American Handbook of Psychiatry

BIOLOGICAL RHYTHMS AND PSYCHIATRY

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> Our body is like a clock; if one wheel be amiss, all the rest are disordered, the whole fabric suffers: with such admirable art and harmony is a man composed.
>
> Robert Burton, *The Anatomy of Melancholy* (1628)

Introduction

Rhythms in nature—the alternation of day and night, the tides and the seasons—govern our lives and structure our experience. The degree to which nature's cycles influence culture is obvious. Less obvious is the fact that they are also impressed upon our genes, for we generate within ourselves days, months, and seasons that mirror and anticipate the rhythmic changes around us. Our biological rhythms make each of us a microcosm of the geophysical world.

Unlike the motions of the planets, biological clocks are imprecise, and their synchronization with external rhythms depends upon their being continually reset. For this purpose we possess special sense organs that lock onto external time cues such as the rising and setting of the sun and that make corresponding adjustments. As we live out our lives, our biological self is always tuned to the rhythms of the world around us, and we are forced to

keep time with its march.

Our internal rhythms constitute a kind of temporal anatomy. Each day our body's temperature rises from a predawn nadir to its evening peak. At night the pineal gland secretes a hormone, melatonin. When we fall asleep, growth hormone briefly appears. The adrenals emerge from quiescence abruptly in the middle of sleep and are most active at dawn. And nearly every function of the organism exhibits a 24-hour, or circadian, pattern of variation with its own characteristic timing and waveform. The classical principle of homeostasis must be amended to encompass such physiological variation: cyclic change of the internal milieu is maintained.

Little is known of the functions of our temporal anatomy. We can speculate that biological rhythms help us to adapt to a cyclically changing environment, by modulating a range of specially and sometimes mutually incompatible functions and states that would be impossible in an unchanging organism. A normal temporal anatomy may also be essential to health. Experimental disturbances in circadian rhythms have been shown to adversely affect emotional well-being, mental acuity, longevity, reproductive function, thermoregulation, and restorativeness of sleep.

Interest in the human circadian system has come late to medical science. Perhaps this is because circadian rhythms exist in a temporal rather than a

spatial domain. In addition, there are psychological and technical reasons for the delay: Compared to the contractions of the heart, a rhythm that beats only once in 24 hours is not easily perceived subjectively and is not easily measured objectively. Recently, basic and clinical circadian rhythm research has been greatly stimulated by three developments: (1) the introduction of instruments and techniques for long-term monitoring of physiological and biochemical rhythms in freely moving human subjects; (2) publication of long-term studies of the behavior of circadian rhythms in normal human subjects living in isolation from environmental time cues; and (3) identification of the neuroanatomical site in the hypothalamus of a circadian pacemaker and its connections to the eye.

It is reasonable to suppose that the human circadian system, a central integrative mechanism that programs recurring sequences of physiological and behavioral events and that resides in known neural structures with proven connections to the environment, is subject to disease and disorder. The question of whether there are diseases specific to the human circadian system, however, remains unanswered. It seems likely that such diseases would affect multiple systems, be associated with disruption of function rather than tissue, be of obscure etiology, and have prominent behavioral manifestations, including disturbances of the sleep-wake cycle. In a very general way, this description fits some psychiatric illnesses, especially the affective illnesses—depression and manic-depressive states. In fact, two

classical symptoms of depression, early-morning awakening and diurnal variation in mood, implicate circadian rhythms in their pathophysiology and highlight a paradox: The depressive awakens early but arises late. Georgi, writing in 1947, was one of the first to make this connection:

> In the true endogenous depressive we see a shift in the 24-hour rhythm . . . the night becomes day . . . anyone knowing the material would look for the CNS origin in the midbrain, where the entire vegetative nervous system is controlled by a central clock whose rhythmicity . . . regulates and balances the biological system. (Authors' translation)

This chapter will review the evidence that links affective illness to disturbances in the circadian system. It will also describe a circadian theory of depression and mania and possible circadian mechanisms of drugs and procedures that are used in their treatment.

The Human Circadian System

Circadian rhythms are near-24-hour patterns of variation in biological functions. They are ubiquitous in human physiology. Some circadian rhythms, such as the sleep-wake cycle, are familiar to everyone. Others can only be detected with special techniques of measurement. Some of the most striking patterns occur in the various secretions of the endocrine system, but they can only be observed when plasma is sampled every 20 minutes for 24 hours and subsequently analyzed with sensitive radioimmunoassay procedures.

Circadian rhythms are endogenous and self-sustained; they are not simply passive responses to daily changes in the environment, but originate within the organism. In many cases they continue independently of both sleeping and waking. Their endogenous nature can be appreciated when human subjects are deprived of all external time cues, permitting their circadian rhythms to *free-run* in isolation experiments. In this situation the rhythms persist but with a periodicity that is slightly different (usually longer) than 24 hours. The fact that they persist, together with the fact that their period deviates slightly from 24 hours, is evidence that the rhythms are generated by the organism. (If their period continued to be 24 hours, the influence of a subtle environmental factor could not be ruled out.) Wever and Aschoff, German scientists who pioneered long-term temporal isolation experiments, studied hundreds of normal human subjects and found that the average free-running or *intrinsic period* of the human circadian system is about 25 hours.

Since we are able to adhere to a daily schedule that is shorter than the intrinsic 25-hour period of our circadian system, it is obvious that some mechanism continually resets our biological clocks ahead approximately one hour a day. Somehow, physiologically, the human organism "knows" the correct time each day and adjusts accordingly. This ongoing process of *entrainment* of circadian rhythms to the day-night cycle depends upon the capacity of the organism to automatically perceive and respond to stimuli in

the environment that have the properties of time cues, or *zeitgebers.* Light-dark transitions (dawn and dusk) are powerful *zeitgebers* for all species, including humans, and light-dark cycles alone can entrain human circadian rhythms. Other *zeitgebers* that may be important for humans include the timing of meals and various social stimuli, which are less well characterized.

