PATHOLOGICAL CONDITIONS RESULTING FROM INSTABILITIES IN PHYSIOLOGICAL CONTROL SYSTEMS*

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1. Introduction

A large number of human diseases are characterized by changes in the qualitative dynamics of physiological control systems: Systems that normally oscillate, stop oscillating, or begin to oscillate in a new and unexpected fashion, and systems that normally do not oscillate, begin oscillating. These changes in qualitative dynamics often have a sudden onset, and in many instances it has not been possible to identify the factors that lead to the disease. By *dynamical disease* we mean a disease that occurs in an intact physiological control system operating in a range of control parameters that leads to abnormal dynamics and human pathology.[41] In this paper, the changes in qualitative dynamics associated with the onset of the disease are identified with bifurcations in the dynamics of mathematical models of the physiological control systems. We shall consider in some detail dynamical diseases in the respiratory and haematopoietic systems.

Our starting point is the ordinary differential equation

$$\frac{dx}{dt} = \lambda - \gamma x \tag{1.1}$$

where x is a variable of interest, λ is a production rate for x, γ is the destruction rate of x, and t is the time. For λ and γ constant, $x \to \lambda/\gamma$ in the limit $t \to \infty$. However, in many physiological systems λ and γ at t may depend on x and/or x_τ (the value of x at a time $t - \tau$, where τ is the time lag). We show that instabilities analogous to those found in pathological conditions in humans can be reproduced by assuming that λ and γ in Equation 1.1 are appropriate nonlinear functions of x and/or x_τ.

2. Respiration

Respiratory oscillations in mammals are generated in the brainstem. Several groups have shown that this region is essential for respiration, and that cells located in the brainstem fire phasically during the respiratory cycle. Several dif-

*This research has been supported by a grant from the National Research Council of Canada and the Cancer Research Society of Montreal.

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ferent classes of cells have been identified (e.g., inspiratory cells and expiratory cells which fire during inspiration and expiration, respectively), but the number of different classes of cells, their anatomical location, and interconnections are not agreed upon by workers in the field.[74] A number of mathematical models of the respiratory oscillator have been suggested.[11,14]

Experimental studies have shown that both the frequency and amplitude of the respiratory oscillations can be modulated by a variety of factors including activity in the cerebral cortex, pH and concentrations of CO_2 and O_2 in arterial blood and cerebrospinal fluid, and the amount of stretching in the intercostal muscle in the chest.[24,74] In healthy humans, these inputs act to maintain arterial concentrations of O_2 and CO_2 at constant levels.

Respiratory Disorders[32]

Rapid shallow breathing (panting, tachypnea, or polypnea) occurs in a variety of pathological conditions, for example, as a result of pain in structures moved by breathing, during fever, and under severe hypoxia (low oxygen tension) of long duration. In dogs, panting is a normal response to heat stress, and brief periods of panting (frequency 300–400 min^{-1}) alternate with periods of normal breathing (frequency 20–40 min^{-1}).[63] Superimposed on the panting rhythm may be an occasional deep breath to give a *sighing* pattern.

There are a variety of patterns in which periods of apnea alternate with periods of breathing. We call these *apneic patterns.* Apneic patterns are referred to by clinicians generically as "periodic breathing." The variety of apneic patterns that have been described include Cheyne-Stokes respiration, Biot breathing, and infant apnea.

Cheyne-Stokes breathing is characterized by a regular waxing and waning of breathing amplitude separated by periods of distinct apnea (FIGURE 1). This is the most common apneic pattern encountered clinically, and is often found in obese patients, patients with congestive heart failure, and patients with certain neurological deficits. It is also seen in normal humans after arrival at high altitude. It is interesting that a regular waxing and waning of breathing amplitude *without* apnea (a "wavy" pattern), is more commonly observed than Cheyne-Stokes respiration[65] and is not necessarily associated with pathological conditions (FIGURE 1).

Biot breathing refers to alternating periods of breathing with apnea. The regular alternations of Cheyne-Stokes respiration are absent, and marked irregularity is observed. Biot breathing is often observed just prior to death.

Infant apnea refers to the pronounced periods of apnea found in most premature and many full term infants (FIGURE 2).[66] The apnea generally occurs during rapid eye movement sleep. It has been speculated that there is a causal relation between the sudden infant death syndrome and infant apnea.

Although we have classified apneic patterns into a small number of discrete classes, intermediate patterns also exist. Unfortunately, extended records of pathological breathing patterns are not generally available.

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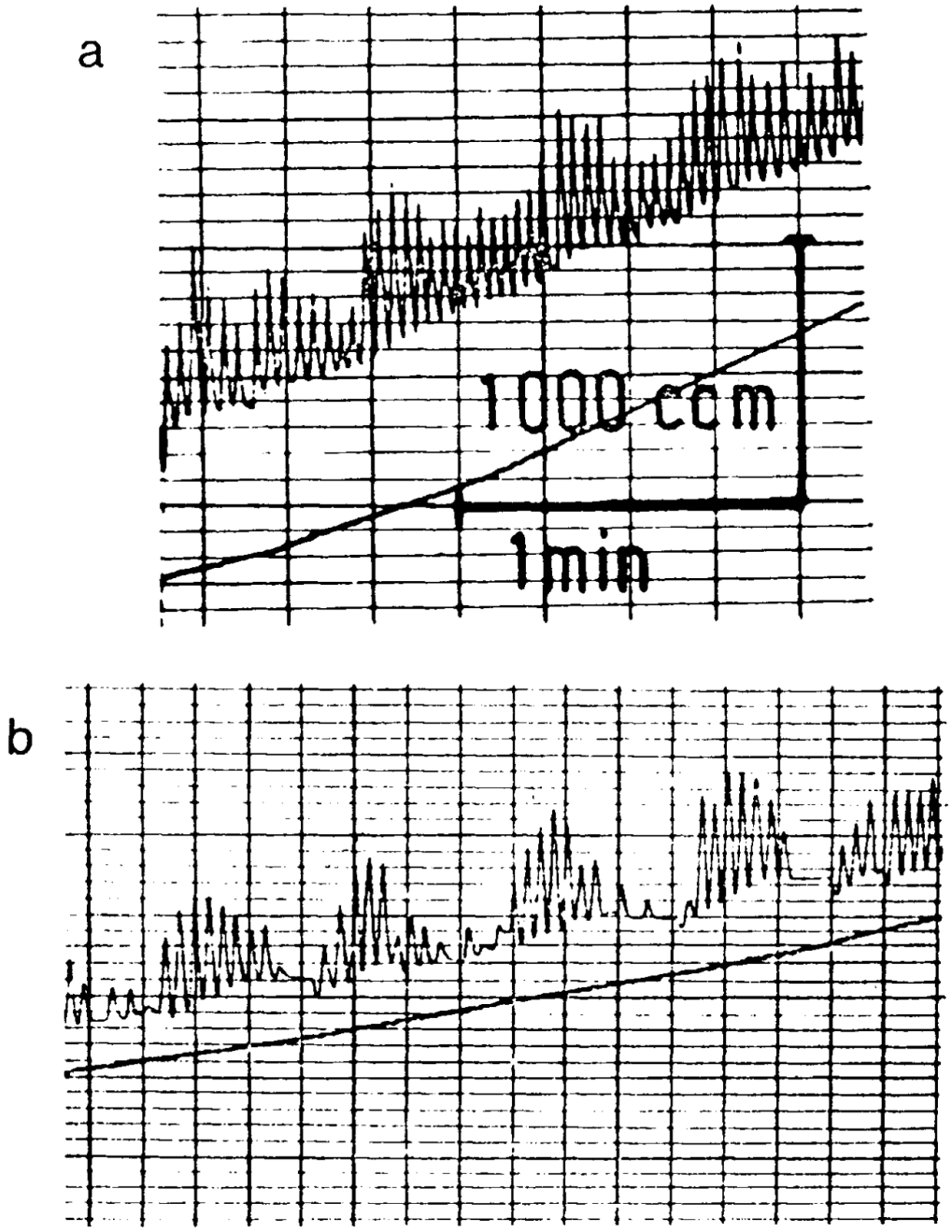

FIGURE 1. (a) A wavelike respiration pattern. (b) Cheyne-Stokes respiration in a 29-year-old man (5 horizontal divisions = 1 min, 10 vertical divisions = 1 liter). (From Sprecht and Fruhman.[65] By permission of *Bulletin Européen de Physiopathologie Respiratoire*.)

