Chapter 3

Circadian Rhythms

Contents

	Page
GENERAL PROPERTIES OF CIRCADIAN RHYTHMS	37
THE CELLULAR CLOCK	38
THE PACEMAKER IN THE BRAIN	40
HUMAN CIRCADIAN RHYTHMS	41
The Body Circadian	42
The Timing of Sleep	45
Human Performance	47
DISRUPTION OF CIRCADIAN RHYTHMS	49
Aging and the Body Clock	49
Sleep Disorders	51
Chronobiology and Mood Disorders	51
CONTROLLING CIRCADIAN RHYTHMS IN HUMANS	53
Light	53
Melatonin	55
Benzodiazepines	56
Other Chemical Substances and Diet	57
Activity	57
SUMMARY AND CONCLUSIONS	58
CHAPTER PREFERENCES	58

Boxes

Box	*Page*
3-A. Circadian Rhythms and Drugs	43
3-B. Cycles That Last From Minutes To Days	44
3-C. Napping	46
3-D. Jet Lag	48

Figures

Figure	*Page*
3-1. Circadian Rhythm	37
3-2. Synchronized and Free-Running Circadian Rhythms	38
3-3. Phase Response Curve	39
3-4. Gene Expression in the Pacemaker	40
3-5. The Transplanted Pacemaker	41
3-6. Human Circadian Rhythms	42
3-7. Human Circadian Rhythms in the Absence of Time Cues	46
3-8. Sleepiness During the Day	47
3-9. Circadian Rhythms of Alertness	49
3-10. Aging and the Pacemaker	50
3-11. Levels of Light	52
3-12. Resetting the Human Pacemaker With Light	54
3-13. Bright Light and Air Travel	55
3-14. Melatonin Rhythms and Light	56

Table

Table	*Page*
3-1. Differences Between Rapid Eye Movement (REM) Sleep and Slow Wave Sleep (SWS)	45

Chapter 3
Circadian Rhythms

Many biological functions wax and wane in cycles that repeat each day, month, or year. Such patterns do not reflect simply an organism's passive response to environmental changes, such as daily cycles of light and darkness. Rather, they reflect the organism's biological rhythms, that is, its ability to keep track of time and to direct changes in function accordingly. Biological rhythms that repeat approximately every 24 hours are called circadian rhythms (from the Latin *circa*, for around, and *dies*, for day) (61) (figure 3-l).

Human functions, ranging from the production of certain hormones to sleep and wakefulness, demonstrate circadian rhythms. This chapter summarizes the basic properties of circadian rhythms and addresses the following questions:

- How are circadian rhythms generated?
- How are they influenced by the environment?
- What specific human functions display circadian rhythms?
- What implications do these rhythms have for health and performance?
- How can circadian rhythms be manipulated?

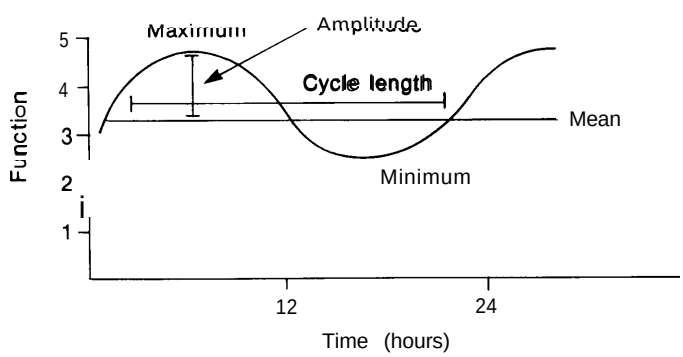
GENERAL PROPERTIES OF CIRCADIAN RHYTHMS

Circadian rhythms display several important characteristics. First, circadian rhythms are generated by an internal clock, or pacemaker (9,124). Therefore, even in the absence of cues indicating the time or length of day, circadian rhythms persist. The precise length of a cycle varies somewhat among individuals and species. Although organisms generate circadian rhythms internally, they are ordinarily exposed to daily cycles in the environment, such as light and darkness. The internal clock that drives circadian rhythms is synchronized, or entrained, to daily time cues in the environment (figure 3-2). Animal research has shown that only a few such cues, such as light-dark cycles, are effective entraining agents (12). In fact, the light-dark cycle is the principal entraining agent in most species, and recent research suggests that it is very powerful in synchronizing human circadian rhythms. The sleep-wake schedule and social cues may also be important entraining agents in humans.

An entraining agent can actually reset, or phase shift, the internal clock (12). Depending on when an organism is exposed to such an agent, circadian rhythms may be advanced, delayed, or not shifted at all. This variable shifting of the internal clock is illustrated in a phase response curve (PRC) (figure 3-3). PRCs were first derived by exposing organisms housed in constant darkness to short pulses of light (40,65,125). The organisms were isolated from all external time cues. When light pulses were delivered during the portion of the organism's internal cycle that normally occurs during the day (therefore called subjective day), they had little effect on circadian rhythms. In contrast, when light pulses were delivered late during the organism's nighttime, circadian rhythms were advanced. Light pulses delivered early during subjective night delayed circadian rhythms.

Several factors make it difficult to identify time cues that can reset the internal clock. First, there is no way to examine the function of the circadian pacemaker directly. The pacemaker's activity can only be evaluated through the circadian rhythms it drives, but unfortunately such functions are subject to other influences. Environmental stimuli may alter a particular circadian rhythm without disturbing the

Figure 3-l—Circadian Rhythm



Circadian rhythms have a single cycle length of approximately 24 hours. The amplitude, a measure of the degree of variation within a cycle, is the difference between the maximum value and the mean.

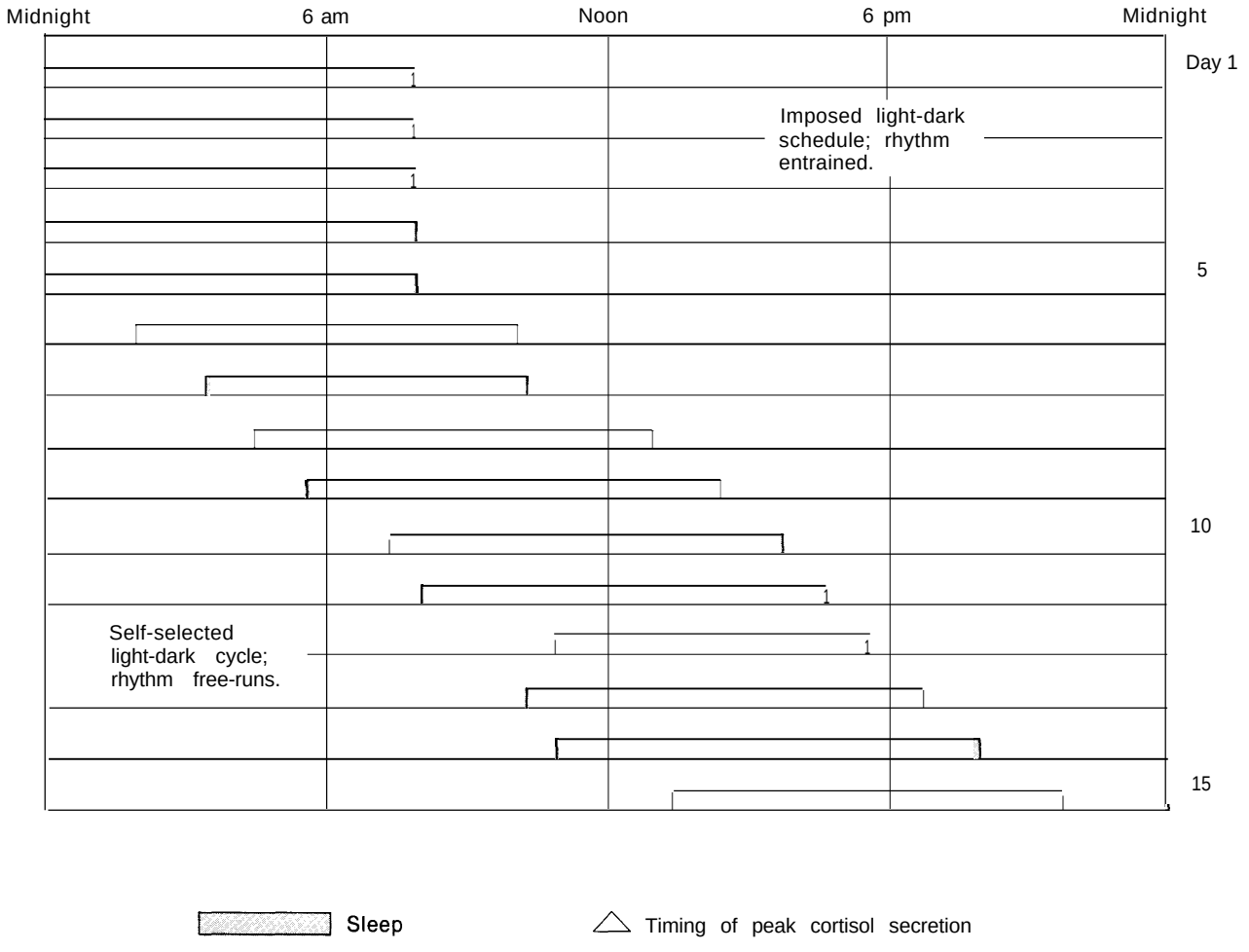
SOURCE: Office of Technology Assessment, 1991.

pacemaker at all. For example, going to sleep causes a temporary lowering of body temperature, without shifting the circadian cycle. Second, a function that exhibits a circadian rhythm may be controlled by both the circadian pacemaker and other systems in the body. For example, the timing and quality of sleep are controlled by circadian rhythms and other factors. Finally, classical techniques used to evaluate the pacemaker in animals and to generate a PRC involve complete isolation from all time cues (e.g., constant darkness) for several days, a difficult approach in human studies. Alternative methods for evaluating potential entraining agents in humans have been devised (see later discussion).

THE CELLULAR CLOCK

Circadian rhythms exist even in single cells. In fact, studies have shown that a wide range of cell functions exhibit circadian rhythms (159). Precisely how cells generate circadian rhythms is not known, but protein synthesis is critical to the process (50,168).

Figure 3-2-Synchronized and Free-Running Circadian Rhythms



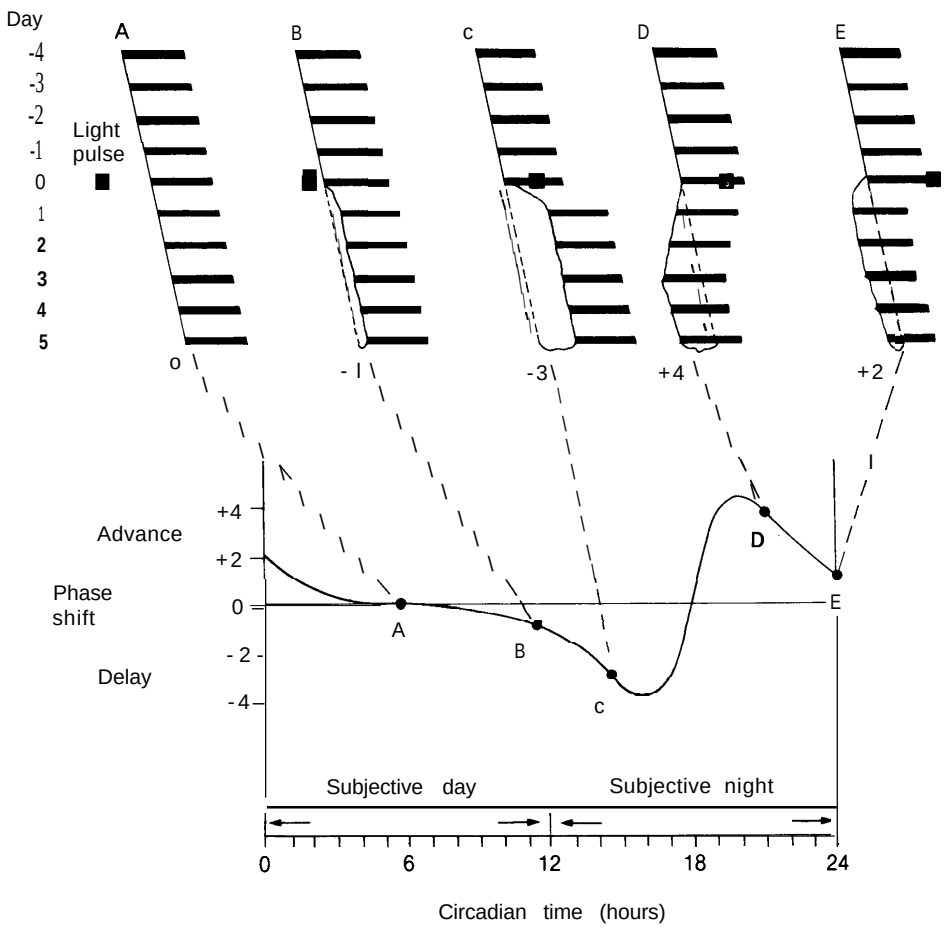
Plot of human sleep and maximum cortisol secretion when synchronized to the environment and when free of environmental input.

SOURCE: Adapted from G.S. Richardson and J.B. Martin, "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," *Progress in NeuroEndocrinImmunology* 1:16-20, 1988.

Specific genes code for circadian rhythms. Genetic control of circadian rhythms has been examined most extensively in the fruit fly *(Drosophila melanogaster),* an organism that has played a key role in the study of genes and inheritance (63,76,142). Initially, painstaking studies were conducted, using chemicals that cause genetic mutations to alter circadian rhythms (77). It was found that mutations on the X chromosome disrupted the fruit fly's circadian rhythms by accelerating, slowing, or eliminating them. A specific gene on the X chromosome, called the per gene, has been identified, cloned, and characterized (15,25,64,202).

Other genetic mutations influencing circadian rhythms have been identified in the fruit fly (71), and genes other than the per gene have been found to control circadian rhythms in other species. The frq gene, for example, controls circadian rhythms in bread mold *(Neurospora crassa) (52,63).* A genetic mutation altering circadian rhythms in hamsters has been identified (13 1). In these experiments, a mutant

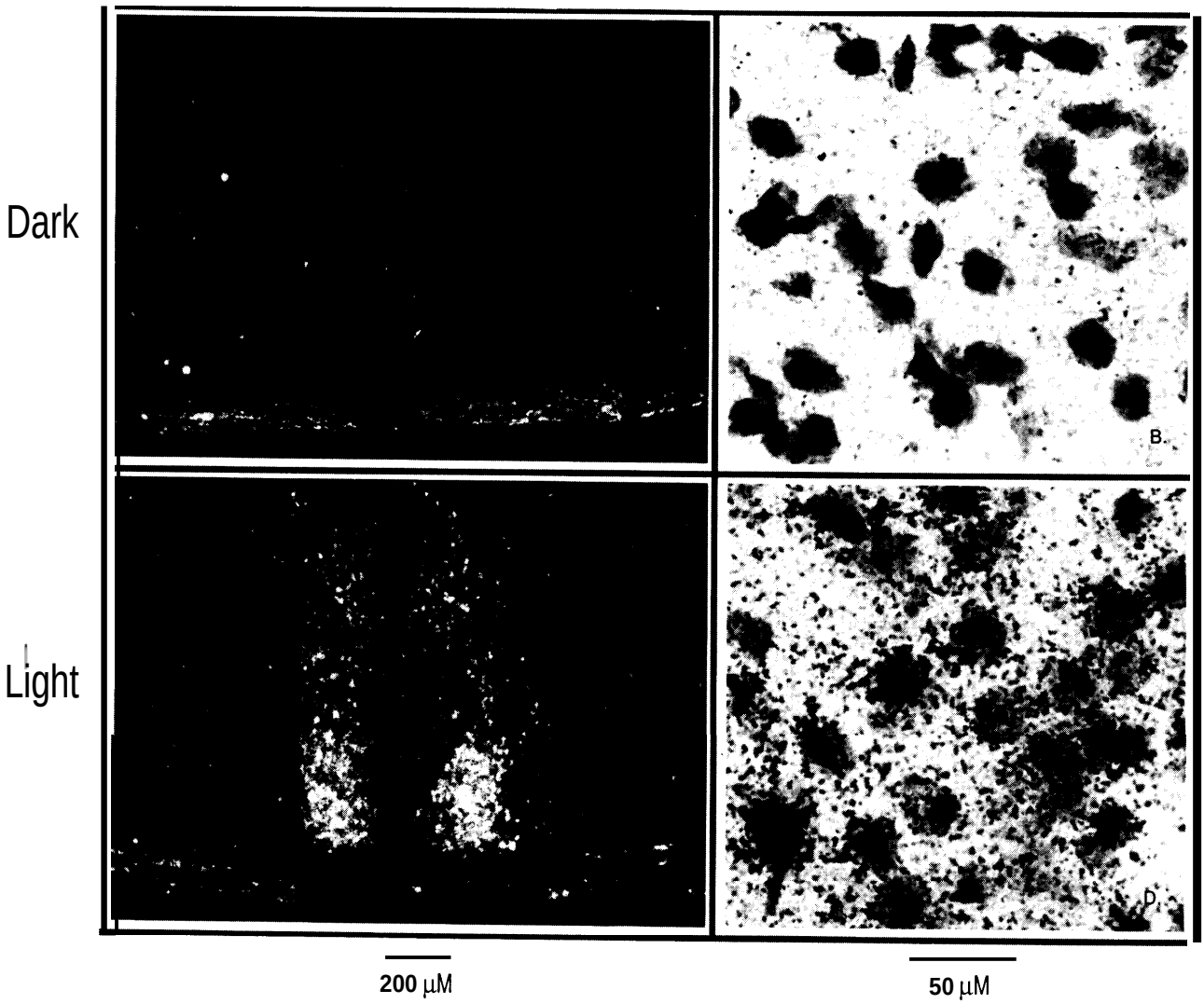
Figure 3-3-Phase Response Curve



Experiments demonstrate that exposure to light at different points in a single circadian cycle variably shifts the internal pacemaker (A-E). The pulse of light given in mid-subjective day (A) has no effect, whereas the light pulses in late subjective day and early subjective night (B and C) delay circadian rhythms. Light pulses in late subjective night and early subjective day (D and E) advance circadian rhythms. In the lower panel, the direction and amount of phase shifts are plotted against the time of light pulses to obtain a phase response curve.