The effect of a *zeitgeber* depends upon the phase of the circadian cycle during which it is presented. If, for example, a light stimulus occurs near the expected time of dawn (in an animal whose intrinsic period is longer than 24 hours), circadian rhythms will be shifted earlier, or *phase-advanced;* if the stimulus occurs long after the expected time of dawn, they will be shifted later, or *phase-delayed.* The magnitude and direction of such shifts are a function of how early or late the stimulus occurs. By presenting light stimuli at various phases of the circadian cycle it is possible to define a *phase-response curve* that describes this function. Typically, such curves show an apparent discontinuity, or *switchover point,* during the circadian phase that corresponds to the middle of the night. If, at this time, a maximally delaying stimulus is shifted a few minutes later, it becomes a maximally advancing stimulus; that is, light at 1 A.M. is perceived as a very late dawning of the previous day and causes a large compensatory phase-delay, whereas light at 2 A.M. is perceived as a very early dawning of the next day and causes a large compensatory phase-advance. The switchover point of the phase-response curve could be an important element in a circadian rhythm theory of affective

illness, since the depressive and manic switch processes tend to occur in the middle of the night and appear to be associated with phase-shifts of circadian rhythms.

The human circadian system can be entrained to artificial "days" shorter or longer than 24 hours. The limits of the *range of entrainment* are normally about 21 and 27 hours. The range of entrainment is partly a function of the intrinsic period of the circadian system. Subjects with relatively long free-running circadian periods entrain to long "days" more easily than to short "days"; the converse is true for subjects with relatively short free-running circadian periods. The range of entrainment normally includes the 24-hour period of the day-night cycle, although this might not be the case in diseases of the circadian system.

When a circadian rhythm is entrained to the day-night cycle, it adopts a characteristic timing, or *phase-position,* relative to it. In other words, the peak and trough of the rhythm recur at particular times each day. The phase-position of an entrained circadian rhythm varies slightly from one person to another and is partly a function of the intrinsic period that a person's rhythm would exhibit if it were free-running. A person who has a long intrinsic period (for example, 25.5 hours) and thus free-runs relatively slowly will adopt a relatively late phase-position when entrained to the day-night cycle. Someone whose intrinsic period is short (for example, 24.5 hours) and free-runs

relatively fast will adopt a relatively early phase-position when entrained to the day-night cycle. For example, the peaks of the rhythms of the two individuals might occur at 5 P.M. and 3 P.M. respectively. Knowledge of this relationship could be useful if circadian rhythm phase-disturbances prove to be important in disease. An abnormally early or late phase-position of a circadian rhythm could indicate that the intrinsic period of that rhythm is abnormally short or long. There is evidence that the phase-position of depressed patients' circadian rhythms is abnormally early relative to the day-night cycle. A possible interpretation is that their intrinsic circadian period is abnormally short.

In the normal situation where the circadian system is entrained to the 24-hour day-night cycle, its intrinsic period is only a latent characteristic—the period its oscillations would exhibit if it were free-running and isolated from external time cues. Obviously, the (latent) intrinsic period is an important characteristic of the circadian system, since it determines whether or not a circadian rhythm can be entrained to a given schedule (the range of entrainment) as well as the phase-position that rhythm will adopt relative to that schedule if entrainment is achieved. The intrinsic period of the circadian system is relatively stable, but it can be altered by certain agents or conditions. The intrinsic period is *history dependent;* for example, if an organism has been entrained to a 22-hour "day," its intrinsic period will gradually become shorter than would be the case if the organism had been

entrained to a 25-hour "day." Light intensity, drugs, and hormones can also alter the intrinsic period. In some species, estrogen and testosterone affect the intrinsic period, which varies with the estrous cycle. These effects of reproductive hormones may be relevant to a circadian rhythm theory of affective illness in light of the increased incidence of depression and mania after puberty, in the puerperium, in association with the menstrual cycle, and during menopause.

Many animals, including humans, exhibit seasonal or annual cycles in behavior and physiology. These cycles regulate levels of sexual, metabolic, and motoric activity related to reproduction, growth, hibernation, and migration. Seasonal rhythms are relevant to the present discussion because they have a circadian basis. Animals use a circadian clock to measure the interval between dawn and dusk (the *photoperiod*). Since the photoperiod varies in length during the year, being shortest at the winter solstice and longest at the summer solstice, these measurements can be used to determine the time of year and to trigger appropriate biological and behavioral changes. Seasonal rhythms have been described in humans, and there are reasons to believe that they depend on photoperiodic mechanisms. Affective illness shows seasonal patterns of recurrence which might have a circadian basis in the photoperiodic mechanism, and at least one type of treatment, partial sleep-deprivation in the second half of the night, artificially lengthens the photoperiod by advancing "dawn."

Most of our knowledge of the human circadian system is derived from the behavior of free-running circadian rhythms in temporal isolation experiments. In general, two types of circadian rhythms have been simultaneously monitored: the rest-activity (sleep-wake) cycle and the circadian temperature rhythm. Subjects in these experiments live in caves, underground bunkers, or aboveground apartments sealed off from the outside world. They wear indwelling rectal temperature probes that are connected to recording equipment. Devices worn on the wrist, or sensors in the floor, detect motion; and the times of switching on and off lights and bedrest is monitored. Sometimes sleep electroencephalogram (EEG) recordings, performance tests, and frequent blood or urine sampling are done. The subjects remain in their quarters from a few weeks to as long as six months, with no knowledge of the time of day or calendar day. They prepare their own meals and select their own times of going to bed and arising. Usually they entertain themselves with books and music and often undertake long-term projects such as the writing of a thesis. When subjects are released into free-running, they typically go to bed and get up about one hour later each day, and the sleep-wake cycle and the circadian temperature rhythm usually oscillate together with the same 25-hour period. However, at some point during free-running their oscillations may spontaneously become dissociated, so that the two rhythms run with different periods and beat in and out of phase with one another every few days. When dissociation of the

two rhythms occurs, the subject no longer sleeps regularly at the same phase of his temperature rhythm but goes to sleep and arises at progressively different phases. Sometimes he may sleep while his body temperature is high and be awake while it is low—a reversal of the normal relationship. During this phase-inversion, subjects sometimes report mild psychological and somatic discomforts. Dissociation of the rest-activity cycle and the circadian temperature rhythm, reported by Aschoff, Gerecke, and Wever in 1967, and subsequently observed in many subjects, indicates that the human circadian system consists of at least two potentially separate driving oscillators. Because the two circadian oscillators, which are coupled together in ordinary conditions, sometimes spontaneously dissociate during free-running experiments, it has been possible to learn something of their individual characteristics. Studies by Wever and Aschoff conducted over the past 20 years, and those conducted more recently by Weitzman, Czeisler, Zimmerman, Moore-Ede, and Kronauer indicate that the controlling oscillator of the circadian temperature rhythm is a much stronger oscillator than the one which controls the sleep-wake cycle. The intrinsic period of its rhythm is very stable and remains close to 25 hours, even after many months of free-running. Besides body temperature, the strong oscillator also appears to control circadian rhythms in the hypothalamic-pituitary-adrenal axis and in rapid-eye-movement (REM) sleep (see figure 3-1). The weak oscillator, which controls the sleep-wake cycle, however, has a labile intrinsic period that can

deviate quite substantially from 24 hours. Sometimes the period of the weak oscillator is much shorter than 24 hours; more often it becomes much longer, reaching 40 or 50 hours per cycle when it dissociates from the strong oscillator during free-running experiments (see figure 3-2). In the latter case, the subject may remain awake for 30 hours or more during each sleep-wake cycle with no perceived need for sleep. At the end of such experiments, subjects are often surprised to learn that many more calendar days have passed than their total number of subjective "days" in isolation.

