A Clinician's Primer on the Circadian Clock: Its Localization, Function, and Resetting

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Editor's Introduction

Considering how dependent on the daily cycle of light and darkness our biological functions are, intensive investigation of the brain's remarkable clock by which we adapt to the earth's rotation is long overdue. This deficit in clinical research, however, is being rapidly corrected, stimulated perhaps by air and space travel, and more pragmatically by the frequency of sleep disturbances incurred by work around the clock, aging, and bad sleep habits. Dr. William Schwartz admirably updates us on recent advances in the understanding of what the circadian clock is, how it works, and what we can do to manipulate its cycle.

G.H. Stollerman

And God said: "Let there be light." And there was light. And God saw the light, that it was good; and God divided the light from the darkness. And God called the light Day, and the darkness He called Night. And there was evening and there was morning, one day.

Genesis I, 3–5

Since the beginning of life on Earth, plants and animals have been forced to adapt to the planet's daily rotation about its axis. Biologic rhythms that are synchronized to the periodic alternation of day and night have been known since antiquity. The recognition that such rhythmicity is an *innate* feature of organisms, however, has come about only much more recently.[1] Usually credited with this discovery is the French astronomer Jean Jacques d'Ortous de Mairan, who in 1729 reported that the daily leaf movements of a heliotrope plant persisted in the absence of sunlight; in 1832 Augustin de Candolle demonstrated that these leaf openings occurred in constant darkness an hour or two earlier each day, i.e., they showed a *circadian*

(Latin; *circa* = about; *dies* = day) rhythm of 22 to 23 hours. The interpretation of these observations—that an endogenous clock mechanism oscillates independent of geophysical cues—is now generally accepted, but it was still the subject of debate as recently as 1960.[1]

The purpose of this chapter is to provide an introductory overview of this remarkable physiologic timekeeping system. The objectives are to (1) summarize our current understanding of the basic biology of circadian rhythmicity; (2) highlight some aspects of internal timing in humans that should be of interest to clinicians; and (3) survey some putative "clock" disorders and the possible means to treat them.

The Concept of a Circadian Clock

Ordinarily, the biologic activities of plants and animals are synchronized (entrained) to the natural day-night cycle by environmental light and darkness. However, even in an aperiodic environment, many rhythms continue to oscillate with frequencies only slightly different from that of the daily cy-

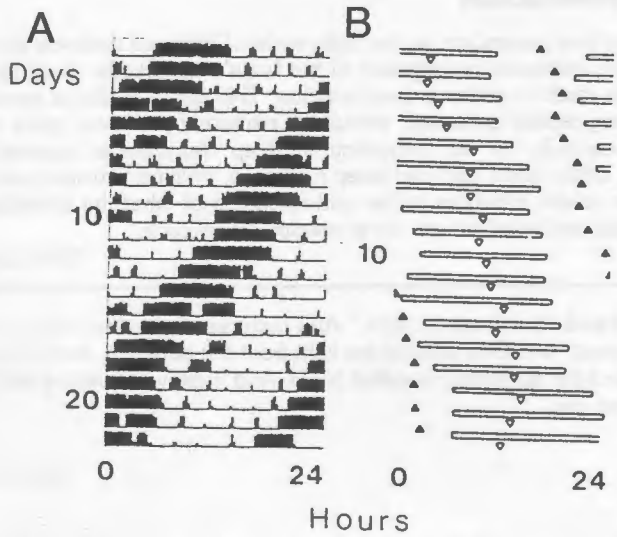


FIG 1.
Free-running circadian rhythms of activity in mouse **(A)** and human **(B).** The data are presented as "actograms," i.e., activity over the course of each 24-hour interval is plotted horizontally from *left* to *right,* with succeeding days stacked vertically from *top* to *bottom.* The onset of wheel-running by the mouse in a constant (time-free) environment begins earlier each day, i.e., it expresses a free-running circadian period of less than 24 hours. Activity in the human tends to start later each day, i.e., a greater than 24 hour period. Also shown for the human are maximal *(open triangles)* and minimal *(closed triangles)* values of rectal temperature. (Modified from Schwartz WJ, Zimmerman P: *J Neurosci* 1990; 10:3685–3694 and Wever RA: *Sleep* 1984; 7:27–51.)

cle to which they were previously entrained; that is, they "free run" with approximate 24-hour (circadian) periods (Fig 1). The persistence and properties of such environmentally independent, self-sustaining rhythms suggests the existence of an innate timekeeping mechanism, i.e., a "biologic clock."[4–6] The fact that the clock's endogenous period is not exactly 24 hours does not mean that it is imprecise. Rather, this property allows for more stable entrainment by environmental cycles and for organisms to successfully adapt to seasonal changes in day length (photoperiod).

The clock consists of three formal functional components: (1) an input (afferent) pathway for entrainment to light-dark cycles; (2) a circadian pacemaker that actually generates the oscillation; and (3) an output (efferent) pathway for expression of overt, measurable rhythms (Fig 2). Figure 2 highlights some of the problems inherent in experimental investigations of this system. For example, a pharmacologic or surgical treatment might abolish an overt circadian rhythm either by inactivating the pacemaker or by merely uncoupling an output pathway from the still oscillating pacemaker. Thus, arrhythmicity of a measured function may represent loss of the "hands" of the pacemaker rather than damage to its "gears." This difficulty emphasizes the possible confound when clock activity is assessed by measurements limited to a single output. On the other hand, experimental treatments that affect the free-running period of the oscillation must reflect changes in pacemaker behavior, either by a direct action on the pacemaker or by an indirect action via an input pathway. In general, the interpretation of circadian studies is made easier when data are continuously recorded from individual subjects, each monitored over several circadian cycles (see Fig 1). More confusing results can arise when a group of subjects is pooled and sampled at only a few phases of a single cycle, especially if the rhythms among the individual subjects are not synchronous. For example, apparent arrhythmicity of a population of subjects may be attributed either to a loss of rhythmicity of each subject or to a desynchronization of rhythmicity between subjects because each of the individuals expresses a rhythm that differs in phase or period.

In actuality, the real circadian clock is much more complex than the open-loop block scheme of Figure 2. Specifically, the system seems to include some closed-loop features: the pacemaker's photic input appears to be gated by a rhythm of visual sensitivity in the eyes,[7] and some of the pacemaker's rhythmic outputs may feed back to modulate the endogenous

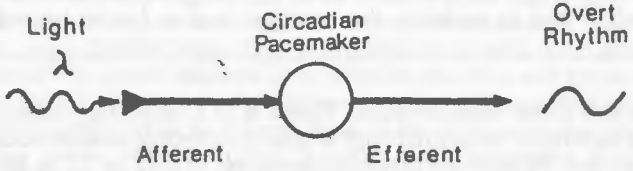


FIG 2.
Components of a circadian clock. (Modified from Takahashi JS, Zatz M: *Science* 1982; 217:1104–1111.