SOURCE: M.C. Moore-Ede, F.M. Sulzman, and C.A. Fuller, *The Clocks That Time Us* (Cambridge, MA: Harvard University Press, 1982).

Figure 3-4-Gene Expression in the Pacemaker



Photographs from the pacemaker (the suprachiasmatic nucleus) of hamsters housed in darkness (A and B) or following a pulse of light (C and D). The silver grains indicate the activation of the c-fos gene. Data show that exposure to light that would reset circadian rhythms stimulates the c-fos gene.

SOURCE: J.M. Kornhauser, D.E. Nelson, K.E. Mayo, et al., "Photic and Circadian Regulation of c-fos Gene Expression in the Hamster Suprachiasmatic Nucleus," *Neuron* 5: 127-134, 1990.

gene was linked to a shortened circadian cycle. Finally, recent research has implicated the c-fos gene in resetting the internal clock (figure 3-4) (see next section).

THE PACEMAKER IN THE BRAIN

The circadian rhythms of various functions in humans, such as hormone production, body temperature, and sleepiness, are normally coordinated—i.e., they bear a specific relationship to each other. This temporal organization suggests that some biological timekeeping device must drive, regulate, or at least integrate various circadian rhythms. In mammals, considerable experimental evidence indicates that a region of the brain called the suprachiasmatic nucleus (SCN) is the circadian pacemaker (98). The SCN, composed of a cluster of thousands of small nerve cells, is located within a region of the brain, the hypothalamus, that controls

such basic functions as food intake and body temperature.

Various lines of evidence pinpoint the SCN as the primary mammalian pacemaker. Nerve cells in the SCN can generate circadian rhythms when isolated from other areas of the brain (59,60,70,98,136, 147,158,161,180). The integrity of the SCN is necessary for the generation of circadian rhythms and for synchronization of rhythms with light-dark cycles (70,185). Compelling evidence that the SCN functions as the primary circadian pacemaker comes from animal studies of SCN transplantation (41,48,83,129,155). In these experiments, the SCN is destroyed, abolishing circadian rhythms. When fetal brain tissue containing SCN nerve cells is transplanted into the brains of these animals, circadian rhythms are restored (129) (figure 3-5).

Light in the environment influences mammalian circadian rhythms by synchronizing the SCN. Light activates cells in the eye, which in turn activate the SCN (122,149,154). Recent animal experiments have shown that light activates the c-fos gene within cells in the SCN (figure 3-4) (79,132,150). The c-fos gene is a proto-oncogene, which is associated with growth, stimulation of nerve cells, and, in pathological conditions, tumor formation.

Figure 3-5-The Transplanted Pacemaker

Photograph of transplant of fetal hamster suprachiasmatic nucleus (arrow) into the brain of an adult hamster.

SOURCE: P.J. DeCoursey and J. Buggy, "Circadian Rhythmicity After Neural Transplant to Hamster Third Ventricle: Specificity of Suprachiasmatic Nuclei," *Brain Research* 500:263-275, 1989.

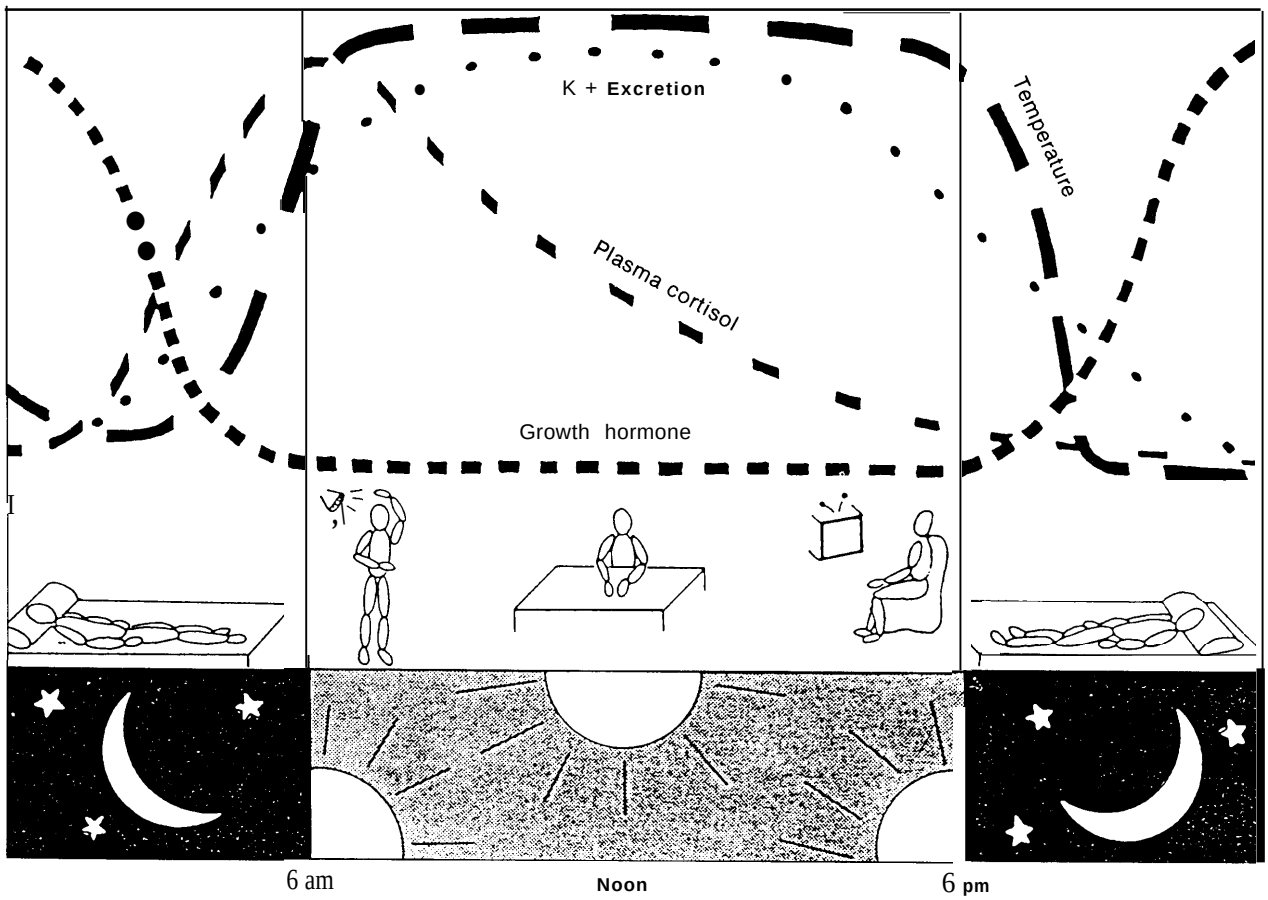
It is clear that the SCN serves as the primary circadian pacemaker in mammals, but there are still many unknowns concerning its activity. How does the SCN, with its tens of thousands of nerve cells and a wide variety of brain chemicals, generate circadian rhythms? How does the SCN coordinate or drive overt circadian rhythms in the animal? Little is known about how the SCN interacts with other parts of the brain to generate and synchronize overt rhythms. Is the SCN the only circadian pacemaker in mammals? There is evidence that other areas of the nervous system produce circadian rhythms. For example, data suggest that cells in the mammalian eye are capable of generating circadian rhythms (135,169). Also, circadian rhythms of meal anticipation and temperature have been reported to persist despite destruction of the SCN (147).

HUMAN CIRCADIAN RHYTHMS

Consider the following reported data: the frequency of heart attacks peaks between 6 a.m. and noon (117, 140); asthma attacks are most prevalent at night (96); human babies are born predominantly in the early morning hours (57,73). While these patterns do not necessarily indicate that the events are driven by the circadian pacemaker, they do suggest temporal order in the functioning of the human body. This temporal organization appears to be beneficial; the human body is prepared for routine changes in state, such as awakening each morning, rather than simply reacting after shifts in demand (113) (figure 3-6). In addition, these regular cycles in the body present considerations for diagnosis of health problems and for the timing of medical treatment (62,102) (box 3-A).

Although daily fluctuations in various human functions have been documented for more than a century, that does not prove that they are controlled by the circadian pacemaker. Not until individuals were examined in temporal isolation could human circadian rhythms be verified. The first studies sequestering humans from all time cues were reported in the early 1960s (10). During the course of these and other studies, which lasted days, weeks, and even months, individuals inhabited specially designed soundproof and lightproof rooms that

Figure 3-6-Human Circadian Rhythms



Circadian rhythms of sleep, body temperature, growth hormone, cortisol, and urinary potassium in a human subject.

SOURCE: Adapted from G.S. Richardson and J.B. Martin, "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," Progress *in NeuroEndocrinImmunology* 1:16-20, 1988.

excluded any indication of the time of day, such as clocks, ambient light, or social interactions. In this temporal vacuum, individuals were instructed to sleep and eat according to their bodies' clocks. These studies indicated that daily fluctuations in some human functions are generated by an internal clock (35,192). While these studies of humans isolated from time cues provide insight into the operation of the human circadian pacemaker, the approach presents difficulties; it is time-consuming and expensive, and it is difficult to recruit subjects for extended study. Alternative methods have been developed for evaluating human circadian rhythms, and these are discussed in subsequent sections.

In the following sections, an overview of various human circadian rhythms is presented, as are some medical implications (boxes 3-A and 3-B). Data on human sleep and performance rhythms, which are intimately related to shift work concerns, are discussed in detail.

The Body Circadian

Several hormones are secreted in a cyclic fashion (181). The daily surge of prolactin and growth hormone, for example, appears to be triggered by sleep (182,183). Sex hormones are secreted at varying levels throughout the day, the pattern of secretion reflecting the fertility, reproductive state, and sexual maturity of the individual. Secretions of glucose and insulin, a hormone important for regulating the metabolism of glucose, also exhibit circadian rhythms. Glucose concentrations in the

Box 3-A-Circadian Rhythms and Drugs

Since the human body is not static Or constant in its function over time, its responses to drugs are likely to vary over time. Thus, not only the dosage, but also the timing of administration influences a drug's effects, both therapeutic and toxic. Chronopharmacoloy, the study of circadian rhythms and the timing of drug treatment, has important clinical implications.

From the time a drug is administered until it is eliminated from the body, it is acted on by many organs, including the intestines, the cardiovascular system, the liver, and the kidneys. Absorption, distribution, and elimination of drugs--i. e., pharmacokinetics—are subject to circadian variation. A tissue's responsiveness to a drug, which may reflect the number of receptors, or binding sites, on target cells or their metabolic activity, also exhibits circadian rhythms. Changes in the effects of a drug when administered at different times over the course of a 24-hour period stem from the circadian variation in pharmacokinetics and tissue responsiveness. Proper timing of drug administration can enhance its therapeutic actions and diminish unwanted side effects.

The most advantageous schedule of administration must be determined for each drug. Even drugs with only slight differences in structure maybe handled differently by the body. For example, injection of the anticancer drug adriamycin into the abdomen of rats leads to toxic effects on bone marrow; intravenous injection has toxic effects on the heart. Different scheduling of these two modes of adriamycin injection significantly reduced these side effects. Ideally, the administration of drugs in clinical situations should be adapted to each patient's circadian rhythms.

The main reason to consider circadian rhythms when timing drug administration is the balance between the toxicity of a compound and its therapeutic. effects. Anticancer drugs are the most prominent example. Many anticancer drugs currently in use kill replicating cells—all replicating cells, malignant or not. The side effects associated with these drugs generally limit the amounts that are administer@ seriously restricting their effectiveness. Attempts to minimize the toxic side effects of anticancer drugs, thus permitting increased doses, presumably with improved effectiveness against the disease, lie at the root of the search for an optimal drug delivery schedule.

Optimal drug delivery schedules for more than 29 anticancer agents have been determined in animal studies. Furthermore, the action of newer agents, including tumor necrosis factor and interleukin-2, has demonstrated a sensitivity to circadian rhythms. Studies have also been implemented to determine the optimum timing of anticancer drugs used in combination, a common medical practice for the treatment of cancer.

The chronopharmacology of several anticancer agents has been studied in humans. Specific therapies evaluated include the agents 5-fluoro-2-deoxyuridine (FUDR) for the treatment of metastatic adenocarcinoma and the combination of doxorubicin and cisplatin for ovarian and bladder cancer. The regimens chosen were found to diminish side effects significantly and in some cases to extend survival time. FUDR was delivered by an automatic pump, which can be programmed to release drugs at a variable rate over time. This device is surgically implanted in the patient and can be noninvasively programmed by an external computer.' Drug supplies in the pump are replenished via simple injection, In general, clinical studies to date, while preliminary, suggest that by carefully timing the administration of anticancer drugs, their therapeutic effects maybe improved, toxic effects diminished, or both.

SOURCE: Office of Technoiogy Assessment, 1991.

blood peak late at night or early in the morning (181), and insulin secretion peaks in the afternoon (118).

The secretion of cortisol, a steroid hormone important for metabolism and responses to stress, fluctuates daily, peaking in the very early morning hours and falling to a negligible amount by the end of the day (181). Besides its use as a marker for the internal pacemaker, the circadian rhythm of cortisol secretion may drive other rhythms in the body and has important clinical implications. For example, blood tests used to diagnose suspected excess cortisol production will be most sensitive during the evening. Also, cortisol-like steroid hormones used therapeutically to treat asthma and allergies and to suppress the immune system, are best administered in the morning, when they interfere least with the body's own cortisol production.

Circadian rhythms in cardiovascular function have long been recognized. Indicators of heart and

Box 3-B-Cycles *That Last From Minutes To Days*

Circadian rhythms are a basic and well-recognized feature of human physiology and behavior. However, biological rhythms that repeat more or less frequently than every 24 hours are also fundamental to the body's function. In general, ultradian rhythms (those with a length of less than 24 hours) and infradian rhythms (those with a length greater than 24 hours) do not coincide with conspicuous environmental cues, and how they are generated is not well understood.

Sleep cycles were one of the first ultradian rhythms characterized in humans. A complete cycle of dreaming and nondreaming takes place about every 90 minutes. This finding prompted researchers to hypothesize that cycles of enhanced arousal followed by diminished activity typify both waking and sleeping periods, This theory of a basic rest-activity cycle has led to many studies of ultradian cycles in alertness-sleepiness, hunger, heart function, sexual excitement, urine formation, and other functions.

Hormones are also released in ultradian cycles. Many are secreted in a more or less regular pattern every few hours. More frequent cycles of release, every few minutes, have also been documented. Although the mechanisms of hormone secretion have not been uncovered, patterned release has been shown to be extremely important for proper functioning. For example, experiments have shown that, when replacing a deficient hormone, pulses of the hormone, not a continuous supply, are required for effectiveness. Also, abnormalities in the production cycle of hormones have been correlated with altered function. Although these cycles do not appear to be tightly coordinated, it is clear that ultradian rhythms with a cycle of 90 minutes, as well as with cycles of a few minutes to several hours, are a basic component of many human functions. How they are generated is unknown.

The most prominent infradian rhythm in humans is the menstrual cycle. Through a series of complex interactions between the brain and reproductive organs, an egg is released by an ovary approximately every 28 days, and the reproductive organs are prepared for possible fertilization. During each cycle, hormones are secreted in varying amounts, and the reproductive tract and breast tissue are altered. Other systems, such as those involved in immune function, may also be affected.

Although the menstrual cycle has long been recognized, how it is generated and how it interacts with other factors have not been completely detailed. It is clearly affected by circadian rhythms. For example, a peak in the secretion of luteinizing hormone, which triggers ovulation, usually occurs in the early morning hours. Also, phase shifts, such as those produced by transmeridian flight, may interfere with the menstrual cycle. The menstrual cycle may also have therapeutic implications. A recent study of the timing of breast cancer surgery in relationship to the menstrual cycle has found fewer recurrences and longer survival inpatients whose surgery occurred near the middle of the menstrual cycle rather than during menstruation. That biological rhythms are often ignored is also indicated in this study: less than half of the records evaluated in the study recorded the time of the last menstrual period.

