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THE THYROID-PITUITARY HOMEOSTATIC MECHANISM

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The paper develops a mathematical theory of thyroid-pituitary interaction. It is assumed that the pituitary gland produces thyrotropin, which activates an enzyme of the thyroid gland. The rate of production of thyroid hormone is considered to be proportional to the concentration of that enzyme. It is further assumed that in the absence of the thyroid hormone the rate of production of thyrotropin is constant, but, in general, it is a linear function of the concentration of the thyroid hormone. This picture leads to a system of non-linear differential equations, which present great difficulties. This system, however, may be conveniently "linearized," by considering that the relations between different variables are linear, but that within different ranges of the variables the coefficients are different. Using this approximation, it is possible to show that the system admits periodic solutions of the nature of relaxation oscillations.

Such oscillations are actually observed in some mental disorders, such as periodic catatonia. The study of the effects of different parameters of the system suggests different possible approaches to clinical treatment. In the light of this theory, the experimental determination of the parameters of the system becomes desirable and important.

The system which controls the amount of thyroid hormone in the body is a feed-back regulator which can be described approximately by a set of differential equations. In a previous paper, Danziger and Elmergreen (1954) presented the following non-linear equations in which θ and π are concentrations of system hormones at any time, t, and the remaining quantities are positive real constants:

$$d\theta/dt = k_1 m\pi/(1 + m\pi) - b\theta = P(\theta, \pi) \tag{1}$$

$$d\pi/dt = c - k_2 n\theta/(1 + n\theta) - g\pi = Q(\theta, \pi) \tag{2}$$

$$\theta \geq 0, \quad \pi \geq 0.$$

This system of equations successfully describes most of the observed functions and malfunctions of the thyroid-pituitary ap-

paratus, but fails to account for the existence of sustained oscillations of the hormone levels believed to produce the mental disorder known as periodic relapsing catatonia. To show that sustained oscillations are not possible in the system of (1) and (2), we apply the First Theorem of Bendixon as given by Minorsky (1947), which states that limit cycles cannot exist in systems of this form if $\partial P/\partial\theta + \partial Q/\partial\pi$ does not change sign. This negative criterion is satisfied by (1) and (2), and we can conclude that the nonlinearities present are not of the type which can produce sustained oscillation in this system. For purposes of stability study, therefore, the Langmuir adsorption terms in (1) and (2) may be linearized.

To account for the observed sustained oscillations, we postulate here a system of three first-order differential equations which are similar to the linearized form of (1) and (2), but which includes a specific mechanism by which the pituitary stimulates the thyroid. It will be shown that this linear, third-order system will yield the same information as the set (1) and (2) and will also permit sustained oscillations of the hormone levels under proper conditions.

The following symbols will be employed:

π is the concentration of thyrotropin at time, t;
E is the concentration of activated enzyme at time, t;
θ is the concentration of thyroid hormone at time, t;
b, g and k are loss constants;
a, h and k are constants expressing the sensitivity of the glands to stimulation or inhibition;
c is the rate of production of thyrotropin in the absence of thyroid inhibition.

As in our previous communication, we assume that the rate of thyrotropin production is reduced by an amount proportional to the concentration of thyroid hormone and that the rate of loss of thyrotropin is proportional to the thyrotropin concentration. Equating, then, the rate of change of π to the rate of production minus the rate of loss, yields

$$d\pi/dt = (c - h\theta) - g\pi \quad \text{when} \quad \theta \leq c/h \tag{3}$$

which is the linearized form of (2). The restriction placed on (3) is now required because the periodic solutions to be investigated will permit thyroid hormone levels of sufficient magnitude to sup-

press the production of thyrotropin. The production-rate term, $(c - h\theta)$, can apply only for $\theta \leq c/h$ as the pituitary gland can produce no output in the presence of thyroid concentrations greater than c/h. To describe the system for large values of θ, we must include the degenerate form of (3),

