MEDICAL PROGRESS

CIRCADIAN TIMEKEEPING IN HEALTH AND DISEASE

Part 1. Basic Properties of Circadian Pacemakers

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THE study of circadian (approximately 24-hour) rhythms has within the past decade evolved from a biologic curiosity to a science with enormous implications for clinical medicine. The concurrent maturation of circadian oscillator theory, the anatomic definition of circadian pacemakers in mammals, and the identification of a considerable number of persons with malfunctions of the circadian timing system have formed the basis of a new medical discipline.[1]

Circadian rhythms relate to clinical medicine in two major ways. First, circadian rhythmicity is such a pervasive element of human physiology that its recognition has required a reassessment of many clinical diagnostic and therapeutic procedures. Measurement of many fundamental clinical indexes, including serum and urine constituents, body temperature, and even performance and mood, all must be considered in the light of the timing system that controls this intrinsic rhythmicity. Similarly, the responses to the various forms of medical therapy — pharmaceutical drugs, radiation, and surgery — have also been shown to vary markedly with the time of day.

Second, there is a growing recognition that disorders of circadian timekeeping may underlie a number of important diseases, many of them of modern origin. The human race evolved on a rotating planet with a day–night cycle that has always had a periodicity of close to 24 hours. It is only within the past century, with the advent of electric light and the ability to travel rapidly by air across time zones, that disruptions of the circadian timing system have become a serious public-health problem.[2] However, circadian disorders are not always modern or of environmental origin. Malfunctions of circadian timing processes can occur as a result of various diseases. For example, the pathophysiology of a variety of disorders, including certain sleep disorders, endocrine disorders, and manic-depressive illness, may have a circadian basis. This review will start with a discussion of the fundamental properties of circadian pacemakers and then outline their physiology and neuroanatomy before proceeding in Part 2 to the clinical implications for therapy and the pathophysiologic mechanisms that are thought to underlie specific circadian disorders.

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Dedicated to the memory of Elliot David Weitzman, M.D.

NORMAL FUNCTIONS OF THE CIRCADIAN TIMING SYSTEM

Since the discovery of circadian rhythmicity, an enormous effort has been devoted to the cataloging of rhythmic variables.[3] Circadian rhythmicity has been shown to be a ubiquitous phenomenon, both across phylogeny and within individual organisms. It is now worthy of note when the rare variable is identified that does not display circadian variation. This ubiquity is perhaps the most eloquent evidence of the fundamental importance of circadian rhythms in nature; successful adaptation to the temporal organization of the environment appears to confer on the organism a selective advantage that is entirely analogous to that conferred by the specialized beaks of the Galápagos finches.[4,5]

Figure 1A shows the normal circadian rhythms in a few variables — including sleep, body temperature, plasma concentration of cortisol and of growth hormone, and urinary excretion of potassium — in a young adult living on a regular day–night schedule. It is clear from this graph that physiologic rhythms may have a variety of wave forms. The rhythm may have a relatively square-shaped wave, as does the body-temperature rhythm; it may consist of a regularly repeating episodic series of pulses, as in the rhythm of plasma concentration of cortisol, or it may consist of a single pulse each day, as in the typical pattern of growth hormone secretion. Each rhythm has its own characteristic "phase relationship" (relative position in time) with respect to the environmental day–night cycle as well as with respect to each other. This internal counterpoint of rhythmic structure is remarkably stable and consistent between individuals. Indeed, it appears that a major function of the circadian timing system is the internal sequencing of physiologic events and metabolic processes so that interdependent functions are coordinated and incompatible processes separated in time.[6]

Many rhythms show anticipation of a periodic environmental event, such as dawn or dusk. For example, as shown in Figure 1A, body temperature starts to rise in advance of the light's being switched on or the subject's awakening in the morning. Similarly, the plasma cortisol concentration starts to rise in the middle of the daily sleep episode, reaching a peak just before the subject awakes. Animal studies have shown that food-seeking behaviors [8,9] and the activity of gastrointestinal enzymes[10] are activated in anticipation of a regu-

