Dynamical Diseases

MICHAEL C. MACKEY[a] AND JOHN G. MILTON[b,c]

[a]*Department of Physiology*
School of Medicine
McGill University
Montreal, Quebec H3G 1Y6

[b]*Department of Neurology*
Montreal Neurological Institute
McGill University
Montreal, Quebec H3A 2B4

INTRODUCTION

Many phenomena in physiology and clinical medicine recur at regular, or almost regular, intervals. In 1963, Reimann[1] drew attention to a diverse group of diseases in which symptoms recurred at seven-day intervals, or integer multiples thereof, which he collectively referred to as periodic diseases. In all of these diseases, oscillations appeared in physiological systems not normally characterized by oscillations. Although in most of his patients these were regular oscillations, he noted that in some patients symptoms recurred in a more irregular manner.

It is more common to observe oscillations in physiological control systems that occur on a more rapid time scale, that is, milliseconds to hours. Moreover, abnormalities in many of these physiological rhythms are of major clinical importance. For example, an abnormality in the cardiac rhythm, ventricular fibrillation, is a common life-threatening medical emergency. In addition to their clinical importance, observations of these oscillations demonstrate that there is a rich variety of dynamics that many physiological control systems can exhibit, ranging from rhythms with differing periodicities to irregular "noise-like" phenomena.

As an extension of the concept of periodic diseases, the concept of a dynamical disease has been introduced.[2-4] A dynamical disease is defined as a disease that occurs in an intact physiological control system operating in a range of control parameters that leads to abnormal dynamics. The signature of a dynamical disease is a change in the qualitative dynamics of some observable nature as one or more parameters are changed. These changes in dynamics would correspond mathematically to bifurcations in the relevant nonlinear equations describing the physiological system.

This paper reviews the applicability of the concept of dynamical disease as it has developed over the past few years.

ROUTES TO PERIODIC DISEASES

TABLE 1 lists several examples of physiological systems in health and disease in which both regular and irregular dynamics have been observed. Though it is undoubtedly true that normal, intact physiological control systems can be shown to

[c]To whom correspondence should be addressed.

undergo such transitions *in vitro* and/or in animal models, it must be recognized that in many of the clinical situations in which abnormal dynamics occur, there are also coexisting pathological structural abnormalities as well as changes in the physiological control parameters. The interplay between structural and control parameter alterations in producing abnormal dynamics is not presently understood. However, even in the setting of a pathologically altered physiological control system, it is possible for changes in dynamics to occur, reflecting alterations in control parameters, although admittedly the control system may not be functioning in the same way as seen in health.

TABLE 1. Examples of Regular and Irregular Dynamics in Health and Disease

Field	Regularly Recurring	Irregularly Recurring	Reference
Behavior	Affective disorders "rapid cyclers"	"Rapid cyclers"	5–7
Cardiology	Sinus rhythm Ventricular bigeminy Wenckebach phenomenon	Atrial fibrillation Ventricular fibrillation	8
Electrophysiology			
beta cells			9–10
molluscan neuron	Rhythms and bursts	Irregular spiking	11–12
thalamus			13
EEG	Spike and wave	Background activity	14
recurrent inhibition	Hippocampal activity	Penicillin epilepsy model	15
Hematology	Periodic hematopoiesis Autoimmune hemolytic anemia	Periodic CML Cyclical thrombocytopenia	16
Movement			
locomotion	Gait	Cerebellar gait	17–18
coordinated activity	Tremors Hiccups	Choreo-athetosis Myoclonus	
Nerve-Muscle	Fibrillations Myotonic discharges Myokimia	Fasciculations	19–20
Neuro-ophthalmology			21–24
pupil diameter	Pupic cycle time	Hippus	
eye movements	Nystagmus	Opsoclonus	
Respiration	Periodic breathing Cheyne-Stokes	Ataxic breathing Cluster breathing	25–26

In general, three types of qualitative changes in dynamics have been observed: (1) the appearance of a regular oscillation in a physiological control system not normally characterized by rhythmic processes, (2) the development of new periodicity in an already periodic process, and (3) the disappearance of a rhythmic process. Dynamical changes of these types are readily observed in the cardiac, respiratory, and hematological systems, but will be discussed elsewhere (see below and the paper by Glass in this volume). Here, we briefly discuss some neurological examples.

Appearance of Rhythms

The appearance of a regular, or almost regular, rhythm in a normally stable physiological process has long attracted clinical interest. Examples include the periodic

diseases described by Reimann,[1] as well as a number of phenomena in clinical neurology[17-20] such as tremors, ankle clonus in corticospinal tract diseases, ocular nystagmus in brainstem disease, and muscle fibrillations observed electromyographically in neurogenic muscle disease.

FIGURE 1 shows an example of a physiological control system in which transitions from irregular to regular dynamics occur in response to changes in the underlying control parameters. The diameter of the pupil of the eye undergoes spontaneous fluctuations in size, which have variously been referred to as hippus or pupillary unrest.[23,24] The cause and significance of these fluctuations are subjects of considerable debate and controversy. The possibility that these fluctuations may have a deterministic origin is suggested by the observations in FIGURE 1, which shows the diameter of the pupil as a function of time of a sleepy narcoleptic patient in complete darkness with his eyes open.[24] As he becomes less alert, regular oscillations in pupil diameter appear, with the regularity again disappearing as he becomes more alert. Alertness is related to activity in a part of the brainstem referred to as the ascending reticular activating system (ARAS),[25] and activity in the ARAS regulates the activity of a parasympathetic nucleus involved in the control of pupil diameter, the Edinger-Westphal (EW) nucleus.[21] It is tempting to speculate that the changes in pupillary dynamics shown in this figure reflect differing dynamical signatures corresponding to different functional activity levels in the light reflex pathway.