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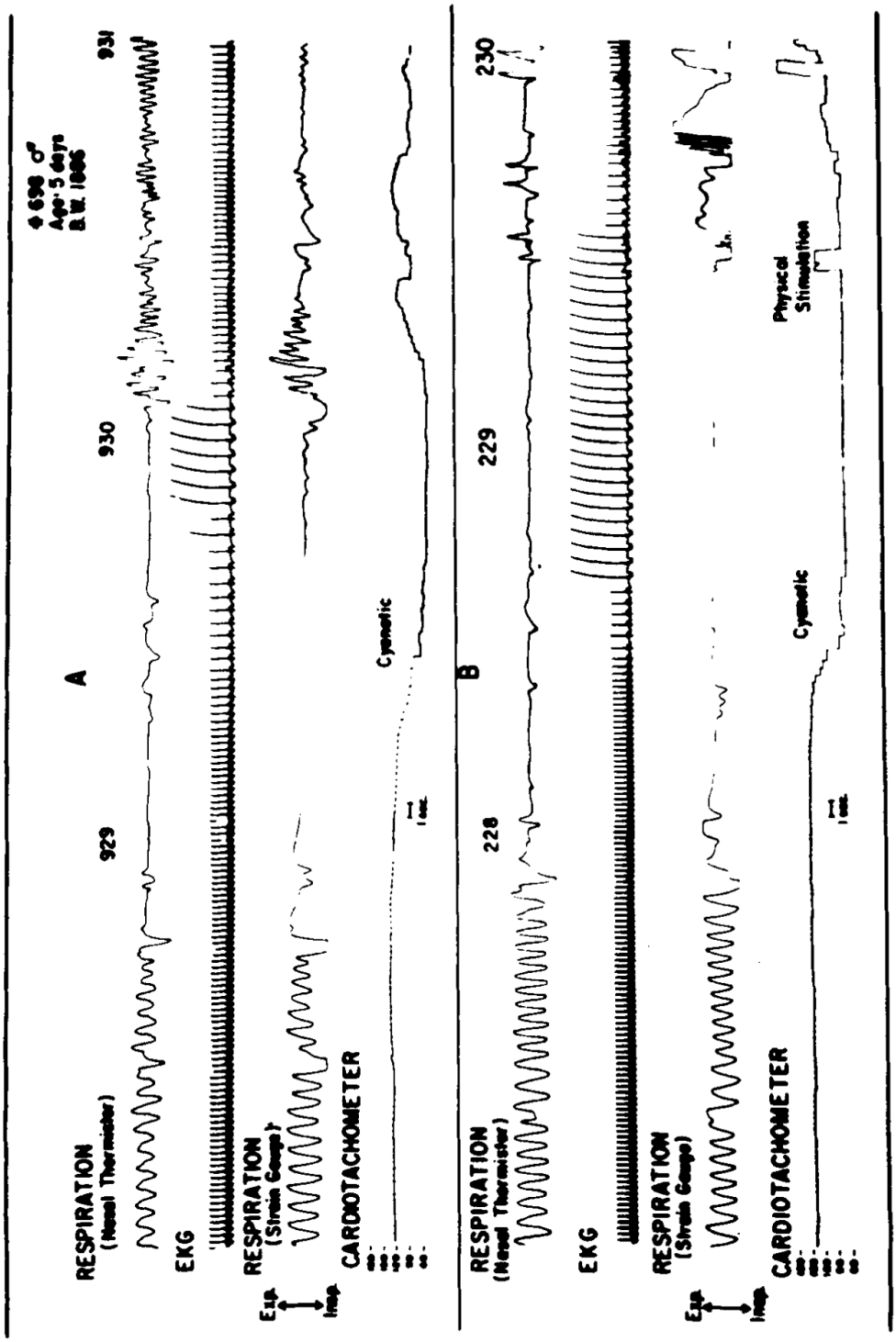

FIGURE 2. Apneic episodes leading to severe bradycardia and cardiac arrhythmia in a 5-day-old infant: (A) breathing spontaneously returned, (B) physical stimulation was applied. (From Steinschneider.[66] By permission of *The Canadian Foundation for the Study of Infant Deaths.*)

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Mathematical Models of Respiratory Disorders

Theoretical studies of the mechanism of Cheyne-Stokes respiration ascribe the slow oscillations observed to instabilities in the respiratory control system.[4,37,47,48] It is known that the total ventilation increases monotonically as the CO_2 concentration in arterial blood increases. However, since the blood is oxygenated in the lungs but the receptors, which are sensitive to the CO_2 concentration, are believed to be present in the brainstem, there is an inherent time lag τ in the respiratory control system. Several investigators have developed complex systems of differential-delay equations to describe the production, transport, and elimination of CO_2 in humans.[37,47,48] Since the mathematical properties of these complex systems of equations are not easily deduced, we have proposed a simplified schematic model which displays similar qualitative features to the more complex models.[41]

The ventilation V at time t is assumed to depend on $x(t - \tau)$, the CO_2 concentration at time $t - \tau$. We also assume that CO_2 elimination is proportional to the product of CO_2 concentration (x) and ventilation. Experimental studies indicate that ventilation is an increasing monotonic function of CO_2 concentration.[24] Assuming that the dependence of the ventilation on CO_2 concentration is described by the Hill function $V = V_{max} x_\tau^n/(\theta^n + x_\tau^n)$, we obtain,

$$\frac{dx}{dt} = \lambda - \frac{\alpha V_{max} x_\tau{}^n x}{\theta^n + x_\tau{}^n} \tag{2.1}$$

where V_{max} is the maximum ventilation and n, θ and α are parameters chosen to agree with experimental data.[41]

The stability of (**2.1**) in the neighborhood of the steady state can be analyzed (at the steady state $dx/dt = 0$). Denoting the values of x and V at the steady state by x_0 and V_0, and setting $S_0 = (dV/dx)_{x_0}$ and $\alpha = \lambda/x_0 V_0$, the first-order equation in x and x_τ is,

$$\frac{dx}{dt} = -\frac{\lambda}{x_0}(x - x_0) - \frac{\lambda S_0}{V_0}(x_\tau - x_0) \tag{2.2}$$

The stability criteria for (**2.2**) are well known.[21] In general, for the first-order linear differential-delay equation,

$$\frac{dz}{dt} = Az + Bz_\tau \tag{2.3}$$

the eigenvalues of the steady state $z = 0$ have negative real parts if and only if,

$$\begin{aligned} &A\tau < 1 \\ &A\tau < -B\tau < \sqrt{(A\tau)^2 + a_1{}^2} \end{aligned} \tag{2.4}$$

where $a_1 \in (0, \pi)$ is the root of the equation,

$$a \cot a = A\tau \tag{2.5}$$

and $a_1 = \pi/2$ if $A\tau = 0$. Applying (**2.4**) to determine the stability of the steady

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state of (**2.1**), we find that the steady state will be stable provided,

$$\frac{\lambda S_0 \tau}{V_0} < \sqrt{\left(\frac{\lambda\tau}{x_0}\right)^2 + a_1^2} \tag{2.6}$$

where a_1 is found by solving,

$$a \cot a = -\frac{\lambda\tau}{x_0} \tag{2.7}$$

Further analysis requires numerical values for the parameters in (**2.6**) and (**2.7**). Approximate values of the parameters for normal humans are readily obtained from the experimental literature.[41] We take,

$$\begin{aligned} x_0 &= 40 \text{ mm Hg} \\ \lambda &= 6 \text{ mm Hg/min} \\ V_0 &= 7 \text{ liter/min} \\ S_0 &= 4 \text{ liter/min mm Hg} \\ \tau &= 0.25 \text{ min} \end{aligned} \tag{2.8}$$

From (**2.8**) we find that $\lambda\tau/x_0 = 0.0375$. A numerical solution of (**2.7**) gives $a_1 = 1.5943$. Since $a_1 \sim \pi/2$, and for the parameters in (**2.8**), $a_1 \gg \lambda\tau/x_0$, the condition for a stable steady state can be given approximately as,

$$S_0 > \frac{\pi V_0}{2\lambda\tau} \tag{2.9}$$

The period of the oscillation is about 4τ.