The different strengths of the two coupled oscillators cause them to respond differently to one another and to external forces acting upon them. For example, because its oscillations are weak, the controlling oscillator of the sleep-wake cycle adjusts more easily to time zone shifts after jet travel than the controlling oscillator of the temperature rhythm. The lag between the time it takes the sleep-wake cycle to shift to a new local time (a day or so) and the time it takes the circadian temperature rhythm to shift (many days) is "jet lag."

Because the forces that tend to couple the two oscillators continue to operate even when they dissociate during free-running, they perturb one another's oscillations as they beat in and out of phase. This means that they tend to keep step with one another for a few cycles, then break away from one another, keep step, then break away, in a kind of recurring tug-of-war in

which the slower oscillator acts as a drag on the faster one, and the faster one pulls the slower one ahead of its natural rhythm, until the inherent discrepancy between their respective intrinsic periods wins out and they part company. This pattern of keeping step, then recurrently breaking out of synchrony has been called *relative coordination* (in contrast to absolute coordination) of two coupled oscillators. At those times when the two relatively coordinated oscillators are temporarily in step with one another, their compromise rhythm is largely determined by the intrinsic period of the stronger, dominating oscillator. Because of this asymmetry, relative coordination can cause the sleep-wake cycle to exhibit runs of short cycles near 25 hours that are periodically interrupted by one or more long cycles 40 or more hours in length, while the circadian temperature rhythm only slightly slows down and speeds up gradually as it breaks in and out of synchrony with the sleep-wake cycle. These features of dissociation and relative coordination of two circadian oscillators may well be connected with circadian rhythm disturbances seen in rapidly cycling manic-depressive patients.

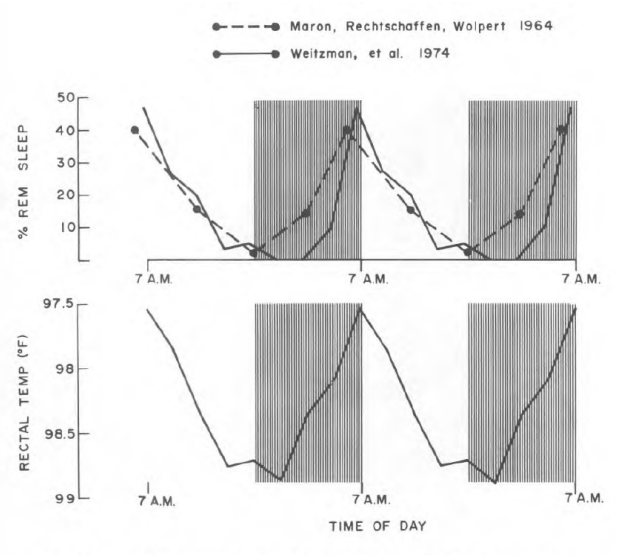


Figure 3-1.
REM sleep propensity circadian rhythm and its relationship to body temperature circadian rhythm. REM sleep changes in depression may be interpreted as a shift to the left (phase-advance) of the REM rhythm.

Note: Maron, L., Rechtschaffen, A., and Wolpert, E.A. "Sleep Cycle During Napping," Archives of General Psychiatry, 11 (1964): 503-598. Weitzman, et al. "Effects on Sleep Stage Pattern and Certain Neuroendocrine Rhythms," Transactions of the American Neurological Association, 93(1968): 153-157.

This model of the human circadian system involves a strong and a weak oscillator that normally are coupled bi-directionally to one another and uni-directionally to the day-night cycle. Richard Kronauer, guided by actual data from human free-running experiments, has developed a mathematical model that produces realistic computer simulations of the behavior of this two-oscillator system. A key feature of the model is the absence of direct coupling

between the strong oscillator and the external day-night cycle that entrains it. There is a hierarchy of coupling such that the strong oscillator, which controls the circadian temperature, REM propensity, and HPA-axis rhythms, is entrained by the weak oscillator, which controls the sleep-wake cycle and which in turn is entrained directly by the day-night cycle. Thus, the strong oscillator is entrained to the day-night cycle indirectly via the weak oscillator. This hierarchy of coupling is the only model that successfully simulates certain transient behaviors of the system that occur immediately after release into free-running.

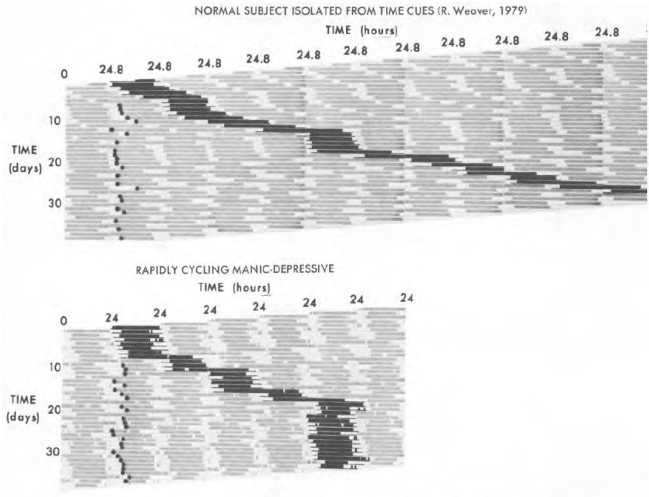


Figure 3-2.
Activity-rest (sleep-wake) cycles in a normal subject (whose circadian rhythms are free-running in isolation from external time cues) and in a rapidly cycling manic-depressive patient living on a 24-hour hospital schedule. Waking activity is indicated by dark bars, sleep or rest by open spaces between bars. Data are plotted in rasters of consecutive 24.8 hour (top) or 24.0 hour (bottom) segments. Courses of consecutive sleep-wake cycles are emphasized in black. Both the free-running normal subject and the entrained manic-depressive repeatedly exhibit double length (48-hour or circa-bi-dian) sleep-wake cycles, as well as cycles of ordinary length. These may indicate that the driving oscillator of the sleep-wake cycle is escaping from its normal one-to-one mode into a one-to-two mode of coupling to other circadian rhythms and, in the patient, to the external day/night cycle. Black dots indicate that the activity onset times remain highly synchronized with an underlying cyclic process having a period near 24 hours. In the patient, 48-hour sleep-wake cycles occurred in conjunction with switches out of depression into mania.