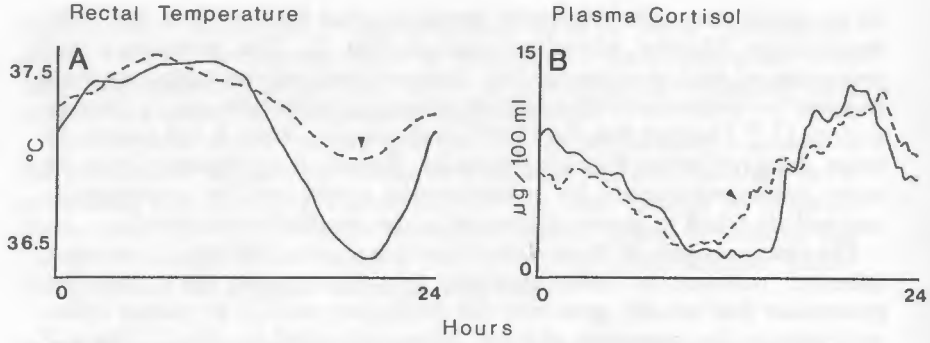
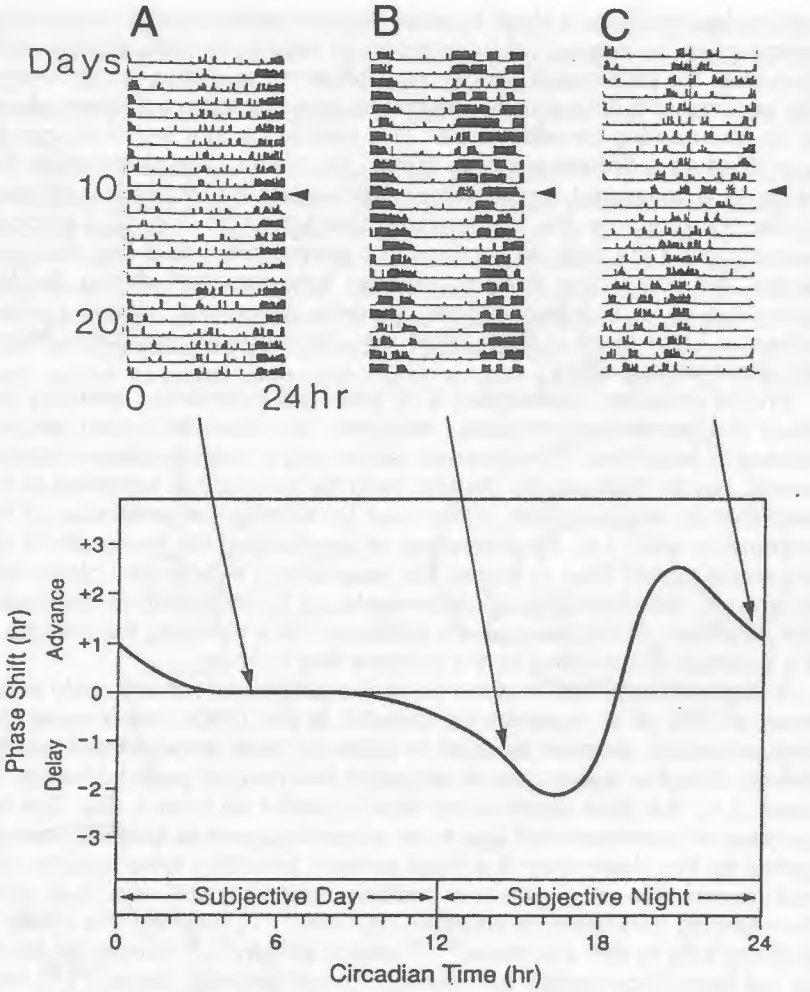


FIG 3.
Masking of rectal temperature **(A)** and plasma cortisol **(B)** rhythmicity by sleep. Temperature and cortisol rhythms during a normal routine of alternating activity and sleep *(solid lines)* are compared to the patterns during sleep deprivation *(dotted lines)*. Sleep lowers body temperature for the entire sleep period and inhibits cortisol secretion for the first 4 hours of the sleep period *(arrows)*. (Modified from Wever RA: *Experentia* 1985; 41:332–342 and Weitzman ED, Zimmerman JC, Czeisler CA, et al: *J Clin Endocrinol Metab* 1983; 56:352–358.)

period of the pacemaker itself.[8, 9] Another important complication not on the diagram is the fact that a manifest rhythm's amplitude and shape are governed not only by the underlying pacemaker but also by influences that can bypass the pacemaker, such as changes in activity, posture, and the environment. Light, for example, may directly modulate or modify an overt rhythm's waveform (light as a *masking* effect) in addition to its entraining role in synchronizing the rhythm's phase by resetting the pacemaker's oscillation (light as a *zeitgeber* [German; *zeit* = time; *geber* = giver]). Importantly, an overt rhythm of one variable may "mask" the expression of others. As one example, the patterns normally observed for the rhythms of body temperature[10] and plasma cortisol[11] are partly under pacemaker control and partly secondary to the rhythmic superimposition of sleep, which by itself lowers temperature and inhibits cortisol secretion (Fig 3). In an effort to minimize such factors that mask the circadian pacemaker's specific contribution to rhythmicity, researchers use a 24-hour "constant routine" protocol,[12] in which human subjects remain awake continuously, eat an identical snack hourly, and are housed in an environment of constant light, temperature, noise, and social cues.