FIGURE 3 shows numerical integration of (**2.1**) for two values of S_0 in the unstable region with the other parameters given in (**2.8**). Choosing a value of S_0, the parameters in (**2.1**) can be found from the relations,

$$\begin{aligned} n &= \frac{x_0 V_{\max} S_0}{V_0(V_{\max} - V_0)} \\ \theta &= x_0 \frac{(V_{\max} - V_0)^{1/n}}{V_0} \end{aligned} \tag{2.10}$$

Note that both a "wavy" pattern and apneic pattern are found in the figure.

These results are of interest for several reasons. Investigators have noted an increased CO_2 sensitivity (S_0) and delay time in patients displaying Cheyne-Stokes respiration.[3,33] Further, the numerical values computed using (**2.8**) for the unstable regime fall in a range outside accepted values for normals. For example, given V_0, λ, τ in (**2.8**) instability is predicted for $S_0 > 7.44$ 1/min/mm Hg, which is above normal.[24] However, the crudeness of the model makes detailed quantitative comparisons questionable. Other workers, who have investigated stability for mathematical models of respiration, have noted an approximate hyperbolic relation between S_0 and τ, leaving the other parameters of the system

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fixed.[37,47,48] The boundary separating stable and unstable regions in the S_0, τ-plane, given by (**2.9**), is a hyperbola.

The Piecewise Linear Case

Numerical integration of (**2.1**) indicates that, in the unstable regime, the oscillations approach a stable limit cycle oscillation. The problem of determining the asymptotic behavior of time-delay differential equations is complex, and only

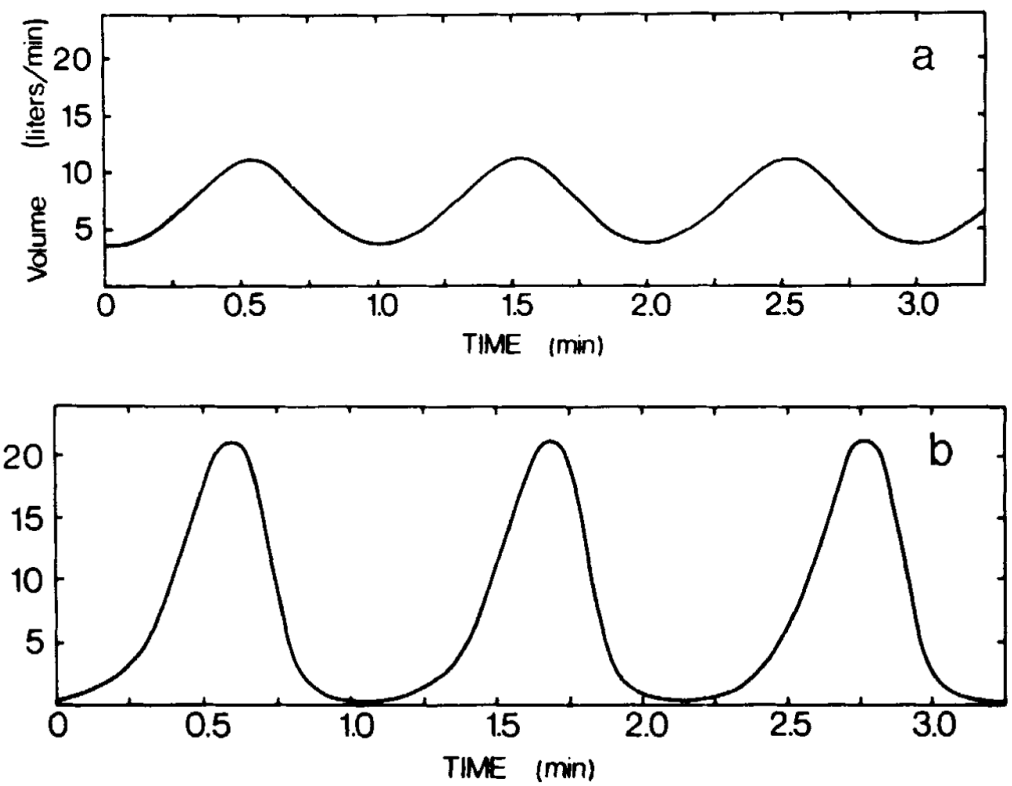

FIGURE 3. Numerical solutions to Equation 2.1. The time course of $x(t)$ as computed from (**2.1**), using parameters listed in (**2.8**) with the exception of S_0. (a) S_0 = 7.7 l/min mm Hg. (b) S_0 = 10.0 l/min mm Hg. With these values of S_0, n and θ in (**2.1**) were computed using (**2.10**). (From Mackey and Glass.[41] By permission of *Science*.)

limited results have been achieved to date.[6,23,44] In the limit $n \to \infty$, Equation 2.1 becomes piecewise linear, and explicit solutions can be constructed.

In the limit $n \to \infty$, (**2.1**) can be written,

$$\frac{dx}{dt} = \begin{cases} \lambda - \gamma x, & x_\tau > \theta \\ 0, & x_\tau = \theta \\ \lambda, & x_\tau < \theta \end{cases} \tag{2.11}$$

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where $\lambda/\gamma < \theta$. Assume that for $t < 0$, $x = x_0$, where $x_0 < \theta$. For $t > 0$, we assume that (**2.11**) holds. By direct integration of (**2.11**), the time course of x can be explicitly computed. From (**2.11**), x initially increases and at some time t_0, $x = \theta$. For $t > t_0$, the temporal evolution of x is given by

$$\begin{aligned}
x(t) &= \theta + \lambda\,(t - t_0), && t_0 \le t \le t_1 \\
x(t) &= (\theta + \lambda\tau)e^{-\gamma(t-t_1)} + \frac{\lambda}{\gamma}\left[1 - e^{-\gamma(t-t_1)}\right], && t_1 \le t \le t_2 \\
x(t) &= \theta e^{-\gamma(t-t_2)} + \frac{\lambda}{\gamma}\left[1 - e^{-\gamma(t-t_2)}\right], && t_2 \le t \le t_3 \\
x(t) &= (\theta - \lambda/\gamma)e^{-\gamma\tau} + \frac{\lambda}{\gamma} + \lambda(t - t_3), && t_3 \le t \le t_4
\end{aligned} \tag{2.12}$$

where:

$$\begin{aligned}
t_1 - t_0 &= \tau \\
t_2 - t_1 &= \frac{1}{\gamma}\log\left[\frac{\theta + \lambda\tau - \lambda/\gamma}{\theta - \lambda/\gamma}\right] \\
t_3 - t_2 &= \tau \\
t_4 - t_3 &= \frac{(\theta - \lambda/\gamma)(1 - e^{-\gamma\tau})}{\lambda}
\end{aligned} \tag{2.13}$$

During the ascending and descending phases, Equation 2.12 is continuous and differentiable. The derivatives are discontinuous at $t = t_1$ and $t = t_3$. Note that $x(t_4) = \theta$, so that for all times $t > t_4$ the solution repeats with a cycle period of,

$$T = 2\tau + \frac{1}{\gamma}\log\left[\frac{\theta + \lambda\tau - \lambda/\gamma}{\theta - \lambda/\gamma}\right] + \frac{(\theta - \lambda/\gamma)(1 - e^{-\gamma\tau})}{\lambda} \tag{2.14}$$

The solution defined by Equations 2.12 and 2.13 is also a solution of Equation 2.11 with $\tau_m = \tau + mT$. As a consequence, for τ fixed, there is a family of solutions, so the solution is not unique.