SOURCE: Office of Technology Assessment 1991.

blood vessel function that demonstrate daily rhythms include blood pressure, heart rate, blood volume and flow, heart muscle function, and responsiveness to hormones (84). The daily fluctuations in cardiovascular function are further illustrated by symptoms of disease. Data have shown that abnormal electrical activity in the heart and chest pains peak at approximately 4 a.m. in patients suffering from coronary heart disease (189,190). As stated earlier, the number of heart attacks has been shown to peak between 6 a.m. and noon (1 17,140). These temporal characteristics of cardiovascular disease indicate the importance of careful timing in their assessment, monitoring, and treatment (120).

The widely recognized pattern of nighttime increases in asthma symptoms highlights the circadian rhythms of the respiratory system. Which respiratory functions are responsible for nocturnal asthma symptoms? Exposure to allergy-producing substances, the respiratory system's responsiveness to compounds that can initiate an asthma attack, daily changes in the secretion of certain hormones, cells in the lung and blood that may be important mediators of asthma, and the recumbent position have all been suggested as possible mechanisms (16,163). The prevalence of asthma attacks at night has led to drug treatment approaches that take circadian rhythms into account.

Other organ systems also reveal circadian fluctuations. Kidney function and urine formation vary over the course of a 24-hour period; there are daytime peaks in the concentrations of some substances in

the urine (sodium, potassium, and chloride) and nighttime peaks in others (phosphates and some acids) (78). Urine volume and pH also peak during the day. Immune system and blood cell functions cycle daily, as do cell functions in the stomach and intestinal tract (85,1 12).

The Timing of Sleep

Daily cycles of sleep and wakefulness form the most conspicuous circadian rhythm among humans. Traditionally, about 8 hours each night are devoted to sleep. While neither the function of sleep nor how it is regulated is completely understood, it is clear that sleep is a basic requirement that cannot be denied very long. Even a modest reduction in sleep leads to decrements in performance, especially at night. Furthermore, when deprived of a night or more of sleep, individuals can find sleep impossible to resist, especially in monotonous situations, and they experience brief episodes of sleep, called microsleeps (45,104).

Classic studies indicate that sleep is not a homogeneous state (42,75). Polysomnography, the measurement of electrical activity in the brain, eye movement, and muscle tone, has revealed distinct stages of sleep (table 3-l). During stages 1 through 4, sleep becomes progressively deeper. In stages 3 and 4, which constitute slow wave sleep (SWS), the eyes do not move, heart rate and respiration are slow and steady, and muscles retain their tone but show little movement. Dreams are infrequent. As sleep continues, dramatic changes occur: brain activity appears similar to that seen during wakefulness, heart rate and respiration increase and become erratic, dreams are vivid and frequently reported, and the eyes move rapidly. This stage of sleep is rapid eye movement (REM) sleep. Typically, cycles of non-REM sleep (stages 1 through 4) and REM sleep repeat every 90 to 100 minutes throughout the course of a night's sleep.

When synchronized to the 24-hour day, the timing of sleep usually bears a characteristic relationship to the environment and to other circadian rhythms in the body. In general, humans retire for sleep after dark, when body temperature is falling. Morning awakening coincides with an upswing in body temperature. With the exception of an occasional afternoon lull (box 3-C), wakefulness continues throughout the day, and body temperature reaches its zenith during the late afternoon.

Studies of humans isolated from all time cues have unveiled several characteristics about the timing of the sleep-wake cycle and the circadian pacemaker. In isolation, circadian rhythms are approximately 25 hours long (figure 3-7). While the sleep-wake and body temperature cycles are a similar length at first, their relationship gradually changes, until body temperature decreases during wakefulness and increases during sleep (34,35).

Prolonged temporal isolation, for many days or weeks, sometimes leads to a dramatic dissociation of

Table 3-l—Differences Between Rapid Eye Movement (REM) Sleep and Slow Wave Sleep (SWS)

Factors concerning sleep	REM sleep	SWS (stages 3 and 4)
Brain		
Measured activity	High	Low
Cerebral blood flow	High	Low
Oxygen consumption	High	Low
Temperature	High	Low
Body		
Eyes	Rapid movements	No movements
Pupils	Dilated	Normal
Heart rate	Increased and variable	Slow and steady
Respiration	Increased and variable	Slow and steady
Behavior		
Movements	Occasional twitches	None
Dream reports	Frequent and vivid	Infrequent and vague
Deprivation	Agitated and impulsive	Withdrawn and physical complaints

SOURCE: Office of Technology Assessment, adapted from D.F. Dinges, "The Nature and Timing of Sleep," *Transactions & Studies of the College of Physicians of Philadelphia* 6:177-206, *1964.*

Box *3-C—Napping*

Are human beings biologically programmed to nap? Divergent lines of evidence, both direct and indirect, suggest that midafternoon napping is an inherent aspect of human behavior. No other species exhibits exclusively once-a-day, or monophasic, sleep patterns. Indeed, as children develop, the midafternoon nap is generally relinquished only when school interferes. Adult napping is more prevalent than most Americans realize, especially in other cultures and among persons who may be sleep-deprived, More than 50 percent of all college students, for example, nap at least once a week. Napping also appears to increase among retired Americans.

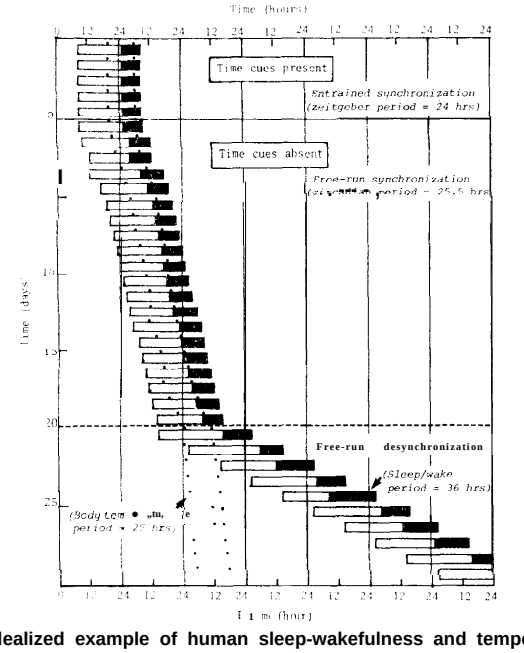
There are other indications that a midafternoon nap is natural in humans. When human circadian rhythms are analyzed in a time-free environment, napping is common. The postlunch dip, or the midafternoon decrease in human performance regardless of food intake, may reflect a proclivity for sleep at that time. Decreased human performance presumably accounts for the midafternoon peak in traffic accidents. Moreover, the decline in human performance corresponds to peaks in sleepiness. Measures of sleepiness using the multiple sleep latency test demonstrate a more rapid onset of sleep in the afternoon. Pathological conditions, such as narcolepsy, or frequent, uncontrolled sleeping, also exhibit a midafternoon peak in sleep episodes.

Insight into human napping behavior may have some practical implications. While mood and subjective feelings of sleepiness may not be affected by napping, performance during extended periods of work can be improved. In addition, the scheduling of brief episodes of sleep during sustained periods of work maybe optimized: research suggests that napping before, rather than after, extended periods of work is best for reducing the effects of sleep loss.

SOURCE: Office of Technology Assessment, 1991.

body temperature and sleep-wake cycles, a state called internal desynchronization (10) (figure 3-7). In some individuals, while the body temperature cycle maintains a 25-hour length, the sleep-wake cycle may become 30 to 50 hours long, with sleep occupying 6 to 20 hours per cycle. Despite the apparent lack of synchrony between sleep-wake and body temperature cycles, further studies show that a relationship is maintained between the two (34,204). REM sleep is more prevalent as body temperature

Figure 3-7—Human Circadian Rhythms in the Absence of Time Cues



An idealized example of human sleep-wakefulness and temperature rhythms in a time-free environment.

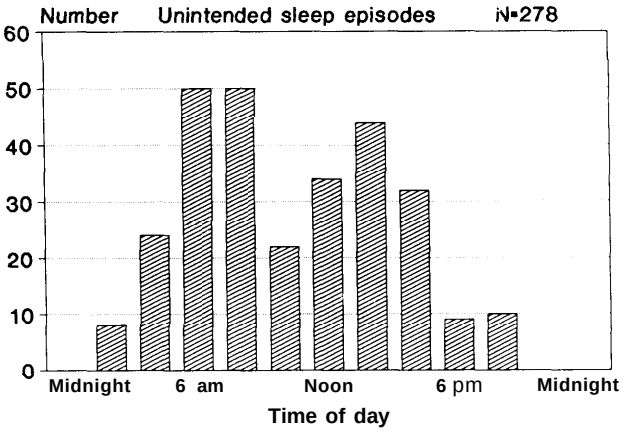
SOURCE: D. F. Dinges, "The Nature and Timing of Sleep," *Transactions & Studies of the College of* Physicians of Philadelphia 6: 177-206.1984.

rises. Similarly, wake times correlate to rising body temperature, regardless of when the sleep period began. Sleep is of short duration if it begins at the body temperature's low point; sleep is long if it begins near the peak of the body temperature rhythm, with wake time occurring at the next body temperature peak. These studies indicate that circadian rhythms influence total sleep time (165).

Other characteristics of the timing of sleep and wakefulness have been discerned. How long it takes to fall asleep in a sleep-promoting environment at different times throughout the day can be measured using the multiple sleep latency test. Studies using this technique have shown that individuals fall asleep most rapidly at two times, during the middle of the night and during the middle of the afternoon (figure 3-8) (19, 138). Conversely, experiments have demonstrated that there are times during the course of the day when falling asleep is very difficult (81).

In summary, sleep is a necessary component of life. When synchronized to the 24-hour day, sleep typically occurs during the night hours and bears a constant, if complex, relationship to other circadian

Figure 3-8-Sleepiness During the Day



Episodes of unintentional sleep over the course of a day.

SOURCE: M.M. Mitler, M.A. Carskadon, C.A. Czeisler, et al., "Catastrophes, Sleep, and Public Policy: Consensus Report," *Sleep* 11:100-109, 1988.

rhythms. Particular components of sleep, including total amount of sleep and sleepiness, are governed by the circadian clock. Therefore, periods of sleep are not readily rescheduled, deferred, or resisted. The requirement for sleep and the control of its timing have important implications for work schedules and shift work (see ch. 5).

Human Performance

Physiological variables such as body temperature, hormone levels, and sleep are not the only human functions that exhibit circadian rhythms. Human performance, including psychological processes and mental functions, also exhibits circadian fluctuations (26). Diverse components of human performance, including memory, reaction time, manual dexterity, and subjective feelings of alertness, have been dissected experimentally to ascertain when they peak during the course of a day and how they are affected by circadian rhythm disruption.

Research conducted during the first half of this century indicated that some aspects of human performance improve over the course of the day, climaxing when peak body temperature is achieved. Subsequent experiments determined that the timing of peak performance varied with the nature of the task being assessed. Several factors, including perceptual involvement, the use of memory, and the amount of logical reasoning required, appear to be important in determining when particular types of performance peak during the circadian cycle. Performance of tasks involving manual dexterity, simple recognition, and reaction time appears to parallel the circadian rhythm of body temperature, peaking when body temperature is highest, in the late afternoon (54,107,110,111). Verbal reasoning seems to peak earlier in the circadian cycle and may adjust more quickly than other types of performance to such disruptions as jet lag (box 3-D) (69,107, 110,11 1). An individual's assessment of mood and alertness also exhibits circadian rhythms. For example, when subjects are asked to indicate their level of alertness, weariness, happiness, or other moods on a visual scale at regular times throughout the course of the day, consistent circadian patterns emerge (figure 3-9) (54,106,108,109,173).

Variation in performance may also reflect subtle differences between tasks and the way in which a task is approached (53). For example, when subjects were asked to identify the larger of two spheres, it was found that, if speed of identification was assessed, the usual relationship with temperature held—that is, subjects became faster over the course of the day. However, if accuracy of response became the benchmark, peak performance occurred in the morning (27,107). Short-term and long-term memory also appear to peak at different times during the 24-hour cycle (53). Motivation can influence performance, too. It has been shown that when an incentive is offered, such as a significant sum of money, circadian decrements in performance maybe overcome to some extent (26,68). The latter study (68) indicated, however, that sleep deprivation and circadian rhythms can overcome even the strongest incentive influencing performance. Further complicating the picture is the observation that individuals are not always accurate judges of their own mood, alertness, or ability. For example, a short nap maybe able to counteract decrements in performance caused by lack of sleep without alleviating subjective feelings of sleepiness (56).

Many aspects of human performance decline to minimal levels at night, reflecting not only the influence of the circadian pacemaker, but also the lack of sleep (14). Sleep deprivation, even for one night, is one of the most important disrupting factors of human mental and physical function (46). Sleep loss influences several aspects of performance, leading to slowed reaction time, delayed responses, failure to respond when appropriate, false responses, slowed cognition, diminished memory, and others.

Box 3-D—*Jet Lag*

Transmeridian air travel, especially across several time zones, can severely disrupt circadian rhythms. It may produce an unpleasant and somewhat disabling constellation of symptoms collectively labeled jet lag. Jet lag varies among individuals and may include trouble sleeping, daytime sleepiness, gastrointestinal disruption, and reduced attention span. Physical and mental performance may also be seriously diminished following transmeridian flight.

What precipitates jet lag? Stress and loss of sleep associated with air travel certainly contribute to postflight fatigue; however, these factors alone do not interrupt circadian rhythms. Rather, conflict between the traveler's own circadian clock and external rhythms in a new time zone is the primary agent of jet lag. The timing of meals, activity, and sleep no longer coincides with that customary in the new time zone. Furthermore, environmental cues, especially light, promote synchronization between circadian rhythms and the new time zone. Since different circadian rhythms may adjust to the new time zone at different rates, the air traveler experiences a period when internally generated rhythms are no longer in synchrony with each other. The lack of synchrony between internal and external rhythms, as well as among different internal rhythms, probably results in the malaise and diminished performance associated with jet lag.

How long it takes to adjust to a new time zone and recover from jet lag depends on several factors, including the number of time zones crossed, the direction of travel, differences among individuals, age, and the particular circadian rhythm involved. The number of time zones crossed, or hours phase shifted, significantly influences the occurrence and duration of jet lag; resetting the circadian system can take as many as 12 days following a 9-hour flight across several time zones. Even a l-hour time shift can require at least a day for complete adjustment.

The direction of air travel may also influence the severity of jet lag. Most, but not all, studies indicate a more rapid adjustment to westward than to eastward travel. Also, the severity and duration of jet lag vary markedly among individuals. One rule of thumb is that persons with less variable body temperature rhythms become synchronized to a new time zone more rapidly. (Older persons, who may exhibit a reduction in circadian variation, generally have more difficulty adjusting to a new time zone.) What mechanisms determine how quickly phase shifts occur is not known. As mentioned, various circadian rhythms adjust to external cues at various rates. For example, it may take 2 days for the sleep-wake cycle to adjust to a 6-hour time zone shift but 5 or more days for body temperature rhythm to be entrained. Furthermore, recovery from jet lag may not proceed linearly: some data indicate that sleep and performance may improve the first day following a phase shift and languish the next.

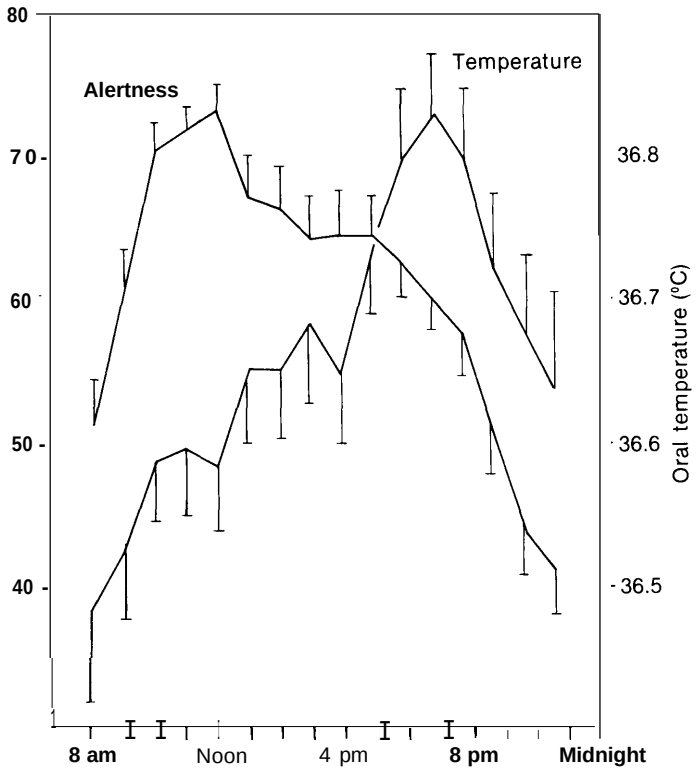
Measures to hasten adjustment to a new time zone, including the use of certain drugs, bright light, exercise, and diet, are under investigation. Improved understanding of human circadian rhythms has prompted recommendations from scientists about how best to confront jet lag. Short trips of only a few days across time zones probably do not warrant an attempt to adjust to the local time zone. In these situations, it is best to try to schedule activities and sleep as close to one's internal clock as possible in order to avoid jet lag. For longer trips, suggestions for resetting one's interred clock include adopting the new schedule immediately and maximizing exposure to environmental cues, especially light at specific times (figure 3-12). The problems are very complex for international air crews, who fly rapid sequences of transmeridian flights (see ch. 4) combined with irregular hours of work and rest. The kinds of jet lag countermeasures that may suffice for occasional transmeridian travelers (use of hypnotics, scheduled bright light exposure, and so on) are generally not practical-and may even be hazardous-for individuals exposed to repeated time zone changes. These issues are being addressed in a broad program of field and laboratory research being conducted by the Aviation Human Factors Branch at the National Aeronautics and Space Administration's Ames Research Center (see app. B).