$$d\pi/dt = -g\pi \quad \text{when} \quad \theta \geq c/h. \tag{4}$$

To describe the mechanism in the thyroid gland, we assume that thyrotropin activates a thyroid enzyme, which, when activated, catalyzes the production of hormone, θ. Such an effect of thyrotropin has been observed by Vanderlaan and Greer (1950), by Ghosh, Woodbury and Sayers (1951), and by others, who reported that the thyroid of hypophysectomized animals was unable to trap radioactive iodide, and that this ability was restored by the administration of thyrotropin. While it is not necessary to identify the enzyme involved, we may imagine it to be a peroxidase which oxidizes iodide to iodine before its incorporation into the thyroid hormone molecule. Thyroid hormone production, according to this assumption, will depend on the concentration of activated enzyme and not directly on the level of thyrotropin. To describe this enzyme action, we equate the rate of change of activated enzyme to the rate of activation, assumed proportional to π, minus the rate of inactivation, assumed proportional to E. This yields

$$dE/dt = m\pi - kE. \tag{5}$$

Similarly, equating the rate of change of thyroid hormone concentration to the rate of production minus the rate of loss, yields

$$d\theta/dt = aE - b\theta, \tag{6}$$

which is similar to the linearized form of (1) except that the production-rate term is now a function of the activated enzyme level rather than the thyrotropin concentration.

Equations (3), (4), (5), and (6) now represent the feed-back regulator action of the thyroid-pituitary system. The physical condition that the hormones and enzyme cannot have negative values is now inherent in these equations and need not be stated separately.

This system agrees with the observations in various clinical situations. If the pituitary gland is removed, c will become zero, π will fall exponentially with time, E will follow π, and θ will follow E. If E is unable to function, because of the presence of some enzyme poison or of inadequate supply of iodide, the rate of pro-

duction of thyroid hormone is reduced in magnitude, and the resulting increase in π will not overcome the effect of the poison or the deficiency. If the thyroid gland is removed, θ will fall exponentially with time, and π will approach the value c/g.

A more convenient form of the equations may be obtained by means of variable changes. Let

$x = (g/h)\pi$ be a new variable proportional to π;
$y = (gk/hm)E$ be a new variable proportional to E;
$C = c/h$ be a controlling parameter;
$K = (ahm/bgk)$ be a dimensionless over-all gain constant;
$T_1 = 1/g$, $T_2 = 1/k$ and $T_3 = 1/b$ be system time constants.

Substitution of these quantities in (3), (4), (5), and (6) yields

$$T_1 dx/dt + x = C - \theta \quad \text{when} \quad \theta \leq C \tag{7}$$

$$T_1 dx/dt + x = 0 \quad \text{when} \quad \theta \geq C \tag{8}$$

$$T_2 dy/dt + y = x \tag{9}$$

$$T_3 d\theta/dt + \theta = Ky. \tag{10}$$

As a first step in the analysis of the set of equations (7) through (10), the steady-state levels of the dependent variables will be determined. For a normal system, the steady state may be characterized by zero rates of change of the hormone and enzyme levels; further, the steady-state level of θ must be less than C. Setting, then, the derivatives in (7), (9), and (10) equal to zero and solving for the steady-state levels of the hormones yields

$$x_s = C/(1 + K) \tag{11}$$

$$\theta_s = CK/(1 + K). \tag{12}$$

These steady-state equations correlate the behavior of the thyroid-pituitary regulator with the system constants. The parameter $C = c/h$ is seen to control the steady-state levels of both hormones, while the gain constant $K = (ahm/bgk)$ has a large effect on x_s and a relatively small effect on the steady-state level of thyroid hormone. It can be shown that typical values of K will be sufficiently large to permit the approximation $K/(1 + K) = 1$ so that (12) may be written as

$$\theta_s \cong C = c/h. \tag{13}$$

Since the controlled quantity in the thyroid-pituitary system is the level of thyroid hormone, equations (12) and (13) are of primary

importance. These equations show that if the thyroid gland is normal the steady-state level of thyroid hormone is essentially dependent on the pituitary constants c and h, whereas if K is large the effects of the sensitivity constants a and m and of the loss constants b, g, and k are almost completely nullified by feed-back action. This result is analogous to that of feed-back amplifiers or servo-mechanism systems where the output-input ratio can be made practically independent of system parameters. The thyroid-pituitary system, therefore, can be considered to be a feed-back regulator which, in terms of the servo-mechanism analog, has an input C, an output θ and an open loop gain K.

