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MATHEMATICAL THEORY OF PERIODIC RELAPSING CATATONIA*

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Two first-order, non-linear differential equations are presented to describe the interaction of the thyroid and pituitary glands and to explain some of the phenomena of periodic relapsing catatonia. Topographical study of these equations shows a mechanism in which either random fluctuations of hormone levels or system stability may occur. The variations in hormone concentrations are assumed to be caused by system malfunction, while stability is shown to result from the administration of exogenous thyroid which, if supplied at an optimum rate, suppresses the output of both glands. The system, under treatment, shows a zero level of thyrotropin and a thyroid concentration which is larger than the equilibrium level in the untreated system. The theory is consistent with what is known of the course and proper treatment of periodic relapsing catatonia.

Periodic relapsing catatonia, first described and successfully treated by R. Gjessing (1939), is a type of mental disorder marked by fairly regular variations in the patient's behavior. These variations persist, usually until death, unless the patient is given appropriate amounts of thyroid extract or thyroxin; and they return if the daily intake of thyroid falls below a level which is critical for the patient. Shock therapy may relieve the symptoms temporarily, but often is without effect and is never of lasting benefit.

Gjessing (*loc. cit.*), Danziger *et al.* (1948), A. G. Gornall *et al.* (1953), and G. Mall (1952) observed that the clinical condition is correlated with fluctuations in the basal metabolic rate (BMR). In very elegant experiments, Gjessing found regular changes in the nitrogen balance, which we believe reflect changes in the BMR.

In explaining these findings, we postulate the following concepts of thyroid-pituitary interactions: The pituitary makes a hormone, thyrotropin, which stimulates the thyroid gland to make thyroid hormone, which in turn inhibits the production of thyrotropin. If the pituitary is removed, the production of thyroid hormone falls to zero, while if the thyroid gland is removed, the production of thyrotropin proceeds un-

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checked at a rate which we assume is constant. If a sufficient quantity of thyroid extract is administered by a physician, the production of thyrotropin is driven to zero. The two hormones are assumed to stimulate and inhibit in accordance with the Langmuir adsorption isotherm (Langmuir, 1916) and are assumed to be excreted or otherwise lost at rates which are proportional to the hormone concentrations. These ideas may be expressed mathematically by the following non-linear differential equations:

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

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

$$\theta > 0 ; \quad \pi > 0 ,$$

where

θ is the level of thyroid hormone in the system at any time t,
π is the level of thyrotropin in the system at any time t,
c is the rate of production of thyrotropin in the absence of thyroid inhibition,
k_1 is a constant equal to the theoretical maximum production rate of the thyroid gland,
k_2 is a constant assumed to be greater than c so that the production of thyrotropin may be zero for sufficiently large θ,
m and n are the constants in the Langmuir adsorption equations, and
b and g are the loss constants.

These equations state that the rate of change of either hormone concentration is equal to the difference in the rate of production and the rate of loss of the hormone. As the production rates of either hormone depend upon the level of the other hormone, (1) and (2) describe a feed back system which will be shown to be a stable regulating mechanism whose apparent function is to maintain the equilibrium level of the two hormones.

The action of the regulating system governed by equations (1) and (2) may be shown conveniently by plotting the locus of successive states in the $\theta - \pi$ plane. Eliminating time from (1) and (2) yields

$$\frac{d\pi}{d\theta} = \frac{Q(\theta, \pi)}{P(\theta, \pi)}, \qquad (3)$$

which describes the family of integral curves or the trajectories of the representative point (θ, π) in the $\theta - \pi$ plane. A topographical solution of (3) for any initial point (θ_0, π_0) may be obtained by the method of isoclines (Minorsky, 1947). A simplified analytical procedure employing the concept of isoclines will be employed to show the general shape of any trajectory. The two limiting isoclines, $d\pi/d\theta = 0$ and $d\pi/d\theta = \infty$, may be obtained by setting (3) equal to zero and infinity respectively, yielding for $d\pi/d\theta = 0$ the curve,

$$Q(\theta, \pi) = 0, \tag{4}$$

and for $d\pi/d\theta = \infty$ the curve,

$$P(\theta, \pi) = 0. \tag{5}$$

As shown in Figure 1, the limiting isoclinal curves divide the $\theta - \pi$ plane