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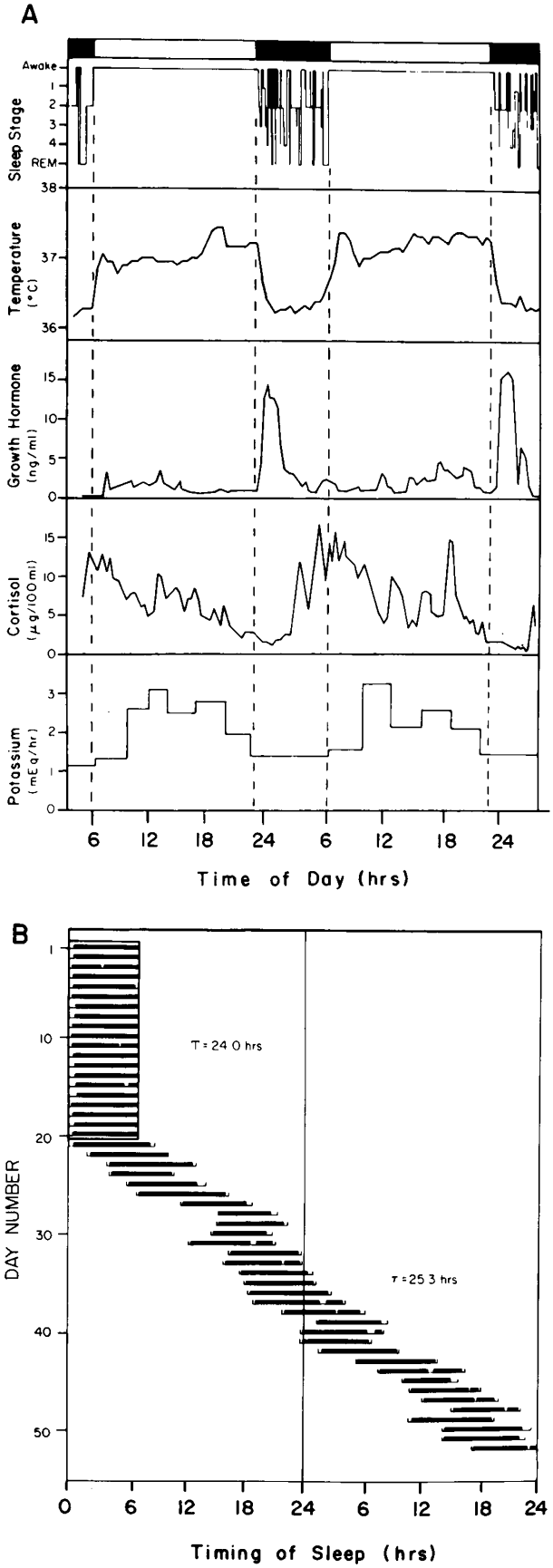

larly timed meal, provided that the timing of meals has a nearly 24-hour periodicity at a regular phase of the circadian day. This anticipation of environmental events that have a nearly 24-hour periodicity enables animals to predict when regularly recurring daily events will occur and to initiate appropriate behavioral and physiologic responses sufficiently in advance of the event that the optimal response is obtained with a minimal time lag.

Properties of Circadian Pacemakers

Diurnal rhythmicity in the activity of animals and plants must have been recognized from humankind's earliest contemplations of the temporal order of nature. The most obvious explanation for diurnal variations — that they represent a passive response to environmental periodicity — was even incorporated into ancient Greek myth. The heliotrope plant, which raises its leaves by day and lowers them by night, was said to represent the immortal incarnation of the unrequited love of Clytie, daughter of the King of Babylon, for the sun god Helios. As Helios rode his chariot into the eastern sky, Clytie raised her arms in greeting; as Helios disappeared in the west, she dropped her arms forlornly, to await his return.

Two hundred fifty years ago the French astronomer Jean-Jacques d'Ortous de Mairan[11] used a heliotropic plant in the first experiment to challenge the theory that circadian rhythms are mere passive responses to the environment. Placing the plant in his closet, where it was isolated from diurnal variations in illumination, de Mairan was surprised to find that the plant continued to raise and lower its leaves on schedule. Since then, most daily cycles in plants and animals have been demonstrated to persist similarly in constant environmental conditions — i.e., when light, food, temperature, and sound are held at steady levels around the clock — suggesting that circadian rhythms are truly endogenous to the organism.

In 1832, Augustin de Candolle added a second very

Figure 1. Circadian Rhythms in Sleep, Body Temperature, Plasma Concentration of Growth Hormone and of Plasma Cortisol, and Urinary Excretion of Potassium Measured over 48 Hours in a Normal Human Subject (A) and 55-Day Recording of Circadian Sleep–Wake Cycle in a Normal Human Subject in a Schedule-Free Environment (B).