Appearance of New Periodicities

Situations occur in which an oscillation with a new periodicity and waveform replaces a previously oscillatory process. Well-known examples are the development of

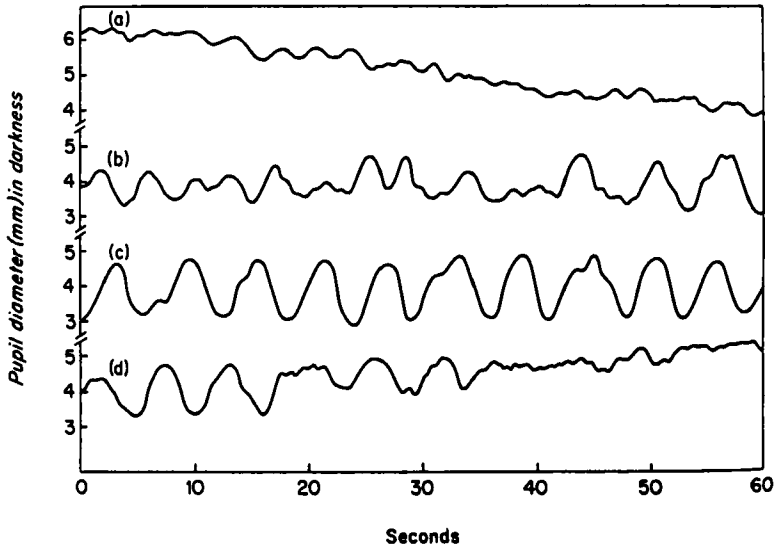

FIGURE 1. Pupil diameter measured in complete darkness for four consecutive minutes (a to d, respectively) in a sleepy patient with narcolepsy. The patient becomes more drowsy at ~110 seconds and then more alert at ~200 seconds. (From Yoss *et al.*[24] With permission from The American Journal of Ophthalmology.)

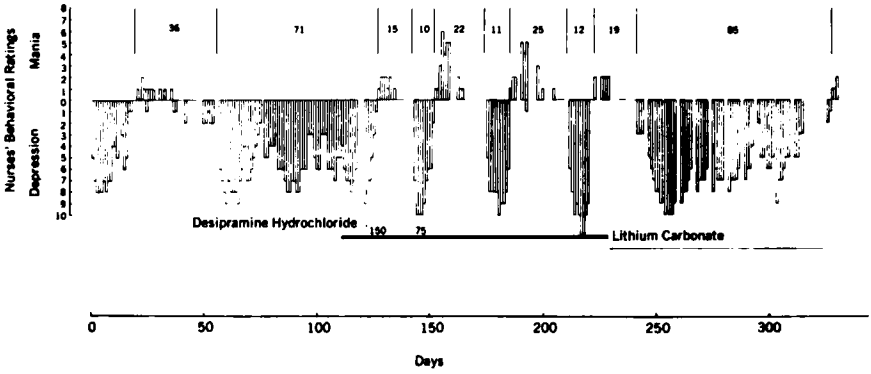

FIGURE 2. Daily mood ratings in a patient with rapid cycling manic-depressive illness.[5] Vertical lines above ratings indicate where switches into mania or depression occurred; numbers above indicate days elapsed between switches in either direction. Desipramine dose indicated above line; lithium carbonate dose was 750 mg. (With permission from T. A. Wehr.)

AV block and bigeminal arrhythmias in the cardiac cycle,[8] and the appearance of abnormal respiratory cycles such as Cheyne-Stokes respiration.[25,26] Here we discuss an example in which such transitions appear to occur in response to medication.

Manic-depressive illness is a pathological biological rhythm whose characteristics have been extensively explored.[5-7] In some cases, the illness takes a rapid cycling form with manic and depressive phases alternating four or more times yearly. Changes in the manic-depressive rhythm which, at least superficially, resemble period doubling bifurcations occur in "rapid cyclers." For example, the period of the cycle may sometimes suddenly lengthen by doubling. In addition, these patients quite commonly experience one or more consecutive 48-hour sleep cycles, that is, there is a doubling of the 24-hour sleep-wake cycle such that there are alternate nights without sleep, when they switch from depression to mania. Initially depressed patients can sometimes be made to undergo such a change by artificially depriving them of a night's sleep. In others, the period of the cycle appears to change in response to certain medications, notably antidepressants.[5] FIGURE 2 illustrates a change in periodicity of a rapid cycler in response to the antidepressant desipramine. With the introduction of this medication, the patient cycles more rapidly, only to apparently return to his previous rhythm following discontinuation of the medication.

Loss of Rhythmicity

The final situation occurs in which there is the disappearance of a rhythmic process. Examples of this include the replacement of the normal cardiac rhythm by atrial or ventricular fibrillation,[8] and the development of apneic respiratory rhythms.[25,26] Here, we give an example of this phenomenon in a periodic disease.