System malfunction characterized by abnormal steady-state hormone levels, such as hyperthyroidism or hypothyroidism, in conditions not involving deficiencies of raw materials or enzymes, arise, as shown by (13), from a defect in the pituitary gland which would produce an abnormal ratio c/h. In toxic goiter, for example, the presence of excessive levels of thyrotropin, as well as of thyroid hormone, indicates a higher than normal c/h. Thyroidectomy would reduce the level of thyroid hormone but would increase the level of thyrotropin. This can be seen by making the constant, a, in (6) and hence the value of K, zero. From (11) and (12), then, ϖ_s becomes equal to C and θ_s becomes zero. From this we conclude, in accordance with clinical observation, that thyroidectomy would relieve some, but not necessarily all, of the symptoms of toxic goiter. Thyroidectomy followed by administration of sufficient thyroid extract to keep the thyrotropin concentration low would seem to be a more efficient treatment of the disorder.

Hypothyroidism may result from a variety of causes. The pituitary type is due to abnormally low values of c/h and, hence, to a malfunction of the production mechanism of the pituitary gland; it is associated with low values of thyrotropin. The type caused by goitrogens, which inhibit E, is due to failure of the production mechanism of the thyroid gland; it is associated with high values of thyrotropin. Analysis of the steady-state levels for the condition of iodine deficiency requires further discussion of the production-rate term in (6), which has been assumed to be linear for all positive values of activated enzyme, E. This term will be linear only as long as a sufficient amount of iodine is present to permit thyroid-hormone production at the rate demanded by the level of E.

If iodine intake is severly limited, the term aE will express the thyroid production rate only so long as the rate of iodine utilization does not exceed the rate of iodine intake. Mathematically, we may define a critical value of enzyme, E_c, for which iodine is used as fast as it becomes available. Then for $E \geq E_c$, the thyroid production rate would be constant at the value aE_c. If the normal steady-state level of activated enzyme is greater than E_c, the system is limited by the supply of iodine, and the steady-state thyroid hormone level must be less than normal.

The last system malfunction which we shall discuss is the mental disorder called periodic relapsing catatonia (Gjessing, 1939, 1953), which is characterized by fairly regular variations in the basal metabolic rate (BMR) and in the severity of the psychosis. In applying equations (7) through (10) to this condition, we assume the observed variations in the BMR are due to sustained oscillations in the thyroid hormone level and that the periodic nature of the solution of the system equations is due to instability for $\theta < C$.

To investigate the stability of the system, we obtain the third-order differential equations describing the variation of thyroid hormone with time. Eliminating x and y from (7), (8), (9), and (10) yields the pair of linear equations

$$a_3 d^3\theta/dt^3 + a_2 d^2\theta/dt^2 + a_1 d\theta/dt + (1+K)\theta = KC\,, \quad \theta < C \tag{14}$$

$$a_3 d^3\theta/dt^3 + a_2 d^2\theta/dt^2 + a_1 d\theta/dt + \theta = O\,, \quad \theta > C \tag{15}$$

where the coefficients are the positive real numbers given by

$$\begin{aligned} a_3 &= T_1 T_2 T_3 \\ a_2 &= T_1 T_2 + T_1 T_3 + T_2 T_3 \\ a_1 &= T_1 + T_2 + T_3 \end{aligned} \tag{16}$$

Employing the classical operator $D = d/dt$, the characteristic equations of both (14) and (15) may be written as

$$a_3 D^3 + a_2 D^2 + a_1 D + a_0 = 0\,, \tag{17}$$

where $a_0 = 1 + K$ for (14) and $a_0 = 1$ for (15).

Stability of (14) and (15) may be discussed in terms of a factored form of (17) which is

$$[D - \beta][(D - \alpha)^2 + \omega^2]\,, \tag{18}$$

where α, β and ω are functions of the coefficients. The roots of (17), expressed in terms of the factors of (18) are

$$D = \beta, \quad D = \alpha \pm i\omega, \tag{19}$$

where ω may be real or imaginary.