The circadian system functions both to recognize the local time of day (as a sundial) and to measure the passage of time (as an hourglass). The

FIG 4.
Derivation of a phase-response curve. Panels **A** to **C** show free-running circadian rhythms of locomotor (wheel-running) activity in individual rodents housed in continuous darkness. Animals are previously entrained to a 12 hr:12 hr light-dark cycle before exposure to constant conditions. By convention, circadian time (ct) 12 is the onset of nocturnal locomotor activity; "subjective day" (ct 0–12) corresponds



to the 12 hour interval when the lights would have been on during the preceding light-dark cycle; and "subjective night" (ct 12–24) corresponds to the 12 hour interval when the lights would have been off. A 15 minute light pulse *(arrows)* is applied at different phases across the free-running circadian cycle. A pulse presented during mid-subjective day **(A)** has little or no effect; a pulse during early subjective night **(B)** is interpreted as a late dusk and delays the succeeding rhythm; and a pulse during late subjective night **(C)** is interpreted as an early dawn and causes a phase advance. The phase-response curve plots the direction and amount of such phase shifts against the times the light pulses are given. When pulses span the entire free-running circadian cycle, the waveform of the phase-response curve follows the *solid line* shown. (Modified from Schwartz WJ, Zimmerman P: *J Neurosci* 1990; 10:3685–3694 and Moore-Ede MC, Sulzman FM, Fuller CA: *The Clocks That Time Us: Physiology of the Circadian Timing System.* Cambridge, Mass, Harvard University Press, 1982.)

pacemaker works as a clock because its endogenous period is accurately entrained to the external 24-hour period by daily light-induced phase shifts that reset the pacemaker's oscillation. Advances or delays occur because the pacemaker is differentially sensitive to light exposure at different phases of its free-running circadian cycle. This rhythm of light sensitivity can be quantified as a "phase-response curve" by plotting the phase shifts that occur in a measured rhythm when light pulses are applied at different phase points across the free-running circadian cycle (Fig 4). Light presented during the early subjective night is interpreted as a late dusk and delays the succeeding rhythm, whereas light exposure during the late subjective night is interpreted as an early dawn and causes a phase advance. Light given at times other than the subjective night has little or no phase-shifting effect.

Precise circadian timekeeping is of profound importance, ensuring that body rhythms are appropriately integrated for concerted action and entrained to local time. The temporal sequencing of various clock-controlled events can be dramatically affected both by varying the sensitivity of the organism to environmental cycles and by altering the properties of the pacemaker itself, i.e., by shortening or lengthening the pacemaker's endogenous period (thus changing the pacemaker's steady-state phase relationship to the entraining light-dark cycle) or by increasing or decreasing the amplitude of the pacemaker's oscillation (thus changing the strength of the pacemaker's coupling to the rhythms that it drives).

It is important to note that the principles summarized above apply to humans as well as to experimental animals. In the 1960s, experiments that kept subjects in temporal isolation in cellars or caves demonstrated that the human circadian system has an apparent free-running period of about 25 hours, i.e., the clock tends to run slow by about an hour a day. The importance of environmental light as an entraining agent in humans was suggested by the observation that blind persons, including those living in normal society who are exposed to multiple periodic social cues, may show free-running (unentrained) circadian rhythms.[13, 14] Recently, the ability of ambient light to shift the phase[15–19] and/or entrain[20–22] human rhythmicity has been documented, and human "phase-response curves"[23, 24] have been generated. Photic effects in humans,[25] unlike those in laboratory rodents or monkeys,[26] require high light intensity, i.e., daylight (on the order of thousands or tens of thousands of lux) rather than indoor lighting (on the order of a few hundred lux).

Localization of a Clock to the Suprachiasmatic Nuclei of the Hypothalamus

There is now strong evidence (mostly but not exclusively in rodents) that the suprachiasmatic nuclei (SCN) in the anterior hypothalamus are the site of the mammalian circadian pacemaker.[27, 28] The SCN are paired nuclei straddling the midline, bordering the third ventricle, bounded anteroven-

trally by the optic chiasm (Fig 5). No other discrete area of mammalian brain has yet been found with the circadian pacemaking properties of the SCN. The homologue of the nuclei also appears to play a crucial timekeeping role in a few species of lizards and birds that have been examined.

In rodents, electric or pharmacologic stimulation of the nuclei causes predictable phase shifts of overt circadian rhythms, whereas destruction of the SCN results in a breakdown of the entrainment or generation of a wide array of such rhythms. More than 75% of the nuclei must be ablated to eliminate expressed rhythmicity, and no recovery of function is found even after prolonged postoperative survival. Three intrinsic properties of the SCN (energy metabolism, neuronal spike activity, and vasopressin secretion) exhibit circadian rhythmicity both in vivo and in vitro; all of these

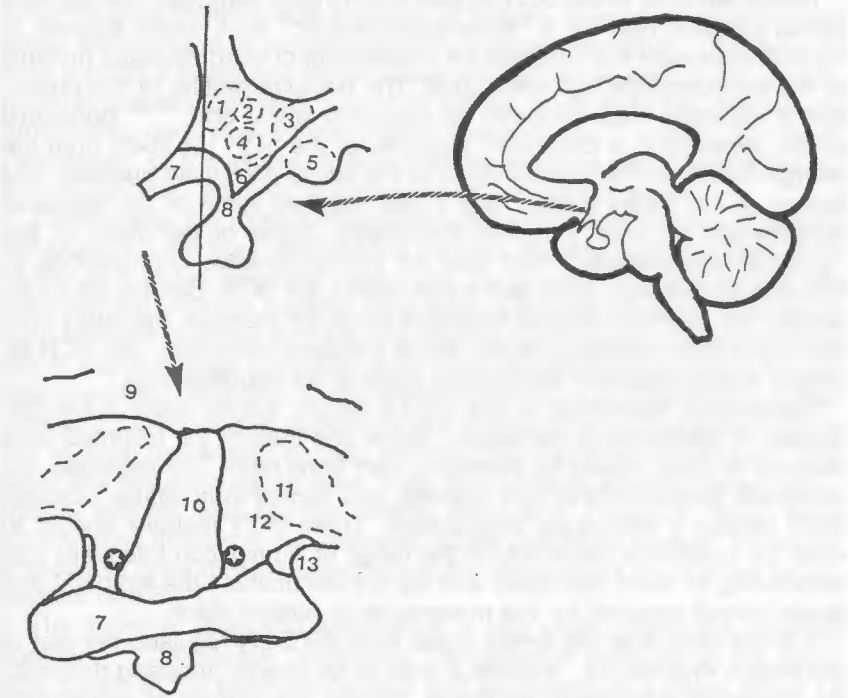


FIG 5.
Location of the human SCN *(stars)*. **Top,** sagittal views of whole brain *(right)* and hypothalamus *(left)*; **bottom,** coronal section at the level of the line through the hypothalamus. *1* = paraventricular nucleus; *2* = dorsomedial nucleus; *3* = posterior nucleus; *4* = ventromedial nucleus; *5* = mammillary body; *6* = arcuate nucleus; *7* = optic chiasm; *8* = infundibular stalk; *9* = anterior commissure; *10* = third ventricle; *11* = nucleus of the diagonal band of Broca; *12* = preoptic area; *13* = supraoptic nucleus. (Modified from Klein DC, Moore RY, Reppert SM (eds): *Suprachiasmatic Nucleus: The Mind's Clock.* New York, Oxford University Press, 1991 and Schwartz WJ, Busis NA, Hedley-White ET: *J Neurol* 1986; 233:1–4.)

rhythms peak during the subjective day in both diurnal and nocturnal mammals. Finally, neural grafts of SCN tissue reestablish overt rhythmicity in arrhythmic, SCN-lesioned recipients, and the rhythms restored by the transplants display properties that are characteristic of the circadian pacemakers of the donors rather than those of the hosts.