In a few patients with epilepsy, seizures occur regularly.[27] In a small proportion of patients with cyclic epilepsy, seizures cannot be controlled with medication, but the rhythmicity can be destroyed. FIGURE 3 shows two such examples. Both patients show a circadian pattern to their seizure recurrences and the patient in FIGURE 3a also appears to show an ultradian pattern of recurrence as well. However, both patterns

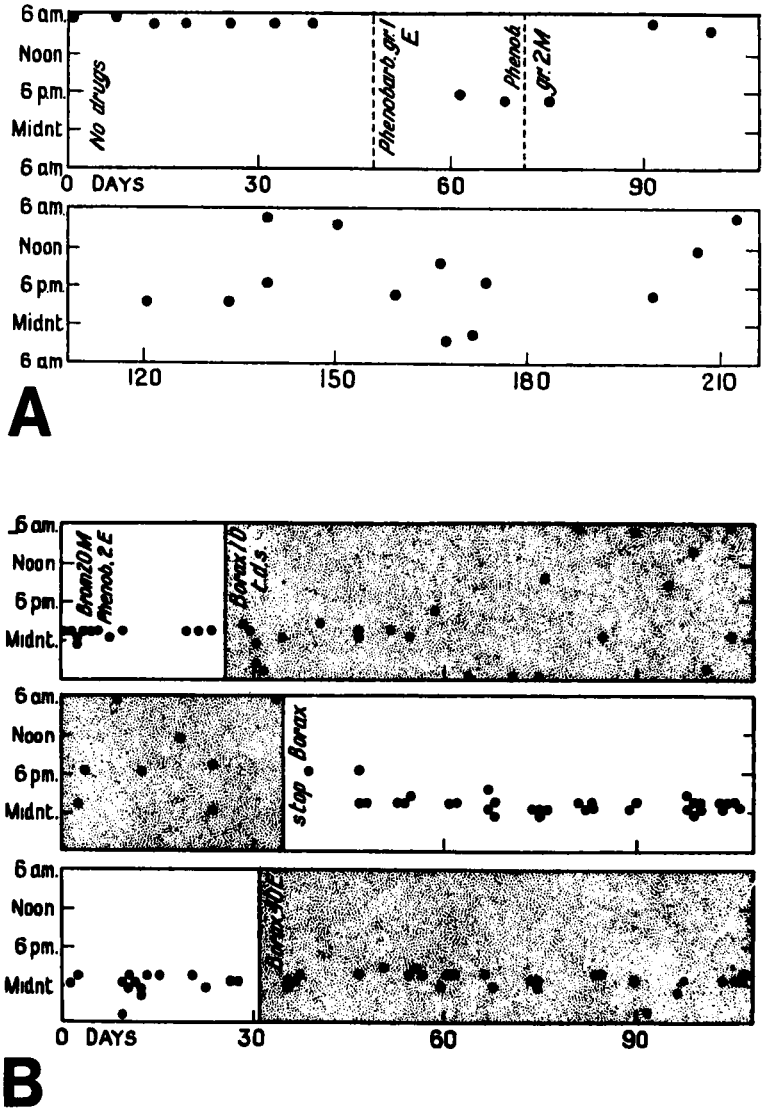

FIGURE 3. Seizure diaries for two patients with epilepsy. The occurrence of each seizure has been indicated by a ●. (From Griffiths & Fox.[27] With permission from *Lancet*.)

were lost once the patients received medication, only to reestablish themselves following cessation of the medication.

MODELS OF DYNAMICAL DISEASES

It is safe to say that all physiological systems contain significant feedback mechanisms and, in many of these, time delays are extremely important. These time delays may arise because, for example, of the time required for a cell to mature, of the time for the nerve impulse to travel along the axon and across the synapse, or the time for hormonal signals to travel from their site of production to target organs by diffusion and/or passage through the circulation. Here we consider several highly simplified mathematical models for time-delayed physiological control systems that have dynamics like those observed experimentally and clinically.

Let $x(t)$ be some controlled variable. Then typically the net rate of change of x, denoted by dx/dt or $\dot{x}(t)$, will be given by the difference between its production rate P and its rate of destruction Dx. Mathematically, this may be written as

$$\dot{x}(t) = P - Dx(t). \tag{1}$$

Since $\dot{x}(t) > 0$ for $x < P/D$, and $\dot{x}(t) < 0$ for $x > P/D$, this system can be thought of as a simple feedback system with a set point P/D. As is well known, when P and D are constant, x cannot oscillate but will monotonically approach the value P/D. However, if important time delays are present so P and/or D are not constant but depend on the variable x at some time T in the past, i.e., on $x(t - T)$, then $x(t)$ may not only display sustained and regular oscillations, but it may also display a type of very irregular or "chaotic" dynamics. To illustrate the importance of these types of behaviors, we consider three examples of physiological control systems with time-delay systems.[28]

Cheyne-Stokes Respiration

There is a well-characterized breathing pattern known as Cheyne-Stokes respiration (FIG. 4a) in which there is a regular waxing and waning of ventilation.[25,26] Cheyne-Stokes respiration often occurs in congestive heart failure, in obese individuals, and after neural brainstem lesions.

To see how simple considerations of physiological control systems may play a role in understanding Cheyne-Stokes respiration, we focus on the control of ventilation by blood CO_2 levels.[2,3] Bearing in mind equation 1, let x denote pCO_2, the partial pressure of arterial CO_2. The CO_2 is produced by body tissues at a constant rate, P, under constant conditions. The CO_2 elimination rate from the body, D, is proportional to the ventilation, V, which is a monotonic increasing function of arterial CO_2 levels some time T in the past,[29] as shown schematically in FIGURE 5a. This delay T is due to the blood transit time from the brainstem (where ventilation is determined by chemoreceptors and by the "respiratory oscillator") to the lungs (where CO_2 elimination takes place).