3. Haematopoiesis

In the normal mammal, circulating levels of the formed elements of the blood (the white and red blood cells, platelets, and lymphocytes) are maintained at fairly constant levels. In response to various assaults by the environment, however, one or more of these blood cell types may change their relative concentrations in a transient fashion.[73]

It is generally believed that there exists a self-maintaining *pluripotential stem cell* population (PPSC) in the marrow capable of producing committed cells for the erythroid, myeloid, or thromboid lines. These populations are not self-maintaining but depend on a cellular flux from the PPSC for their continued integrity. Cells at the committed level undergo four to five effective divisions (nuclear divisions

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for the myeloid and erythroid series; cytoplasmic divisions for the thromboid series) before losing their nuclei to enter a maturation phase. Cells are then released from this marrow maturational compartment to enter the blood as a mature white blood cell, red blood cell, or platelet.[73]

There is control operating in the erythroid series between the circulating erythrocyte and the PPSC. Decreases in oxygen levels lead to the release of a substance called *erythropoietin* (EP), which acts to increase the cellular flux from the PPSC.[1,67] A number of investigators have looked for similar regulators in the myeloid and thromboid series, and to date the existence of putative *granulopoietins* (GP)[59] and *thrombopoietins* (TP)[7] has been claimed. In addition to this stimulatory effect on cell production, there have been numerous reports concerning the partial isolation of mitotic inhibitory substances in the myeloid and erythroid lines, which are termed *chalones*.[28,62] These chalones appear to be produced by mature granulocytes and erythrocytes, and inhibit proliferation at the myeloblast or erythroblast stage.

In addition to the feedback from circulating blood cells to the PPSC, control mechanisms are believed to exist within the PPSC itself, acting to control cell population numbers.[1] Although the details are not clear, it seems that the PPSC regulates its size by adjusting the rate at which cells enter active proliferation on the basis of the number of resting (G_0) phase cells.[31,46,53,69]

Dynamic Hematologic Disorders

In the hematology literature, there are a number of well-documented pathologies characterized by periodic oscillations in the formed elements of the blood in an apparently constant environment, and in the absence of any clinical intervention. Pathologies in which blood elements remain approximately constant at abnormal levels are also well known.

Cyclical neutropenia is characterized by an oscillation in circulating neutrophil numbers from normal to low values (FIGURE 4).[17] In humans, the majority of cases display a period in the range of 17 to 28 days. All grey collies have a similar disorder, with an oscillatory period of 11 to 12 days.[7,10] In both humans and grey collies, a concomitant oscillation of all the formed blood elements, with the exception of the lymphocytes, is observed.[9,10,22] These elements oscillate with the same period as the neutrophils, but with phase differences consistent with the known differences in maturation times for each of the cell types. Thus, this disorder is more appropriately termed *periodic haematopoiesis* (PH). In *aplastic anemia* (AA), there are severely depressed levels of all circulating elements of the blood, as well as a hypoplastic marrow. There is experimental evidence that the defect giving rise to PH and AA is contained in the PPSC,[2] and a common mechanism has been hypothesized to underly both diseases.[38,39]

Chronic myelogenous leukemia (CML) is a neoplastic disorder of the haematopoietic system generally characterized by a massive increase in circulating cells of the myeloid and thromboid series, and approximately normal erythroid elements.[73] In the past decade, reports in the clinical literature establish the existence of an interesting and provocative periodic variant, *periodic CML* (PCML). In the handful of patients in which PCML has been found, the peripheral leukocyte and

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thrombocyte counts oscillate around elevated levels with a period of 30 to 70 days depending on the patient (FIGURE 5).[5,12,58,68] Oscillations are commonly noted in all of the myeloid and thromboid series elements of these patients, and in two patients there is clear evidence of oscillations in the erythrocyte levels.[5,58] As in PH and AA, the PPSC is implicated as the source of the defect giving rise to CML and PCML.[73]

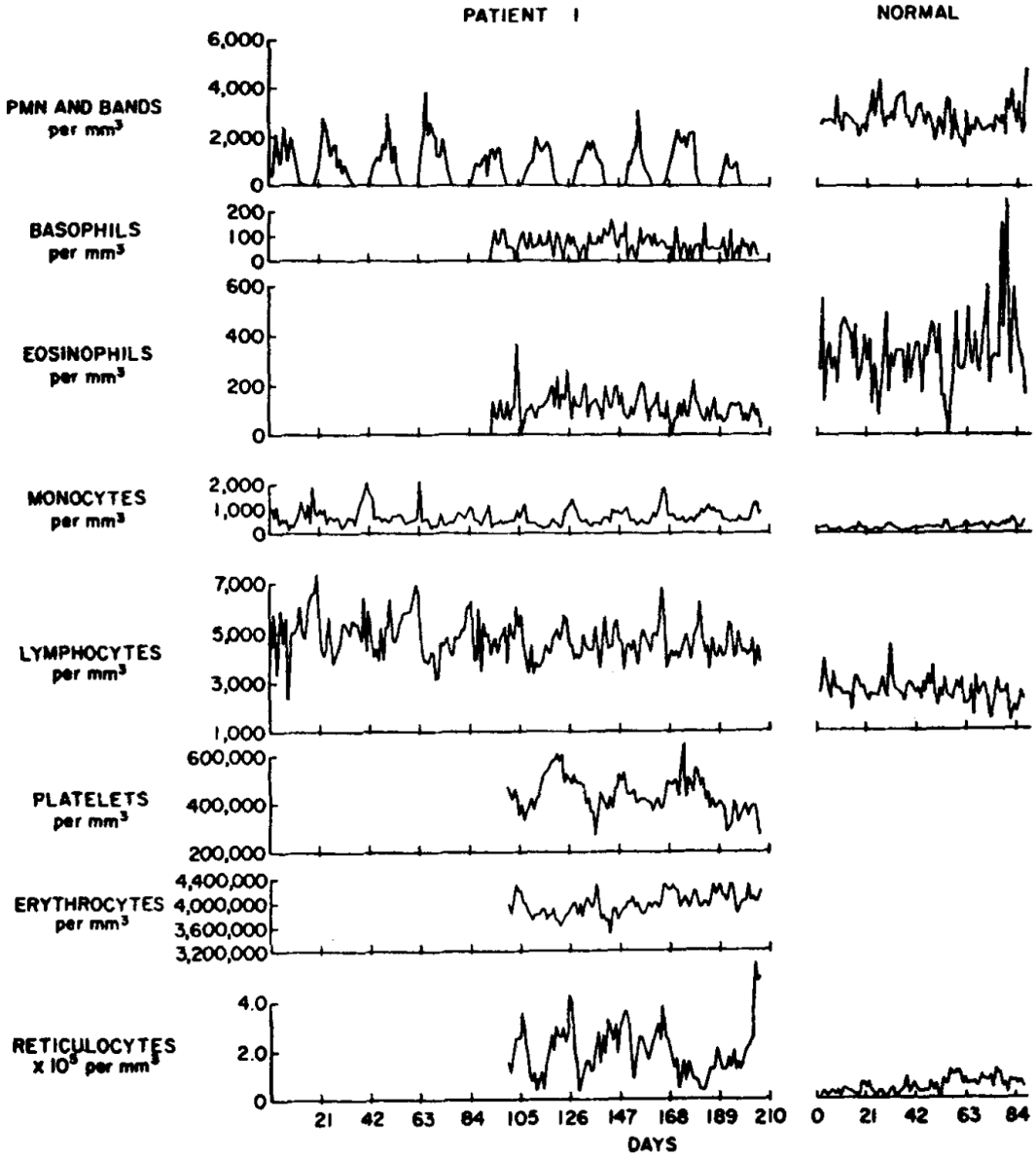

FIGURE 4. An example of human cyclic neutropenia (left-hand side) compared to a normal volunteer. The marked periodicity in the neutrophil count, with a period of 20 days, is also reflected in the monocytes, lymphocytes, platelets, and reticulocytes to a significant degree (period-gram analysis). (From Guerry *et al.*[17] By permission of *Journal of Clinical Investigation.*)