The architecture of the SCN has been studied extensively. The SCN cells are among the smallest in the brain, are very densely packed, and contain a number of neural peptides (vasopressin, vasoactive intestinal polypeptide, somatostatin, gastrin releasing peptide, enkephalin, atrial natriuretic peptide, and angiotensin). Most SCN axons terminate locally within the nuclei amidst a myriad of synaptic interactions, including dendro-dendritic contacts. Gamma-aminobutyric acid (GABA) is the most plentiful substance identified in SCN axons and boutons.

Neural afferents to the SCN include visual inputs conveyed directly from retinal ganglion cells via a "retino-hypothalamic" tract, which appears to be both necessary and sufficient for entrainment of overt circadian rhythms to the environmental light-dark cycle. The neurotransmitter of this projection is uncertain but is probably an excitatory amino acid.[29, 30] Additional photic information is channeled indirectly to the SCN via fibers from the intergeniculate leaflet (a subdivision of the lateral geniculate nucleus), and lesions of the leaflet suggest that it may mediate some of the effects of lightintensity on overt circadian rhythmicity. Some of the fibers of this "geniculo-hypothalamic" tract stain for immunoreactive neuropeptide Y. Plentiful serotonergic fibers also ramify within the SCN. Besides neural afferents, the SCN also receive hormonal input; for example, the nuclei contain high-affinity receptors for the pineal hormone melatonin. The SCN efferents mainly innervate neighboring parts of the hypothalamus.

Extracellular recordings of the SCN's electric activity show a low frequency of spontaneous discharges. About one third of the recorded units respond to light, usually by increasing their firing rates. The responses are sustained, proportional to light intensity, and elicited from diffuse receptive fields lacking a retinotopic organization. These SCN neurons appear to code for luminance (especially in the range of illumination intensities corresponding to dawn and dusk) and do not discriminate the temporal and spatial stimuli required for eye movements or pattern vision.

It is not clear how the timing signal from the SCN regulates the rest of the brain's rhythms, i.e., whether it does so by directly imposing rhythmicity, entraining subservient oscillators, filtering the outputs of subordinate systems so that their overt expression occurs only at specific times, or by combining a number of these mechanisms. Also unknown are the cellular and molecular processes that constitute the SCN's actual timekeeping machinery. In fact, for no circadian pacemaker (including those in unicellulars, fungi, insects, and molluscs) is this mechanism understood. Neuropharmacologic approaches have been difficult.[31] Nicotinic or glutamatergic antagonists block light-induced phase shifts of overt circadian rhythms in rodents and inhibit SCN neuronal responses to optic nerve stimulation in hypothalamic slices, although administration of the agonists (carbachol or

glutamate) to the animals does not exactly reproduce light's phase-shifting action. Manipulation of brain GABA-ergic and serotonergic systems also alters the circadian pacemaker's responsivity to light and entrainment to the light-dark cycle, but the observed effects are quite complex.

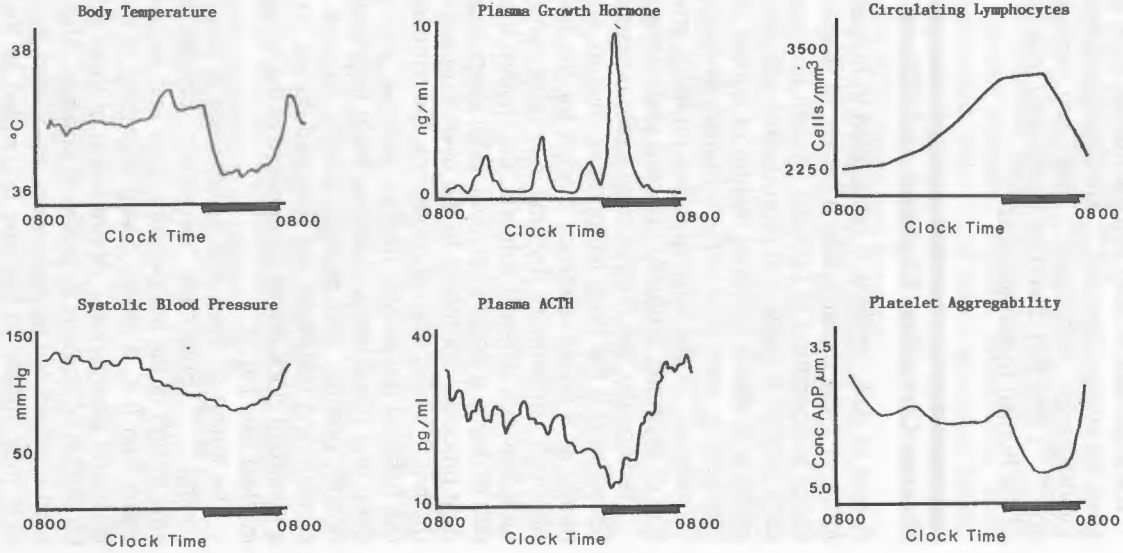
It is important to note that the human SCN have also been clearly identified by cytoarchitectural,[32] immunohistochemical,[33, 34] and receptor autoradiographic techniques[35]; that they receive a direct retinal innervation[36, 37]; and that disturbed rhythmicity may follow damage to this region of the human hypothalamus.[38, 39]

Human Circadian Rhythms and Effects on Medical Practice

A host of daily rhythms is catalogued in humans (Fig 6).[40–42] The waveforms of these rhythms take a variety of shapes, from relatively sinusoidal (body temperature) to pulsatile (growth hormone secretion). The phase of each rhythm is stable and reproducible with respect to time of day. Rhythmicity is in fact a universal feature of normal physiologic and psychologic functioning, even very early in human development.[43] Indeed, the classic "constancy" of the internal milieu probably emerges only through the action of rhythmic, mutually opposed underlying control systems.