This model of the circadian system was developed entirely by analyzing the formal properties of the behavior of circadian rhythms in various conditions. It is remarkable that during the past decade nearly all of the

neuroanatomical substrates of the model have been tentatively identified in experimental animals and, to a certain extent, in humans. The weak oscillator, which controls the sleep-wake cycle, appears to reside in neurons of the suprachiasmatic nuclei (SCN) of the hypothalamus. These paired structures are situated in the anterior hypothalamus just above and behind the optic chiasm on either side of the third ventricle. They are innervated by a small group of nerve fibers coming directly from the retina via the retinohypothalamic tract (RHT), which emerges from the chiasm and enters the SCN. It has not been possible to lesion the RHT selectively. However, interruption of optic pathways, which include these fibers, destroys the animal's capacity to entrain to light-dark cycles. Bilateral destruction of the SCN essentially destroys the sleep-wake (or rest-activity) cycle. After lesioning, animals exhibit short bouts of activity and sleep, distributed randomly over time.

It is presently unclear whether SCN lesions destroy the circadian temperature rhythm. Several recent studies suggest that the neural substrate of the controlling oscillator of the circadian temperature rhythm, the strong oscillator, may lie elsewhere, possibly in the hippocampus. Two groups have recently identified structures corresponding to the SCN in postmortem human brain tissue. Although technical difficulties have prevented identification of the retinohypothalamic tract in humans, two experimental findings suggest strongly that the pathway exists. Czeisler and associates have demonstrated

that human circadian rhythms can be entrained to a light-dark cycle alone. Another group has shown that human melatonin secretion by the pineal gland can be suppressed by light (this response is known to be mediated by light acting on the SCN via the RHT in experimental animals). It is therefore likely that a homologous pathway exists in humans.

The neurochemistry, neurophysiology, and neuropharmacology of the SCN are presently the focus of intensive investigation. The visual field of the SCN has been mapped and is very broad; essentially the SCN respond to light impinging on any portion of the retina. The SCN contain the largest concentration of serotonergic nerve terminals in the hypothalamus. These fibers originate in cell bodies in the raphe nuclei. The functions of the serotonergic input to the SCN are unknown; raphe lesions do not alter their rhythmic behavior. Injections of various neuropharmacological agents into the third ventricle adjacent to the SCN indicate that some of the effects of light may be partially mediated by cholinergic mechanisms.

Studies of the effects of light on the putative human RHT-SCN-pineal pathway revealed an interesting difference between humans and other animals (including primates). The threshold for light intensity sufficient to elicit a response is considerably higher in humans. Because of this difference humans are able to discriminate between the brightness of ordinary artificial light and natural light. It is possible that the discovery of fire some 100,000

years ago has shaped human evolution in this respect.

Before concluding this discussion of the human circadian system, an important methodological problem warrants attention. Circadian oscillators are not the only factors that govern body temperature, waking, and sleeping. Changes in our physiological state are also evoked by stress, physical activity, meals, and other variables that strongly reflect the time-structure of our social and physical environment. Evoked physiological responses are superimposed on, and may even obscure, changes related to the circadian rhythm, making it difficult to measure and characterize.

Distortion of the circadian pattern by evoked responses is referred to as *masking.* Another form of masking occurs when one circadian rhythm affects the expression of another. For example, sleep lowers body temperature, and activity raises it; therefore, the timing of the sleep-wake cycle relative to the temperature rhythm will determine the waveform of the rhythm that is being measured. Thus, there are two forms of masking: internal and external. Circadian rhythms in some variables can only be observed in special conditions; for example, the circadian rhythm in REM sleep is expressed only when the subject is asleep. In this case sleep is said to have a *positive masking effect.* The problem of masking highlights the fact that an overt rhythm is only an indirect measure of the oscillator that drives it. In clinical studies of circadian rhythms we must assume that an abnormality in phase-position of a

circadian oscillator, if present, will be masked to some extent by sleep schedules and other influences emanating from the temporal structure of the environment.

In summary, the human circadian system is controlled by at least two endogenous, self-sustained, coupled oscillators: a strong one controlling body temperature, REM sleep propensity, and cortisol secretion, and a weak one controlling the sleep-wake cycle and sleep-related neuroendocrine activity. Ordinarily, the longer than 24-hour rhythm of the coupled oscillator system is adjusted to 24 hours exactly by periodic environmental stimuli, such as dawn light, which act on the weaker oscillator through its connections to the eye. Light acting on circadian oscillators is also the basis of seasonal and annual biological rhythms. The normal phase-relationships between the two circadian oscillators and their overt rhythms can be temporarily disturbed by phase-shift experiments and rapid trans-meridian travel. Furthermore, the two oscillators may spontaneously dissociate and oscillate with unequal periods when humans are experimentally deprived of external time cues. The circadian oscillators and their connections to the environment have a physical reality in specific nerve cells and tracts in the hypothalamus. The timing of circadian rhythms relative to the day-night cycle and to one another is homeostatistically controlled and partly reflects the period of the intrinsic rhythm of their driving oscillators.

There are several ways in which such a system might be altered by disease and treatment interventions. There could be alterations in coupling between oscillators, coupling of the oscillators to the external day-night cycle, or in the intrinsic periods of the oscillators. These changes could be expected to affect the phase-position of circadian rhythms entrained to the day-night cycle, and may even affect their capacity to be entrained at all. Clinical studies of circadian rhythms are difficult because of the requirement for longitudinal, around-the-clock monitoring of multiple variables and the confounding effect of masking of circadian rhythms by sleep and by exogenous social factors. (In the next section we will examine evidence from many different sources that strongly suggests, but does not yet establish, that affective illness is an expression of pathology in the human circadian system.)

Circadian Rhythm Disturbances in Affective Illness

Historically, four clinical features of depression have stimulated interest in the idea that circadian rhythm disturbances are involved in the disease: early-morning awakening, diurnal variation in symptom severity, seasonality of the illness, and cyclicity of the illness.