SOURCE: Office of Technology Assessment, 1991.

The circadian clock also leads to a nighttime minimum in many types of performance (26,104). Thus, sleep deprivation combined with the influence of the circadian pacemaker can severely curtail performance at night. These factors have important implications for shift work (see ch. 5).

In summary, circadian rhythms can cause performance to vary according to the nature of the task or mood assayed. Other factors, such as fatigue and motivation, also profoundly influence human performance. Furthermore, a discrepancy may exist between an individual's own assessment of his or her ability to perform and the performance that is actually demonstrated. When individuals are synchronized to the natural day-night cycle, many types of performance reach minimum levels during the

Figure 3-9-Circadian Rhythms of Alertness



The circadian rhythms of subjective alertness and body temperature from persons synchronized to a 24-hour day.

SOURCE: T.H. Monk, M.L. Moline, J.E. Fookson, et al., "Circadian Determinants of Subjective Alertness," ***Journal of Biological Rhythms*** **4:393-404, *1989.***

night, reflecting the combined influence of the circadian pacemaker and the lack of sleep.

DISRUPTION OF CIRCADIAN RHYTHMS

When rhythms generated by the body conflict with those in the environment, function is compromised until the rhythms are realigned. Patterns of sleep are disrupted, performance may be impaired, and a general feeling of malaise may prevail. Data linking disrupted circadian rhythms with some mental and sleep disorders also point to the importance of an intact circadian system for health. The following section discusses specific situations, other than shift work, that may be associated with altered or disrupted circadian rhythms. Shift work is discussed in chapter 5.

Aging and the Body Clock

Are circadian rhythms altered by the aging process? The stereotypes of diminished daytime alertness and early morning rising among the elderly[1] hint at possible circadian alterations. Studies confirm that many physiological and behavioral functions that typically display circadian rhythms are altered with advancing age in humans. For example, there are usually conspicuous changes in sleep habits, such as earlier onset of sleepiness, early morning awakening, and increased daytime napping (93,101). During sleep, there is an increase in the number and duration of waking episodes, there is a reduction in the nondreaming phases of sleep, the first REM phase occurs earlier in the night, and the tendency to fall asleep is increased during the day (18,20,29). Other circadian rhythms, such as body temperature, activity, and the secretion of hormones, including cortisol, are also altered with age (29,93,138,193).

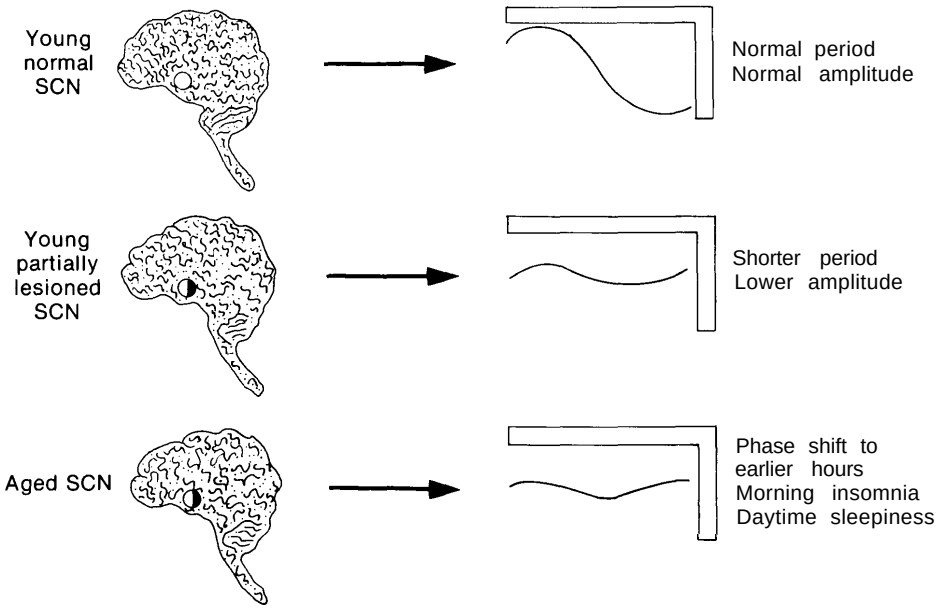
While factors such as changing social habits, medication, and disease processes can impinge on functions that exhibit circadian rhythms, such as sleep, activity, alertness, and hormone secretion, research suggests that aging affects the circadian system itself. A decrease in the amplitude and length of various cycles with age has been observed in animal studies, including longitudinal studies (114, 126,196).[2] Studies of various circadian rhythms in humans have suggested that the length of the circadian cycle shortens with age and that the amplitude of circadian rhythms is blunted (28,105,160,186,193). Furthermore, coordination of various circadian rhythms, such as body temperature, hormone levels, and the sleep-wake cycle, may be lost with age (105,186).

What is the basis for these changes in circadian rhythms with age? It has been suggested that a decreased number of nerve cells in the SCN corre-

[1]Changes in circadian rhythms associated with aging, as discussed in this section, may refer to different populations of older people. Most research on sleep parameters focused on subjects age 65 or older. Anatomical changes in the brain have been observed in subjects over 80. Difficulties associated with shift work or jet lag have generally been studied in subjects age 45 or older.

[2]Longitudinal studies involve analysis of a particular function in individual subjects over a period of time. They are especially useful for determining effects that exhibit a great deal of variation among individuals, as circadian rhythms do. While longitudinal data concerning circadian rhythms in animals have been collected (114, 126), no similar data are available on humans.

Figure 3-10-Aging and the Pacemaker



The influence of the pacemaker (SCN) on the length and amplitude of circadian rhythms, linking the decreased amplitude in rhythms with disturbed sleep among the elderly.

SOURCE: Adapted from G.S. Richardson and J.B. Martin, "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," Progress *in NeuroEndocrinImmunology* 1:16-20, 1988.

lates with a decrease in cycle length and perhaps dampened amplitude (figure 3-10) (29,139). Support for this idea is derived from several studies: when some SCN neurons are destroyed in young animals, the length and amplitude of circadian rhythms are diminished, much as they diminish with advancing age (37,123). A decrease in the number or function of SCN neurons has been associated with aging in rats (24,141). Similarly, a decrease in the number of SCN neurons and the overall size of the SCN was documented in humans over the age of 80 (66, 166,167).

Other biological changes with age may impinge on circadian rhythms. For example, relay of synchronizing cues, such as light, may be hampered. There is evidence that some eye problems that occur with age may impede the transmission of light information to the SCN (162). It is possible that changes in the eye may precede and even induce changes in the SCN. Several studies of humans and animals have reported diminished responsiveness to synchronizing cues with age, despite a decrease in the amplitude of circadian rhythms, which normally eases synchronization (29).

While many elderly people fail to report any circadian rhythm-based problems, some studies have illuminated difficulties. For example, adjusting to rotating shift work schedules and transmeridian flight is more difficult among older people (134). In addition, advanced sleep phase syndrome, a disorder in which sleep occurs earlier than usual, appears to be common among the elderly (174). A considerable proportion of older people complain of sleep problems: one study found that 33 percent of older people visiting a general practitioner complain of frequent early morning awakening (97). Lessened performance and alertness during the day may result from fatigue or the lack of synchrony among circadian rhythms. Thus, changes in circadian rhythms with age may cause a broad spectrum of effects, ranging from no complaints whatsoever, to disturbances of everyday life, to severe health problems.

Sleep Disorders

Just as the timing of sleep is the most prominent indicator of circadian rhythms in humans, it may also be the cycle most susceptible to disruption (32). It is now recognized that some types of insomnia most likely result from abnormalities in circadian rhythms. In the recently revised *International Classification of Sleep Disorders (2),* several sleep disorders are ascribed to problems with circadian rhythms, including:

- advanced sleep phase syndrome,
- delayed sleep phase syndrome, and
- non-24-hour sleep-wake disorder.

Advanced sleep phase syndrome is a common sleep disorder among the elderly, affecting up to one-third of that population (97). It involves early onset and offset of sleep. Research indicates that diminished circadian cycle length and amplitude underlie the disorder (28,193). Advanced sleep phase syndrome may have several consequences, including decreased daytime alertness, overuse of hypnotics and other drugs, and social disruption.

Delayed sleep phase syndrome, or insomnia, is characterized by abnormal delay of sleep onset and waking (2). Persons with this form of insomnia are generally teenagers and young adults. They complain that, on retiring at a bedtime common for most individuals, they are unable to fall asleep. Waking in time for early morning classes or work is also difficult, and they may suffer from fatigue caused by inadequate sleep at night. If individuals with this disorder are permitted to retire and arise at a later hour, although out of step with the environment and society, they can achieve an adequate amount of sleep. It is postulated that the cause of this disorder may be either an abnormally long circadian cycle or a diminished responsiveness to cues in the environment that reset the circadian pacemaker each day (33,119).

Non-24-hour sleep-wake disorder is also likely to reflect disruption of the circadian system. Individuals suffering from this disorder find themselves retiring for and waking from sleep at progressively later times (2). When the timing of sleep onset and awakening coincides with that of the world around them, individuals with this disorder are asymptomatic. When their circadian rhythms are not in synchrony with the environment, individuals with this disorder complain of insomnia, difficulty awakening, and fatigue. One survey showed that 40 percent of blind persons may suffer from non-24-hour sleep-wake disorder (100). These data indicate that the inability to perceive light-dark cycles probably causes the disorder.

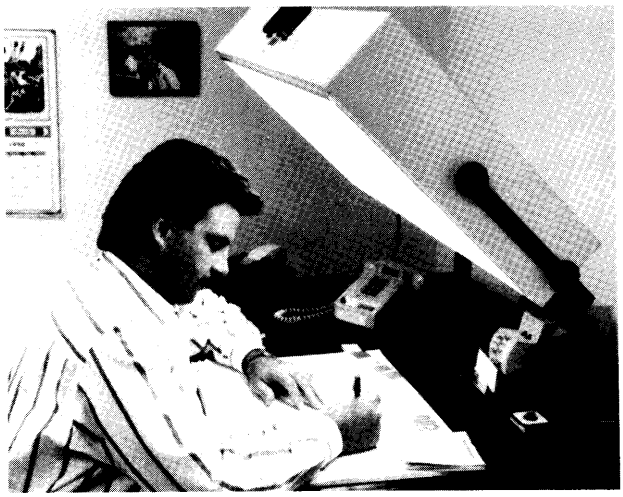


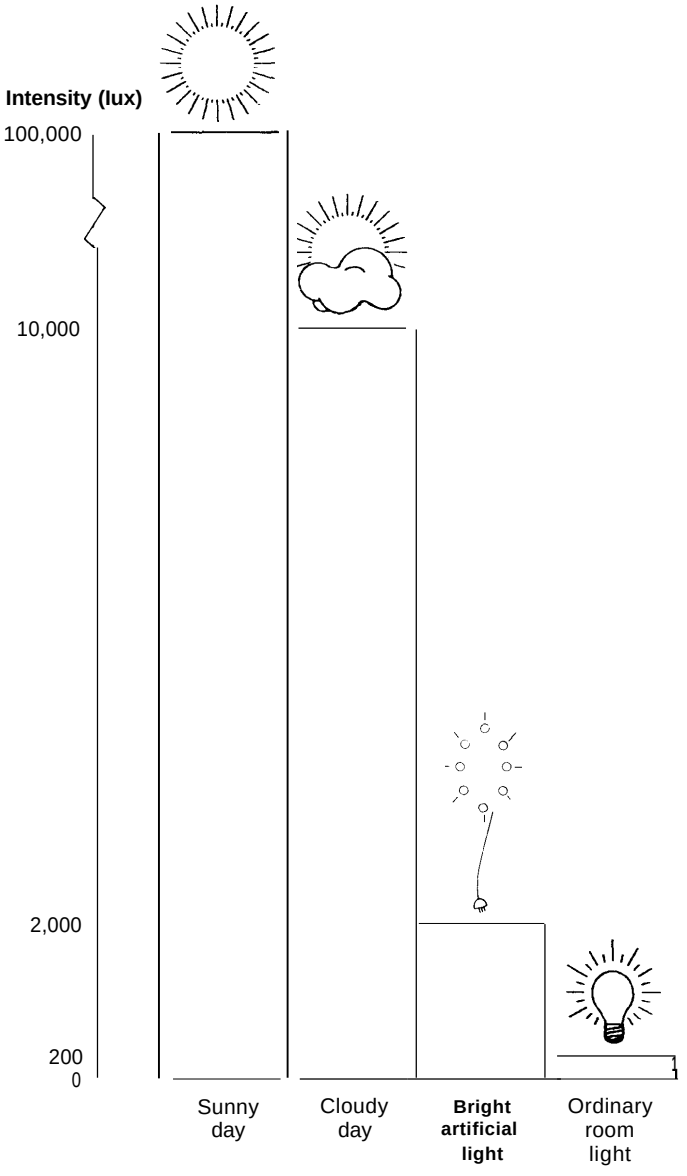
Photo credit: Neal Owens, Sun Box Co., Rockville, MD

A light box used for the treatment of SAD.

Chronobiology and Mood Disorders

While seasonal tendencies in mood disorders have been noted for hundreds of years, the recent surge in research into circadian rhythms has triggered a systematic examination of this phenomenon. Several current hypotheses suggest that an alteration of circadian rhythms leads to various mood disorders. Furthermore, exposure to bright light appears to be an effective therapeutic intervention in some cases. Continued research is necessary, however, to verify the link between circadian rhythm disruption and mood disorders. In the 1980s, researchers first documented a mood disorder involving a recurring autumn or winter depression (144). Currently, this form of seasonal affective disorder (SAD) is the subject of extensive study; although the symptoms and diagnostic criteria are somewhat disputed, SAD and its treatment with bright light are generally recognized by the psychiatric community (1,17,58). Each fall or winter, individuals suffering from SAD may tire easily, crave carbohydrates, gain weight, experience increased anxiety or sadness, and exhibit a marked decrease in energy (144,146). With protracted daylight in the spring, patients emerge from their depression and sometimes even display

Figure 3-1 l—Levels of Light



The comparative intensity of light. Bright artificial light is effective for shifting human circadian rhythms.

SOURCE: A. Lewy, Oregon Health Sciences University, 1991.

modest manic symptoms. Epidemiological studies indicate that SAD is related to latitude, with the number of cases increasing with distance from the equator (127,143).

Although there is no agreement about how light therapy works, data from several studies suggest that it is a useful treatment for SAD (144,170). The recommended protocol for treatment involves exposure to light with an intensity of 2,500 lux (which is equivalent in intensity to outdoor light at dawn) for 2 to 5 hours per day (figure 3-1 1). Some researchers have asserted that shorter periods of exposure to very bright light (e.g., 10,000 lux for 30 minutes) may also relieve symptoms (170,172). Data from several studies suggest that morning exposure to light is most effective in relieving symptoms of SAD, although this issue is unresolved (17,89,170,172).

The cause of SAD and the way in which light therapy alleviates it are not known. It has been hypothesized that circadian rhythms are delayed or possibly that the amplitude is dampened (17,86,89). To date, however, SAD has not been proven to be a circadian rhythm disorder. Problems that plague this area of research include heterogeneous populations of study subjects, small sample sizes, lack of adequate controls, lack of longitudinal studies, and the absence of controls for the effects of sleep, activity, and light on circadian rhythms (17,1.72). Further studies are necessary to delineate the basis of SAD.

Nonseasonal depression is a significant cause of mental illness in the United States, affecting nearly 1 in 12 Americans. Although not proven, several observations **suggest a** link between altered circadian rhythms and nonseasonal depression (17,32). Among persons suffering from depression, mood typically fluctuates daily, with improvement over the course of the day. Persons also demonstrate seasonal patterns, with an apparent increase in the incidence of depression, as indicated by hospital admissions, electroconvulsive therapy, and suicide records, in the spring and autumn. Various physiological functions may exhibit an altered circadian pattern in depression, notably the timing of REM sleep. In people suffering from depression, the frost REM episode occurs earlier after sleep begins, and REM sleep is abnormally frequent during the early hours of sleep (80). Rhythms of body temperature, hormone and brain chemical secretion, and sleep-wake cycles deviate during episodes of depression, peaking earlier than is the norm or, more commonly, exhibiting dampened amplitude.