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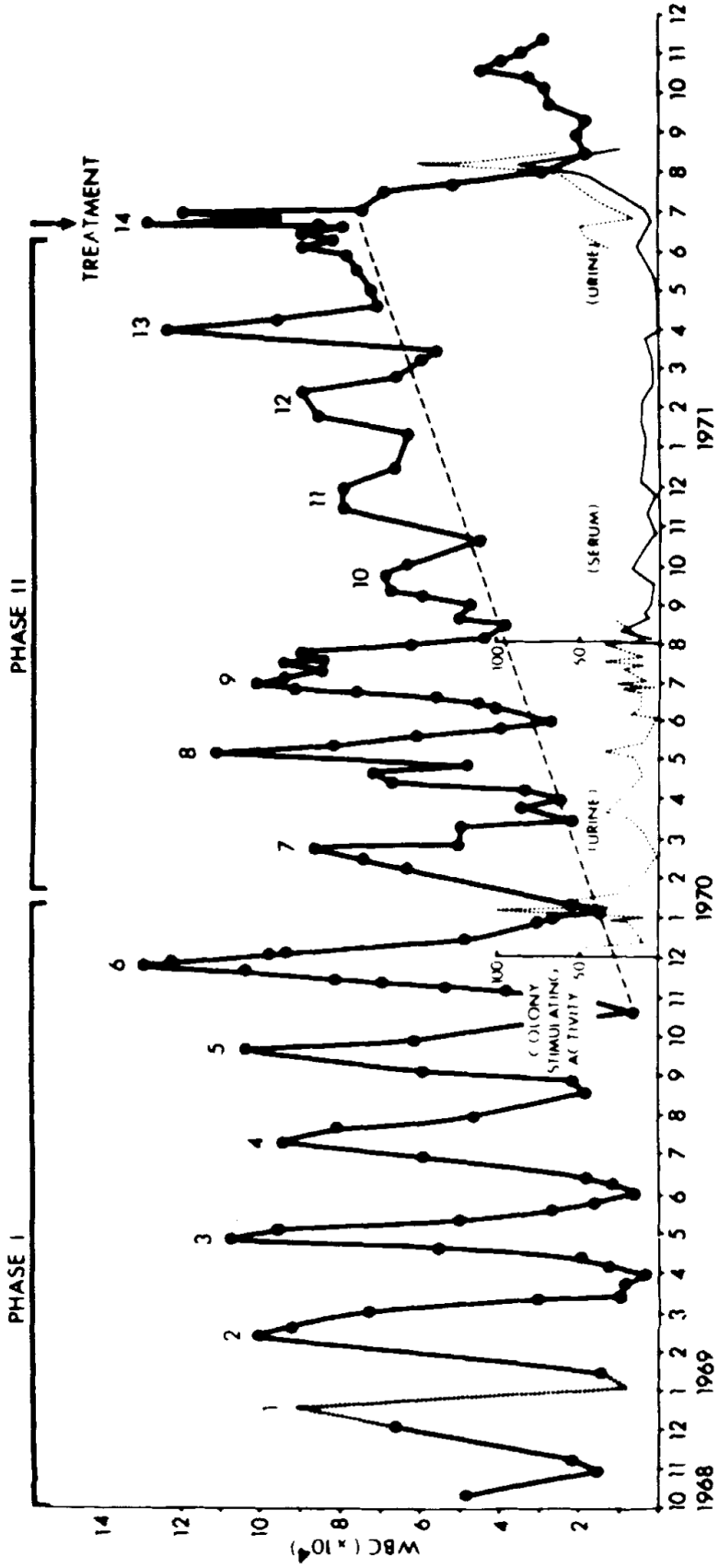

FIGURE 5. Periodic chronic myelogenous leukemia. In this young girl (12 years old at the start of the figure) with CML, the white blood cell count spontaneously oscillates with a period of approximately 70 days in the absence of any therapy. (From Gatti *et al.*[12] By permission of *Blood*.)

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Cyclical thrombocytopenia is a rare disease in which rhythmic changes in platelets and megakaryocytes from normal to low values are observed to occur with a period of about 28 days.[34] There are documented cases in the literature in which the presence of these platelet cycles has persisted for up to 12 years.

Mathematical Models of Dynamic Hematological Diseases

In this section we consider two problems: the first is related to peripheral control over circulating cell numbers (e.g., as exercised via erythropoietin), and the second is related to control within the PPSC compartment. In both cases, our models are similar to models proposed by others for coupled stem cell-peripheral control systems in granulopoiesis,[25,60,71] erythropoiesis,[27] and thrombopoiesis.[15]

Peripheral Control in Haematopoiesis

We first consider a simple model for the control of peripheral blood cell numbers via a humoral feedback mechanism. Let $x(t)$ be the concentration of circulating cells (cells/kg) and assume that cells are randomly lost from the circulation at a rate $\gamma(\text{day}^{-1})$ proportional to their concentration. To reproduce the effects of poietin feedback control from the circulating population of cells, we assume that the flux (λ in cells/kg/day) into the circulation from the stem cell compartment depends on x at time $t - \tau$, and thus the dynamics of $x(t)$ is governed by,

$$\frac{dx}{dt} = \lambda(x_\tau) - \gamma x \tag{3.1}$$

We have examined two forms for $\lambda(x)$:

$$\lambda(x) = \begin{cases} \dfrac{\lambda_0 \theta^n}{\theta^n + x^n} & (3.2) \\[2ex] \dfrac{\lambda_1 \theta^n x}{\theta^n + x^n} & (3.3) \end{cases}$$

where n, θ (cells/kg), λ_0 (day^{-1}), and λ_1 (kg/day-cell) are parameters.[41] The control function (**3.2**) is a simple monotone decreasing function of x for $x \geq 0$, while that of (**3.3**) is a single-humped function.

Combining Equation 3.1 with the equations for λ thus gives two possible equations governing the evolution of $x(t)$,

$$\frac{dx}{dt} = \frac{\lambda_0 \theta^n}{\theta^n + x_\tau^{\,n}} - \gamma x \tag{3.4}$$

and

$$\frac{dx}{dt} = \frac{\lambda_1 \theta^n x_\tau}{\theta^n + x_\tau^{\,n}} - \gamma x \tag{3.5}$$

An equation similar to (**3.4**) has been proposed for the control of erythropoiesis.[6,70]