Early-morning awakening is one of the hallmarks of endogenomorphic depression. Typically, the depressed patient awakens abruptly at 4 or 5 A.M. and finds he cannot return to sleep, but instead lies in bed wracked with

depressive ruminations. Some patients have observed that they are better able to tolerate this problem if they simply accept that they are not going to be able to return to sleep, get out of bed, and begin their day's activities. Early awakening has been regarded as merely one manifestation of a more fundamental insomnia. However, it can also be regarded as a normal event—simply waking up—that occurs at an abnormally early time. In fact, some patients find that they are also able to go to sleep early. The shift in time of awakening has been interpreted to mean that a circadian rhythm is abnormally phase-advanced.

Diurnal variation in mood, with depression worse in the morning, is another hallmark of endogenomorphic depression. Patients awake in the depths of depression. As the day wears on, depressive symptoms abate somewhat, especially after the midafternoon. Sometimes in the evening patients feel nearly normal, or even better than normal, but they always dread going to sleep because depression will return at its worst the following morning. This pattern has suggested to some that the depressive process is tied in some way to a circadian rhythm, possibly a normal one. Papoušek, in her elegant and pioneering theoretical paper, interpreted the paradoxical early awakening and late functioning of the depressive as an internal phase-displacement of two circadian rhythms (sleep-wake and "waking-readiness"), one being too early, the other too late.

The seasonality of depression and mania is a striking phenomenon that can be seen in epidemiological studies as well as in individual cases. For depressives, it seems, “April is the cruelest month”: Depressive hospital admissions, electroconvulsive treatments, and suicides occur most frequently in the spring. Some studies show secondary peaks in the fall as well. Mania also appears to recur seasonally, although studies differ on whether it is most frequent in the spring, late summer, or fall. Kripke has proposed that seasonal patterns of mania and depression could be atavistic expressions of vestigial seasonal behavioral rhythms based on photoperiodic mechanisms involving the circadian system.

The cyclicity of affective illness need not express itself seasonally. It is characteristic that whenever affective episodes occur, they run their course and remit spontaneously, only to return again at some future time. The recurrent nature of the illness has been repeatedly confirmed by epidemiological studies. Halberg proposed that such long-term cycles of relapse and remission could occur if depression resulted from an abnormal internal phase relationship between two circadian rhythms and if at least one of those rhythms was no longer entrained to the day-night cycle but was free-running and beating slowly in and out of phase with the other rhythm. And Kripke has published striking results of longitudinal studies of circadian rhythms in a few rapidly cycling manic-depressive patients that support Halberg’s hypothesis.

Some of the first clinical studies of circadian rhythms in depression were carried out in England in the 1950s and 1960s. They were inspired by Lewis and Lobban's discovery that the timing of one circadian rhythm relative to another within the same person could be altered experimentally by placing subjects on unusual schedules during the Arctic summer. The clinical studies were designed to explore whether early-morning awakening in depressives is related to an analogous but pathological internal phase-disturbance. Early studies sometimes showed dramatic phase-disturbances in depressives, but no consensus about the significance and pattern of these changes emerged, even after thirty years in which more than twenty studies of circadian rhythms in depressives have been carried out. The results of these studies, to the authors' knowledge, have never been systematically related to one another and have remained on the periphery of psychobiological research in depression. Perhaps this is because there was no context based on normal circadian physiology in which to place their findings. Also, the investigative groups have been widely separated geographically, and the studies widely separated in time. In contrast to circadian rhythms, the sleep of depressives has been intensively studied by several active groups continuously for fifteen years, and a consensus regarding their findings has emerged. Ironically, the results of sleep EEG studies have rekindled interest in a circadian rhythm hypothesis of affective illness, for they can be interpreted as indicating that the circadian rhythm of REM sleep propensity is phase-advanced in

depressives.* In light of this finding, the authors retrospectively analyzed published data describing a variety of physiological and biochemical circadian rhythms in depressives as compared with controls (see figure 3-3). These results are compatible with the REM sleep finding and with a *circadian rhythm phase-advance hypothesis of depression.* In the next section this hypothesis and the evidence that supports it will be discussed. In a following section some recent findings about circadian rhythms in mania will be presented.

Circadian Rhythm Phase-Advance Hypothesis of Depression

Phase-Advance of the REM Sleep Circadian Rhythm

REM sleep was discovered by Aserinsky and Kleitman in 1953- Episodes of REM sleep lasting 10 to 30 minutes occur about 80 to 90 minutes after sleep onset, then recur cyclically each 90 minutes through the night. It has been called paradoxical sleep because while the EEG shows signs of arousal and the eyes exhibit bursts of vigorous lateral movements, skeletal muscles are profoundly relaxed. In 1957, Dement and Kleitman observed that the distribution of REM sleep during a night's sleep was skewed, with more REM occurring toward the end of the night than at the beginning. Studying naps in 1965, Maron and colleagues found that afternoon naps contained relatively high amounts of REM while evening maps contained little. Linking their own findings with those of Kleitman and Dement's, they proposed that the

propensity for REM sleep is governed by a process that exhibits a circadian rhythm independent of sleep. They also noted that the REM rhythm was more or less inverse to the rhythm of body temperature, and they went on to propose that the two circadian rhythms might be fundamentally related. Subsequent research has borne out their speculations (see figure 3-1). Much about the relationship between the circadian temperature rhythm and REM sleep has been learned from EEG sleep studies of free-running subjects whose sleep-wake cycle and circadian temperature rhythms dissociate and beat in and out of phase with one another. In these subjects, the window of sleep through which REM sleep is observed passes repeatedly across all the phases of the temperature rhythm, making it possible to record all 360 degrees of the circadian rhythm of REM sleep. Results of these studies reveal that REM sleep propensity is maximal just after the body temperature falls to its minimum level. When the propensity of REM sleep is high, REM episodes are long and REM latency (the time from sleep onset to REM onset) is short. Also the percentage of sleep that is REM sleep is high. Normally the temperature minimum occurs in the latter half of the sleep period, so that REM sleep is maximal near dawn. The close association between REM sleep, body temperature, and cortisol secretion suggests that their respective circadian rhythms are controlled by the same oscillator—the stronger of the two coupled circadian oscillators.