This model for the control of pCO_2 levels has been discussed in detail elsewhere.[2-4] Designate the values of x and V at the steady state, i.e., $\dot{x}(t) = 0$, by x_0 and V_0, respectively, and set $S_0 = V'(x = x_0)$ so that S_0 is an index of the sensitivity of the

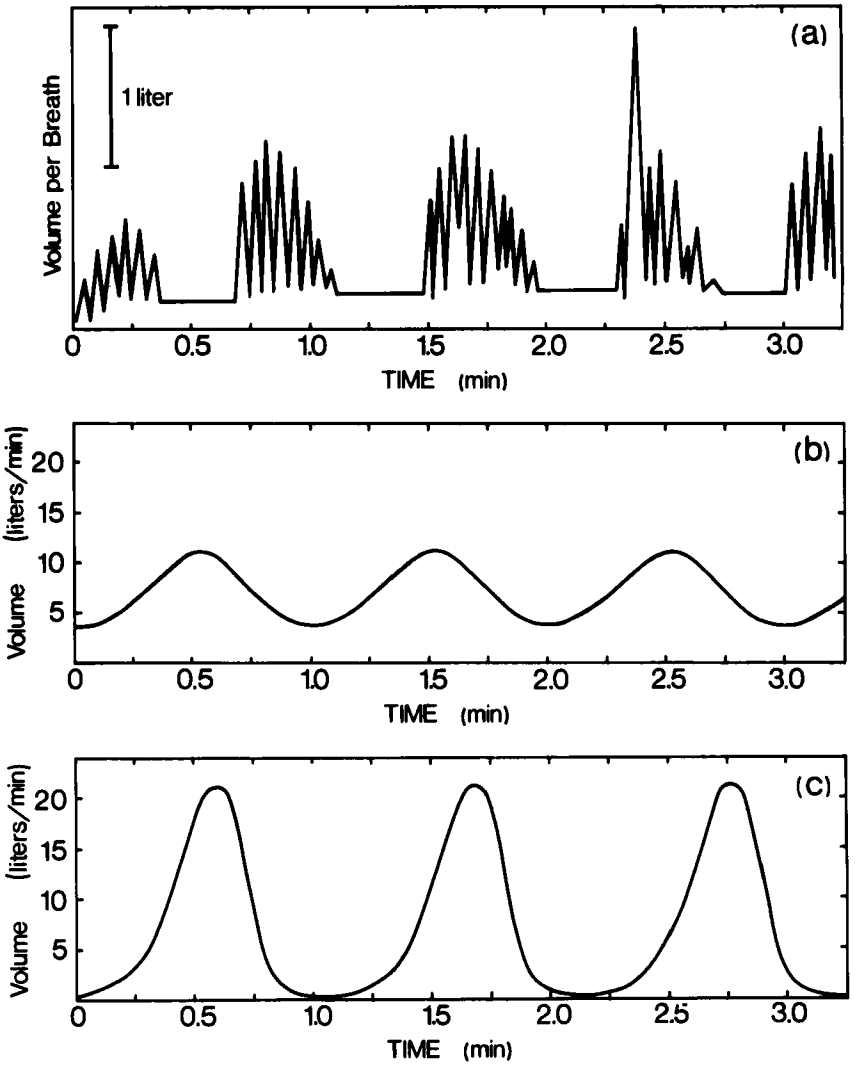

FIGURE 4. Dynamics of Cheyne-Stokes respiration.[2] (a) Ventilation as a function of time in a 29-year-old patient suffering from Cheyne-Stokes respiration.[26] (b) and (c) The results of simulations from a simple model for arterial CO_2 control (see text) in which the sensitivity S_o of the ventilatory response curve at steady state is increased (S_o = 7.7 and 10.0 liters/min mm Hg in b and c, respectively) past the critical value for stability. Compare the pronounced periods of apnea in (a) and (c).

ventilatory response curve to changes in CO_2 levels near the steady state. Then it is straightforward to show that the steady-state arterial pCO_2 will be unstable whenever $S_o > \pi V_o/2PT$, and that there will be an oscillation in pCO_2 and, consequently, in the ventilation with a period approximately equal to $4T$ (FIGS. 4b and c).

The inequality resulting from this stability analysis, i.e., $S_o > \pi V_o/2PT$, predicts

that there are four possible ways in which the steady-state pCO_2 level, x_0, may become unstable and start to oscillate: (1) If either the sensitivity (S_0) of the CO_2 control function at the steady state, the time delay (T), or the whole body CO_2 production rate (P) is increased sufficiently or (2) if the steady-state ventilation (V_0) is decreased sufficiently.