The action of various antidepressant drugs and therapies provides further evidence for a link between circadian rhythm disruption and depression (49,58). Some animal studies have shown that several classes of antidepressant drugs either lengthen the circadian cycle, delay distinct circadian rhythms, or influence synchronization with environmental cues. Studies showing that late-night sleep deprivation temporarily alleviates depression also suggest,

but do not prove, a link between circadian rhythms and nonseasonal depression. Assessment of 61 studies, with more than 1,700 patients, indicated that missing one night's sleep halted depression immediately in 59 percent of the patients (the next sleep episode usually resulted in the return of depression, and in more than a quarter of the patients a manic episode was triggered) (198).

While this information suggests a potential causative relationship between circadian rhythm disruption and depression, little direct evidence supports the hypothesis that nonseasonal depression is a circadian disorder. For example, only a few studies have indicated a phase advance or blunted circadian amplitude. Most studies share similar problems as those described above for SAD, including heterogeneous samples, small sample sizes, and failure to evaluate circadian rhythms isolated from the influence of the environment.

CONTROLLING CIRCADIAN RHYTHMS IN HUMANS

Interest in manipulating the internal clock has grown with improved understanding of human circadian rhythms and increasing awareness of circadian rhythm disruption, whether precipitated by intrinsic factors (e.g., sleep disorders, blindness, mental disorders, or aging) or extrinsic factors (e.g., air travel across time zones and shift work) (box 3-D). Several agents are under investigation or have been proposed for use in manipulating circadian rhythms. In order to assert that an agent's primary action is on the circadian system, several questions must be addressed, including: How are circadian rhythms modified? Are all circadian rhythms altered or only certain rhythms, such as the sleep-wake cycle? How is the circadian pacemaker influenced? Does the effect vary at different times during the circadian cycle (i.e., has PRC been evaluated)? Does the agent have any side effects or drawbacks? Several agents show promise for manipulating human circadian rhythms, including:

- light,
- melatonin,
- benzodiazepines,
- other chemical substances and diet, and
- activity.

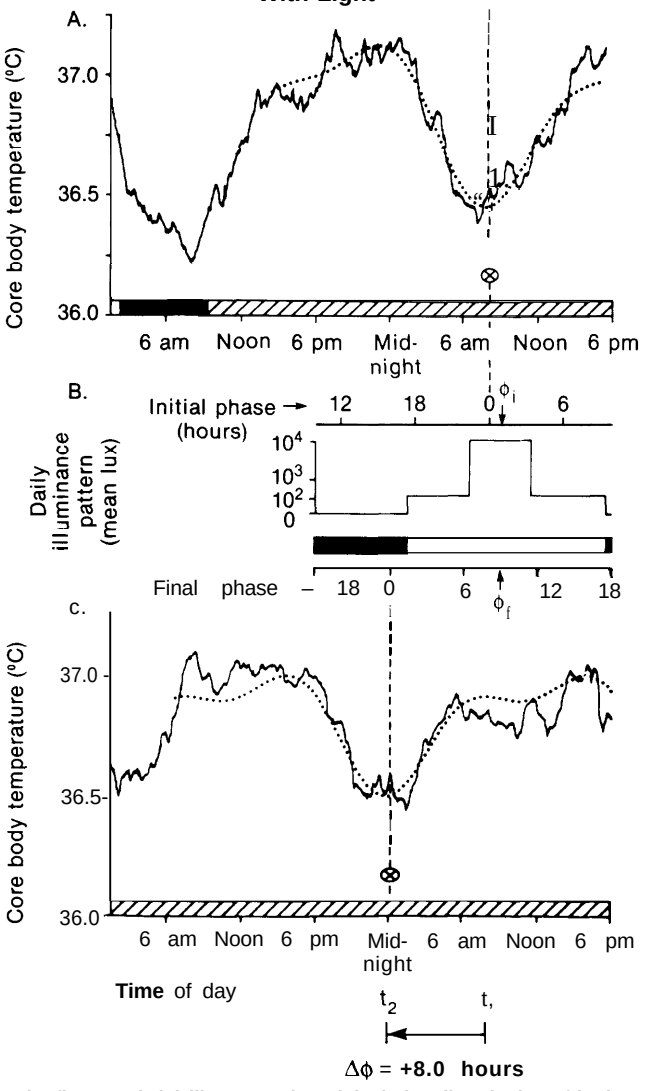
Light

Light-dark cycles are the single most important environmental cue for synchronizing the internal clock to the Earth% 24-hour cycle. As mentioned, light's ability to reset the internal clock was first discovered by exposing organisms to pulses of light at "different times throughout the circadian period (40,65,125). In these experiments, exposure to light at night produced the largest shifts in rhythms, with late-night pulses advancing rhythms and pulses during the early part of the night delaying them. Other studies have shown that the phase-shifting effects of cycles of light and dark are similar to those of light pulses.

The synchronizing effect of light on human circadian rhythms has only been recognized in the last 10 years (33). Previously, social contacts were thought to synchronize human circadian rhythms, since light-dark cycles apparently failed. This conclusion was questionable, for several reasons. First, subjects were permitted to use lamps at will in the original study and therefore were never completely limited to an imposed light-dark cycle. Also, the design of the studies prevented discrimination between the effects of social contact and those of rest, activity, or eating. A subsequent study reported synchronization of human circadian rhythms when an absolute light-dark cycle was imposed, but the experiment did not differentiate between the effects of the light-dark cycle and the timing of sleep on circadian rhythms, since subjects always retired to bed at the time lights were turned out.

The discovery that bright light (2,500 lux) suppresses the production of the human hormone melatonin (92) triggered a reassessment of light's effects on human circadian rhythms. In one study, light-dark cycles were shown to significantly synchronize human circadian rhythms (195). Subsequent studies illustrated the phase-shifting effects of light on humans. For example, in one study, exposure to 4 hours of very bright light (7,000 to 12,000 lux) was shown to delay circadian rhythms in a single subject whose rhythms were unusually advanced (figure 3-12) (28). These and other studies support the hypothesis that bright light shifts human circadian rhythms, the size and direction of the shift depending on when in the cycle exposure takes place (38,39,43,44,47,67,9O,91,1O3, 195).

Figure 3-12—Resetting the Human Pacemaker With Light



The first graph (A) illustrates the original circadian rhythm of body temperature. Following exposure to bright light, as illustrated in B, the rhythm of body temperature was significantly shifted (C).

SOURCE: C.A. Czeisler, R.E. Kronauer, J.S. Allan, et al., "Bright Light Induction of Strong (Type O) Resetting of the Human Circadian Pacemaker," *Science* 244:1328-1332, 1989.

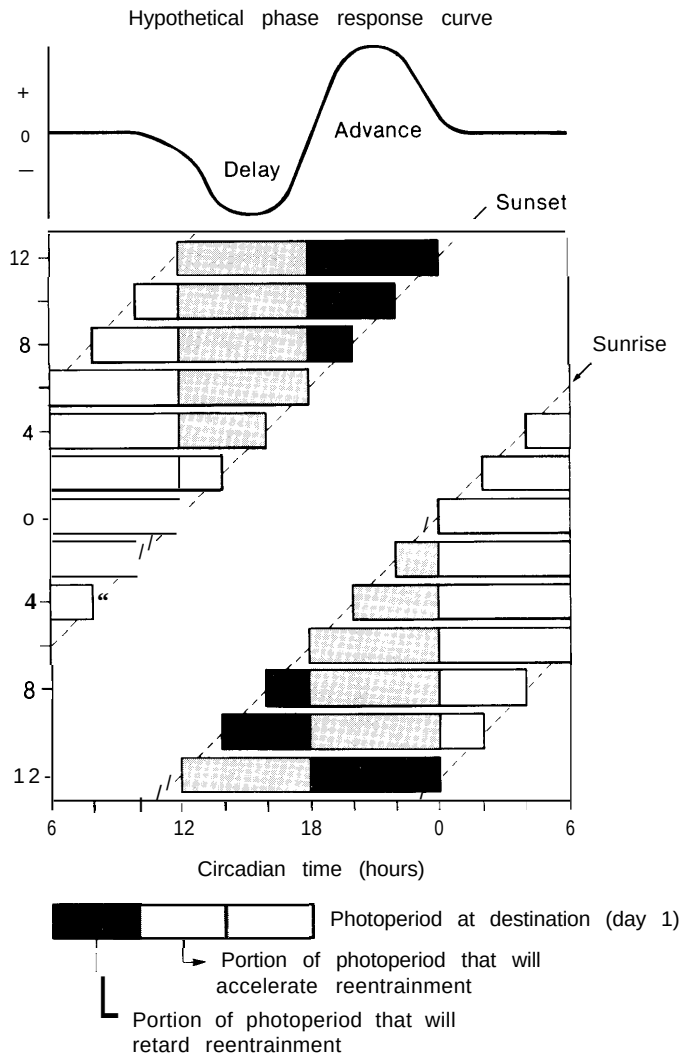
More recent studies report a human PRC to light (31,194). For example, one study exposed human subjects to varying cycles of very bright light (7,000 to 12,000 lux), ordinary room light, and darkness (31). The greatest shift in circadian rhythms (several different rhythms were measured) was produced when the exposure to very bright light occurred approximately 3 hours before the usual waking time; exposure immediately preceding or following this time maximally delayed or advanced rhythms, respectively. This study also suggested that low-intensity light (150 lux) modifies the phase-shifting effects of very bright light, a pattern that resembles the effect of light on circadian rhythms in other organisms. Recent experiments have provided further evidence of the similarity of light's effects on human and other species' circadian rhythms (72).

The methods used in these human studies to evaluate and manipulate circadian rhythms differ from the methods used in animal studies, leaving room for speculation concerning the mechanism by which light produces its effects. The influence of sleep, fatigue, or darkness in these studies is not known, nor is the mechanism by which light influences human circadian rhythms well defined. However, accumulating evidence shows that, as in other animal species, light, especially bright light, is effective in shifting human circadian rhythms. The phase-shifting properties of bright light have been applied in several situations:

- Exposure to bright light is now used in certain clinical centers and research settings to treat some sleep disorders and elderly persons suffering from circadian rhythm disruption.
- A published research plan for exposure to sunlight has been proposed to speed recovery from jet lag (figure 3-13) (36).
- Recent studies have evaluated the influence of bright light and darkness cycles on the circadian rhythms, sleep, and performance of workers at night (see ch. 5) (30).
- Although the basis for SAD has not been definitely linked to circadian rhythm disruption, bright light therapy appears to be beneficial for patients (145,170).

The potential adverse effects of using light to reset circadian rhythms (as well as in the treatment of SAD) have not been systematically studied. Since it is a nonpharmacological intervention, it probably presents fewer detrimental effects. It has been argued that since the intensity of light used to modulate human rhythms is far less than the intensity of outdoor daylight, there is little risk involved. However, experience with SAD has led to some concern that artificial bright light may present a risk of damage to the eye (171). To date, studies evaluating the health of the eye following bright light therapy for SAD have failed to document any damage, although the risk of long-term effects has not been ruled out. Also, it is not clear what harmful consequences, if any, would result from repeated

Figure 3-13-Bright Light and Air Travel



Exposure to bright light following travel across time zones may influence circadian rhythms. For example, after flying 2 hours from the west to the east, it is suggested that bright light exposure begin at dawn for 2 hours.

SOURCE: S. Daan, and A.J. Lewy, "Scheduled Exposure to Daylight: A Potential Strategy To Reduce Jet Lag Following Transmeridian Flight," *Psychopharmacology Bulletin* 20:566-568, *1984.*

resetting of the circadian pacemaker, such as when using bright light to help shift workers adjust to their changing work schedules.

Exposure to ultraviolet *(W)* radiation is another potential concern raised by the use of bright lights. In research and clinical settings (for the treatment of SAD), fluorescent lighting, both that emitting *W* radiation and that designed to limit it, has been used. One study reported that exposure to *W* light was within established safety guidelines following several hours of exposure to wide-spectrum fluorescent light of 7,000 to 12,000 lux (30). Evidence shows that *W* radiation is not necessary for adjusting rhythms, although it may have some effect on them. Bright light may also produce unpleasant but transient side effects of irritability, eyestrain, headaches, or insomnia.

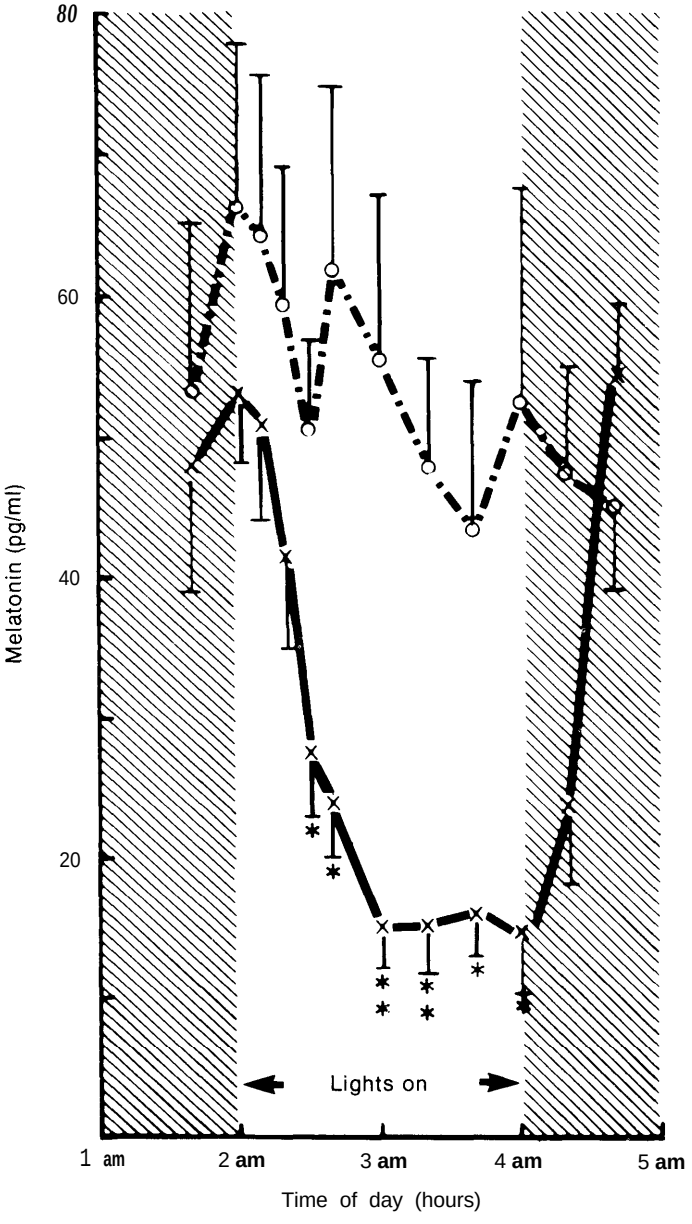
Melatonin

The hormone melatonin is produced by the pineal gland, a small, pealike structure that in humans sits deep within the brain. In lower vertebrates, the pineal gland is positioned near the top of the skull and detects light directly, thus its designation as the third eye *(3). In* mammals, including humans, information about light in the environment is transmitted from the eye through multiple **nerve cells** to the pineal gland *(74,200).* Melatonin secretion is normally limited to nighttime hours, a pattern of secretion that is. regulated in two ways: 1) light suppresses the pineal gland's production of melatonin, and 2) melatonin secretion is regulated by the circadian pacemaker, exhibiting a circadian rhythm even in the absence of environmental cues (figure 3-14) (94,95). For this reason, melatonin can be used as a marker for circadian rhythms (90,91); however, its usefulness may be limited because it is so readily inhibited by light.

In many species, melatonin is a gauge of day length, or photoperiod. Seasonal changes in day length alter the amount and duration of melatonin secretion, thereby regulating the timing of fertility, birth of offspring, and other functions. Although responsiveness to day length generally has not been considered a prominent human feature, several human functions, including the onset of puberty, semen production, and some forms of depression (see earlier discussion), display seasonal patterns.

The pineal gland's nighttime secretion of melatonin is postulated to be important for circadian rhythms in many species (178). In some species, including some birds, the pineal gland serves as the circadian pacemaker (99,203). In other species, the pineal gland does not serve as the primary pacemaker, but its removal disrupts circadian rhythms (8,156). Studies have shown that daily melatonin injection can synchronize circadian rhythms in rats, apparently by a direct effect on the pacemaker in the brain (7,21-23,133,137). These and other data sug-

Figure 3-14—Melatonin Rhythms and Light



Exposure to bright light shown to inhibit human melatonin production (indicated by solid line) when compared to controls (dashed line).

SOURCE: A. Lewy, T.A. Wehr, F.K. Goodwin, et al., "Light Suppresses Melatonin Secretion in Humans," *Science* 210:1267-1269, 1960.

gest that the pineal gland and melatonin production may synchronize various circadian rhythms in at least some mammals.

The effect of melatonin on circadian rhythms has also been examined in humans. In some early studies, melatonin both succeeded and failed to act as a synchronizing agent. Other studies reported that melatonin counteracted subjective feelings of jet lag (4,8,121) (see box 3-D), although how it did so was not clear. Some data indicated that melatonin directly influenced circadian rhythms *(4,8);* however, others failed to confirm this effect ***(6).*** Furthermore, the effects of melatonin on jet lag varied considerably among individuals (4). It was suggested that melatonin counters jet lag by facilitating sleep, since it has sedative properties.