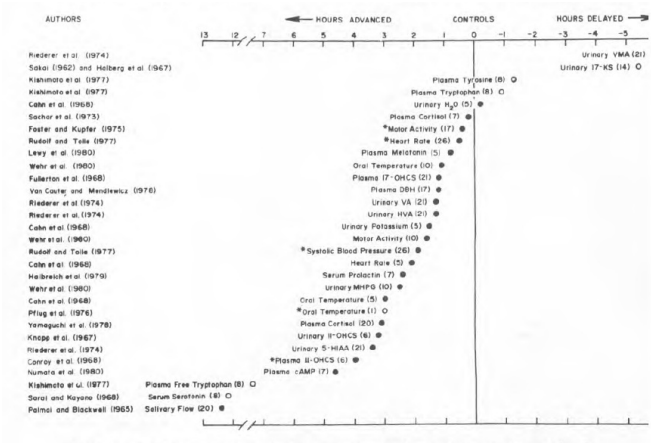


Figure 3-3.
Early timing (phase-advance) of circadian rhythms in depressives compared with controls. Phase was defined as the time of the peak (acrophase) of a cosine function, f(t) = mean + amplitude X cos (frequency XU phase), fitted to published data by the method of least squares. Open circles indicate studies where no data was obtained during sleep. Asterisks indicate studies where control group was not normal.

In one of the first EEG studies of sleep in depressives, Gresham and Agnew found that the normal skewed distribution of REM sleep was altered. Depressives had more REM sleep in the first third of the night and less REM sleep in the last third of the night than did the controls (see figure 3-4). In a way, most subsequent EEG sleep studies of depression have described variations on this theme. Kupfer has emphasized the short REM latency in depressives, and this finding has been extensively replicated. Vogel found that the first REM episode in depressives is sometimes quite long, and that on nights when first REM episodes are long, subsequent episodes are short. All of

these changes in the temporal' distribution of depressives' REM sleep could result from a phase-advance of the circadian rhythm in the propensity to have REM sleep, such that its maximum, instead of occurring near dawn, occurs nearer to the beginning of sleep. Probably the first person to propose this interpretation was Snyder who, in 1968, noted a similarity between the sleep of normal subjects whose sleep period was experimentally shifted later relative to their REM sleep rhythm and depressed patients whose REM sleep was shifted earlier relative to their sleep period. Papoušek stated the interpretation more explicitly in 1975.

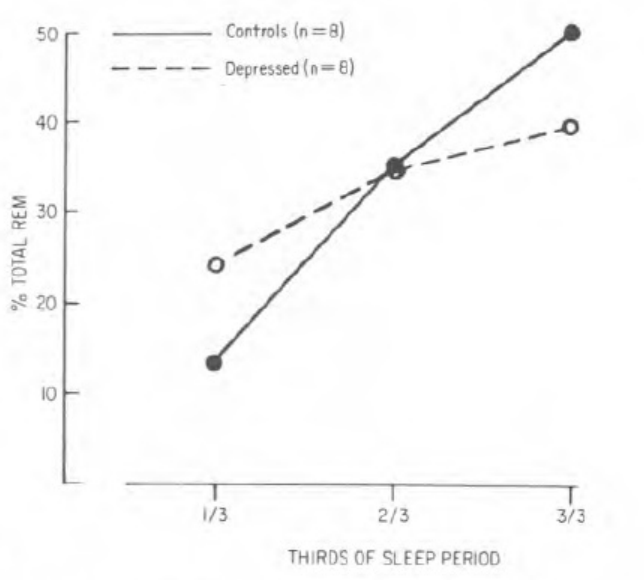


Figure 3-4.
Early temporal distribution of REM sleep in depressives compared with controls. Many studies indicate that early occurrence of REM sleep in depressives sleep period is expressed in their short REM latency (time from sleep onset to REM onset) and long first REM episodes.

SOURCE: Gresham, S.C., Agnew, W.F., and Williams, R.L. "The Sleep of Depressed Patients," Archives of General Psychiatry, 13 (1965): 503-507.

Somnopathy in depressive patients is based on an internal and external desynchronization. . . . the reduced REM latency, the relative increase in REM sleep at the beginning of the night and the shortening of the REM cycles . .. find a new interpretation as the expression of a phase displacement of the circadian rhythm of REM activity. (Authors' translation)

Vogel has conducted well-controlled studies of depressive sleep and,

working in a different conceptual framework, he arrived at a conclusion that is compatible with Papoušek's formulation. Emphasizing the advance of REM sleep within depressives' sleep period, he noted striking similarities between depressive sleep at the beginning of the night and normal sleep in the morning when it is extended past the usual wake-up time.

Because of the close association between circadian rhythms in REM sleep, body temperature, and cortisol secretion, a phase-advance in the latter two rhythms in depressives would tend to support the circadian phase-advance interpretation of the REM sleep abnormalities. Some—but not all—studies of temperature and cortisol rhythms in depressives tend to support this hypothesis.

Phase-Advance of the Circadian Temperature Rhythm

There are surprisingly few studies of the circadian temperature rhythm, considering the ease with which this variable can be measured. In one of the first studies, Cahn and colleagues hourly recorded depressed patients and controls' temperatures. Subjects were housed in a special chamber and elaborate precautions were taken to ensure that measurements were uniformly made and as free as possible of exogenous influences. Five patients were studied. If their results are compared to those of the five controls whose ages are most similar, the depressives show a statistically significant phase-

advance (3 hours) in the time of their temperature peak (see figure 3-3).

Nikitoupoulou and Cramer studied manic-depressives in both phases of their illness. In depression, the patients' temperature rhythms became bimodal with two peaks and two troughs per day. This result is difficult to interpret. However, in the authors' studies of normals it was observed that a 180-degree reversal of the timing of sleep relative to the temperature rhythm sometimes results in bimodal patterns; of the two temperature minima, one is related to the true minimum of the circadian temperature rhythm that now occurs late in the waking phase, and the other is related to a lowering of temperature evoked by sleep—a masking effect. If an analogous internal phase-shift is responsible for the patients' bimodal patterns, the phase-displacement of the temperature rhythm would be very great indeed. In the manic phase, the temperature rhythm reverted to its normal unimodal pattern.