From these observations, we may now qualitatively understand why Cheyne-

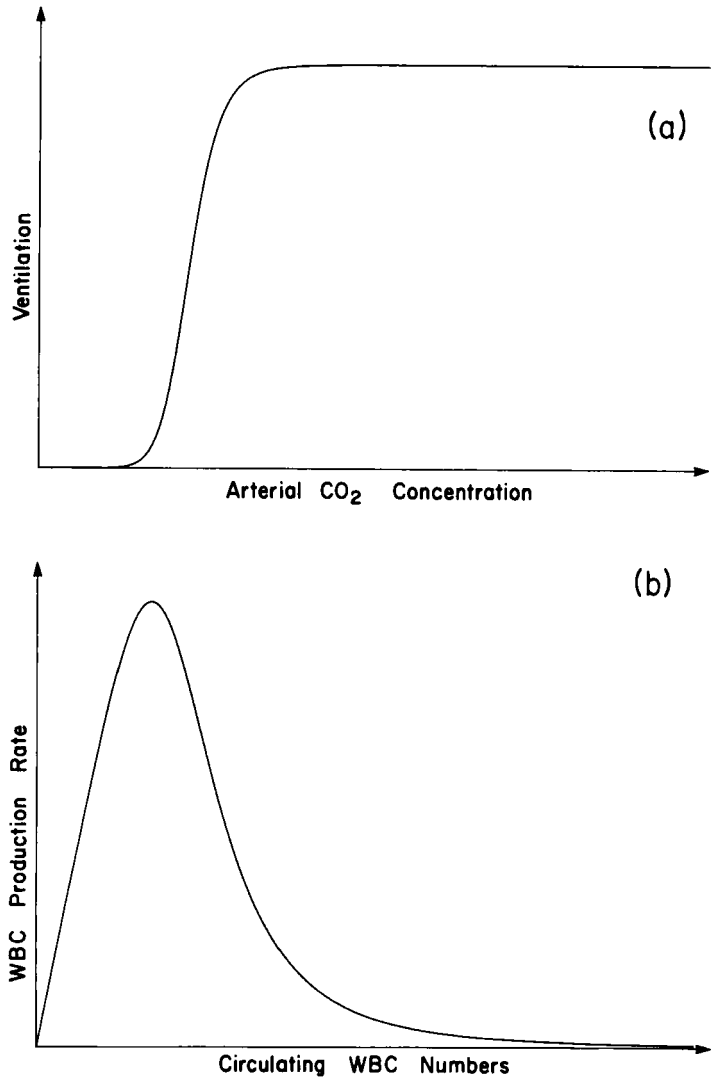

FIGURE 5. Schematic forms of nonlinear feedback functions. (a) Ventilatory response to arterial CO_2 levels as an illustration of controlled destruction. (b) The neutrophil production rate is shown as a function of circulating white blood cell (WBC) numbers to illustrate controlled production.

Stokes respiration often occurs in the pathological condition of congestive heart failure since it is associated with increased circulatory time from the lungs to the chemosensitive centers in the brainstem regulating ventilation. Cheyne-Stokes respiration has also been induced in normal dogs by increasing the circulatory time with the addition of an arterial extension.[30] Further, in obese individuals, the CO_2 production rate P is increased, and finally after neural brainstem lesions, an increased sensitivity (S_0) of the ventilatory CO_2 response function has been reported. All of these factors will dispose the system controlling arterial CO_2 levels to instabilities and consequent oscillation.

More complex mathematical models for the control of ventilation than that considered here have been developed to account for changes in both O_2 and CO_2, but they are generally sufficiently complex to preclude detailed theoretical analysis of stability properties.[31-33]

Periodic Hematological Diseases

As a second example of a physiological feedback system in which time delays are important, we consider the control of white blood cell production and the curious dynamics observed in some patients suffering from chronic myelogenous leukemia (CML). CML is a neoplastic disorder of the hematopoietic system generally characterized by a massive increase in circulating neutrophils. In the past two decades, clinical reports have established the existence of an interesting variant in which the neutrophil counts oscillate around elevated levels with a period of 30 to 70 days depending on the patient.[34] FIGURE 6a shows the serial white cell counts in a 12-year-old girl with the periodic version of CML.[35]

Again keeping equation 1 in mind, let x be the density of circulating neutrophils, D be the random neutrophil destruction rate, and P be the flux of new neutrophils into the blood. Since the committed neutrophil precursor cells require a period of time T (normally about five days) to produce mature neutrophils, P is a function of the white blood cell population a time T ago. Thus, in this system, the effective time delay is the cell maturation time.

Over a wide range of circulating neutrophil levels, the neutrophil production rate P is a decreasing function of increasing neutrophil density. However, due to a variety of factors, it is expected that at very low neutrophil levels the production rate will fall to zero. Thus, for P, we pick[36] a mixed positive/negative type feedback function as shown in FIGURE 5b. Note that in contrast to the ventilatory control system of the previous example, the rate constant for the destruction of cells is now fixed, but the rate of production of cells is under feedback control. Further, instead of having only one steady state, the dynamical equation for neutrophil production may have two steady states: $x_0 = 0$, and a second steady state $x_1 > 0$.

The steady state $x_0 = 0$ turns out to be uninteresting for our understanding of periodic CML. However, the second (nonzero) steady state may be locally stable or unstable depending on the values of a variety of parameters. The condition for the local stability of this second steady state is complicated, and we do not write it down here.[36] Several investigators believe that CML is generally accompanied by an increase in the transit time T through the cellular maturation compartments. As the maturation time T increases in the model, the steady state will eventually become unstable. When this happens, an oscillatory number of circulating neutrophils with a period between $2T$ and $4T$ will result. This local analysis, however, does not even begin to uncover the

behavior that this deceptively simple model for the control of neutrophil production is capable of producing. To see this, we must abandon analytic tools in favor of numerical studies.

In FIGURE 6b, we show the numerically determined neutrophil numbers predicted by this simple model when all parameters are maintained at their estimated normal values, except the maturation time (T) has been increased from its normal value of 5 days to a value of 20 days. With these parameters, the stability analysis predicts that the steady-state numbers of neutrophils should be unstable. Note the evident instability as well as the extreme irregularity of the solution to the totally deterministic model

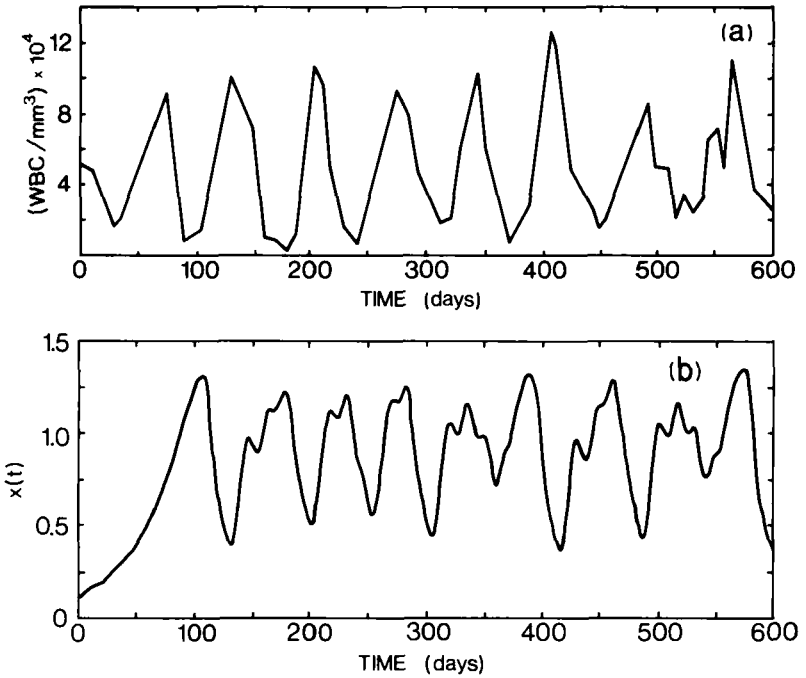

FIGURE 6. Dynamics in chronic myelogenous leukemia (CML). In (a) we have redrawn[35] the WBC counts from a 12-year-old girl suffering from periodic CML. There was no treatment during this period. (b) The pattern of WBC levels predicted by the simple model described in the text after increasing the neutrophil precursor maturation time from the normal value of 5 days to 20 days.