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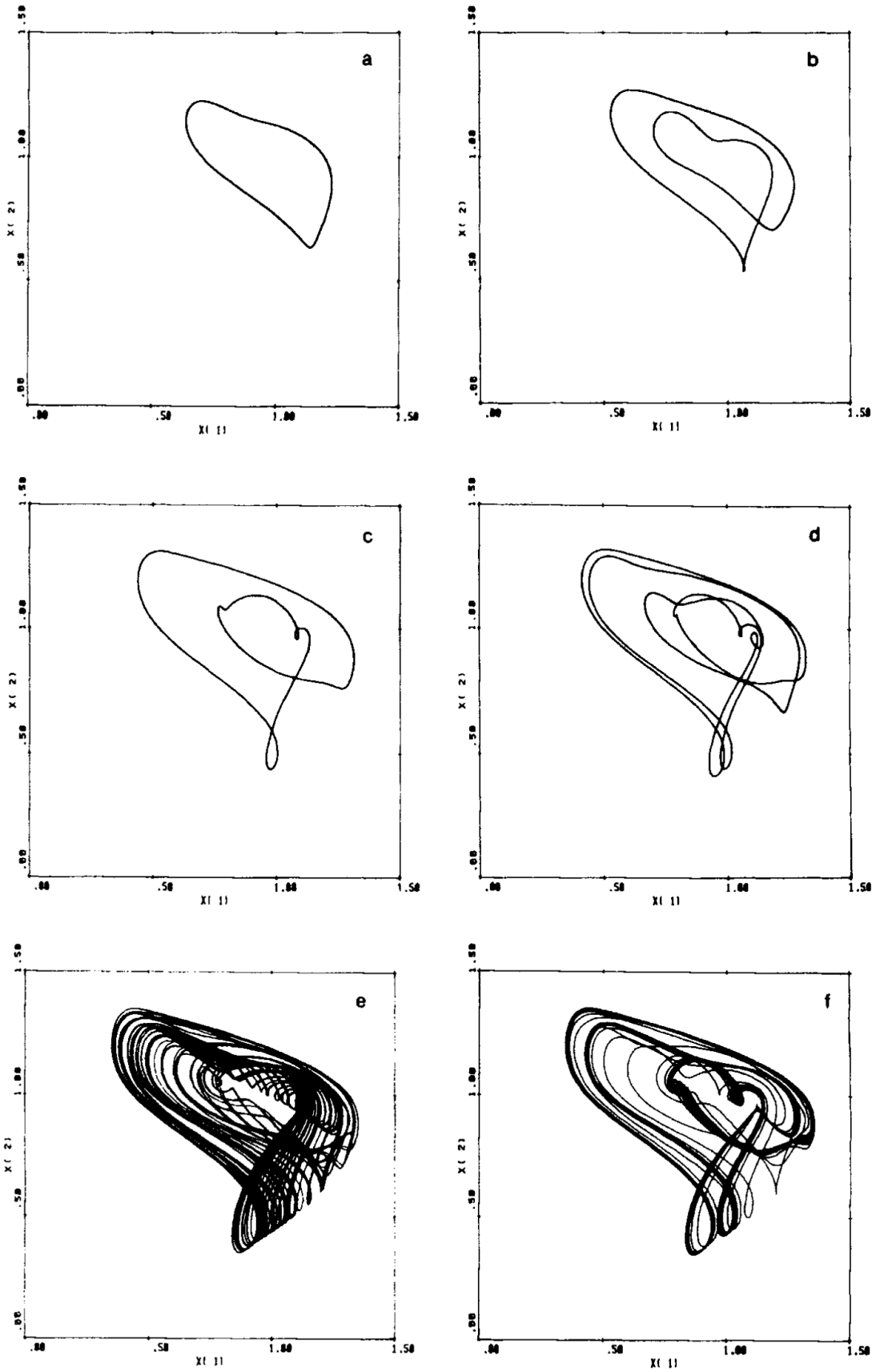

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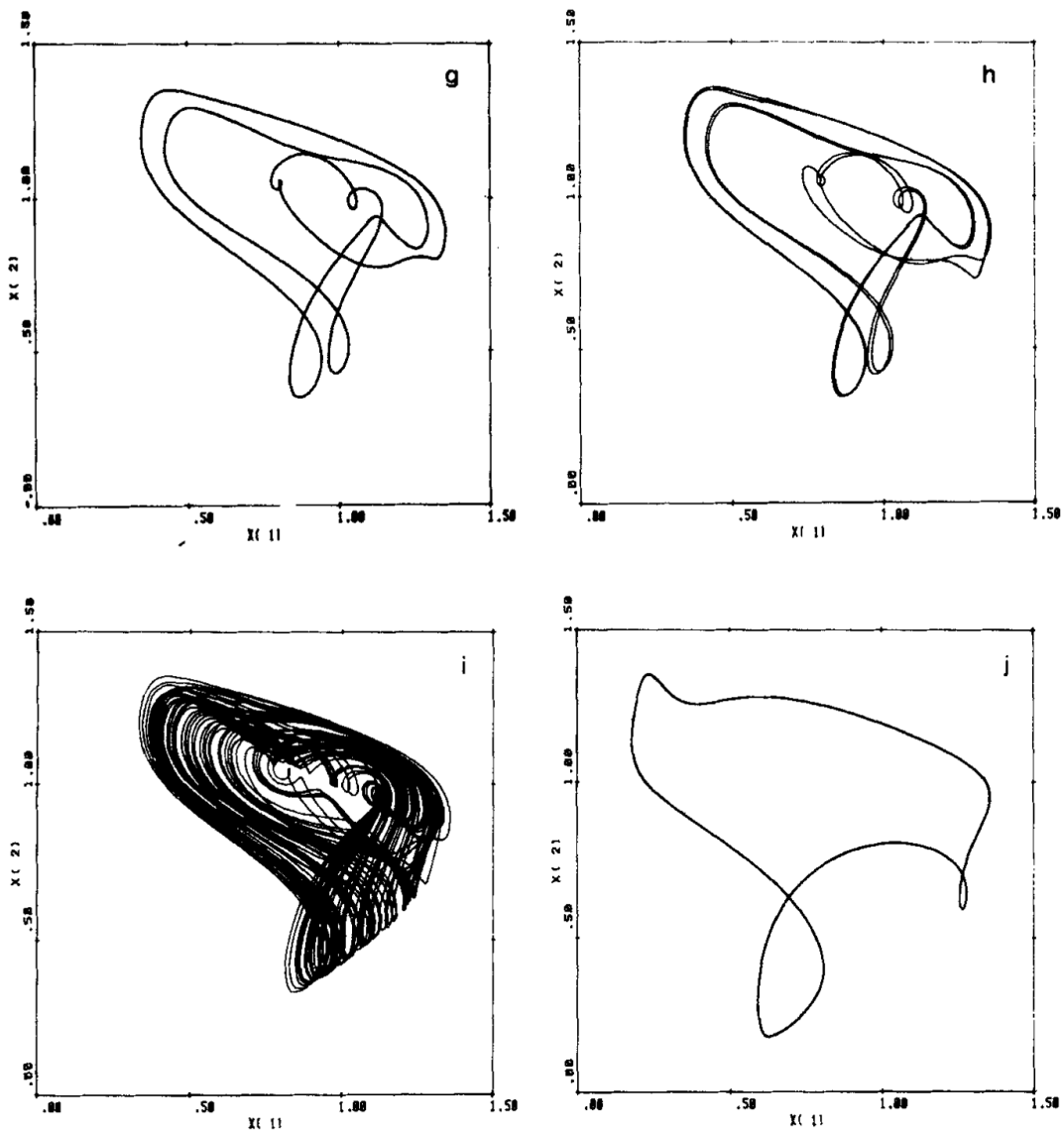

FIGURE 6. Bifurcating solutions to Equation 3.5. Here we show the numerically determined solutions to this equation in the form of phase plots of $x_\tau = x(2)$ versus $x = x(1)$. The integrations were carried out with a step size of 0.05 using a predictor-corrector method, assuming $\gamma = 1$, $\lambda_1 = 2$, $\theta = 1$, $\tau = 2$, and an initial condition on x and x_τ of 0.50.

(a) $n = 7$, $100 \le t \le 150$
(b) $n = 7.75$, $150 \le t \le 200$
(c) $n = 8.50$, $200 \le t \le 250$
(d) $n = 8.79$, $300 \le t \le 400$
(e) $n = 9.65$, $300 \le t \le 600$
(f) $n = 9.69715$, $300 \le t \le 800$
(g) $n = 9.6975$, $300 \le t \le 400$
(h) $n = 9.76$, $300 \le t \le 400$
(i) $n = 10.0$, $300 \le t \le 600$
(j) $n = 20.0$, $300 \le t \le 400$

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The nonzero steady states x_0 of these equations may be calculated and the local behavior of the solutions examined near x_0 as in the section on respiratory models. The results of these computations indicate that increases in n, τ, or λ_0, or decreases in γ or λ_1 may lead to a loss of stability at x_0 and the appearance of oscillatory solutions about x_0.

To investigate the behavior of (**3.4**) and (**3.5**) away from the region of applicability of this linear analysis, we have numerically integrated the equations using either a predictor-corrector or a Runge-Kutta integration scheme. For Equation 3.4, we have found only two qualitatively different behaviors: 1) either a stable steady state or 2) a stable limit cycle oscillation—for any set of parameters only one or the other behavior is found.