Sleep stages (A) include rapid-eye-movement (REM) sleep and non-REM sleep, Stages 1 through 4. Body temperature was measured rectally. The light–dark cycle is indicated by the horizontal bar at top.

In Part B, thick horizontal bars represent time asleep, and thin horizontal lines represent time awake in bed. The abscissa is "double-plotted" over 48 hours (top line, Day 1 to Day 2; next line, Day 2 to Day 3) to allow uninterrupted precession of free-running rhythms. The ordinate represents successive 24-hour days. On Days 1 through 20, bedtimes and waking times were scheduled on a regular 24-hour cycle. After Day 20, the subject was allowed to go to bed and arise at will, and the sleep-wake rhythm "free-ran" with a period τ of 25.3 hours.

Part A is adapted from Czeisler,[32] and Part B from Czeisler et al.[7] with the permission of the publishers.

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important piece of evidence for the endogenous nature of circadian rhythms when he demonstrated that under constant conditions, the period of the daily cycle of leaf movements in plants ceased to be precisely 24 hours.[12] This, too, was shown to be a general feature of circadian rhythms, with rhythms in some species having periods of less than 24 hours, and in others, of more than 24 hours. Thus, under constant conditions, organisms consistently gain or lose time with respect to the environment and are said to be "free-running from the 24-hour clock."[13] The characteristic period, which approximates but does not equal 24 hours, is the basis for the term "circadian" (from "circa," meaning approximately, and "dies," meaning day).[13] A period offset from 24 hours is not a result of imprecision in the circadian rhythm; it has been demonstrated that a non–24-hour period is necessary if the circadian rhythm is to achieve a stable phase relation with the environmental cycle,[14] and it may allow animals to adapt more precisely to seasonal changes in day length.

The endogenous free-running period has been demonstrated to persist throughout the life span of an animal[15] and, indeed, through many successive generations reared in the absence of any environmental periodicity.[16] The free-running period is remarkably stable in most species; studies in hamsters have demonstrated average standard deviations in period length of only a few minutes from one day to the next.[17] Furthermore, circadian rhythms appear to be elaborately insulated from environmental factors that might confound their ability to measure time precisely. Circadian rhythms are temperature compensated[18-20]; they do not speed up as much as most metabolic processes with changes in temperature, and some species actually overcompensate; their clocks slow down slightly as the temperature is raised. Temperature compensation is an important consideration for organisms whose body temperature varies with the environment. The period length is somewhat sensitive to light intensity in nocturnal species but shows relatively little sensitivity in diurnal mammals.[21] Remarkably few chemical agents influence the endogenous free-running period, although those that do (e.g., lithium,[22,23] gonadal steroids,[24,25] and possibly the tricyclic antidepressants[26]) raise some fascinating questions to which we will return in Part 2.

The first studies of endogenous circadian rhythms in human subjects isolated from time cues were conducted by Aschoff and Wever[27] in a cellar under a Munich hospital and independently by Siffre[28] and his colleagues in an underground cavern in the French Alps. In those environments, subjects were isolated from knowledge of day and night in the outside world and from normal periodic variations of light, temperature, and humidity. Under these conditions, human beings, just like most other mammalian species, had a persisting rhythmicity in the rest–activity, body temperature, and other cycles. Since that time — largely through the efforts of workers in Germany,[29,30] England,[31] and this country[2,7,32,33] — the fundamental properties of the human circadian system have been more thoroughly defined. Human beings have a free-running period of approximately 25 hours, and thus, if their circadian pacemakers were not reset, the timing of their endogenous rhythms would "lose" about one hour with respect to clock time each day. Figure 1B shows the timing of the sleep–wake cycle of a subject who was first synchronized to a 24-hour day and then allowed to "free-run" in an environment free of time cues.[7] In this situation, the rhythm had a period of 25.3 hours, with sleep episodes occurring an average of 1.3 clock hours later each day.