generating the behavior. The results of the simulation results shown in FIGURE 6b are of immediate interest when contrasted with the data presented in FIGURE 6a, as they mimic the observed pathological dynamics quite well.

This simple model for the production of neutrophils was the first association of intrinsic "chaos" in a continuous time deterministic system with a pathological process. Thus in contrast to random inputs leading to random fluctuations in output, here the levels of circulating neutrophils in the model appear random simply as a consequence of their own deterministic evolution.

A variety of other periodic and aperiodic hematological disorders have been modelled in a similar fashion including autoimmune hemolytic anemia,[37] cyclical neutropenia (also known as periodic hematopoiesis), aplastic anemia,[38] and cyclical thrombocytopenia.[39] In every case, it has been possible to associate known or inferred clinical alterations in the pathophysiological state with bifurcations in the models.

A number of investigators have shown that it is possible to induce oscillatory dynamics in hematological control systems by either the application of chemotherapeutic drugs in normal dogs[40] and in chronic myelogenous leukemia patients,[41] or the application of marrow-seeking radioactive compounds in normal mice.[42] Thus, bifurcations to periodic and aperiodic behavior may be produced by alterations in the number of cells allowed to complete the DNA synthesis, mitosis, and cytokinesis sequences.

Recurrent Inhibition

As a final example of how time delays and nonlinearities may play an important role in the generation of irregular dynamics in physiological feedback systems, we consider a model that may be of importance in understanding some of the processes leading to the onset of epileptic seizures. In an attempt to understand the complex sequence of events leading to the onset of petit mal and grand mal epileptic seizures, neurophysiologists and neurologists have often employed the penicillin-induced epilep-

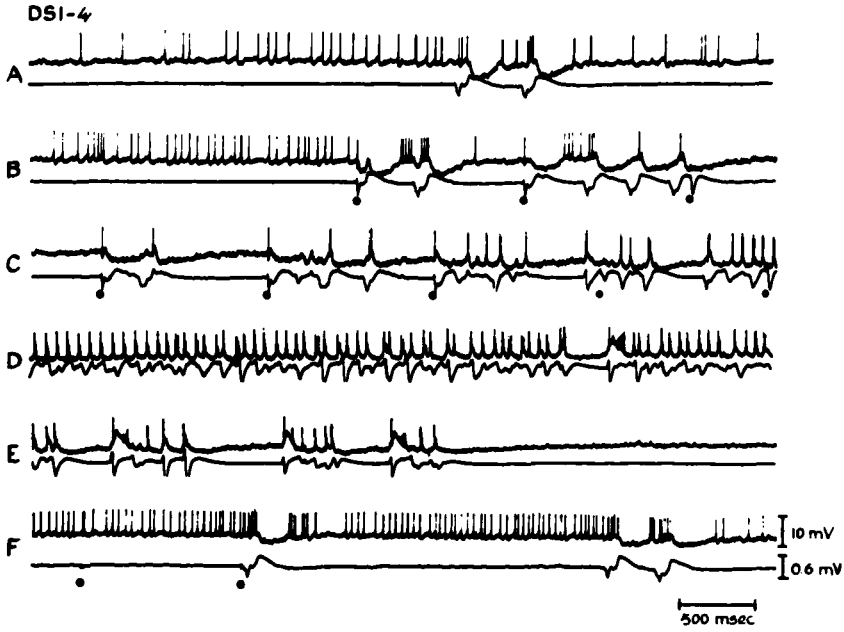

FIGURE 7. Penicillin-induced alterations in the neuronal discharge. This figure shows a noncontiguous sequence of recordings from a neuron in the pericruciate cortex of cat. (From Prince.[15] With permission from the publisher.)

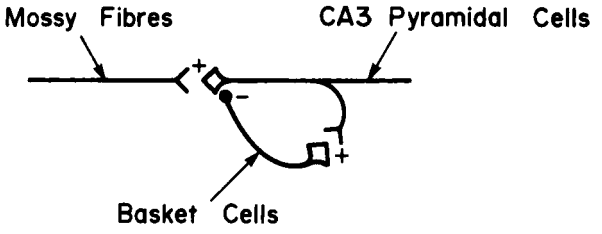

FIGURE 8. A schematic representation of some recurrent inhibitory interconnections in the hippocampus.

tic discharge model. In this preparation, the topical application of penicillin to various cortical structures leads to a discharge pattern in cortical neurons quite similar to those observed in naturally occurring epileptic seizures. These patterns are generally characterized by a gradual shift from low frequency burst like firing patterns to one in which there is continuous and sustained high frequency irregular neuronal firing. FIGURE 7 illustrates the type of firing patterns observed in a cortical neuron following the application of penicillin.[15]

Of all cortical structures that have been studied using this technique, probably the most popular has been the hippocampus, for which a great deal of knowledge exists concerning the type of neural connections present. In the hippocampus, a widely studied neural circuit is the recurrent inhibitory pathway formed by the CA3 pyramidal cells, the mossy fibers, and the basket cells. Recurrent inhibition is a process that has been described in almost every type of neural tissue in species ranging from the lowest invertebrates through man. In the hippocampus, this process is characterized by presynaptic cells (the mossy fibers) delivering excitation to postsynaptic cells (the CA3 pyramidal cells, FIG. 8). The postsynaptic cells then generate action potentials, and one effect of these action potentials is to activate inhibitory interneurons (the basket cells) via axon collaterals from the postsynaptic cell axons. These interneurons in turn deliver inhibitory activity back to the postsynaptic cells from which their original activation was derived. A number of investigators[46–49] have evolved models of varying complexity to treat the dynamics of recurrent inhibition.