However, the qualitative behavior of (**3.5**) in response to parameter changes are quite different. To illustrate this behavior we assume that $\gamma = 1$, $\lambda_1 = 2$, $\theta = 1$ (so $x_0 = 1$), and $\tau = 2$. Equation 3.5 was integrated starting from an initial condition $x(t) = 0.50$, $-\tau < t < 0$, using a predictor-corrector integration routine with a step size of $\Delta = 0.05$ for various values of n.

The linear analysis of (**3.5**) indicates that with these parameters, $x_0 = 1$ should be stable for $n < 5.0404$, and, as stability is lost for $n \sim 5.0404$, periodic solutions of period $T \sim 5.49$ should appear. Numerical solutions of (**3.5**) in the neighborhood of $n = 5.04$ bear out the accuracy of this analysis, and indicate that the periodic solutions are stable.

In FIGURE 6 we show the dynamics of (**3.5**) in the $x_\tau - x$ phase plane for several values of n. Notice that as n is increased, the oscillation undergoes a sequence of bifurcations. Further, this sequence is analogous to the sequence of bifurcations observed in a class of finite-difference equations in 1-dimension.[35,42,43,45] Notice that the oscillatory patterns in FIGURE 6a and b are analogous to the "period 2" oscillation; FIGURE 6b and 6c are analogous to the "period 4" oscillation; FIGURE 6d is analogous to the "period 8" oscillation; FIGURE 6g is analogous to the "period 3" oscillation; FIGURE 6h is analogous to the "period 6" oscillation; FIGURE 6e and 6i are analogous to the "chaotic regimes." In FIGURE 6f we observe that the "period 3" oscillation has almost "condensed" out of the chaotic regime. FIGURE 6j shows a stable oscillation, which appears for large n.

At the moment we are not aware of any clinical data concerning circulating levels of blood elements that displays similar sequences of bifurcations in their qualitative dynamics. However, (**3.4**) can be used[40] to describe the periodic fluctuations in circulating red blood cell numbers observed in an auto-immune hemolytic anemia[52] (increased cell destruction rate γ).

Control Within The PPSC

To examine the possible origins of PH within the PPSC, we assume that[38,39]: 1) cells in the PPSC are either proliferating or in the resting phase (G_0) cells, 2) cells travel through proliferation to undergo mitosis at a fixed time τ (days) from their time of entry into the proliferative phase, 3) all cells enter G_0 upon the completion of mitosis, and 4) cells in G_0 exit randomly to differentiate either irreversibly into one of the haematopoietic lines (myeloid, erythroid, or thromboid) at a rate α (day^{-1}) or reenter proliferation at a rate β (day^{-1}) propor-

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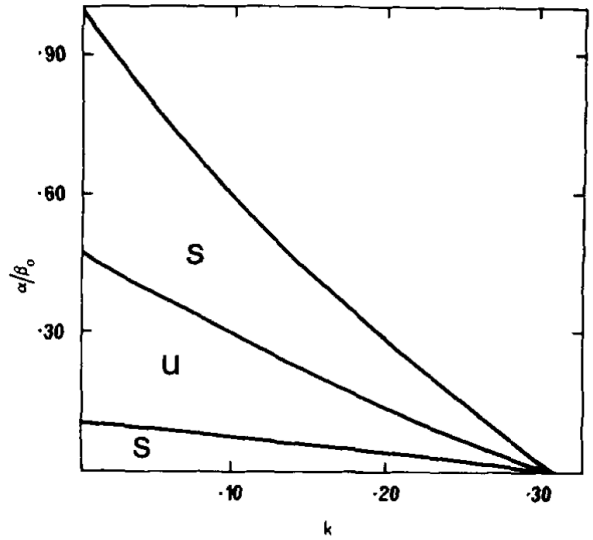

FIGURE 7. Linear stability analysis for Equation 3.7. Here we show the predicted regions of local stability of the steady state x_0 of Equation 3.7, assuming $n = 3$, $\tau = 2.22$ days, $\beta_0 = 1.77$ days^{-1}; u denotes the region where x_0 is not stable according to the linear analysis, while s denotes stability. For all parameter values $(k, \alpha/\beta_0)$ above the top curve, a positive steady state does not exist.

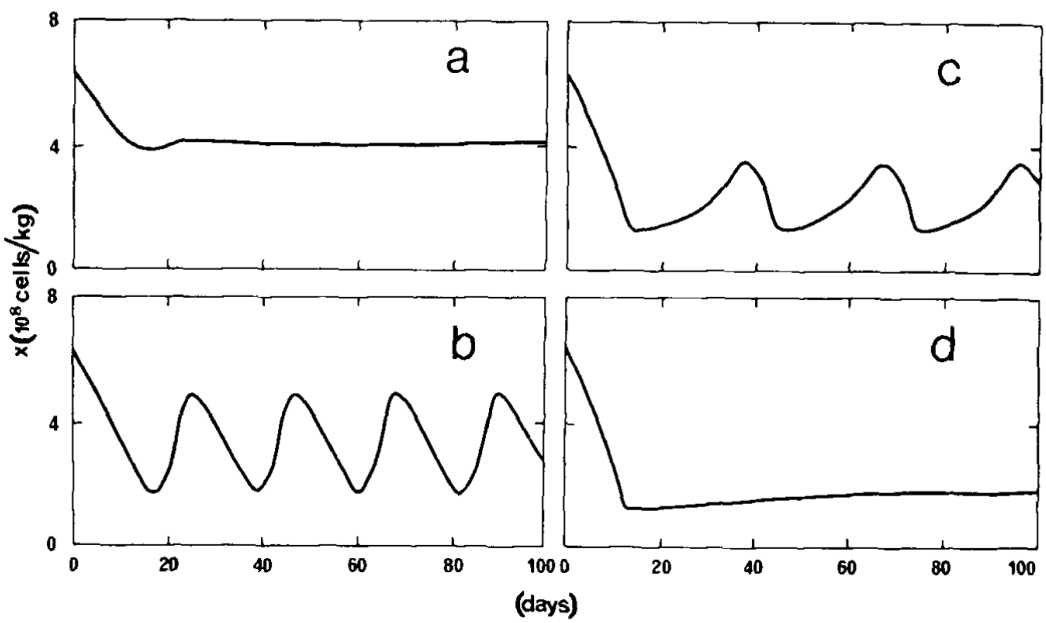

FIGURE 8. Numerical solutions to Equation 3.6: Here we illustrate the time course of $x(t)$ as computed from Equation 3.6 using a predictor-corrector integration scheme with an integration step size of 0.05, $n = 3$, $\alpha = 0.05$ day^{-1}, $\beta_0 = 1.77$ day^{-1}, $\tau = 2.22$ days, $\theta = 1.98 \times 10^8$ cells/kg, and an initial condition $x(0) = 6.43 \times 10^8$ cells/kg. (a) $k = 0.20$ day^{-1}, (b) $k = 0.25$, (c) $k = 0.28$, and (d) $k = 0.29$. The behavior in (a) and (d) has been interpreted as reflecting the pattern of aplastic anemia, while that of (b) and (c) is similar to periodic haematopoiesis.[39]

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tional to their concentration (in certain pathological states, proliferating phase cells die at a rate k (day^{-1}) proportional to their concentration).

We further assume that control in the PPSC is exercised over the rate β of cell reentry into proliferation and that β is a monotonic decreasing function of G_0 cells. Calling the population density of the G_0 cells x (cells/kg), we obtain,

$$\frac{dx}{dt} = \frac{2\beta_0\theta^n x_\tau}{\theta^n + x_\tau^n}\exp(-k\tau) - \alpha x - \frac{\beta_0\theta^n x}{\theta^n + x^n} \tag{3.6}$$

where θ (cells/kg), β_0 (day^{-1}), and n are parameters characterizing the PPSC.