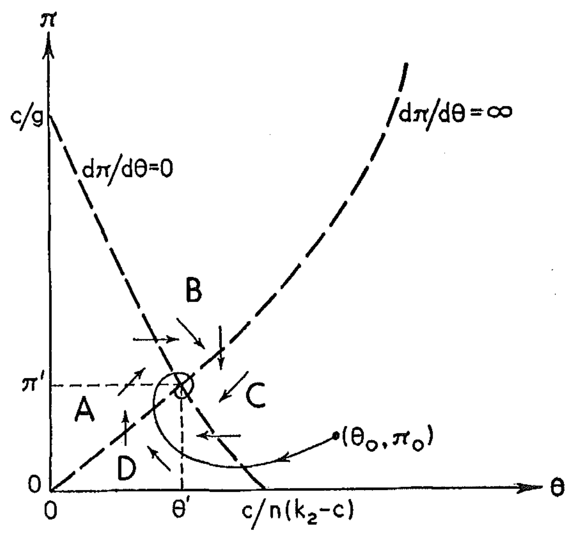

FIGURE 1. The θ-π plane diagram and typical trajectory for equation (3)

into four regions, which by analysis of (1) and (2) may be characterized by the following:

$$\text{Region } A \quad \frac{d\theta}{dt} > 0; \quad \frac{d\pi}{dt} > 0; \quad \frac{d\pi}{d\theta} > 0 \tag{6}$$

$$\text{Region } B \quad \frac{d\theta}{dt} > 0; \quad \frac{d\pi}{dt} < 0; \quad \frac{d\pi}{d\theta} < 0 \tag{7}$$

$$\text{Region } C \quad \frac{d\theta}{dt} < 0; \quad \frac{d\pi}{at} < 0; \quad \frac{d\pi}{d\theta} > 0 \tag{8}$$

$$\text{Region } D \quad \frac{d\theta}{dt} < 0; \quad \frac{d\pi}{dt} > 0; \quad \frac{d\pi}{d\theta} < 0. \tag{9}$$

The shape of any trajectory defined by (3) and the initial point (θ_0, π_0) is now clearly defined by the required values of the trajectory slopes on the limiting isoclines and by the signs of these slopes in the four intermediate regions. Clearly, all trajectories must be clockwise spirals terminating at the singular point (θ', π') which is the equilibrium condition for the system. In the time domain, the spiral trajectories would appear as damped oscillations of θ and π about the equilibrium levels θ' and π'. Figure 1 includes a typical trajectory as well as the trajectory directions on the limiting isoclines and in the four intermediate regions of the $\theta - \pi$ plane.

The action of the thyroid-pituitary regulating system as illustrated by this analysis can be summarized as follows: If, due to any disturbance, the hormone concentrations are driven away from the equilibrium point, the regulating action will return the system to equilibrium by means of rapidly damped oscillations of both hormone levels.

In periodic relapsing catatonia, observed variations in the level of thyroid hormone are sustained with irregular amplitudes. This suggests a recurring malfunction of some part of the system which causes the hormone levels to be driven away from equilibrium. The response of the system of equations (1) and (2) to random disturbances would, if the equations were valid in the intervals between disturbances, consist of trains of damped oscillations of the hormone levels. Although the source of instability is not known, stabilization of the thyroid level can be achieved by rendering the regulating system partially or wholly inoperative by substituting externally added thyroid for all or most of the internally produced hormone. If thyroid is added to the system by daily doses of thyroxin or thyroid extract, the equilibrium level of thyrotropin will be reduced or suppressed entirely while the equilibrium level of thyroid hormone will be increased. These general effects have been partially confirmed by clinical observations and will be shown to result from mathematical analysis of the thyroid-pituitary system modified by an input of exogenous thyroid.

Assume the system of equations (1) and (2) is modified by the daily addition of equal amounts of thyroid extract. As the system time constants are long compared to the 24-hour period between doses, the intake of exogenous thyroid extract can be assumed to be equivalent to a second source of thyroid whose rate of production is constant at a value taken, for convenience, at bK where K is a constant and b is the loss constant in (1). As the rate of change of the thyroid level depends upon the equivalent rate of production, equation (1) will be modified by the factor bK and can be written as

$$\frac{d\theta}{dt} = \frac{k_1 m\pi}{1 + m\pi} - b(\theta - K) . \tag{10}$$

Equation (2) does not change, but equation (3) will contain the factor bK and becomes

$$\frac{d\pi}{d\theta}=\frac{Q(\theta,\pi)}{P(\theta-K,\pi)}. \tag{11}$$

The trajectories of the modified system are now defined by (11) and can be sketched in a manner similar to that previously employed. In the $\theta - \pi$ plane diagram, the isocline $d\pi/d\theta = 0$ is unchanged as $Q(\theta, \pi)$ does not contain the parameter K, whereas the isocline $d\pi/d\theta = \infty$ is shifted to the right by an amount K as $P(\theta - K, \pi)$ in (11) differs from $P(\theta, \pi)$ in (3) only in that $\theta - K$ is substituted for θ. It follows, therefore, that