If one identifies $x(t)$ with the frequency of firing in the CA3 pyramidal cells, then within the context of equation 1 the production P of x is entirely due to the excitatory activity within the mossy fiber population. The rate constant for the destruction of x is determined by two different processes: (1) The natural decay of activity that occurs because of the electrotonic properties of the CA3 pyramidal cell membrane and (2) a mixed (positive/negative, FIG. 5b) type of feedback because of the recurrent inhibitory pathway comprising the basket cells. The final aspect of this process that is important is the time delay in the generation of the recurrent inhibition due to conduction and synaptic delays within the feedback pathway.

The CA3 pyramidal cell–mossy fiber–basket cell complex has been extensively studied, and it is possible to estimate the relevant parameters for a model of this system.[45] It is known that the inhibitory neural transmitter between the basket cells and the CA3 pyramidal cells is gamma-aminobutyric acid (GABA) and that penicillin binds almost irreversibly to the GABA receptors on the CA3 pyramidal cell

membrane. Thus it is natural to examine the behavior of a model for this system as the GABA receptor density is decreased, corresponding to increasing penicillin levels.

In FIGURE 9, we have illustrated the response of this simple model for recurrent inhibition as a function of the number of GABA receptors. As receptor density is decreased to mimic the results of applying penicillin, there is a progressive shift in the cellular activity from regular bursting-like behavior with differing periodicities to a final sustained but irregular firing pattern at low receptor numbers.

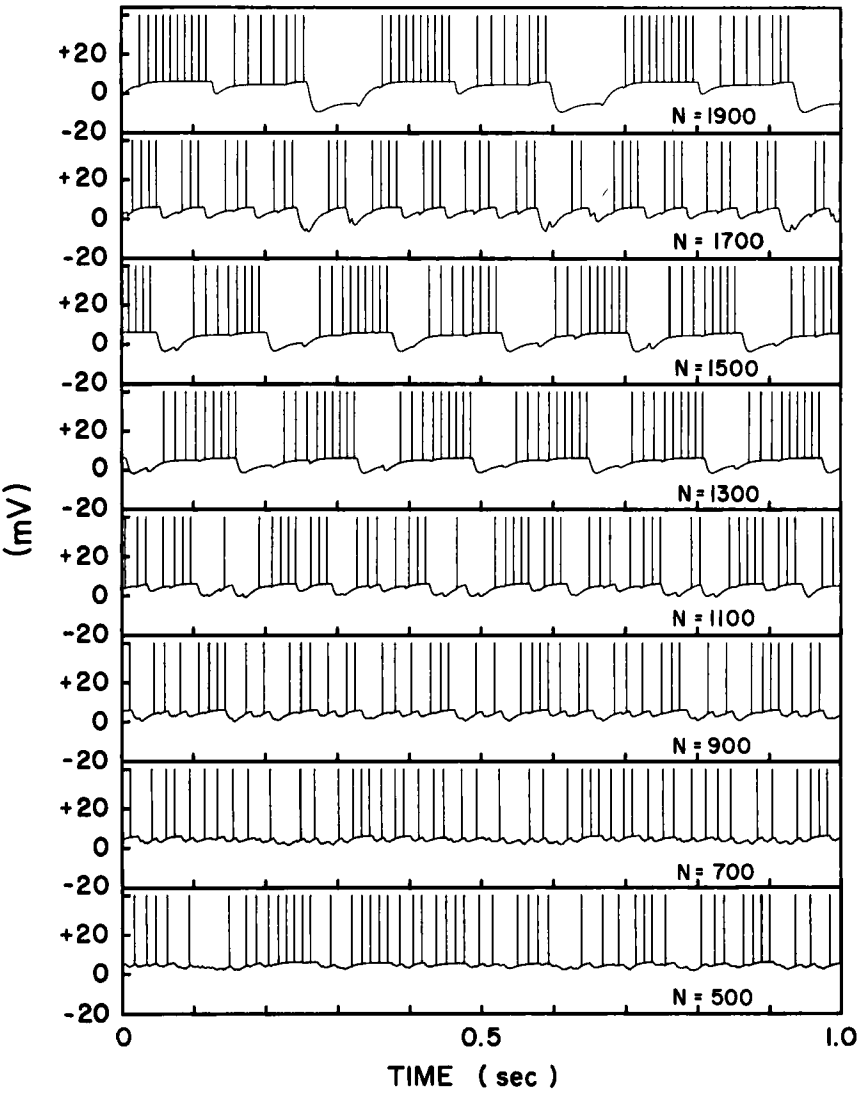

FIGURE 9. Simulated effects of penicillin in the recurrent inhibitory circuit of FIGURE 8. Each panel shows one second of simulated model activity at various densities (N) of GABA receptors as indicated. (Redrawn from M. Mackey & U. an der Heiden.[45])

IS CHAOS SOMETIMES THE NORM?