PH and AA. Based on several lines of evidence, there is good reason to believe that the strange dynamics of PH is intimately connected with the death of cells from the proliferating phase of the PPSC. Further, at least some cases of AA may involve the death of proliferating PPSC cells.[2]

It is possible to estimate the values of the parameters characterizing a PPSC population in a normal ($k = 0$) state. Depending on the values of these parameters, the linear analysis of the stability of the nonzero steady state x_0 of (**3.6**) predicts two possible responses in the PPSC to increases in k (FIGURE 7). For humans, taking $n = 3$, $\tau = 2.22$ days, $\alpha = 0.05$ day^{-1}, and $\beta_0 = 1.77$ days, an increase in k leads to a depression of the steady state x_0. At about $k = 0.235$ day^{-1}, the steady state is no longer stable and periodic solutions of period 19.00 days are predicted. At $k = 0.287$ day^{-1} a stable steady state reappears. For $0.235 < k < 0.287$, numerical studies indicate stable limit cycle oscillation. These behaviors are illustrated in FIGURE 8. Since both depression of cell densities and periodic dynamics can be accounted for in this single model and the numerical values obtained are reasonable, it has been suggested that both AA and PH can be accounted for by varying rates of cell destruction during proliferation of stem cells.[39]

4. MISCELLANEOUS DYNAMICAL DISEASES

During the course of our research we have become aware of a large number of other pathological conditions with striking dynamical behavior. Although some of the conditions are well known to the layman, others are obscure and often not even accurately diagnosed. We mention some representative examples, and recent references, which can be consulted for extensive bibliographies.

Cardiac Arrhythmias[36,61]

The heart is capable of beating in a variety of different regular and irregular oscillatory patterns. These patterns can be visualized by the electrocardiogram (ECG) shown in FIGURE 9. Normally the cardiac cycle is initiated by the sinoatrial (S-A) node that acts as a pacemaker, initiating activity that travels through the cardiac tissue to the atrioventricular (A-V) node. Excitation at the S-A node leads to contraction of the atria and excitation at the A-V node leads to ventricular contraction.

However, most heart tissue is capable of generating spontaneous rhythms, and

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in many pathological conditions the S-A node partially or completely loses its role as the pacemaker. A few pathologies will be illustrated. FIGURE 9a shows an ECG taken from a patient in which every fourth pulse generated by the S-A node is ineffective in driving the ventricular rhythm (the Wenkebach phenomenon). In the same patient, at a slightly higher pulse rate (FIGURE 9b) every other pulse generated by the S-A node is ineffective. In another pathology, the ventricles display high-frequency contraction, apparently out of control of the S-A node. This condition (ventricular tachycardia) may have sudden onset and cessation (FIGURE 9c). Ventricular fibrillation is characterized by "chaotic, irregular, and disorganized ventricular activity,"[36] and usually leads to death within a few minutes (FIGURE 9d).

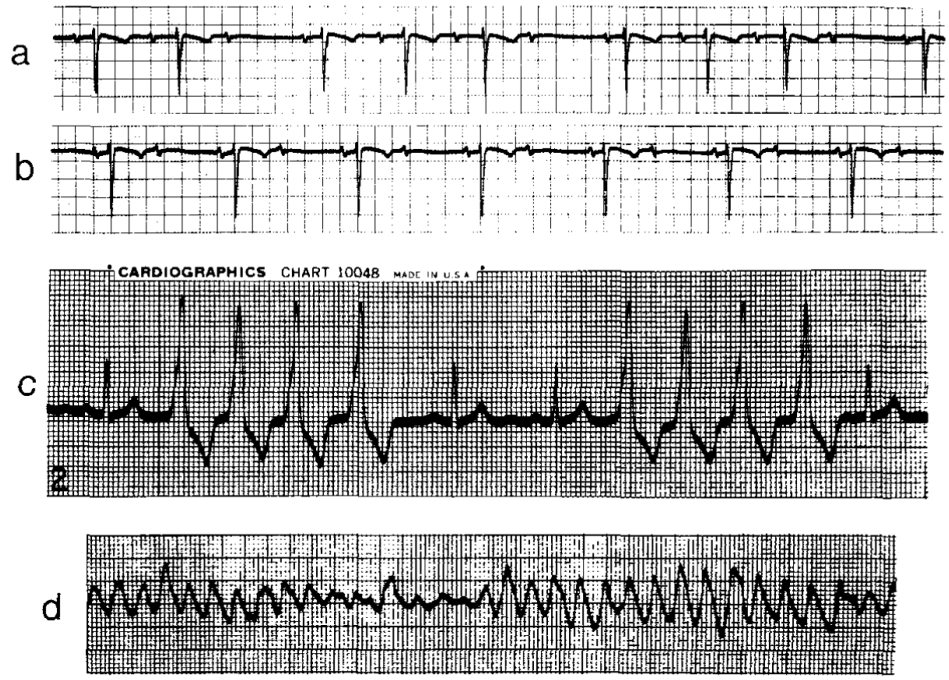

FIGURE 9. Electrocardiograms of four pathological cardiac arrhythmias: (a) 2:1 A-V block, (b) The Wenkebach phenomenon, (c) Ventricular tachycardia, (d) Ventricular fibrillation. (From Lindsay and Budkin.[36] By permission of *Year Book Medical Publishers*.)

There is an intriguing and widely scattered theoretical literature dealing with mechanisms of cardiac arrhythmias. In an early paper, van der Pol and Mark[54] generated oscillatory patterns similar to those shown in FIGURE 9 by coupling nonlinear oscillators with different natural frequencies. There has been additional theoretical work that attributes other arrhythmias to abnormal patterns of wave propagation in the excitable tissue of the heart.[29,49,72]

Psychological and Neurological Disorders

There are a variety of psychological and neurological disorders including insomnia, epilepsy, manic-depressive episodes, and schizophrenia that have been reported to display a variety of regular and irregular oscillatory patterns with

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periodicities ranging from several days to several years.[57] Theoretical work has been done on the analysis of a proposed mechanism for periodic catatonic schizophrenia.[8]

Cancer

There is a large body of theoretical work that ascribes cancerous growth to instabilities in the dynamics of the cell cycle,[18,19] or in feedback control systems regulating mitosis.[16,64] It has been observed that cancer, if untreated, does not necessarily grow "without limit."[30] Further, some cancerous growth, (e.g., the CML referred to above) may have a periodic time course (see the section on haematopoiesis).

Miscellaneous

There are a large number of other diseases that can display regular and irregular oscillatory dynamics; e.g., periodic synoviosis (swelling of the articulated joints), periodic peritonitis (swelling of the gut), periodic fever, and periodic pancreatitis.[55-57] Although it is plausible that some of these diseases arise from instabilities in feedback control mechanisms similar to those we have discussed here,[51] we are not aware of detailed theoretical analyses. Finally, the importance of periodic factors in both normal and pathological conditions in humans have been emphasized in the work of Halberg *et al.*[20]

5. Discussion

Physiological control systems are extremely complex. Moreover, there are large differences in the details of the structure of these systems among different species, and even different members of the same species. As a consequence, those interested in studying dynamical diseases face numerous experimental difficulties. Experimentation on normal and diseased humans must be of an extremely limited kind. Since human experimentation is difficult, most of the systematic information that has been gathered about physiological control systems is from other mammals. Although principles of organization may be the same in these animals as in humans, extrapolation of quantitative results to humans is not easily done. Even more subtle problems arise. Many experimental paradigms that have been adopted by physiologists tend to obscure variability in a single animal during the course of an experiment, as well as the differences among different animals. Typically, data from a number of animals are lumped together, and average data are reported. Since diseases tend to be rare, abnormal dynamical behavior (if it occurs at all), which might be most relevant from the standpoint of dynamical disease, is often disregarded or lumped with enough other data to give "good statistics." One experimental approach to the study of dynamical disease is to develop animal models of the disease in which animals, after a variety of manipulations, display similar qualitative dynamics to those displayed in the human counterpart of the disease. Clearly, studies such as these can not be used to identify the cause of the disease in humans, but simply to generate plausible hypotheses.

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The existence of classificable dynamical diseases in humans suggests a correspondingly rich theory of bifurcations in nonlinear ordinary, partial, and functional differential equations which model physiological control systems. At this point a sufficient body of data is not yet available for actual testing of theories of dynamical diseases. In our view, close collaboration between theorists and clinicians is needed to clarify the bases of these dynamical diseases.

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