Some hint of the propensity for human sleep to drift to later hours is provided by everyday experience. During weekends, when they are freed from the pressure of external schedules, most people tend to go to bed a little later and arise a little later than they do during the week. This can account for what some call the "Monday morning blues." By the end of the weekend the accumulated drift has left the circadian system several hours out of synchrony with the day–night schedule required on weekdays. On Monday one is therefore forced to arise several hours earlier than is normal within the endogenous cycle (for example, 7 a.m. by the clock on Monday morning may occur at the equivalent of 4 a.m. on the biologic time scale).

Organization of the Circadian Timing System

There is increasing evidence that the circadian system, particularly in human beings, may be more complex than was originally supposed. In their pioneering studies of human beings in environments free from external time cues, Wever[29] and Aschoff[30] showed that on some occasions, internal desynchronization occurred between the rest–activity cycle and the rhythm of body temperature, so that the rest–activity cycle might have a period of approximately 33 hours, whereas the body-temperature rhythm had a 24.5-hour period.

Subsequent research[33,34] has demonstrated that when internally desynchronized circadian rhythms develop in a subject, the various physiologic and behavioral indexes cluster into two groups, tracking either with the rest–activity cycle or with the body-temperature rhythm. It has been proposed that under normal conditions physiologic systems receive signals from both pacemakers, which are referred to as "X" (body-temperature driving) and "Y" (rest–activity cycle driving). Circadian rhythms observed in each variable are the net result of signals from both sources. However, under constant conditions, the X and Y systems can dissociate, and the physiologic variables tied to each system assume the respective period. Thus, for example, slow-wave sleep and growth hormone release follow the Y pacemaker, whereas the propensity for rapid-eye-movement sleep and cortisol secretion follow the X pacemaker. Recent theoretical math-

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ematical simulations of coupled oscillator interactions have been remarkably successful in reproducing and predicting experimental findings and have given substantial credence to this hypothesized organization,[35] although several alternative models have also been proposed.[36]

Identifying the Pacemakers

The conclusion that circadian rhythms are endogenous to the organism suggests that there should be identifiable anatomic correlates. In recent years tremendous progress has been made in the identification and characterization of "biological clocks."

The first evidence that specific neuroanatomic sites act as circadian pacemakers was provided by the work of Richter.[8,37] Using the free-running activity rhythm of blinded rats as his marker of the circadian system, he subjected his animals to "almost every conceivable kind of metabolic, endocrinologic and neurologic interference." This included removal of the gonads, the pancreas, or the adrenal, pituitary, thyroid, or pineal glands; electroshock therapy; induced convulsions; prolonged anesthesia; and alcoholic stupor. Remarkably, each of these procedures failed to disrupt the rats' free-running activity rhythm. In the next step of his investigations, Richter placed hundreds of lesions in various parts of the rat brain. The only location where lesions were found to influence the free-running rhythm was the hypothalamus. From a series of 200 hypothalamic lesions, he was able to identify a general area of the ventral hypothalamus where lesions resulted in a loss of circadian organization in the timing of activity, feeding, and drinking.

The specific localization of a circadian pacemaker in the mammalian brain, however, required the use of a new technique. Tritiated amino acids injected into the vitreous humor of the eye are taken up by the retinal ganglion cells and then transported through the neural projections from the retina. In the hands of Moore and Lenn,[38] this technique was used to identify a unique monosynaptic retinohypothalamic projection, which terminated specifically in the suprachiasmatic nuclei of the hypothalamus. Shortly thereafter, Moore and Eichler[39] showed that destruction of the suprachiasmatic nuclei resulted in the apparent loss of the circadian rhythm in adrenal corticosterone, and Stephan and Zucker[40] independently showed a similar loss of circadian rhythmicity in drinking and locomotor activity in hamsters.

Since that time, a considerable body of evidence from a variety of sources has shown that the most important role of the suprachiasmatic nuclei is the coordination of circadian rhythms.[41,42] The firing rate of neurons in these nuclei exhibits a circadian pattern in rodents whether they are maintained under light–dark cycles or constant environmental conditions. This rhythmic neural activity appears to be an inherent property of suprachiasmatic neurons, since it persists after isolation of the suprachiasmatic nuclei from adjacent hypothalamic tissue by Halasz knife cuts (Fig. 2A),[43] and recent studies have shown persisting circadian rhythms of neural activity in vitro in slices of hypothalamic tissue containing the suprachiasmatic nuclei.[46,47] In addition, studies of the glucose uptake of suprachiasmatic neurons in vivo using the 2-deoxyglucose method indicate that, unlike other hypothalamic tissue, the suprachiasmatic nuclei have a circadian pattern of glucose uptake in rodents housed under either cyclic or constant lighting conditions (Fig. 2B).[45,48]