Traditionally, the rhythm most easily measured longitudinally in individual subjects is the body temperature rhythm, and this rhythm is used commonly as a phase reference marker for the human circadian pacemaker. Although temperature rhythms may differ somewhat in phase and amplitude between different subjects, the rhythm is remarkably consistent from day to day in a single individual. Both sleep-dependent and sleep-independent processes contribute to the overt expression of the body temperature rhythm.[10] Under normal conditions, the temperature cycle is influenced by our habitual rest-activity rhythm, exercise, and ambient temperature. Both sleep and recumbency decrease body temperature, whereas wakefulness, upright posture, and physical activity increase it. However, when these confounding influences are removed during "constant routine" protocols, a persistent clock-driven component of the temperature rhythm can be unmasked (see Fig 3).

The timing of sleep and wakefulness is also under prominent circadian control.[44–47] Subjective "sleepiness" corresponds primarily to the nighttime trough of the temperature cycle and secondarily to a phase about 12 hours later (i.e., a siesta). Sleep attempted at times other than these is difficult and disorganized. Appreciation of these relationships has been aided by studies of humans in temporal isolation. After prolonged experiments in such unscheduled environments, associated rhythms within individual subjects may appear to become uncoupled as their free-running phase and period relationships become desynchronized. Such "internal desynchronization" occurs as the rest-activity cycle adopts a period of approximately 33 hours while body temperature rhythmicity persists with a 25 hour period. Sleep under these circumstances occurs at various phases of the tem-


Body Temperature
38
°C
36
0800
0800
Clock Time
Plasma Growth Hormone
10
ng/ml
0
0800
0800
Clock Time
Circulating Lymphocytes
3500
Cells/mm3
2250
0800
0800
Clock Time
Systolic Blood Pressure
150
mm Hg
50
0800
0800
Clock Time
Plasma ACTH
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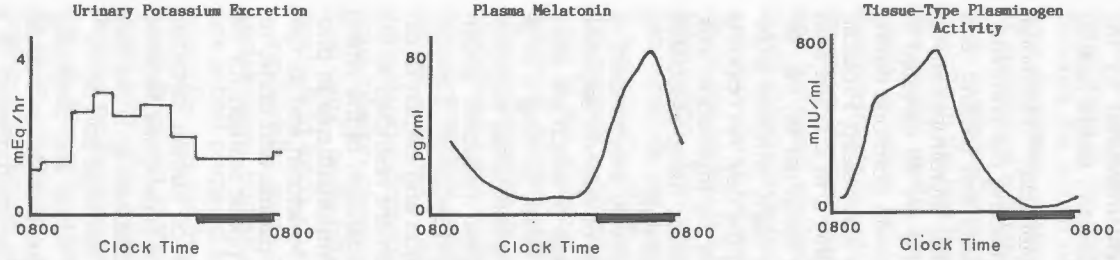

FIG 6.

Some physiologic, endocrine, and hematologic human rhythms. *Dark bar* represents the sleep period. *ACTH* = adrenocorticotropic hormone. (Modified from Moore-Ede MC, Sulzman FM, Fuller CA: *The Clocks That Time Us: Physiology of the Circadian Timing System.* Cambridge, Mass, Harvard University Press, 1982; Arendt J, Minors DS, Waterhouse JM (eds); *Biological Rhythms in Clinical Practice.* Bristol, England, John Wright, 1989; Van Cauter E: *Horm Res* 1990; 34:45–53; and Muller JE, Tofler GH, Stone PH: *Circulation* 1989; 79:733–743.)

perature rhythm. In these studies, the architecture of rapid eye movement sleep and the duration of sleep episodes depend on the phase of sleep onset within the circadian cycle; subjects tend to awaken as their free-running body temperature rhythms rise toward maximum. On the other hand, the "intensity" of sleep within an episode, as putatively measured by the amount of slow wave activity on the electroencephalogram, seems heavily influenced by the length of prior wakefulness.[48]

Much work has also focused on endocrinologic rhythmicity.[49] Hormonal rhythms typically exhibit complicated waveforms, reflecting the combined actions of circadian influences, masking effects of sleep and feeding, and pulsatile secretion. Plasma growth hormone, prolactin, thyrotropin stimulating hormone (TSH), and luteinizing hormone (LH) are all elevated in humans during sleep at night. The major surge of growth hormone during the first 2 hours of sleep is associated with deep slow wave sleep. Prolactin levels are elevated for a longer duration, subsiding only 1 to 2 hours after awakening. Both hormones are strongly affected by sleep per se, i.e., secretion is blunted when sleep is prevented during the night, whereas secretory peaks can be induced when subjects nap during the day. An opposite effect of sleep is exerted on TSH levels; sleep inhibits the thyrotropic axis, with TSH levels nearly doubled during sleep deprivation. Sleep-associated LH secretion occurs during early puberty in boys and girls.

Other neuroendocrine rhythms, however, are relatively independent of sleep. Plasma corticosteroids exhibit a complex profile of episodic secretion over 24 hours (perhaps 6 to 9 episodes per day, some of which are associated with meals). Most of the peaks begin late in sleep, forming a large daily surge from 3:00 to 9:00 A.M., and morning corticosteroid secretion persists during sleep deprivation. The pineal hormone melatonin undergoes a dramatic nocturnal increase in its synthesis and secretion. Environmental light acts to both suppress melatonin production and entrain its circadian rhythm, ensuring that high levels of melatonin are restricted to the dark phase in both nocturnal and diurnal animals regardless of the timing of their sleep. The hormone is believed to play an important role in photoperiodic behaviors as a transducer of day length. Melatonin and its metabolite 6-sulphatoxymelatonin can be measured in plasma and urine, respectively, and these rhythms are proving useful as phase markers for the human circadian pacemaker.[50]

The enormous clinical and practical importance of human circadian rhythmicity is now better realized.[5, 41, 42] Performance capabilities decrease at night, and it is probably no coincidence that the disasters at Three Mile Island, Chernobyl, and Bhopal all occurred between midnight and dawn.[51] In the hospital, proper interpretation of laboratory values and diagnostic tests hinges on a working knowledge of human endocrinologic and physiologic rhythmicity. Every practitioner knows that the interpretation of a plasma cortisol level depends on the time of day that the sample is drawn. It is also well known that an oral glucose tolerance test given in the afternoon will yield plasma glucose values nearly double those obtained by tests in the morning.[49] Even immune reactivity has a circadian basis; the

area of induration after tuberculin (purified protein derivative) skin testing varies threefold as a function of the time of antigenic challenge.[52]