In the authors' study of manic-depressive patients during depression it was found that the phase-position of the temperature rhythm was approximately 1 hour advanced compared with controls, although the difference was not statistically significant. Kripke and others reported similar results. Two German groups, Pflug and associates and Lund and associates found an early temperature minimum in depression. However, Lund's group observed that, for a given patient, nights when the temperature minimum was

particularly early did not necessarily correspond to nights when REM sleep occurred earliest (that is, when REM latency was shortest). Because of the relative ease of measurement, longitudinal studies of the temperature rhythm are possible in individual patients; these are of interest because the patient can serve as his own control and the process of change in circadian phase can be correlated with change in the clinical state. Pflug studied a patient with recurrent depressions for over a year. Marked advances in the phase-position of the circadian temperature rhythm were associated with depressive episodes. Both the San Diego group- and the authors' group have studied longitudinal changes in temperature rhythms in rapidly cycling manic-depressive patients. In five patients, the point of maximal phase-advance of the circadian temperature rhythm coincided with the switch into the depressive phase of the mood cycles (see figure 3-5). In summary, a small number of preliminary cross-sectional and longitudinal studies of the circadian temperature rhythm tend to support the idea that the early timing of REM sleep in depression is related to a phase-advance of a circadian oscillator.

Phase-Advance of the Circadian Cortisol Rhythm

In 1967, Doig and colleagues noted that the 24-hour pattern of secretion of cortisol was "shifted to the left," that is, phase-advanced in depressives. Subsequent studies of fairly large numbers of patients by Fullerton and

associates, Conroy and Mills, and Yamaguchi and colleagues have confirmed this finding. (Sachar and coworkers, however, found no shift in the timing of the rhythm.) In the Fullerton study, the degree of phase-advance of the cortisol rhythm was correlated with the severity of the depression. The change in timing of the cortisol rhythm in depressives is accompanied by a change in its waveform. The nadir of the rhythm as well as the time of the daily upsurge in secretion are shifted earlier; the peak of secretion, however, continues to occur near dawn, as in normals. A possible explanation for this change in waveform is that the early hours of sleep suppress cortisol secretion—a masking effect. In other words, the "true" maximum of the circadian rhythm of cortisol excretion may be blunted and obscured by the effects of sleep. An analogous change in waveform can be seen when the cortisol rhythm becomes phase-advanced relative to sleep in normal subjects during free-running experiments (see figure 3-6).

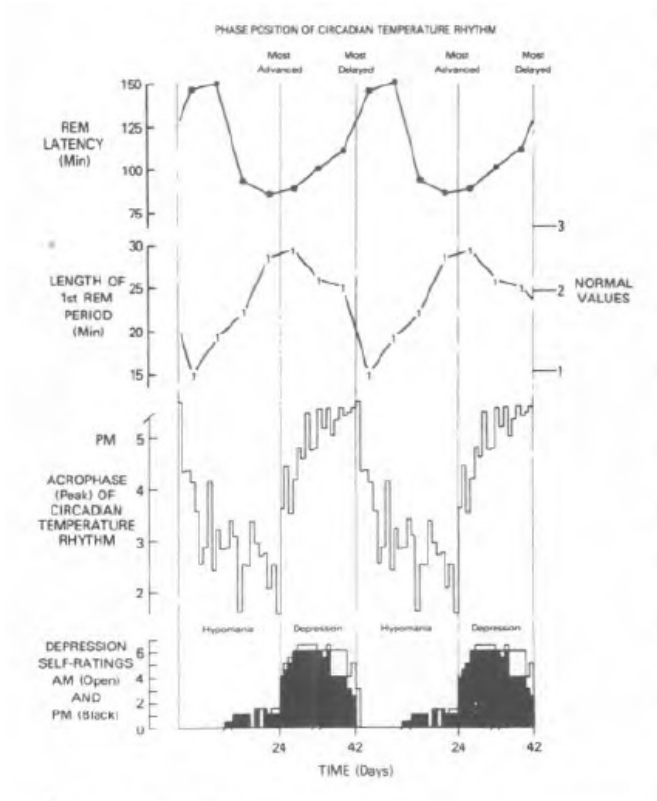


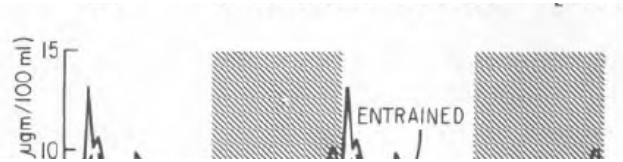
Figure 3-5.
Phase-advance of circadian temperature rhythm is associated with shortest REM latency (time from sleep onset to REM onset) and longest first REM episodes at switch into depression in a rapidly cycling manic-depressive. Points shown are medians of data obtained in five manic-depressive cycles studied longitudinally.

In most studies of depression there is also evidence of cortisol hypersecretion in depression. Increased activation of the adrenocortical system is also reflected in a tendency of depressives to escape dexamethasone

suppression of cortisol secretion.- It is possible that this increase in cortisol secretion in depressives is related to the phase-advance of the circadian rhythm relative to sleep. Analogous shifts in some of the free-running subjects studied by Weitzman and colleagues (see figure 3-6) and by Wever are also associated with increased levels of cortisol secretion. Much more research on the interaction of sleep (or darkness) and the cortisol rhythm is necessary before this explanation of cortisol hypersecretion can be taken seriously. As with temperature, the shift in timing of the daily pattern of cortisol secretion supports a circadian rhythm phase-advance hypothesis of REM sleep changes in depression.

Phase-Advance of Neuro transmitter Metabolite Circadian Rhythms

Alterations of neurotransmitter metabolism have been implicated in the pathophysiology of affective disorders. Circadian rhythms of neurotransmitter metabolites in depression are therefore of special interest. Riederer and colleagues studied urinary metabolites of serotonin (5HIAA), dopamine (HVA), and norepinephrine (VMA, VA). An analysis of their results shows that three of the four rhythms are phase-advanced in depressives compared with controls.



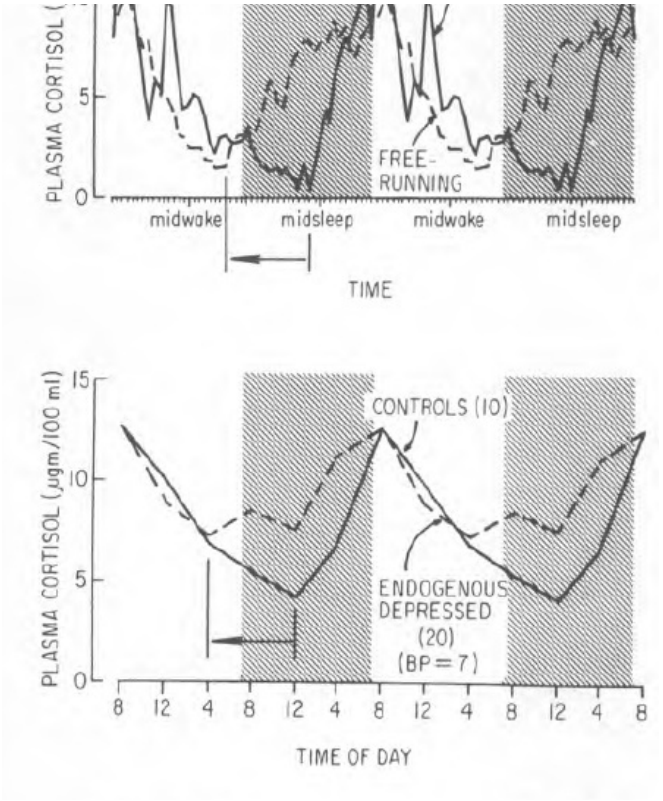


Figure 3-6.
Change in waveform of circadian rhythm of cortisol secretion associated with its internal phase-advance relative to sleep in a free-running normal subject (top) and in a group of depressives compared with controls (below).