A few studies have used blind persons, who are often not synchronized with the environment, to assess melatonin's effect on the circadian pacemaker. In one such study, it was reported that administration of melatonin synchronized the disturbed sleep-wake cycle of a blind individual ***(5). In*** another study, a phase advance was produced by daily administration of melatonin in four of five blind subjects with free-running rhythms (151,152). More recently, orally administered melatonin synchronized circadian rhythms in a blind subject (153). Also, melatonin has been reported to cause circadian phase shifts, the direction and magnitude of which appear to vary with the timing of its administration, in sighted individuals (87,88). While another study failed to demonstrate administered melatonin's ability to synchronize or shift circadian rhythms (55), this failure may be due to the timing of melatonin administration. Further study is necessary to delineate melatonin's action on human circadian rhythms.

Benzodiazepines

Several studies in rodents have shown that treatment with benzodiazepines, a class of hypnotic drugs which includes Valium, can alter circadian rhythms (130,179). The phase-shifting effects of the short-acting benzodiazepine triazolam (trade name Halcion) have been most extensively studied in the golden hamster. In most of these studies, the timing of locomotor activity (i.e., wheel-running) has been used as a measure of circadian rhythms, although hormonal secretions have also been used. Injection of triazolam produced pronounced phase shifts in wheel-running, the particular effect depending on the dose and timing of administration (177). Triazolam's ability to shift wheel-running was attenuated after a few days of repeated administration, indicating a growing tolerance to the drug.

Besides its ability to cause phase shifts in circadian rhythms, triazolam was also shown to synchronize circadian rhythms when regularly administered. Furthermore, when hamsters experienced a shift in the timing of the light-dark cycle, administration of triazolam at the appropriate time expedited their readjustment (187).

Some data suggest that triazolam's influence on circadian rhythms in hamsters is predicated on its ability to induce locomotor activity (1 16). Triazolam treatment of hamsters increases activity (176). When locomotor activity is suppressed in hamsters, triazolam no longer produces phase shifts (188). However, stimulation of activity may not be necessary for triazolam's circadian effects in all species.

Is triazolam, or other benzodiazepines, likely to emerge as a jet lag pill, capable of shifting human circadian rhythms? Preliminary studies in humans have suggested that it may facilitate shifts in circadian rhythms, or at least promote sleep when circadian rhythms are in conflict with the environment (184). In addition, the activity and safety of this class of drugs have been well characterized in humans, since benzodiazepines are commonly used to manage insomnia and anxiety. However, while benzodiazepines are useful pharmaceutical agents, they do carry the risk of serious side effects, including memory problems and agitation. They can also exacerbate depression. Long-term use of this type of drug can lead to dependency; therefore, repeated use of benzodiazepines for circadian rhythm adjustment is not tenable. Furthermore, any effects of benzodiazepines on circadian rhythms in humans have yet to be thoroughly evaluated. As is the case for their effect on activity, the effects of benzodiazepines on circadian rhythms in humans may be very different from their effects on hamsters.

Other Chemical Substances and Diet

Researchers have speculated that several other chemicals may manipulate circadian rhythms in mammals, including carbachol, phenobarbital, theophylline, and lithium (11,148,175,191,197). Many of these agents affect specific chemical systems in the brain that are important for nerve cell communication and impinge on the circadian pacemaker. Other agents are characterized by generalized stimulatory or sedative properties (157,164). There are no data, however, indicating that these substances influence human circadian rhythms. Furthermore, powerful unwanted side effects cast doubt on the usefulness of many of these substances in counteracting jet lag or shift work.

A popularized diet has been said to manipulate circadian rhythms and has been promoted as an antidote for jet lag (51,199). These claims are based on hypothetical effects of the diet on chemical systems in the brain. Specifically, it has been asserted that morning meals rich in proteins boost concentrations of catecholamines in the brain and consequently stimulate activity. Evening meals rich in carbohydrates purportedly increase concentrations of serotonin, a sleep-inducing chemical in the brain. While a few animal studies suggest that diet can modulate these brain chemicals (82), the protocol used in these experiments does not relate directly to the recommendations for humans. This dietary protocol has not been shown to influence circadian rhythms in humans.

Activity

That the timing of arousal and physical activity is intimately linked to the time of day and circadian rhythms appears self-evident; a few studies suggest that physical activity or arousal can synchronize the internal clock (176). The apparent link between triazolam's stimulation of activity and its circadian effects on hamsters has renewed interest in this 30-year-old proposal (9,176). In fact, many agents purported to alter circadian rhythms also alter the amount of activity in animals.

Experiments in rodents demonstrated that simply having access to a running wheel changes the length of the circadian cycle (13,201). A few other studies indicated that when specific periods of physical activity or other forms of arousal are provided, a phase shift in the circadian cycle can be produced (116,128,176). One study reported phase response to "doses" of activity: variable phase shifts resulted from periods of arousal or social activity at different times during the 24-hour period (115).

Although these studies suggest that activity modulates circadian rhythms in animals, further experimentation is necessary to characterize this effect. Since the state of being active or aroused is so general, there is some question as to what specific features of this state affect circadian rhythms. Finally, the impact of activity and arousal on circadian rhythms has yet to be carefully evaluated in humans.

SUMMARY AND CONCLUSIONS

Research has indisputably demonstrated that living organisms, ranging from single cells to humans, are able to keep track of time and to direct changes in function accordingly. Such functional cycles that repeat approximately every 24 hours are called circadian rhythms. Circadian rhythms are generated by living organisms and are genetically determined. Environmental cues synchronize circadian rhythms in organisms, the most important cue being light-dark cycles. In mammals, including humans, a region of the brain called the suprachiasmatic nucleus serves as the circadian pacemaker.

Most organs in the human body display circadian rhythms. Especially significant for shift work are sleep-wakefulness and performance rhythms. Daily cycles of sleep and wakefulness are a conspicuous circadian rhythm in humans. Studies have shown that the circadian pacemaker significantly influences the timing and quality of sleep. Therefore, periods of sleep are not easily rescheduled, deferred, or resisted. Human performance, assessed by measures of reaction time, cognitive processes, and mood, also displays circadian rhythms, which vary according to the nature of the task or mood assayed. Factors such as fatigue and motivation also profoundly influence human performance. When individuals are synchronized to the natural day-night cycle, many performance rhythms diminish to minimal levels at night. This nighttime attenuation of performance reflects the combined effects of circadian rhythms and the lack of sleep.

Research during the last few decades has demonstrated that humans have an internal clock and suggests that violation of its temporal order may exact a price in health and performance. When internally generated circadian rhythms conflict with environmental cycles, which happens following transmeridian flight and in some schedules of shift work, performance may be impaired, sleep disordered, and a general malaise experienced. Data indicate that the generation of circadian rhythms is altered with aging and in certain sleep disorders. Circadian rhythms may also be altered in certain mental disorders.

Several agents, including light, melatonin, benzodiazepines, other chemical substances, diet, and activity, are under investigation for their ability to adjust or shift circadian rhythms. Data indicate that bright light, the most extensively studied agent, can shift human circadian rhythms. How it does so, however, is not completely understood. Further research is necessary to substantiate the circadian effects of the other agents in humans.

CHAPTER 3 REFERENCES

1. American Psychiatric Association, ***Diagnostic and Statistical Manual of Mental Disorders (III-R)*** (Washington, DC: 1987).
2. American Sleep Disorders Association, The ***International Classification of Sleep Disorders. Diagnostic and Coding Manual*** (Lawrence, KS: Allen Press, **1990).**
3. Arendt, J., "Melatonin and the Pineal Gland," ***Biological Rhythms in Clinical Practice,*** J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).
4. Arendt, J., Aldhous, M., English, J., et al., "Some Effects of Jet-lag and Their Alleviation by Melatonin," ***Ergonomics 30:1379-1393, 1987.***
5. Arendt, J., Aldhous, M., and Wright, J., "Synchronization of a Disturbed Sleep-Wake Cycle in a Blind Man by Melatonin Treatment," ***Lancet*** 1:772-773, 1988.
6. Arendt, J., and Broadway, J., 'Light and Melatonin as Zeitgebers in Man," ***Chronobiology International 4:273-282, 1987.***
7. Armstrong, S. M., "Melatonin: The Internal Zeitgeber in Mammals?" ***Pineal Research 7:157-202, 1989.***
8. Armstrong, S.M., Cassone, V.M., Chesworth, M.J., et al., "Synchronization of Mammalian Circadian Rhythms by Melatonin," ***Journal of Neural Transmission 21(supp.):375-394, 1986.***
9. Aschoff, J., "Exogenous and Endogenous Components in Circadian Rhythms," ***Cold Spring Harbor Symposium on Quantitative Biology 25:11-26, 1960.***
10. Aschoff, J., "Circadian Rhythms in Man: A Self-Sustained Oscillator With an Inherent Frequency Underlies Human 24-Hour Periodicity," ***Science 148:1427-1432, 1965.***
11. Aschoff, J., "Circadian Activity Rhythms in Hamsters and Rats Treated With Imipramine in the Drinking Water," ***Chronobiologia 16:9-20, 1989.***
12. Aschoff, J. (cd.), ***Handbook of Behavioral Neurobiology,*** vol. **4,** ***Biological Rhythms (New*** York NY: Plenum Press, 1981).
13. Aschoff, J., Figala, J., and Poppel, E., "Circadian Rhythms of Locomotor Activity in the Golden Hamster ***(Mesocricetus auratus)*** Measured With Two Different Techniques," ***Journal of Comparative Physiology and Psychology 85:20-28, 1973.***

14. Aschoff, J., Giedke, H., Poppel, E., et al., "The Influence of Sleep-Interruption and of Sleep Deprivation on Circadian Rhythms in Human Performance,' ***Aspects of Human Efficiency: Diurnal Rhythm and Loss of Sleep,*** W.P. Colquhoun (cd.) (London: English University Press, 1972).
15. Bargiello, T.A., Jackson, F.R., and Young, M.W., "Restoration of Circadian Behavioral Rhythms by Gene Transfer in Drosophila," *Nature 312:752-754, 1984.*
16. Barnes, P.J., "Circadian Rhythms in the Respiratory System," ***Biological Rhythms in Clinical Practice,*** J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).
17. Blehar, M. C., and Lewy, A.J., "Seasonal Mood Disorders: Consensus and Controversy," ***Psychopharmacology Bulletin 26:465-494, 1990.***
18. Carskadon, M.A., "Daytime Sleepiness: Clinical Consequences and Treatment," ***The NIH Consensus Development Conference on the Treatment of Sleep Disorders of Older People*** (Bethesda, MD: National Institutes of Health, 1990).
19. Carskadon, M.A., and Dement, W. C., "Daytime Sleepiness: Quantification of a Behavioral State," ***Neuroscience & Biobehavioral Reviews 11:307-317, 1987.***
20. Carskadon, M. A., Van den Hoed, J., and Dement, **W.c.,** "Insomnia and Sleep Disturbances in the Aged: Sleep and Daytime Sleepiness in the Elderly," ***Journal of Geriatric Psychiatry 13:135-151, 1980.***
21. Cassone, V. M., Chesworth, M.J., and Armstrong, S.M., "Dose Dependent Entrainment of Rat Circadian Rhythms by Daily Injection of Melatonin," ***Journal of Biological Rhythms 1:219-229, 1986.***
22. Cassone, V.M., Chesworth, M.J., and Armstrong, S.M., "Entrainment of Rat Circadian Rhythms by Daily Injection of Melatonin Depends on the Hypothalamic Suprachiasmatic Nuclei," ***Physiology and Behavior 36:1111-1121, 1986.***
23. Cassone, V.M., Roberts, M.H., and Moore, R.Y., "Effects of Melatonin on 2-deoxyglucose Uptake Within the Rat Suprachiasmatic Nucleus,' ***American Journal of Physiology 255:332-337, 1988.***
24. Chee, C.A., Roozendaal, B., Swaab, D.F., et al., ' 'Vasoactive Intestinal Polypeptide Neuron Changes in the Senile Rat Suprachiasmatic Nucleus," ***Neurobiology of Aging 9;307-312, 1988.***
25. ***Citri, Y.,*** Colot, H.V., Jacquier, A. C., et al., "A Family of Unusually Spliced and Biologically Active Transcripts Encoded by a Drosophila Clock Gene," ***Nature 326:42-47, 1987.***
26. Colquhoun, P., "Rhythms in Performance,' ***Handbook of Behavioral Neurobiology, VOL 4, Biological Rhythms,*** J. Aschoff (cd.) (New York, NY: Plenum Press, 1981).
27. Craig, A., and Condon, R., "Speed-Accuracy Trade-Off and Time of Day,' ***Acta Psychological 58:115-122, 1985.***
28. Czeisler, C.A., Allan, J. S., Strogatz, S.H., et al., "Bright Light Resets the Human Circadian Pacemaker Independent of the Timing of the Sleep-Wake Cycle, "Science ***233;667-671, 1986.***
29. Czeisler, C.A., Dumont, M., Richardson, G. S., et al., "Disorders of Circadian Function: Clinical Consequences and Treatment," ***The NIH Consensus Development Conference on the Treatment of Sleep Disorders of Older People*** (Bethesda, MD: National Institutes of Health, 1990).
30. Czeisler, C.A., Johnson, M.P., Duffy, J.F., et al., "Exposure to Bright Light and Darkness To Treat Physiologic Maladaptation to Night Work" New ***England Journal of Medicine 322:1253-1259, 1990.***
31. Czeisler, C.A., Kronauer, R.E., Allan, J. S., et al., "Bright Light Induction of Strong (Type O) Resetting of the Human Circadian Pacemaker," ***Science 244:1328-1332, 1989.***
32. Czeisler, C.A., Kronauer, R.E., Mooney, J.J., et al., "Biologic Rhythm Disorders, Depression, and Phototherapy: A New Hypothesis,' ***Psychiatric Clinics of North America 10:687-709, 1987.***
33. Czeisler, C.A., Richardson, G. S., Zimmerman, J.C., et al., "Entrainment of Human Circadian Rhythms by Light-Dark Cycles: A Reassessment," ***Photochemistry and Photobiology 34:239-247, 1981.***
34. Czeisler, C.A., Weitzman, E.D., Moore-Ede, M. C., et al., 'Human Sleep: Its Duration and Organization Depend on Its Circadian Phase,' *Science 210:1264-*1267, 1980.
35. Czeisler, C.A., Zimmerman, J. C., Ronda, J.M., et al., "Timing of REM Sleep Is Coupled to the Circadian Rhythm of Body Temperature in Man," ***Sleep 2:329-346, 1980.***
36. Daan, S., and Lewy, A.J., "Scheduled Exposure to Daylight: A Potential Strategy To Reduce Jet Lag Following Transmeridian Flight," ***Psychopharmacology Bulletin 20:566-568, 1984.***
37. Davis, F. C., and Gorski, R.A., "Unilateral Lesions of the Hamster Suprachiasmatic Nuclei: Evidence for Redundant Control of Circadian Rhythms," ***Journal of Comparative Physiology, A 154:221-232, 1984.***
38. Dawson, D., Morris, M., and Lack, J., "Average Phase Response Curves in Humans for a 4 Hour Exposure to Evening Light," ***Sleep Research 18:413, 1989.***
39. Dawson, D., Morris, M., and Lack, J., "The Phase-Shifting Effects of a Single 4 Hour Exposure to Bright Morning Light in Normals and DSPS Subjects," ***Sleep Research 18:415, 1989.***