Daily rhythms such as these may be important in the pathophysiology of disease.[5, 41, 42] In fact, one of the inherited dystonias is essentially *defined* by its marked daily fluctuation.[53] Asthmatics display heightened bronchial constriction in the early morning, at the time that normal subjects also experience the trough of their rhythm of peak expiratory flow rate.[54] Nighttime decreases of airway patency and dynamic compliance and increases of pulmonary resistance and vagal tone serve to magnify asthmatic sensitivity to environmental triggers. Also showing a marked daily rhythm (but peaking in the late morning) is the incidence of myocardial infarction, sudden cardiac death, and ischemic stroke.[55, 56] Symptoms and signs of myocardial ischemia, including angina pectoris, ST segment displacement, and positive treadmill tests, are more frequent 4 hours after awakening in the morning. Increased circulating catecholamine levels, decreased fibrinolysis, and increased platelet aggregation also occur in the morning hours and could trigger thrombus formation.

It should not be surprising that the efficacy, side effects, and toxicity of drugs are greatly influenced by time of day.[5, 41, 42] Both drug disposition (absorption, distribution, metabolism, and elimination) as well as target organ sensitivity are susceptible to body rhythmicity. Thus, a given drug dose is not equally effective (or toxic) throughout the day. The clinical utility of this concept is exemplified by the practice of administering exogenous steroids in the morning (rather than in the evening or in divided doses) to minimize adrenocortical suppression. In addition, the study of rhythmic pharmacokinetics of anticancer drugs has led to some novel scheduling strategies for enhancing effectiveness and minimizing toxicity.[57] It is important to note that constant drug delivery does not ensure a temporally invariant drug effect. Indeed, constant intravenous infusion of heparin results in rhythmic anticoagulation, maximal at night.[58] Even the seemingly innocuous infusion of saline is more likely to cause iatrogenic edema at night than day,[59] partly because of renal rhythms that affect the handling of imposed fluid loads.

Incidentally, some practical tips on daily living come from an intimate knowledge of human circadian rhythmicity. Although it seems intuitive that one is best prepared to confront the dentist early in the morning, circadian principles suggest instead that the visit be postponed until after lunch, when threshold to tooth pain and duration of anesthesia are greatest.[4] For those who bring extra work home in the evening, it should be of interest that the performance measure that improves over the day, peaking at 8:00 P.M., is the "simple serial search" task (similar to proofreading); the ability to retain information, on the other hand, is lowest at this time.[51] For some persons, the timing of their exercise regimen may be as important as its intensity; patients with classic or Prinzmetal's angina show a greater exercise tolerance in the afternoon than in the morning.[60, 61] Last, and of no surprise to obstetricians and parents, is the pronounced daily rhythm of the initiation of labor, which occurs most frequently from 12:00 A.M. to 4:00

A.M.[42] In fact, mammals generally give birth during their inactive phase; parturition in rats, for example, occurs during the day. This circadian regulation ensures that births occur when the dams are in the burrow and not while they are foraging away from the nest.

Disorders of Clock Function

Rapid Time Zone Change Syndrome ("Jet Lag").—When a new, phase-shifted environmental cycle is acutely imposed in either laboratory[62] or actual field[63] studies, overt circadian rhythms appear to resynchronize at different rates, causing instabilities in the phase relationships among the rhythms. The analysis of this resynchronization is complicated by highly dynamic masking effects, because sleep and meals are taken out of phase and temporarily disrupt the waveforms of marker rhythms (in fact, the circadian pacemaker itself may reentrain much more quickly than the measured waveforms would indicate). This transient temporal disorganization is experienced as the symptoms of "jet lag," which include insomnia, fatigue, headache, irritability, dizziness, and loss of appetite. The insomnia and diminished daytime alertness are caused by a combination of sleep deprivation and circadian phase shift. The number of days required for full resynchronization of rhythms after transmeridian travel depends partly on the number of time zones crossed; it is generally faster after westward flights (phase delay) than after eastward flights (phase advance) of the same magnitude. The conventional rule of thumb is that 1 day is required for each time zone passed. The direction of flight (outbound vs. homeward) and the time of departure (night vs. day) seem to be only minor factors.

Rotating Shift Work Schedules.—About 1 of every 5 working men and women work shifts that alternate between day and night. Although individual tolerance to shift work varies enormously, these workers report sleep-wake disruptions (in large surveys, half of them report falling asleep at least twice a week on the job), gastrointestinal complaints (with documented peptic ulcer disease), and cardiovascular disorders.[64] It appears that most workers are merely "staying up late" on the night shift, rather than adjusting to it. Fatigue on the job is caused by working at the trough of the normal performance and temperature rhythms and by cumulative sleep loss from daytime insomnia. Symptoms may be minimized by rotating the shifts in a phase-delaying manner (day to swing to night) every 3 weeks.[65] Evening personalities ("night owls") are said to tolerate shift work well and tend to take their leisure time after sleep and before work, rather than the usual pattern of leisure after work and before sleep. Studies to prospectively identify those individuals who may not tolerate rotating work schedules have considerable economic and public health implications.

Sleep Disorders.—The "delayed sleep phase syndrome"[66] can be differentiated from other forms of insomnia and has been estimated to account for 10% of all patients who report difficulty with sleeping. Patients cannot fall asleep at the desired clock time required to meet work sched-

ules; they typically finally fall asleep between 2:00 A.M. and 6:00 A.M.. The abbreviated night's sleep then leads to daytime somnolence and fatigue. However, when not required to maintain a strict schedule (e.g., weekends, holidays, and vacation periods), the patient will fall asleep normally if allowed to adopt an idiosyncratic schedule, e.g., going to bed at 3:00 A.M. and arising at 11:00 A.M.. These individuals have normal sleep duration and architecture, but the phase of their sleep period within the 24-hour day is abnormal and must be reset to occur at a socially acceptable clock time. There may be milder forms of this syndrome that present as a sleep-onset insomnia.[67] Less common is the "advanced sleep phase syndrome," in which patients are hypersomnolent in the evening, retire early, and spontaneously awaken in the early morning alert and refreshed. This pattern is similar to the sleep of the normal elderly. Finally, the "hypernychthemeral syndrome"[68] leads to insomnia secondary to a free-running (unentrained) sleep-wake cycle, sometimes caused by either a defective entrainment mechanism (as in blindness) or a weakened appreciation of societal cues (as in some types of personality disorder).