As we have already discussed, there appear to be two major circadian pacemaking systems in human beings (referred to as "X" and "Y"). The question thus remains whether the suprachiasmatic nuclei may contain both pacemakers or only one of them. In an attempt to answer this question, the suprachiasmatic nuclei were destroyed in squirrel monkeys, animals in which multiple variables could be studied. The behavioral rhythms of activity, feeding, and drinking were disrupted, but the body-temperature rhythm was found to persist,[49] thus suggesting that the X pacemaker may be located outside the suprachiasmatic nuclei, whereas the Y pacemaker is contained within it. Although an alternative interpretation might argue that some suprachiasmatic tissue may have remained, subsequent neuroanatomic studies have indicated that an area much larger than that of the suprachiasmatic nuclei, including parts of the preoptic area and lateral

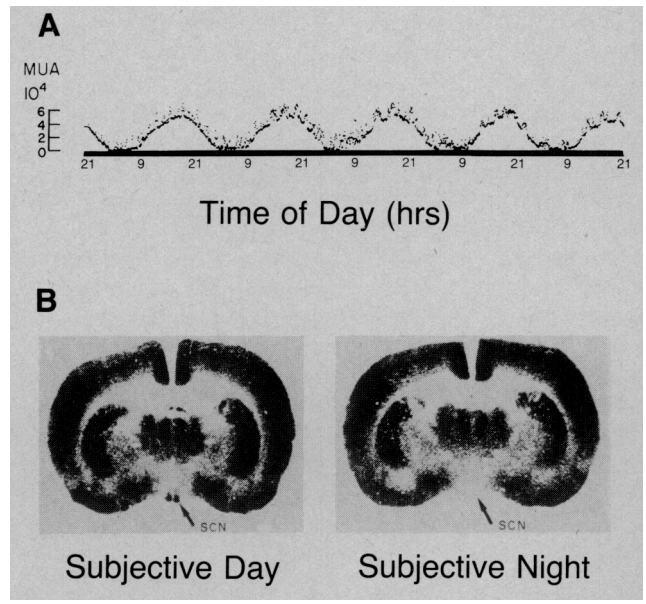

Figure 2. Circadian Rhythm in Neuronal Activity Recorded from Rat Suprachiasmatic Nucleus after Isolation from Surrounding Brain Structures by Halasz Knife Cuts (A) and Comparison of Autoradiographs of 2-Deoxyglucose Uptake in Mid-Subjective Day and Mid-Subjective Night from Rats Maintained in Constant Darkness (B).

MUA (Part A) denotes multiple-unit activity units per five minutes. Suprachiasmatic neurons (Part B) exhibit a clear circadian variation in metabolic activity in contrast to the relatively constant uptake of 2-deoxyglucose by surrounding neural structures.

Part A is adapted from Inouye and Kawamura,[44] and Part B from Schwartz et al.,[45] with the permission of the publishers.

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hypothalamus, was destroyed in these experiments. Further support for the conclusion that the X pacemaker lies outside the suprachiasmatic nuclei has been provided by Reppert et al.,[50] who recently reported a persistent circadian rhythm of the cerebrospinal-fluid concentration of cortisol — an X-driven variable — in rhesus monkeys after total ablation of the suprachiasmatic nuclei. Although it thus appears that the X pacemaker is not located in the suprachiasmatic nuclei, its exact location has not yet been determined and is the current focus of an extensive research effort.

Entrainment by Environmental Time Cues

The fact that the period of circadian rhythms is more or less than 24 hours necessitates a mechanism for daily resetting of the circadian system to maintain synchrony with the earth's rotation and thus with the day–night cycle in the environment. In the case of animals with free-running periods of less than 24 hours (e.g., mice), each cycle must be appropriately lengthened, whereas in organisms with a period longer than 24 hours (e.g., human beings) each cycle must be appropriately curtailed. Furthermore, stable entrainment to the environmental cycle requires accurate perception of a reliable indicator of environmental time called a "zeitgeber" (a German neologism meaning "time giver").[51,52] Although temperature, relative humidity, barometric pressure, and a host of other physical measures all vary diurnally and thus could potentially act as zeitgebers, the most reliable index of environmental time is the regular diurnal alternation of light and darkness. The majority of organisms appear to have circadian mechanisms that use the light–dark cycle as their principal zeitgeber. In fact, however, some species use other indexes of environmental time; marine organisms, for example, use tidal cycles as a zeitgeber.[53]

The advent of artificial lighting has, of course, markedly complicated the entrainment process for human circadian rhythms. It is clear, however, that light–dark cycles can successfully entrain human circadian rhythms.[54] It has been speculated that the timing of meals[55] and social contacts[29,56] may also have a role, although these have never been systematically studied and the mechanism of their action is unknown.