297-935 - 91 - 3 QL 3

40. DeCoursey, P.J., "Daily Light Sensitivity Rhythm in a Rodent," ***Science 131:33-35, 1960.***
41. ***DeCoursey,*** P. J., and Buggy, J., "Restoration of Locomotor Rhythmicity in SCN-lesioned Golden Hamsters by Transplantation of Fetal SCN," ***Neuroscience Abstracts 12:210, 1989.***
42. Demerit, W., and Kleitman, N., "Cyclic Variations in EEG During Sleep and Their Relation to Eye Movements, Body Motility and Dreaming," ***Electroencephalography and Clinical Neurophysiology 9:673-690, 1957.***
43. Dijk, D.J., Beersma, D. G. M., Daan, S., et al., "Bright Morning Light Advances the Human Circadian System Without Affecting NREM Sleep Homeostasis," ***American Journal of Physiology 256:R106-R111, 1989.***
44. Dijk, D.J., Visscher, C.A., Bloem, G. M., et al., ''Reduction of Human Sleep Duration After Bright Light Exposure in the Morning," ***Neuroscience Letters 73:181-186, 1987.***
45. Dinges, D.F., "The Nature of Sleepiness: Causes, Contexts and Consequences," ***Perspectives in Behavioral Medicine: Eating, Sleeping, and Sex,*** A.J. Stunkard and A. Baum (eds.) (Hillsdale, NJ: Lawrence Erlbaum, 1989).
46. Dinges, D.F., "Probing the Limits of Functional Capability: The Effects of Sleep Loss on Short-Duration Tasks," ***Sleep, Arousal and Performance: Problems and Promises,*** R.J. Broughton and R. Ogilivie (MIs.), in press.
47. Drennan, M., Kripke, D.F., and Gillin, J. C., "Bright Light Can Delay Human Temperature Rhythm Independent of Sleep," ***American Journal of Physiology 257:R136-R141, 1989.***
48. Drucker-Colin, R., Aguilar-Roblero, R., Garcia-Hernandez, F., et al., "Fetal Suprachiasmatic Nucleus Transplants: Diurnal Rhythms Recovery of Lesioned Rats," ***Brain Research 311;353-357, 1984.***
49. Duncan, W. C., and Wehr, T.A., "Pharmacological and Non-Pharmacological chronotherapies of Depression," ***Annual Review of Chronopharmacology,*** A. Reinberg, M. Smolensky, and G. Labrecque (eds.) (New York NY: Pergamon Press, 1988).
50. Dunlap, J. C., and Feldman, J.F., "On the Role of Protein Synthesis in the Circadian Clock of Neurospora crassa," ***Proceedings of the National Academy of Sciences, USA 85:1096-1100, 1988.***
51. Ehret, C.F., and Scanlon, L. W., ***Overcoming Jet Lug (New*** York NY: Berkley, 1983).
52. Feldman, J.F., and Dunlap, J. C., "Neurospora crassa: A Unique System for Studying Circadian Rhythms," ***Photochemistry and Photobiology Review 7:319-368, 1983.***
53. Folkard, S., and Monk, T.H., "Circadian Rhythms in Human Memory, ' ***British Journal of Psychology*** 71:295-307, 1980.
54. Folkard, S., Wever, R.A., and Wildgrubert, C.M., "Multi-Oscillatory Control of Circadian Rhythms in Human Performance, ' ***Nature 305:223-225, 1983.***
55. Folkard, S., Arendt, J., Aldhous, M., et al., "Melatonin Stabilizes Sleep Onset Time in a Blind Man Without Entrainment of Cortisol or Temperature Rhythms, ***Neuroscience Letters 113:193-198, 1990.***
56. Gillberg, M., "The Effects of Two Alternative Timings of a One-Hour Nap on Early Morning Performance,' ***Biological Psychology 19:45-54, 1984.***
57. Glattre, E., and Bjerkedal, T., "The 24-Hour Rhythmicity of Birth," ***Acta Obstetrics and Gynecology Scandinavia 62:31-36, 1983.***
58. Goodwin, F. K., and Jamison, K. R., ***Manic-Depressive Illness (New*** York, NY: Oxford University Press, 1990).
59. Green, D. J., and Gillett, R., "Circadian Rhythm of Firing Rate Recorded From Single Cells in the Rat Suprachiasmatic Brain Slice," ***Brain Research 245:198-200, 1982.***
60. Groos, G.A., and Hendriks, J., "Circadian Rhythm in Electrical Discharge of Rat Suprachiasmatic Neurones Recorded in Vitro," ***Neuroscience Letters 34:283-388, 1982.***
61. Halberg, F., "Physiologic 24-hour Periodicity in Human Beings and Mice, the Lighting Regimen and Daily Routine,' ***Photoperiodism and Related Phenomena in Plants and Animals,*** R.B. Withrow (cd.) (Washington, DC: American Association for the Advancement of Science, 1959).
62. Halberg, F., "Implications of Biological Rhythms for Clinical Practice," ***Hospital Practice 12:139-149, 1977.***
63. Hall, J. C., and Rosbash, M., "Mutations and Molecules Influencing Biological Rhythms," ***Annual Review of Neuroscience 11;373-393, 1988.***
64. Hamblen, M., Zehring, W.A., Kyriacou, C.P., et al., ''Germ-Line Transformation Involving DNA From the Period Locus in Drosophila Melanogaster: Overlapping Genomic Fragments That Restore Circadian and Ultradian Rhythmicity to Pep and Per⁻ Mutants," ***Journal of Neurogenetics 3:249-291, 1986.***
65. Hastings, J. W., and Sweeney, B.M., "A Persistent Diurnal Rhythm of Luminescence in Gonyaulax polyedra," ***Biological Bulletin 115:440-458, 1958.***
66. Hofman, M.A,, Fliers, E., Goudsmit, E.L., et al., "Morphometric Analysis of the Suprachiasmatic and Paraventricular Nuclei in the Human Brain: Sex Differences and Age-Dependent Changes," ***Journal of Anatomy 160:127-143, 1988.***

67. Honma, K., and Honma, S., "A Human Phase Response Curve for Bright Light Pulses," *Japanese Journal of Psychiatric Neurology 42:167-168, 1988.*
68. Home, J.A., and Pettitt, A.N., "High Incentive Effects on Vigilance Performance During 72 Hours of Total Sleep Deprivation," ***Acta Psychologica 58:123-139, 1985.***
69. Hughes, D.G., and Folkard, S., "Adaptation to an 8-Hour Shift in Living Routine by Members of a Socially Isolated Community," ***Nature 264:432-434, 1976.***
70. Inouye, S.T, and Kawamura, H., "Persistence of Circadian Rhythmicity in a Mammalian Hypothalamic 'Island' Containing the Suprachiasmatic Nucleus," ***Proceedings of the National Academy of Sciences, USA 76:5962-5966, 1979.***
71. Jackson, F.R., 'The Isolation of Biological Rhythm Mutations on the Autosomes of Drosophila melanogaster," ***Journal of Neurogenetics 1:3-15, 1983.***
72. Jewett, M.E., Kronauer, R.E., and Czeisler, C.A., "Light-Induced Suppression of Endogenous Circadian Amplitude in Humans," ***Nature 350:59-62, 1991.***
73. Kaiser, H., and Halberg, F., "Circadian Periodic Aspects of Birth," ***Annals of the New York Academy of Sciences 98:1056-1068, 1962.***
74. Klein, D. C., ''Photoneural Regulation of the Mammalian Pineal Gland," CIBA Foundation Symposium 17, ***Photoperiodism, Melatonin and the Pineal,*** D. Evered and S. Clark (eds.) (London: Pitman, 1985).
75. Kleitman, N., ***Sleep and Wakefulness*** (Chicago, IL: University of Chicago Press, 1963).
76. Konopka, R. J., "Genetics of Biological Rhythms in Drosophila," ***Annual Review of Genetics 21:227-236, 1987.***
77. Konopka, R.J., and Benzer, S., "Clock Mutants of Drosophila melanogaster," ***Proceedings of the National Academy of Sciences, USA 68:2112-2116, 1971.***
78. Koopman, M. G., Minors, D. S., and Waterhouse, J.M., "Urinary and Renal Circadian Rhythms," ***Biological Rhythms in Clinical Practice,*** J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).
79. Kornhauser, J. M., Nelson, D.E., Mayo, K.E., et al., "Photic and Circadian Regulation of c-fos Gene Expression in the Hamster Suprachiasmatic Nucleus," ***Neuron 5:127-134, 1990.***
800 Kupfer, D.J., Frank E., Jarrett, D. B., et al., "Interrelationship of Electroencephalographic Sleep Chronobiology and Depression," ***Biological Rhythms and Mental Disorders,*** D.J. Kupfer, T.H. Monk, and J.D. Barchas (eds.) (New York, NY: Guilford Press, 1988).
81. Lavie, P., "Ultrashort Sleep-Waking Schedule, III. 'Gates' and 'Forbidden Zones' for Sleep," *Electroencephalography and Clinical Neurophysiology 63:414-425, 1986.*
82. Leathwood, P., "Circadian Rhythms of Plasma Amino Acids, Brain Neurotransmitters and Behavior," ***Biological Rhythms in Clinical Practice,*** J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).
83. Lehman, M.N., Silver, R., Gladstone, W.R., et al., ''Circadian Rhythmicity Restored by Neural Transplant: Immunocytochemical Characterization With the Host Brain," ***Journal of Neuroscience 7: 1626-1638, 1987.***
84. Lemmer, B., "Circadian Rhythms in the Cardiovascular System," ***Circadian Rhythms in Clinical Practice,*** J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).
85. Levi, F., Reinberg, A., and Canon, C., "Clinical Immunology and Allergy," *Biological Rhythms in Clinical Practice,* J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).
86. Lewy, A., and Sack, R., ''Phase Typing and Bright Light Therapy of Chronobiologic Sleep and Mood Disorders,' ***Chronobiology and Psychiatric Disorders,*** A. Halaris (cd.) (New York NY: Elsevier, 1987).
87. Lewy, A., Sack, R.L., and Latham, J., "Circadian Phase Shifting of Blind and Sighted People With Exogenous Melatonin Administration: Evidence for a Phase Response Curve," paper presented at the Second Annual Conference of the Society for Light Treatment and Biological Rhythms, New York NY, May 1990.
88. Lewy, A., Sack, R.L., and Latham, J., "Melatonin and the Acute Suppressant Effect of Light May Help Regulate Circadian Rhythms in Humans," ***Advances in Pineal Research 5:285-293, in*** press.
89. Lewy, A., Sack R.L., Miller, S., et al., "Antidepressant and Circadian Phase-Shifting Effects of Light,' ***Science 235:352-354, 1987.***
90. ***Lewy,*** A., Sack R.L., and Singer, C.M., "Assessment and Treatment of Chronobiologic Disorders Using Plasma Melatonin Levels and Bright Light Exposure: The Clock-Gate Model and the Phase Response Curve," ***Psychopharmacology Bulletin 20: 561-565, 1984.***
91. ***Lewy,*** A., Sack, R. L., and Singer, C.M., "Immediate and Delayed Effects of Bright Light on Human Melatonin production: Shifting "Dawn" and "Dusk" Shifts the Dim Light Melatonin Onset (DLMO)," ***Annals of the New York Academy of Sciences 453:253-259, 1985.***
92. ***Lewy,*** A., Wehr, T. A., Goodwin, F.K., et al., "Light Suppresses Melatonin Secretion in Humans," *Science* 210:1267-1269, 1980.

93. Lieberman, H.R., Wurtman, J.J., and Teicher, M.H., "Circadian Rhythms of Activity in Healthy Young and Elderly Humans," ***Neurobiology of Aging 10:259-265, 1989.***

94. Lynch, H.J., Jimerson, D. C., Ozaki, Y., et al., "Entrainment of Rhythmic Melatonin Secretion From the Human Pineal to a 12-Hour Phase Shift in the Light-Dark Cycle, "Life ***Science 23:1557-1564, 1978.***

95. Lynch, H.J., Wurtman, R. J., Moskowitz, M.A., et al., "Daily Rhythm in Human Urinary Melatonin," ***Science 187:169-171, 1975.***

96. McFadden, E. R., "Asthma: A Nocturnal Disease," ***American Journal of Medicine 85:1-70, 1988.***

97. Mant, A., and Eyland, E.A., "Sleep Patterns and Problems in Elderly General Practice Attenders: An Australian Survey," ***Community Health Studies 12:192-199, 1988.***

98. Meijer, J.H., and Rietveld, W.J., "Neurophysiology of the Suprachiasmatic Circadian Pacemaker in Rodents," ***Physiological Review 69:671-707, 1989.***

99. Menaker, M., "Aspects of the Physiology of Circadian Rhythmicity in the Vertebrate Nervous System," ***The Neuroscience: Third Study Program,*** F.O. Schmitt and F.G. Worden (eds.) (Cambridge, MA: MIT Press, 1974).

100. Miles, L.E.M., and Wilson, M.A., "High Incidence of Cyclic Sleep/Wake Disorders in the Blind," ***Sleep Research 6:192, 1977.***

101. Minors, D. S., Rabbitt, P. M. A., Worthington, H., et al., "Variation in Meals and Sleep-Activity Patterns in Aged Subjects; Its Relevance to Circadian Rhythm Studies," ***Chronobiologia International 6:139-146, 1989.***

102. Minors, D. S., and Waterhouse, J.M., "Chronobiochemistry: An Overview of Circadian Rhythms and Some Applications to Clinical Medicine and Biochemistry,''Annals ***of Clinical Biochemistry 24(supp.): 16-27, 1987.***

103. Minors, D. S., and Waterhouse, J.M., "The Influence of Light on the Entrainment of the Circadian System: An Introduction," ***Studies in Industrial and Organizational Psychology, Shift Work: Health, Sleep and Performance,*** vol. 9, G. Costa, G. Cesana, K. Kogi, et al. (eds.) (Frankfurt am Main: Verlag Peter Lang, 1989).

104. Mitler, M.M., Carskadon, M.A., Czeisler, C.A., et al., "Catastrophes, Sleep and Public Policy: Consensus Report," ***Sleep*** 11:100-109, 1988.

105. Monk, T.H., "Shift Work and the Older Worker," ***The NIH Consensus Development Conference on the Treatment of Sleep Disorders of Older People*** (Bethesda, MD: National Institutes of Health, 1990).

106. Monk, T.H.., Fookson, J.E,, Moline, M.L., et al., "Diurnal Variation in Mood and Performance in a Time-Isolated Environment," ***Chronobiology International 2:185-193, 1985.***

107. Monk, T.H., and Leng, V. C., "Interactions Between Inter-Individual and Inter-Task Differences in the Diurnal Variations of Human Performance,' ***Chronobiology International 3:171-177, 1986.***

108. Monk, T.H., Leng, V. C., Folkard, S., et al., "Circadian Rhythms in Subjective Alertness and Core Body Temperature," ***Chronobiologia 10:49-55, 1983.***

109. Monk, T.H., Moline, M.L., Fookson, J.E., et al., ''Circadian Determinants of Subjective Alertness," ***Journal of Biological Rhythms 4:393-404, 1989.***

110. Monk, T.H., Weitzman, E.D., and Fookson, J.E., "Circadian Rhythms in Human Performance Efficiency Under Free-Running Conditions," ***Chronobiologia 11:343, 1984.***

111. Monk, T.H., Weitzman, E.D., Fookson, J.E., et al., ''TaskVariables Determine Which Biological Clock Controls Circadian Rhythms in Human Performance," ***Nature 304:543-545, 1983.***

112. Moore, J.G., "Circadian Rhythmicity in Gastric Emptying, Acid Secretion and Mucosal Damage by Drugs: Implications for Drug Therapy," ***Chronopharmacology: Cellular and Biochemical Interactions,*** B. Lemmer (cd.) (New York, NY: Marcel Dekker, 1989).

113. Moore-Ede, M.C., "Physiology of the Circadian Timing System: Predictive vs. Reactive Homeostasis," ***American Journal of Physiology, 250:R737-R752, 1986.***

114. MOM, L.P., "Age-Related Changes in Hamster Circadian Period, Entrainment and Rhythm Splitting," ***Journal of Biological Rhythms 3:237-248, 1988.***

115. ***Mrosovsky, N., ''Phase*** Response Curves for Social Entrainment," ***Journal of Comparative Physiology 162:35-46, 1988.***

116. ***Mrosovsky, N.,*** and Salmon, R.A., "A Behavioral Method for Accelerating Reentrainment of Rhythms to New Light-Dark Cycles," ***Nature 330:372-373, 1987.***

117. Muller, J.E., Stone, P.H., Turin, Z.G., et al., "The Milis Study Group: Circadian Variation in the Frequency of Onset of Acute Myocardial Infarction," ***New England Journal of Medicine 313:1315-1322, 1985.***

118. Nejean, L., et al., "Circadian and Ultradian Rhythms in Serum Glucose and Insulin," ***Chronobiology International 5:227-236, 1988.***

119. ***Ozaki, N.,*** Iwata, T., Itoh, A., et al., "Body Temperature Monitoring in Subjects With Delayed Sleep Phase Syndrome, ''Neuropsychobiology 2O: 174-177, 1988.

120. Pepine, C. J., "Circadian Variations in Myocardial Ischemia," ***Journal of the American Medical Asso-***

ciation 265:386-390, 1991.