Affective Illness.—The symptoms of endogenous depression are often periodic, with a prominent diurnal variation of mood. On one hand, this may merely reflect the effect of normal body rhythmicity on the expression of depressive symptomatology; on the other hand, abnormalities of circadian rhythms in these patients have also been noted, including decreased amplitude, distorted waveform, day-to-day instability, and unusual 48-hour periods.[69] Interestingly, some rhythms in some patients appear to be phase-advanced, and the shortened latency of rapid eye movement sleep onset, early morning awakening, and abnormal cortisol and temperature rhythms of depression have been proposed to represent such a phase shift. One of the possible causes of this anomaly would be a circadian pacemaker running faster than normal; when this abnormal oscillation becomes entrained to the 24-hour environmental cycle, its phase would be advanced compared to normals. At present, however, there is insufficient evidence to interpret these rhythm disturbances in depression, and no clear consensus has emerged regarding their nature (i.e., are the altered waveforms because of shifts in phase or merely changes in shape?) or significance (i.e., are the abnormalities trait- or state-specific?). Conclusions have been hampered by the diagnostic heterogeneity of the groups studied, small sample sizes, poorly matched control populations, lack of "constant routine" protocols, and differences in the frequency of sampling and selected phase marker (peak, trough, onset) of measured rhythms.

"Seasonal affective disorder"[70] consists of recurrent depressions occurring annually during the fall and winter, affecting as much as 5% of the general population. In addition to the expected symptoms of decreased activity and libido, there are atypical features of overeating, weight gain, and hypersomnia. Frequently, these patients report amelioration of depression after traveling south. One environmental variable that shows a pronounced seasonal change in temperate latitudes is exposure to sunlight.[71] The notion that a shortened winter day length might be responsible for

this syndrome has led to successful therapies using bright light (see later).

Aging and Dementia.—Elderly persons often have characteristic changes in the timing and pattern of their sleep. It is possible that daytime napping, fragmented sleep, and early morning awakening in the aged might be secondary to reduced amplitude and/or shortened free-running period of the circadian pacemaker's oscillation.[72] Some data on body temperature, motor activity, and neuroendocrine secretory rhythms in the elderly are consistent with this idea.[73–75] Other evidence raises the suspicion that elements of the circadian clock become less tightly coupled with advancing age.[40] An especially intriguing observation is the finding of apparent cell loss in the SCN during normal aging and in patients with Alzheimer's disease.[76] It is important to note that age-associated changes in motor activity levels and sensitivity to environmental cycles may exert masking effects on marker rhythms that could account for some of the differences between young and old subjects.[77] Some preliminary work studying 80-year-olds in a "constant routine" protocol does suggest that age-related deterioration might be occurring mostly in the circadian pacemaker's entrainment and output pathways and not in the oscillatory mechanism itself.[78] In any case, it is tempting to speculate that diminished integrity of the circadian system in Alzheimer's disease,[79, 80] while surely a consequence of the disease itself, might also contribute to symptoms such as fluctuating confusion and "sundowning."

Resetting the Clock

Light.—The discovery that bright light can entrain human rhythms, shift their phase, and suppress melatonin secretion (see earlier) has revolutionized our thinking about resetting the human circadian clock. Advance or delay phase shifts can be predicted by understanding the phase-response curve to light (see Fig 4). In this way, scheduled exposure to daylight (in the afternoon after westward flights, in the early morning after eastward flights) may help reduce the symptoms of jet lag[81]; indeed, subjects allowed outdoors after a flight do seem to resynchronize faster than those kept indoors. Also, patients with the delayed sleep phase syndrome may improve on a regimen designed to phase-advance circadian rhythms, i.e., bright light in the morning and darkness in the evening.[82] Similarly, adaptation to nocturnal shift work can be enhanced by exposure to bright light during the night and darkness during the day.[83, 84] Recently, applied light of a specific timing, intensity, and duration appeared to result in an "arrest" of the circadian pacemaker's oscillation[85]; this finding suggests the exciting future possibility that a properly timed, second light pulse might be used to instantaneously reset the circadian system to any desired clock time.

"Phototherapy" in seasonal affective disorder has received wide attention.[86] A remission rate of 75% has been reported after daily exposure to 10,000 lux for 30 minutes or 2,500 lux for 2 hours; broad-band white light

is more effective than restricted bandwidths,[87] and dim (100 lux) light is not therapeutic. Improvement begins within 4 days, but patients usually relapse if lights are discontinued. Recent evidence suggests that bright light may also help otherwise normal people with the "winter blahs."[88] Nonseasonal depressives, including those with atypical symptoms, do not seem to respond.[89, 90] The explanation for light's antidepressant action is unclear[91, 92] but appears not to depend on sleep deprivation, melatonin suppression, or extension of the environmental photoperiod. A seasonal variation in sensitivity to light may be involved.[93] Light exposure in the morning appears relatively more effective than in the evening, but it has not been conclusively demonstrated whether this is because of a phase shift of circadian rhythmicity, an alteration of rhythm amplitude, or some other, noncircadian mechanism.[94, 95]

There are certain environments with deficient or exotic environmental cycles, and bright light might be profitably employed to promote entrainment in such special circumstances. Astronauts in earth orbit, for example, see a 90-minute day-night cycle, a frequency that lies outside the possible range of entrainment of the human clock; scheduled bright light might help their adaptation. Residents living north of the Arctic Circle experience nearly full darkness around the time of the winter solstice; their "midwinter insomnia" may respond to bright light.[96] Closer to home, the intensive care unit is an environment in which patients generally do not experience the alternation of day and night. Interestingly, delirium and disorientation appear to be more common in a windowless, artificially lit unit than in one with windows open to daylight,[97] and infant outcome is improved in a neonatal nursery with cycles of light and darkness.[98] Last, because patients with Alzheimer's disease typically see less than 1 hour of more than 2,000 lux light per day,[99] the effects of bright light therapy in these patients should be of extraordinary interest.