Anatomic Basis of Entrainment

The most important route by which environmental time cues reach the suprachiasmatic nuclei are the optic pathways (Fig. 3). Within these pathways, the major component appears to be the retinohypothalamic tract,[58-60] a monosynaptic direct path to the suprachiasmatic nuclei from specialized photoreceptors in the retina that are uniquely suited to sensing the ambient illumination level.[61] If the optic nerves, which include the retinohypothalamic tract, are severed bilaterally, blinding the animal, entrainment to light–dark cycles is no longer possible, and the circadian rhythms "free-run"[57] (Fig. 3B). When the

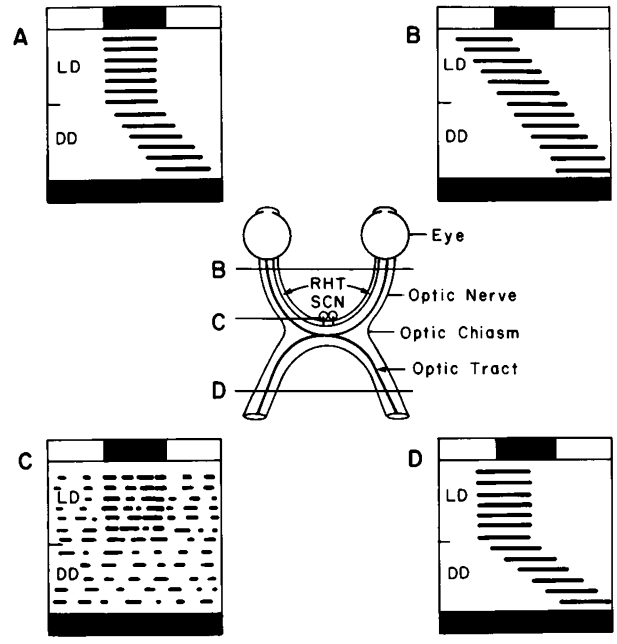

Figure 3. The Neuroanatomic Basis of Entrainment.[57]
The central panel shows neuroanatomic pathways involved in the circadian entrainment to light–dark cycles with the location of lesions referenced to the data in the other panels. Activity rhythm in the intact rat (A) entrains to the light–dark cycle (upper half, designated LD; the black bar indicates darkness) and free-runs in constant darkness (lower half, designated DD). After transection of the optic nerves, entrainment to the light–dark cycle no longer occurs (B), and the activity rhythm free-runs in both a light–dark cycle and in constant darkness. Destruction of the suprachiasmatic nuclei results in some persistent clustering of activity in the dark phase in a light–dark cycle ("masking"; see text), but in constant darkness there is a virtually complete loss of circadian rhythmicity. Transection of the primary and accessory optic tracts posterior to the optic chiasm results in entrainment with an abnormally advanced phase relation (D). The free-run in constant darkness is normal.

pacemaker itself (i.e., the suprachiasmatic nuclei) is destroyed, leaving visual connections intact, some persistent clustering of daylight activity is seen in the light phase of the light–dark cycle (Fig. 3C). This direct effect of light on activity is known as "masking."[16] However, when constant conditions are imposed, the loss of the pacemaker results in a disruption of circadian rhythmicity. In contrast, when the optic tracts are severed behind the optic chiasm (Fig. 3D), entrainment to the light–dark cycle persists although the animal is behaviorally blind. When the animal is placed in constant darkness, the rhythm free-runs normally, demonstrating that the pacemaker remains intact.