In the preceding sections, we have discussed several examples of physiological systems in which irregular, noise-like oscillations appear as certain parameters are altered. In some cases, the onset of irregular oscillations can be identified with a pathological state (TABLE 1). However, on close inspection, most normal physiological oscillations also show variability, albeit sometimes very small, e.g., in interevent intervals and consecutive amplitudes. The usual interpretation of this irregularity, if considered at all, is to attribute it to biological "noise" or "slop." Although in some cases such as interpretation may be reasonable, it is essential to recognize that irregularity may in fact be a reflection of the intrinsic dynamics of the system and thus would be observed even in the complete absence of biological "noise." Examples in which there is some evidence to indicate that the observed variability may, at least in part, be of deterministic origin include the cell generation time,[50–53] interbeat variability in the electrocardiogram,[54,55] background activity in the electroencephalogram,[56] and irregular glucose-induced oscillations in the electrical activity of mouse pancreatic beta-cells.[9,10]

Mathematical techniques are under development to analyze the irregularities noted in experimental data with the goal of learning something about the nature (e.g., the dimension) of the underlying system.[57] However, confirmation that observed irregular dynamics are in fact deterministic chaos is problematic. Indeed, in view of the fact that for almost every time series there are an infinite number of possible deterministic systems that will generate a time series with the same statistical properties,[58] it would seem that obtaining a unique solution, at least for arbitrarily chosen examples of noise-like dynamics, is not possible.

If variability is an intrinsic dynamic ingredient in the operation of normal physiological systems, then its significance is far from clear. It is not difficult to see that an irregular oscillation encodes more information in its varying amplitudes and interevent intervals than does a precisely periodic oscillation. However, it remains to be seen what the purpose of this information is and whether transmitting it by a noisy signal is more faithful in the face of ever-present biological noise.

DISCUSSION

As this paper and others have illustrated, a wealth of dynamical behavior ranging from periodic to irregular, noise-like oscillations can readily be observed in physiological control systems both experimentally and clinically (see for example other papers in this volume). Although many of these situations are familiar to the physiologist, the universal and fundamental aspects of their rich dynamical fabric does not yet appear to be fully appreciated. The importance of these qualities becomes more evident when it is realized that relatively simple nonlinear mathematical models have these same properties, thus implying that dynamic complexity may be the norm rather than the exception in nonlinear systems.

Our observations stress the importance of careful experimental documentation of the time-dependent behavior of physiological control systems in health and disease, particularly in response to changes in control parameters. Such observations not only provide important insights into the nature of the underlying control systems, but also

place constraints on the features that proposed models must contain. Unfortunately, it is uncommon to find published time series for physiological phenomena, particularly in the recent clinical literature. It is quite possible that both interesting and relevant dynamical changes are often observed but not published because their significance is not fully appreciated or the dynamical changes are wrongly ascribed to environmental noise and/or experimental error.

The pooling of data from different experiments or patients often obscures the presence of interesting dynamics in experimental and clinical time records. A fundamental property of chaotic systems is that their dynamics are exquisitely sensitive to small changes in either the values of the control parameters and/or initial conditions. In view of the extensive range of biological variability, it is not surprising that even at the best of times the observed dynamics between two experiments or patients are not precisely the same. Striking examples of interpatient variability in this context are the observations of hippus in sleepy patients with narcolepsy[23,24] and of rapid cycling manic-depressive patients.[5–7] By pooling time series, one could easily submerge interesting dynamics into a monotonous and humdrum noisy sea. A similar problem may occur with the use of signal averagers unless care is taken in the choice of the stimulus used to trigger repetitive sweeps of the averager.

In mathematical models, changes in dynamics correspond to bifurcations that occur as one or more control parameters are varied. Dynamical diseases may similarly arise because of pathological alterations in underlying physiological control parameters. Clearly the hope is that it may eventually be possible to develop diagnostic techniques to identify dynamical diseases as well as the altered control parameters. Therapeutic strategies could then be devised to readjust these altered control parameters by, for example, using mechanical, electrical, or pharmacological stimuli to reposition the control system in a range of parameter space associated with "healthy" dynamical behavior.

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DISCUSSION OF THE PAPER

E. BASAR: You have given three very interesting clinical examples and integrated several mechanisms to explain regular or irregular fluctuations of approximately one-minute duration. Did you think about correlations involving the motions of smooth muscle, oscillations that also have a periodicity of one minute? There are several studies, including some from Russian physiologists, that demonstrate minute rhythms in the brainstem. In Bob Galambos's laboratory in San Diego, Scott Makeig has measured minute rhythms from scalp electrodes. At Lubeck (West Germany), we have measured minute rhythms from smooth muscles and are able to show that smooth muscle rhythms can be chaotic, having fractal dimensions below three. Did you try to correlate this minute rhythm with the other physiological mechanisms you discussed?

M. MACKEY: I know that these rhythms exist in smooth muscle. I think you're suggesting that there may be a correlation between the existence of these approximately one-minute rhythms in brainstem areas and smooth muscle, with the kinds of behavior one sees on Cheyne-Stokes respiration. I would offer the following argument against that notion, not dogmatically, but in the spirit of friendly discussion. One can take this very simple model for the control of arterial CO_2 and instead of changing the sensitivity of the ventilatory response curve, change the time delay; if the time delay becomes long enough, the system should become unstable and should oscillate with a period of approximately four times the time delay. Such experiments were carried out many years ago when Guyton and some of his co-workers introduced arterial shunts in the dog. They found that increasing the time delay past a certain critical value induced oscillations in ventilation, and the oscillations and the ventilation had a period of approximately four times the time delay. So my suspicion is that the oscillation that we are seeing in Cheyne-Stokes respiration might be due, not to what you're suggesting, but to the instability of the global dynamics of the control system. As I said, I'm not being very dogmatic about this; I'd like to talk to you some more about it.