Social Cues.—Although bright light may be the most powerful environmental timing cue,[100] humans living under natural conditions in a modern industrial society probably do not receive sufficient amounts for the purposes of entrainment.[101] Nonphotic societal cues—e.g., knowing the time of day; scheduling meals, activities and sleep; and interacting socially—may be the more relevant entraining factors, given their ubiquity.[102] The critical stimulus for these social cues has been difficult to determine, but recent fascinating experiments in a number of animal species (especially hamsters) are proving informative. Hamster rhythms can be entrained by repeated social contacts between conspecifics, and the phase-response curve to periodic social encounters appears qualitatively different in form from that resulting from light pulses.[103] Unlike the "photic" curve shown in Figure 4, the "social" curve has phase advances during the middle to late subjective day and phase delays during the late subjective night or early subjective day. A similar curve can be generated by a manipulation both *nonsocial* and *nonphotic*, e.g., inducing hamsters to run by placing them in a novel running wheel.[104] Thus, wheel-running activity, itself one of the rhythmic outputs of the circadian pacemaker, also feeds back to entrain the pace-

maker. Of note, appropriately timed locomotion in these animals can accelerate their reentrainment to a new, phase-shifted light-dark cycle.[105] However, more research is needed before exercise can be routinely recommended as an antidote for human jet lag; it may not be physical activity per se but a correlated variable that mediates these circadian effects, e.g., the animals' state of "arousal." In any case, future studies of phase-shifting stimuli in humans will need to attend to any changes in the level or pattern of motor activity.

Meals.—When food is made available for a restricted time (i.e., for a few hours each day), rats can anticipate the meal and increase their locomotor activity before food presentation. The properties of this anticipatory activity have been characterized and indicate that it is mediated by a circadian pacemaker.[106, 107] However, this food-entrainable mechanism is separate from the light-entrainable mechanism based in the SCN, and food-anticipatory rhythms persist in SCN-lesioned rats. The anatomic substrate for this extra-SCN oscillator is unknown and may even reside in the gastrointestinal tract.[106] Importantly, the circadian pacemaker in the SCN usually cannot be entrained by the anticipatory activity of food-deprived rats. Similarly, although the food-driven rhythms of plasma insulin and glucagon are phase-shifted in human subjects consuming a single meal at breakfast or dinner, the rhythms of body temperature and plasma cortisol remain relatively unaffected.[108] Further experiments in rats suggest that entrainment by food depends on the size of the nutrient meal and not on the ingestion of a single or specific foodstuff.[107] There is, therefore, little theoretical or empirical data at present to support the use of any special diets to combat jet lag.

Melatonin.—In animals (and especially well studied in rats), locomotor rhythmicity can be entrained by daily subcutaneous injections of melatonin.[109] In constant conditions, entrainment occurs when the onset of the free-running locomotor rhythm coincides with the time of melatonin administration; this phase relationship between injection time and activity onset seems to be a consequence of melatonin-induced phase advances during the late subjective day. This characteristic is reminiscent of the phase-response curve to social interaction/novelty-induced wheel-running/arousal in hamsters (see earlier). Although this similarity raises the suspicion that melatonin's phase-resetting capacity might be caused by induced changes in sleep or activity, there is also evidence to implicate the SCN as the hormone's site of action: the nuclei contain high-affinity melatonin receptors, SCN lesions prevent melatonin entrainment, and SCN metabolic and electrical activities are altered by melatonin given during the late subjective day.[110, 111] There are also some data to suggest that melatonin administration may hasten the resynchronization of rhythms to a new, phase-shifted light-dark cycle.[112] Of note, all of these melatonin effects may be pharmacologic, because the doses required are supraphysiologic and because pinealectomy has little influence on overt circadian rhythmicity in rats.

These findings in animals now have some human correlates. Melatonin (5 mg orally in the evening) has a phase-advancing action on the free-run-

ning circadian rhythms of blind human subjects,[113] and such an action might be therapeutically used to advance the time of sleep onset in patients with delayed sleep phase syndrome.[114] Both field[115] and laboratory[116] studies of jet lag show that melatonin improves psychologic and physiologic readjustment to an eastward (i.e., phase-advancing) time zone transition. Some of this benefit may be because of the hormone's hypnotic effects, and further well-controlled studies, including westward[117] (i.e., phase-delaying) flights, are needed to assess melatonin's efficacy and safety as a jet lag therapy.

Benzodiazepines.—In hamsters, the short-acting benzodiazepine triazolam (Halcion) affects circadian rhythmicity.[118] A single injection shifts the phase of free-running rhythmicity and accelerates reentrainment to a new light-dark cycle; the phase-shifting effect is blocked by the benzodiazepine antagonist Ro 15-1788.[119] Moreover, repeated daily injections of triazolam can synchronize rhythmicity to the period of the injection regimen[120] and alter the entrained rhythm phase relationship to an external light-dark cycle. However, the dose usually studied in hamsters is very large (2.5 mg), resulting in a peak plasma concentration of nearly 3,500 ng/mL[118]; this compares to a peak of less than 4 ng/mL and a total area under the plasma concentration curve of less than 25 hour ng/mL in human subjects given a standard 0.5 mg dose.[121] The phase-response curve to triazolam in hamsters resembles the nonphotic curves described previously. In fact, the drug causes hyperactivity (not sedation) in rodents, and its phase-shifting ability can be blocked completely if the animals are immobilized.[122] In humans, 0.5 mg of triazolam (but not 0.25 mg) is reported to reverse the sleep loss and daytime sleepiness that results from an acutely shifted sleep-wake schedule,[123] but this is a dose that has been associated with cognitive impairment, including amnesia.[124] Thus, the present rationale for recommending triazolam for jet lag is rather weak, and further research is needed to characterize its phase-shifting activity in humans.[125]

Other Agents.—Currently under investigation are a number of other potential pharmaceuticals. For example, interference with monoaminergic neurotransmission (as with the monoamine oxidase A inhibitor clorgyline[126] or the alpha$_2$-adrenergic agonist clonidine[127]) modifies the free-running period of wheel-running rhythmicity in rodents. Interestingly, lithium slows circadian rhythmicity in a variety of organisms, including algae, plants, insects, molluscs, and mammals.[128] Curiously, Vitamin B_{12} has been reported to improve the sleep-wake scheduling difficulties of a few patients with delayed sleep phase or hypernychthemeral syndromes.[129, 130] The mechanisms for any of these effects are unknown.

Postscript

This overview has only considered biologic rhythmicity in the circadian range; beyond its scope are rhythms of faster frequencies (e.g., hormonal pulses, rapid eye movement sleep cycles) and a host of other phenomena

(e.g., reproductive rhythms, seasonal behaviors, celestial navigation and migration) that depend in part on a daily time sense and the ability to measure day length. The entire spectrum of biologic rhythmicities is critical to the regulation of organisms in the time domain. Such "internal temporal order" helps to optimize the economy of biologic systems, better prepares organisms to anticipate and cope with periodic alterations in the environment, and allows for predictive, in addition to reactive, homeostatic control.[131] The consequences for human health and disease are only now being realized.

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