121. Petrie, K., Conaglen, J.V., Thompson, L., et al., "Effect of Melatonin on Jet Lag After Long Haul Flights," ***British Medical Journal 298:705-707, 1989.***
122. Pickard, G.E., "The Afferent Connections of the Suprachiasmatic Nucleus of the Golden Hamster With Emphasis on the Retinohypothalamic Projection," ***Journal of Comparative Neurology 211:65-83, 1982.***
123. Pickard, G.E., and Turek, F.W., "The Suprachiasmatic Nuclei: Two Circadian Clocks?" ***Brain Research 268:201-210, 1985.***
124. Pittendrigh, C. S., "Circadian Rhythms and the Circadian Organization of Living Systems," ***Cold Spring Harbor Symposium on Quantitative Biology 25:159-182, 1960.***
125. Pittendrigh, C. S., and Bruce, V. G., "An Oscillator Model for Biological Clocks,' ***Rhythmic and Synthetic Processes in Growth,*** D. Rudnick (cd.) (Princeton, NJ: Princeton University Press, 1957).
126. Pittendrigh, C. S., and Daan, S., "Circadian Oscillations in Rodents: A Systematic Increase of Their Frequency With Age," ***Science 186:548-550, 1974.***
127. Potkin, S., Zetin, M., Stamenkovic, V., et al., "Seasonal Affective Disorder: Prevalence Varies With Latitude and Climate," ***Clinical Neuropharmacology*** 9(supp. 4):181-183, 1986.
128. Pratt, B.L., and Goldman, B.D., "Environmental Influences on Circadian Periodicity of Syrian Hamsters," ***Physiology and Behavior 36:91-95, 1986.***
129. Ralph, M.R., Foster, R. G., Davis, F. C., et al., "Transplanted Suprachiasmatic Nucleus Determines Circadian Period," ***Science 247:975-978, 1990.***
130. Ralph, M.R., and Menaker, M., ''Effects of Diazepam on Circadian Phase Advances and Delay s," ***Brain Research 372:405-408, 1986.***
131. Ralph, M.R., and Menaker, M., "A Mutation of the Circadian System in Golden Hamsters," ***Science 241:1225-1227, 1988.***
132. Rea, M.A., "Light Increases Fos-Related Protein Immunoreactivity in the Rat Suprachiasmatic Nuclei," ***Brain Research Bulletin 23: 577-581, 1989.***
133. Redman, J., Armstrong, S., and Ng, K.T., "Free-Running Activity Rhythms in the Rat: Entrainment by Melatonin," ***Science 219:1089-1091, 1983.***
134. Reinberg, A., Andlauer, P., Guillet, P., et al., "Oral Temperature, Circadian Rhythm Amplitude, Aging and Tolerance to Shift Work," ***Ergonomics 23:55-64, 1980.***
135. Reme, C.E., Wirz-Justice, A., and Terman, M., "The Visual Input Stage of the Mammalian Circadian Pacemaking System. I. Is There a Clock in the Mammalian Eye?" ***Journal of Biological Rhythms, in*** press.
136. Reppert, S.M., and Uhl, G.R., "Vasopressin Messenger Ribonucleic Acid in Supraoptic and Suprachiasmatic Nuclei: Appearance and Circadian Regulation During Development,''Endom"nolo# 1202483-2487, 1987.
137. Reppert, S.M., Weaver, D.R., Rivkees, S.A.,et al., "Putative Melatonin Receptors in a Human Biological Clock" ***Science 242:78-81, 1988.***
138. Richardson, G. S., Carskadon, M.A., Orav, E.J., et al., "Circadian Variation of Sleep Tendency in Elderly and Young Adult Subjects," *Sleep* 5:s82-s92, 1982.
139. Richardson, G.S., and Martin, J.B., "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," ***Progress in NeuroEndocrinImmunology 1:16-20, 1988.***
140. Rocco, M.B., Barry, J., Campbell, S., et al., "Circadian Rhythms and Coronary Artery Disease," ***American Journal of Cardiology 59(supp. 1):13C-17C, 1987.***
141. Roozendaal, B., Van Gool, W.A., Swaab, D.F., et al., "Changes in Vasopressin Cells of the Rat Suprachiasmatic Nucleus With Aging," *Brain Research 409:259-264, 1987.*
142. Rosbash, M., and Hall, J. C., "The Molecular Biology of Circadian Rhythms," ***Neuron 3:387-398, 1989.***
143. Rosen, L.N., Targum, S.D., Terman, M., et al., ''Prevalence of Seasonal Affective Disorder at Four Latitudes," ***PsychiatryResearch 31:131-144, 1990.***
144. Rosenthal, N.E., Sack, D.A., Gillin, J. C., et al., ''Seasonal Affective Disorder: A Description of the Syndrome and Preliminary Findings With Light Therapy," ***Archives of General Psychiatry 41:72-80, 1984.***
145. Rosenthal, N.E., Sack, D.A., Skwerer, R.G., et al., "Phototherapy for Seasonal Affective Disorder," ***Seasonal Affective Disorders and Phototherapy,*** N.E. Rosenthal and N.C. Blehar (eds.) (New York NY: Guilford Press, 1989).
146. Rosenthal, N.E., and Wehr, T.A., "Seasonal Affective Disorders," ***Psychiatric Annals 17:670-674, 1987.***
147. Rusak B., "The Mammalian System: Models and Physiology,' ***Biological Clocks and Environmental Time, S.*** Daan and E. Gwinner (eds.) (New York NY: Guilford Press, 1989).
148. Rusak B., and Bina, K. G., "Neurotransmitters in the Mammalian Circadian System,' *Annual Review of Neuroscience 13:387-401, 1990.*
149. **Rusak**, B., and Boulos, Z., "Pathways for Photic Entrainment of Mammalian Circadian Rhythms," ***Photochemistry and Photobiology 34:267-273, 1981.***
150. Rusak B., Robertson, H. A., Eisden, W., et al., "Light Pulses That Shift Rhythms Induce Gene

Expression in the Suprachiasmatic Nucleus," ***Science*** 248:1237-1240, 1990.

151. Sack, R.L., and Lewy, A.J., "Melatonin Administration Phase Advances Endogenous Rhythms in Man," ***Sleep Research 17:396, 1988.***
152. Sack, R.L., Lewy, A.J., and Hoban, TM., "Free Running Melatonin Rhythm in Blind People: Phase Shifts With Melatonin and Triazolam Administration,' ***Temporal Disorder in Human Oscillatory Systems,*** L. Rensing, U. an der Heiden, and M.C. Mackey (eds.) (New York, NY: Springer-Verlag, 1987).
153. Sack, R.L., Stevenson, J., and Lewy, A.J., "Entrainment of a Previously Free-Running Blind Human With Melatonin Administration," ***Sleep Research 19:404,*** 1990.
154. Sadun, A.A., Schaechter, J.D., and Smith, L.E.H., "A Retinohypothalamic Pathway in Man: Light Mediation of Circadian Rhythms," ***Brain Research 302:371-377, 1984.***
155. Sawaki, Y., Nihonmatsu, I., and Kawamura, H., ''Transplantation of the Neonatal Suprachiasmatic Nuclei Into Rats With Complete Bilateral Suprachiasmatic Lesions, ' ***Neuroscience Research 1:67-72, 1984.***
156. Scalabrino, G., Ferioli, M.E., Nebuloni, R., et al., "Effects of Pinealectomy on the Circadian Rhythms of the Activities of Polyamine Biosynthetic Decarboxylases and Tyrosine Aminotransferase in Different Organs of the Rat," ***Endocrinology*** 104:377-384, 1979.
157. Schneider-Helmert, D., and Spinweber, C.L,, "Evaluation of L-Tryptophan for Treatment of Insomnia: A Review," ***Psychopharmacology 89:1-7, 1986.***
158. Schwartz, W., and Gainer, H., "Suprachiasmatic Nucleus: Use of (14C)-labeled Deoxyglucose Uptake as a Functional Marker," Science 197:1089-1091, 1977.
159. Schweiger, H. G., Hartwig, R., and Schweiger, M., ''Cellular Aspects of Circadian Rhythms," ***Journal of Cell Science 4(supp.):181-200, 1986.***
160. Sharma, M., Palacios-Bois, J., Schwartz, G., et al., "Circadian Rhythms of Melatonin and Cortisol in Aging," ***Biological Psychiatry 25:305-319, 1989.***
161. Shibata, S., and Moore, R. Y., "Electrical and Metabolic Activity of Suprachiasmatic Nucleus Neurons in Hamster Hypothalamic Slices," ***Brain Research 438:374-378, 1988.***
162. Shinowara, N.L., London, E.D., and Rapoport, S.I., "Changes in Retinal Morphology and Glucose Utilization in Aging Albino Rats," ***Experimental Eye Research 34:517-530, 1982.***
163. Smolensky, M.H., Barnes, P.J., Reinberg, A., et al., "Chronobiology and Asthma, I. Day-Night Differences in Bronchial Patency and Dyspnea and Circadian Rhythm Dependencies,' ***'Journal of Asthma 23:320-342, 1986.***
164. Spinweber, C.L., "L-Tryptophan Administered to Chronic Sleep-Onset Insomniacs: Late-Appearing Reduction of Sleep Latency," ***Psychopharmacology*** **90:151-155, 1986.**
165. Strogatz, S.H., Kronauer, R.E., and Czeisler, C.A., "Circadian Regulation Dominates Homeostatic Control of Sleep Length and Prior Wake Length in Humans," ***Sleep*** **9:353-364, 1986.**
166. Swaab, D.F., Fisser, B., Kamphorst, W., et al., "The Human Suprachiasmatic Nucleus; Neuropeptide Changes in Senium and Alzheimer's Disease," ***Basic and Applied Histochemistry 32:33-54, 1988.***
167. Swaab, D.F., Fliers, E., and Partiman, T.S., "The Suprachiasmatic Nucleus of the Human Brain in Relation to Sex, Age and Senile Dementia,' ***Brain Research 342:37-44, 1985.***
168. Takahashi, J. S., Murakami, N., Nikaido, S. S., et al., "The Avian Pineal, a Vertebrate Model System of the Circadian Oscillator: Cellular Regulation of Circadian Rhythms by Light, Second Messengers, and Macromolecular Synthesis," ***Recent Progress in Hormone Research 45:279-352, 1989.***
169. Terman, J. S., Reme, C.E., and Wirz-Justice, A., "The Visual Input Stage of the Mammalian Circadian Pacemaker System. II. The Effect of Light and Drugs on Retinal Function, ' ***Journal of Biological Rhythms, in*** press.
170. Terman, J. S., Terman, M., Quitkin, F.M., et al., "Light Therapy for Seasonal Affective Disorder: A Review of Efficacy," ***Neuropsychopharmacology 2:1-22, 1989.***
171. Terman, M., Reme, C.E., Rafferty, B., et al., "Bright Light Therapy for Winter Depression: Potential Ocular Effects and Theoretical Implications," ***Photochemistry and Photobiology 51:781-792, 1990.***
172. Terman, M., Terman, J. S., and Rafferty, B., "Experimental Design and Measures of Success in the Treatment of Winter Depression by Bright Light," ***Psychopharmacology Bulletin 26:505-510, 1990.***
173. Thayer, R.E., "Towards a Psychological Theory of Multidimensional Activation (Arousal)" ***Motivation and Emotion 2:1-35, 1978.***
174. ***Thorpy,*** M.J., "Classification and Definition of Sleep Disorders," ***The NIH Consensus Development Conference on the Treatment of Sleep Disorders of Older People*** (Bethesda, MD: National Institutes of Health, 1990).
175. Turek, F. W., "Pharmacological Probes of the Mammalian Circadian Clock: Use of the Phase Response Curve Approach," ***Trends in Pharmacological Sciences 8:212-217, 1987.***
176. Turek, F. W., "Effects of Stimulated Physical Activity on the Circadian Pacemaker of Vertebrates,"

Biological Clocks and Environmental Time, S. Daan and E. Gwinner (eds.) (New York, NY: Guilford Press, 1989).

177. Turek, F. W., and Losee-Olson, S., "A Benzodiazepine Used in the Treatment of Insomnia Phase-Shifts the Mammalian Circadian Clock" ***Nature 321:167-168, 1986.***

178. Turek, F.W., McMillan, J.P., and Menaker, M., "Melatonin: Effects on the Circadian Locomotor Rhythm of Sparrows," ***Science 194:1441-1443, 1976.***

179. Turek, F.W., and Van Cauter, E., "Altering the Mammalian Circadian Clock With the Short-Acting Benzodiazepine, Triazolam,' ***Trends in Neurological Science 12:535-541, 1988.***

180. Uhl, G.R., and Reppert, S.M., "Suprachiasmatic Nucleus Vasopressin Messenger RNA: Circadian Variation in Normal and Brattleboro Rats,' ***Science 232:390-392, 1986.***

181. Van Cauter, E., "Endocrine Rhythms," ***Biological Rhythms in Clinical Practice,*** J. Arendt, D.S. Minors, and J.M. Waterhouse (eds.) (London: Wright, 1989).

182. Van Cauter, E., L'Hermite, M., Copinschi, G., et al., "Quantitative Analysis of Spontaneous Variations of Plasma Prolactin in Normal Men,' *American Journal of Physiology 241:E355-E363, 1981.*

183. Van Cauter, E., and Refettoff, S., "Multifactorial Control of the 24-Hour Secretory Profiles of Pituitary Hormones," ***Journal of Clinical Endocrinology and Metabolism 8:381-389, 1985.***

184. Van Cauter, E., Van Onderbergen, A., Boosson, D., et al., ''Triazolam Accelerates the Adaptation of the Circadian Rhythm of Cortisol to an 8-Hour Delay of the Sleep-Wake Cycle in Man," ***Society for Neuroscience Abstracts 13:1040,*** 1987.

185. Van Den Pol, A.N., and Powley, T., "A Fine-Grained Anatomical Analysis of the Role of the Rat Suprachiasmatic Nucleus in Circadian Rhythms of Feeding and Drinkřng," ***Brain Research 160:307-326, 1979.***

186. Van Gool, W.A., and Mirmiran, M., "Aging and Circadian Rhythms," ***Progress in Brain Research,*** vol. 70, W.A. Van Gool and F. Van Haaren (eds.) (Amsterdam: Elsevier, 1986).

187. Van Reeth, O., and Turek, F.W., "Adaptation of Circadian Rhythmicity to Shift in Light-Dark Cycle Accelerated by a Benzodiazepine,' ***American Journal of Physiology 253 R204-R207, 1987.***

188. Van Reeth, O., and Turek, F.W., "Stimulated Activity Mediates Phase Shifts in the Hamster Circadian Clock Induced by Dark Pulses or Benzodiazepines," ***Nature 339:49-51, 1989.***

189. von Arnim, T, Hofling, B., and Schreiber, M., ''Characteristics of Episodes of ST Elevation or ST Depression During Ambulatory Monitoring in Patients Subsequently Undergoing Coronary Angiography, " ***British Heart Journal 54:484-488, 1985.***

190. Waters, D.D., Miller, D.D., Bouchard, A., et al., "Circadian Variation in Variant Angina," *American Journal of Cardiology 54:61-64, 1984.*

191. Wee, B.E.F., and Turek, F.W., "Carbachol Phase Shifts the Circadian Rhythm of Locomotor Activity in the Djungarian Hamster," ***Brain Research 505:209-214, 1989.***

192. Weitzman, E.D., Czeisler, C. A., and Moore-Ede, M. C., "Sleep-Wake, Neuroendocrine and Body Temperature Circadian Rhythms Under Entrained and Non-entrained (Free-Running) Conditions in Man," ***Biological Rhythms and their Central Mechanism,*** M. Suda, O. Hayaishi, and ***H.*** Nakagawa (eds.) (Amsterdam: Elsevier, 1979).

193. Weitzman, E.D., Moline, M.L., Czeisler, C.A., et al., 'Chronobiology of Aging: Temperature, Sleep-Wake Rhythms and Entrainment," *Neurobiology 3:299-309, 1982.*

194. Wever, R.A., "Light Effects on Human Circadian Rhythms: A Review of Recent Andechs Experiments," ***Journal of Biological Rhythms 4:161-185, 1989.***

195. Wever, R.A., Polasek, J., and Wildgruber, C.M., ' 'Bright Light Affects Human Circadian Rhythms," ***Pflugers Archives 396;85-87, 1983.***

196. Wise, P.M., Cohen, I.R., Weiland, N.G., et al., "Aging Alters the Circadian Rhythm of Glucose Utilization in the Suprachiasmatic Nucleus," ***Proceedings of the National Academy of Sciences, USA 85:5305-5309, 1988.***

197. Wollnik, F., Turek, F.W., Majewski, P., et al., "Phase Shifting the Circadian Clock With Cycloheximide: Response of Hamsters With an Intact or a Split Rhythm of Locomotor Activity," ***Brain Research 496:82-88, 1989.***

198. Wu, J. U., and Bunney, W.E., "TheBiologicalB asis of an Antidepressant Response to Sleep Deprivation and Relapse: A Review and Hypothesis,' ***American Journal of Psychiatry 147:14-21, 1990.***

199. Wurtman, J.J., ***Managing Your Mind and Mood Through Food (New*** York NY: Rawson, 1986).

200. Wurtman, R.J., Axelrod, J., and Fischer, J.E., ''Melatonin Synthesis in the Pineal Gland: Effect of Light Mediated by the Sympathetic Nervous System," ***Science 143:1328-1330, 1964.***

201. Yamada, N., Shimoda, K., Ohi, K., et al., "Free-Access to a Running Wheel Shortens the Period of Free-Running Rhythms in Blinded Rats," ***Physiology and Behavior 42:87-91, 1988.***

202. Zehring, W.A., Wheeler, D.A., Reddy, P., et al., "P-element Transformation With Period Locus DNA Restores Rhythmicity to Mutant, Arrhythmic Drosophila melanogaster," Cell 39:369-376, 1984.

203. Zimmerman, N.H., and Menaker, M., "The Pineal Gland: The Pacemaker Within the Circadian Systern of the House Sparrow," ***Proceedings of the National Academy of Sciences, USA 76:999-1003, 1979.***

204. Zulley, J., Wever, R., and Aschoff, J., "The Dependence of Onset and Duration of Sleep on the Circadian Rhythm of Rectal Temperature, " ***Pflugers Archives 391:314-318, 1981.***