In addition to the retinohypothalamic tract, other neural pathways may play some part in entrainment to light–dark cycles. Direct connections between neurons of the suprachiasmatic nuclei and axons in the optic chiasm have been demonstrated with electron microscopy.[62] In addition, injections of tritiated proline into the ventral portion of the lateral geniculate nucleus demonstrate projections back to the supra-

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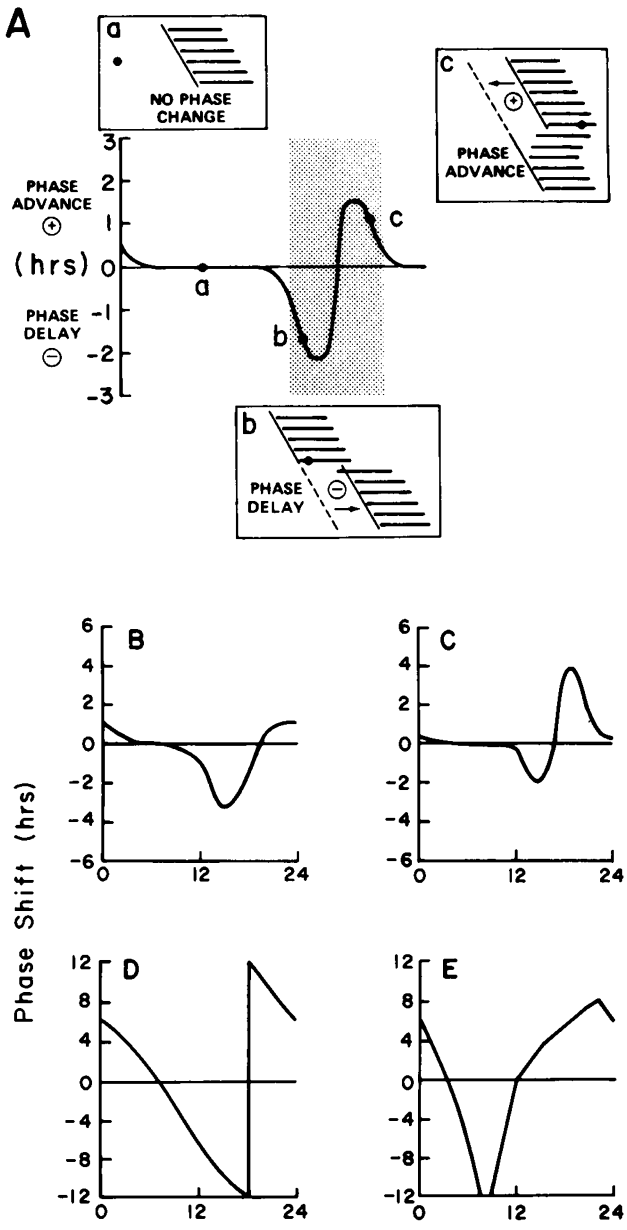

Figure 4. The Derivation of a Phase-Response Curve (A) and Phase-Response Curves for Light Pulses (of 15 Minutes' Duration) to Mice (*Mus musculus*) (B),[14] Direct Electrical Stimulation of Suprachiasmatic Nuclei in Hamsters (*Mesocricetus auratus*) (C),[68] Anisomycin Administration (2.0 μM) to Unicellular Algae (*Gonyaulax polyhedra*) (D),[69] and Theophylline Administration (75 mg per kilogram) to Rats (E).[70]

In Part A, light pulses (or other phase-shifting stimuli) result in no phase change (a), a phase delay (b), or a phase advance (c), depending on the phase of the circadian cycle at which the stimulus occurred.

Part A is reproduced from Czeisler et al.[7] with the permission of the publisher.

chiasmatic nuclei.[63,64] A clue to the role of this latter connection is suggested by studies in which the accessory and posterior optic tracts are severed, cutting off the lateral geniculate nuclei from their visual stimuli, while leaving intact the direct retinal projections to the suprachiasmatic nuclei. As we discussed, entrainment to the light–dark cycle continues, but the activity rhythm is abnormally advanced with respect to the light–dark cycle (Fig. 3D); phase shifts of the entraining cycle are tracked by the activity rhythm, but at an abnormally slow rate.