A general solution of both (14) and (15) may now be written in the form

$$\theta = \theta_s + N\, e^{\beta t} + M\, e^{\alpha t} \sin(\omega t + \Phi), \tag{20}$$

where N, M and Φ are determined by the initial conditions. Clearly, all six of these constants differ for the two solutions included in (20): for (14), $\theta_s = CK/(1 + K)$ and the solution is valid for $\theta < C$; while for (15), $\theta_s = 0$ and the solution is valid for $\theta > C$. Further, a_0 differs for the two cases and hence α, β and ω will necessarily have different values. Stability of (14) and (15) requires that $\lim_{t \to \infty} \theta = \theta_s$ which obtains only if both α and β are negative. Analysis of (17) and (18) shows that β must always be negative for positive real coefficients, while α may take on either positive or negative values depending upon the relative values of the coefficients. A stability criterion for (14) and (15) may then be developed by finding a relation connecting the magnitudes of the coefficients which will encompass all possible values for which $\alpha < 0$. This can be done by considering the critical case with $\alpha = 0$ which separates the stable solutions with $\alpha < 0$ from the unstable with $\alpha > 0$. The quadradic factor in (18) becomes $(D^2 + \omega^2)$, for $\alpha = 0$, and can be divided out of (17) leaving a linear factor $(a_3 D + a_2)$ and a remainder $(a_1 - a_3\omega^2)D + (a_0 - a_2\omega^2)$. If $(D^2 + \omega^2)$ is to be a factor of (17), both terms in the remainder must vanish, yielding

$$\omega^2 = a_1/a_3 = a_0/a_2 \tag{21}$$

and

$$a_0 = a_1 a_2/a_3. \tag{22}$$

The critical solution is then defined by $\alpha = 0$, $\beta = -a_2/a_3$ and $\omega^2 = a_1/a_3$, and occurs when the coefficients are related by (22).

In order to employ (22) as a stability criterion, we need only observe that if $a_0 = 0$, the characteristic equation becomes one of second degree which for positive real coefficients must always have roots with negative real parts. Therefore for small a_0 the

third-order differential equations (14) and (15) are stable with $\alpha < 0$; while for a_0 large enough, $\alpha > 0$ and instability will exist. This leads logically to the criterion that (14) and (15) are stable for all values of coefficients such that $a_0 < a_1 a_2 / a_3$. This result can also be obtained by employing any of the stability tests applicable to linear differential equations with constant coefficients. See, for example, the criterion of Routh or Hurwitz as given by MacMillan (1951).

To apply this stability criterion to (14) and (15), we employ (16) to express the coefficients in terms of the time constants. As T_1, T_2 and T_3 are positive real numbers, it can be shown that $a_1 a_2 / a_3$ has a minimum value of nine when the time constants are equal. Hence, for (14) in which $a_0 = 1 + K$, the solution (20) will be stable for any value of K less than a critical value defined as

$$K_c = a_1 a_2 / a_3 - 1, \tag{23}$$

where K_c is greater than or equal to 8 and corresponds to the critical solution with $\alpha = 0$. For (15), in which $a_0 = 1$, stability will exist for all values of the time constants, the roots of its characteristic equation being $-1/T_1$, $-1/T_2$ and $-1/T_3$ and, hence, all real and negative.

Consider now the case where $K > K_c$. For any set of initial conditions such that $\theta_0 < C$, an unstable system governed by (14) will exist with a solution of the form of (20) in which $\alpha > 0$. This will yield an oscillatory variation of θ with the amplitude of the periodic term increasing exponentially with time. Ultimately, in this mode of variation, θ will reach the value C, and the system will degenerate to the stable system of (15) with a zero steady-state level. To show that the stable solution must exist for a finite time interval, we may use (10) which shows that $d\theta/dt$ must be continuous as neither θ nor y may change value instantaneously. Thus, as $d\theta/dt$ is positive when $\theta = C$ in the unstable mode, the thyroid level must continue to rise before it can begin to fall toward the zero steady-state level of (15). This aperiodic variation of the thyroid hormone can continue only so long as $\theta > C$, and when θ falls to the value C, (14) will again govern the system. Here, again, the continuity of $d\theta/dt$ requires that θ fall below the level C before rising in the unstable mode. Clearly, this sequence of events will give rise to a sustained oscillation of the thyroid hormone concentration about the value C, governed alternately by (14)

and (15) and would obtain for any set of initial conditions. This type of solution, caused by periodic degeneration of an unstable system, is a relaxation oscillation (Minorsky, *loc. cit.*).