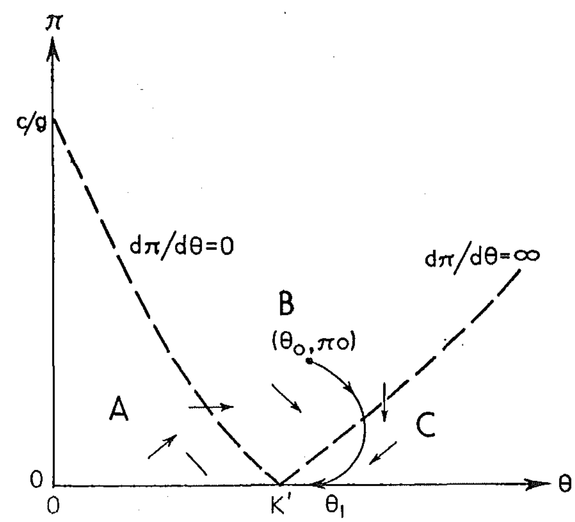

FIGURE 2. The θ-π plane diagram and typical trajectory for equation (11) with $K = K' = c/n(k_2 - c)$.

the equilibrium point (θ', π') for the modified system is shifted so that the equilibrium level of thyrotropin is reduced while the equilibrium thyroid level is increased.

Consider the critical case where $K = K' = c/n(k_2 - c)$, the value of the θ-intercept of the unchanged isocline $d\pi/d\theta = 0$. The $\theta - \pi$ plane diagram for this case is sketched in Figure 2. Here the singular point $(K', 0)$ lies on the θ-axis and at equilibrium, the output of both glands is zero while the system thyroid level is K' and is supplied entirely from the external source. At equilibrium, therefore, the daily intake of thyroid just balances the loss and neither gland is required to deliver hormones to the system.

The response of this modified system with $K = K'$ is now limited to possible momentary output of either or both glands or a change in the loss constant b. A disturbance of the first type would produce an initial point in the part of region B where $\theta > K'$ or in region C, and hence would be followed by a limited spiral trajectory continuing until the representative point reaches the θ-axis. At this point, $(\theta_1, 0)$, equations (2) and (10) would degenerate to

$$\pi = 0 \tag{12}$$

and

$$\frac{d\theta}{dt} + b\theta = bK'. \tag{13}$$

The representative point would, therefore, move along the θ-axis toward the equilibrium point $(K', 0)$ in accordance with the simple exponential time function which is the solution of the linear equation (13). A change in the loss constant b would modify the slope and position of the isocline $d\pi/d\theta = \infty$ and would cause a shift in the equilibrium point. The trajectory produced by an increase in b would be an exponential time decrease of θ toward the new equilibrium point with π remaining zero; and that produced by a decrease in b would be a small spiral originating in region A and proceeding to the new equilibrium point on the θ-axis. A change in the loss constant g would produce no response as the equilibrium level of π is zero.

As clinical observations show that the modification of the system as described here stabilizes the thyroid level without significant subsequent fluctuations, it is probable that the actual disturbing mechanism found in periodic relapsing catatonia is of the type which would produce no response in the modified system; namely, a decrease in the loss constant g or a momentary decrease in the output of either gland.

The transient effects following the initiation of treatment or a change in the magnitude of the daily dose of thyroid extract remain to be discussed. A treatment procedure in which a large initial dose or a series of large doses is administered, followed by smaller daily amounts to maintain the level established, would result in a large overshoot of the total thyroid level which could easily reach dangerous magnitudes. On the other hand, smaller doses, gradually increasing so that the average level of exogenous thyroid would build up to the desired value K', would minimize the transient effects and yield an observational means of determining the optimum rate of thyroid intake. The former method would certainly produce stabilization in a shorter time, and has been described by Gjessing (*loc. cit.*). In this procedure, however, care must be taken to start treatment at an optimum point on the oscillatory cycle and an extended period of preliminary study is required before treatment can begin. The second method allows treatment to be initiated at any time and avoids the danger of large peak values of thyroid concentration.

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