The Phase-Response Curve

One of the major conceptual advances in this field has concerned the mechanisms of entrainment by environmental time cues. DeCoursey,[65] Pittendrigh,[66] and Hastings and Sweeney[67] in the late 1950s realized independently that circadian pacemakers showed a varying responsiveness to environmental time cues, depending on the circadian time of day. A light pulse falling on an animal early in the subjective night caused a phase delay of the circadian system — i.e., a transient lengthening of the cycle. The same light pulse, falling instead late in the subjective night, caused a phase advance. During the middle of the day, light pulses caused no phase shift at all. This relation is illustrated schematically in Figure 4A. An actual phase-response curve for light pulses (in the house mouse *Mus musculus*) is shown in Figure 4B.

The magnitude of the phase shift that is caused by a single light pulse of a given intensity and duration depends on the exact timing of that light pulse. Thus, in most species entrainment can be achieved by a single light pulse every 24 hours, but only when that light pulse falls at the appropriate position on the phase-response curve to effect a shift that bridges the gap between the animal's intrinsic period and the 24-hour day. The curves of the phase response to light for nocturnal and diurnal species are very similar, indicating that the timing of their activity with respect to the day–night cycle is not a function of the pacemaker.

With the identification of the suprachiasmatic nuclei as a circadian pacemaker, it is now possible to study the phase-resetting mechanism at a more fundamental level. Direct electrical stimulation of the suprachiasmatic nuclei has been shown to cause shifts in the circadian phase of the activity cycle with a phase-response curve very similar to that obtained for light[68] (Fig. 4C). Recent research has also demonstrated that the circadian rhythm of the rate of neuronal firing in the suprachiasmatic nuclei shifts in response to light stimulation in the same phase-dependent fashion.[44]

The phase-resetting mechanism is now being investigated at the intracellular level as well. Taylor and Hastings[69] have shown that a number of inhibitors of protein translation on 80S ribosomes (e.g., anisomycin, Fig. 4D) are capable of shifting the phase of bioluminescence rhythms of marine algae (*Gonyaulax polyhedra*). This evidence that the phase of circadian pacemakers may be alterable by chemical means has a number of potential experimental and even clinical applications. Such disorders of circadian phase as "jet lag" (see below) may conceivably be treated with such compounds. Indeed, there is some evidence to suggest that we may already be wantonly treat-

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ing circadian phase disruption on a massive scale with Monday morning cups of coffee; the methylxanthines, including theophylline (Fig. 4E) and caffeine, have been shown to alter the phase of circadian rhythms.[70,71]

Range of Entrainment

The concept of the phase-response curve turns out to be the key to understanding a wide range of circadian disorders and the limits within which human beings (and members of other species) can adapt to imposed environmental light–dark cycles. For example, Figure 4A (top) shows an example in which the maximal phase delay that can be obtained is approximately two hours, and the maximal phase advance is also approximately two hours. This means that if an organism had a 25-hour period (as human beings do), then the maximal length for which the circadian system could be reset in any day would be plus or minus two hours. Thus, there is a "limited range of entrainment"; this hypothetical organism can entrain only to environmental light–dark cycles that have a period within the range of 23 to 27 hours. In fact, recent studies are suggesting that the range of entrainment for the internally synchronized human circadian system may be even more narrow than this (Gander PH et al.: unpublished data). The actual amplitude of the phase-response curve is, of course, determined by the strength of the environmental synchronizer; for example, light pulses that are brighter or of longer duration produce larger phase shifts than weaker or shorter light pulses.

The range of entrainment around the endogenous free-running period also defines the maximal shift that can be achieved on any one day. The typical range of entrainment of approximately 23.5 to 26.5 hours for the synchronized human system easily accommodates normal synchronization to the 24-hour period of the earth's rotation but allows in any one cycle a phase advance with respect to environmental time of only an additional half-hour, while permitting a phase delay of 2.5 hours. This may explain why adaptation for most people is more rapid after westbound travel (requiring a phase delay) than after eastbound travel (requiring a phase advance). It will take several days to resynchronize the circadian system if the environmental phase shift is larger than the maximum achievable according to the phase-response curve. During the process of readjustment, the endogenous circadian rhythms in sleep, alertness, gastrointestinal function, and mood are not synchronized with the new time zone, and the symptoms of malaise and fatigue — known collectively as "jet lag" — occur. There is an interesting group of persons who take considerably longer to resynchronize after flying across time zones. Experiments by Mills et al. in England demonstrated that after an eight-hour phase advance of environmental time cues, these persons may take two weeks to adjust, because their circadian system does not advance by eight hours but instead delays by 16 hours the opposite way around the clock.[72]

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