Any treatment of periodic relapsing catatonia must suppress the oscillation of the hormone levels, which has been shown to be caused by abnormally large gain, $K = (ahm/bgk)$. As it is not feasible to change, by treatment, any of the system constants so as to reduce K, the only procedure which will abolish these oscillations is one which would suppress the thyrotropin output of the pituitary gland and the output of the thyroid gland. The level of thyroid hormone necessary to maintain the BMR would then have to be supplied from an external source. Thyroidectomy followed by administration of thyroid extract would meet these conditions if the thyroid extract added to the system were sufficient to limit the thyrotropin level to safe magnitudes. The administration of sufficient thyroid extract will, however, produce the same results without thyroidectomy. This procedure will be shown to comprise the proper treatment of periodic relapsing catatonia.

If thyroid extract is administered in daily doses such that the effective rate of assimilation is a constant, R, the original equations must be modified to include this second source of thyroid hormone. For this modified system, equation (6) becomes

$$d\theta/dt = aE + R - b\theta \tag{24}$$

and (10) becomes

$$T_3 d\theta/dt + \theta = Ky + T_3 R\,. \tag{25}$$

The total system thyroid, θ, can now be considered to consist of two components: the endogenous hormone, z, and the exogenous hormone T_3R. Substituting $\theta = z + T_3R$ in (7), (8), (9), and (25) with $C' = C - T_3R$, yields

$$T_1 dx/dt + x = C' - z \quad \text{when} \quad z \leq C' \geq O \tag{26}$$

$$T_1 dx/dt + x = O \quad \text{when} \quad z \geq C' \geq O \tag{27}$$

$$T_2 dy/dt + y = x \tag{28}$$

$$T_3 dz/dt + z = Ky \tag{29}$$

for the system under treatment. Note that C' is proportional to the rate of thyrotropin production in the absence of endogenous thyroid hormone inhibition and cannot be negative. If $R \geq C/T_3$, C' must be zero, and (26) becomes (27) for all values of z. The behavior

of this modified system, therefore, will differ for the two cases: (a) $R < C/T_3$ and (b) $R \geqslant C/T_3$.

In case (a), where the rate of assimilation of exogenous thyroid hormone is small, (26) through (29) apply. These equations are the same as the original set (7) through (10) except that z replaces θ and C' replaces C. Considering the endogenous hormone concentrations, x and z, the administration of thyroid extract such that $R < C/T_3$ is equivalent to reducing the controlling parameter C to C', and all of the preceding analyses and conclusions for the unmodified system are applicable. The essential difference between this modified system and the original is the effect on the total system thyroid hormone level. Equation (12) will apply for the steady-state endogenous thyroid hormone with $C = C'$ but the steady state of the total system hormone, being the sum of z_s and T_3R, would become

$$\theta_s = (KC + T_3R)/(1 + K), \tag{30}$$

which is slightly higher than that of the unmodified system. Thyroid extract treatment, therefore, would not be effective in toxic goiter as the thyroid level would increase slightly, although some benefit might result from the reduction of the thyrotropin level. Improvement would result in cases of hypothyroidism with thyroid extract treatment regardless of the cause of thyroid deficiency. In these conditions administration of thyroid extract sufficient to bring the thyroid hormone level up to the required steady-state value would reduce the steady-state thyrotropin concentration without harmful effect. In periodic relapsing catatonia, if $R < C/T_3$, no improvement will result. In this case, oscillations of z about C' will exist, yielding, as in the original system, oscillations of θ about C; the only difference will be a reduction in the average values of the periodic thyrotropin and enzyme variations.

In case (b) where the rate of assimilation of exogenous thyroid hormone is sufficiently large to suppress the production of thyrotropin, only equations (27), (28), and (29) apply. Here $R > C/T_3$, and the system, for any K and any set of initial conditions, is absolutely stable. For unequal time constants, the following general solutions apply:

$$x = X_1\, e^{-t/T_1} \tag{31}$$

$$y = Y_1\, e^{-t/T_1} + Y_2\, e^{-t/T_2} \tag{32}$$

$$z = Z_1\, e^{-t/T_1} + Z_2\, e^{-t/T_2} + Z_3\, e^{-t/T_3}, \tag{33}$$

where $t = 0$ at the instant when treatment starts; $X_1 = x_0$, Y_1 and Y_2 are determined by x_0 and y_0; and Z_1, Z_2, and Z_3 are determined by x_0, y_0, and z_0. These aperiodic transient solutions have zero steady-state values and are independent of the magnitude of R; they are completely determined by the time constants, the gain, K, and the state of the system at $t = 0$. The system with $R > C/T_3$ would ultimately become quiescent with the thyroid hormone being supplied entirely by the external source. For treatment of periodic relapsing catatonia, the rate of intake of exogenous thyroid hormone should be $R = C/T_3$ so that a steady state, $\theta_s = C$, is achieved. This results in complete stabilization of the thyroid hormone concentration at a value which is only $(K + 1)/K$ greater than the normal steady state of (12). If C is abnormally small, then R should be sufficiently large to raise θ_s to the level required for health.

The transient variation of endogenous thyroid hormone, z, will determine the overshoot of the thyroid hormone concentration following the start of treatment with large R. As $\theta = z + T_3R$ and as the steady state is $\theta_s = T_3R$, the single maximum of z, from (33), is the overshoot. This peak value of hormone can reach dangerous magnitudes, and care must be taken in the administration of thyroid extract to hold the overshoot to a low value. Several possible treatment procedures which will minimize the overshoot in thyroid hormone are known. Gjessing (*loc. cit.*) originally favored starting treatment with large values of R and suggested, as an optimum starting point, a time when the BMR is near a minimum in the pretreatment oscillation. This starting point was determined by experiment and produced satisfactory results. We assume that variations in the thyroid hormone level are reflected in variations in the BMR; and, hence, Gjessing's method is equivalent to starting treatment when the oscillatory thyroid hormone is a minimum. Since the thyroid hormone level will jump by the amount T_3R soon after treatment is started, it is evident that a minimum initial value will obtain if θ is a minimum at $t = 0$. The endogenous hormone, z, from (33) will have a maximum after $t = 0$, however, and a more precise identification of the optimum starting point is possible. This would depend upon the system parameters as well as the initial conditions but would not be of much use clinically as none of these quantities can be accurately determined.

A second procedure, suggested by Danziger and Kindwall (1953), starts with small R at any point in the oscillation cycle. The daily intake of exogenous thyroid hormone is then gradually increased until a stabilizing level is achieved. This method permits initiation of treatment without a long period of preliminary study and will yield safe peak values of thyroid hormone.

A third possibility is suggested by inspection of (25), which shows that a maximum θ results when $d\theta/dt = 0$ and y has some value, y_1. This maximum is then

$$\theta_{max} = Ky_1 + T_3R, \tag{34}$$

where the overshoot is Ky_1. If the thyroid enzyme be inhibited before treatment starts so that y_1 is small, treatment with large R could be safely started without regard to the state of the system. This result could be achieved by administration of a thyroid enzyme poison before the start of thyroid extract treatment.

General Remarks

The preceding analysis illustrates the utility of mathematical representation of an endocrine control system. The feed-back aspects of the thyroid-pituitary homeostatic mechanism make possible an analogy with this and perhaps other physiological phenomena on the one hand, and feed-back amplifiers or servo-mechanism systems on the other. A major difference in the philosophy of study in these fields arises from the fact that the electronic or servo-mechanism engineer is interested primarily in synthesis whereas the endocrinologist must necessarily consider analysis of a system in which measurements are difficult and numerical values of parameters are either unknown or known with relatively little accuracy.

In the thyroid-pituitary homeostatic mechanism, particular solutions of the equations presented are of secondary importance. If the system parameters are known or can be estimated, standard procedures can be used to obtain particular solutions. We employed high-speed electronic analogue computer techniques to obtain rapid checks on the conclusions made. For this computer study system parameters were estimated, partly from the literature and partly from the theory developed. This work, Danziger and Elmergreen (1956), illustrated additional advantages of mathematical analysis in the determination of some of the parameter values. In this case,

the time constants, T_1 and T_3, could be estimated from data in the literature while the time constant, T_2, of the thyroid enzyme is unknown. Using relaxation oscillation theory of periodic relapsing catatonia and clinically observed periods of oscillation, the time constant T_2 was evaluated in terms of T_1 and T_3. Further, an estimated value of typical gain, K, was obtained by computing the critical value from (23). The theory developed provided a means for estimating, with a minimum of experimental data, the numerical values of parameters in a typical system.

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