Weitzman, C.D., Czeisler, C.A., and Moore-Ende, M.C. " Sleep-Wake, Neuroendocrine and Body Temperature Circadian Rhythms Under Entrained and Non-Entrained (Free-Running) Conditions in Man," in Suda, M., Hayaishi, O., and Nakagawa, H., eds., Biological Rhythms and Their Central Mechanism, Amsterdam: Elsevier/North Holland, 1979, pp. 199-227

The authors' group studied urinary MHPG, a norepinephrine metabolite partially of central origin, and found the circadian rhythm to be approximately 3 hours phase-advanced in depressed manic-depressive patients compared with controls.

Over the years a variety of circadian rhythms have been studied. Taken together, there is a surprising consistency in nearly all of the studies: The phase position of circadian rhythms is abnormally advanced in depression (see figure 3-3).

One's confidence in the validity of this conclusion, however, is limited by methodological deficiencies in the majority of the studies reviewed. No study in which depressed patients were compared with controls adequately controlled for all the possible effects of age, sex, drugs, or experimental conditions. In a number of studies it is not possible to determine even if these factors were examined. Thus, although the research finding of a circadian rhythm phase-advance is consistent with the clinical observation of early morning awakening, our conclusion about the advanced phase-position of circadian rhythms in depressives must remain tentative until additional, better controlled studies are carried out. The consistency of the results of most of the published studies and their compatibility with sleep EEG findings, justifies further work in this area.

Experiments That Test the Circadian Rhythm Phase-Advance Hypothesis of Depression

Although a circadian oscillator controlling REM sleep, body temperature, cortisol, and other circadian rhythms appears to occupy an abnormally early phase-position relative to the sleep-wake cycle and the day-night cycle in depression, there is very little experimental evidence bearing on the question of whether this phase-disturbance plays a causal role in the illness or is merely a kind of epiphenomenon. There are several ways in which the issue of causality might be explored.

Delaying the time of sleep relative to the REM-temperature-cortisol circadian rhythm (causing an advance in the latter relative to the former) would create the depressive-type phase-disturbance and might be expected to precipitate depression in a predisposed individual. Such an experiment may have been unwittingly carried out. Rockwell and coworkers have reported a retrospective analysis of a phase-shift experiment in which four subjects' sleep-wake schedule was delayed 12 hours. In one subject, the circadian temperature rhythm was somewhat phase-advanced relative to the other subjects (evidence of a predisposition?), and failed to adapt to the shifted schedule and instead remained markedly advanced relative to it. This depressive type of phase-disturbance persisted throughout the remainder of the experiment. Two weeks after the experiment the subject committed suicide. Since the psychiatric evaluation was conducted after the fact, it is

difficult to know whether the subject was clinically depressed and what role, if any, the phase-shift played in his suicide.

In a person who is already depressed, advancing the time of sleep relative to the REM-temperature-cortisol circadian rhythm (causing a delay in the latter relative to the former) would undo the depressive phase disturbance and might be expected to induce a remission. The authors' group conducted such an experiment with a depressed manic-depressive woman who had a history of prolonged stable depressions. On two separate occasions, when her sleep period was advanced six hours earlier than its usual 11 P.M. to 7 A.M. time, so that she was sleeping from 5 P.M. to 1 A.M. (or 11 A.M. to 7 P.M. after the second shift), she experienced a rapid and complete remission that lasted for almost two weeks. She eventually relapsed each time apparently because the REM-temperature-cortisol circadian rhythm gradually adjusted to the shifted schedule and reestablished the preexisting depressive-type phase disturbance (see figure 3-7). The efficacy of the procedure depended, therefore, on a kind of therapeutic jet lag. Two other patients showed partial and less dramatic responses to the procedure.

Another type of intervention, which has been much more extensively used with depressed patients, may be related to the sleep-wake cycle phase-advance experiment just described. Several studies have demonstrated that waking depressives several hours earlier than usual (for example, 1:30 A.M.)

has an antidepressant effect in the majority of cases. In this case, the time of waking is advanced without a corresponding shift in the time of going to sleep. Of course, this procedure results in partial sleep deprivation; however, it is not necessarily sleep deprivation *per se* that induces remission, since sleep deprivation in the first half of the night has no antidepressant effect (see figure 3-8). Total sleep deprivation also induces transient remissions and has been studied much more extensively; its efficacy may also depend on the patient's being awake in the second half of the night (see figure 3-9). Although these procedures confound the variables of phase-shifting and sleep deprivation, they are consistent with a causal role for phase-advanced circadian rhythms in depression.

If being awake in the second half of the night treats depression, then being asleep in the second half of the night presumably sustains it. This apparent interaction of sleep with a specific phase of the circadian system could be a mechanism through which the phase-advance of patients' circadian rhythms could trigger depressive episodes (provided that the causal implications of the hypothesis prove to be correct). In depressives, a phase of the REM-temperature-cortisol circadian rhythm, which is normally associated with the first hours of waking, is advanced into the last hours of sleep (see figure 3-8). Besides the therapeutic efficacy of partial sleep deprivation in the second half of the night, there are other clinical observations that support the idea that this particular consequence of the depressive phase-advance is

pathogenic. First, switches into and out of depression tend to occur most often during the night, that is, near this critical circadian phase. Second, severity of depression is greatest just after and least just before this phase each day (this is just another way of describing depressives' well-known diurnal variation mood). The idea that depression thrives in the dark hours of the morning is not a new one and has been previously discussed by Bunney and associates and Papoušek. The concept of a critical circadian phase that interacts with sleep and wakefulness is similar to photoperiodic mechanisms in which a critical circadian phase interacts with darkness and light. In fact, darkness is a confounding variable in the procedures involving sleep.

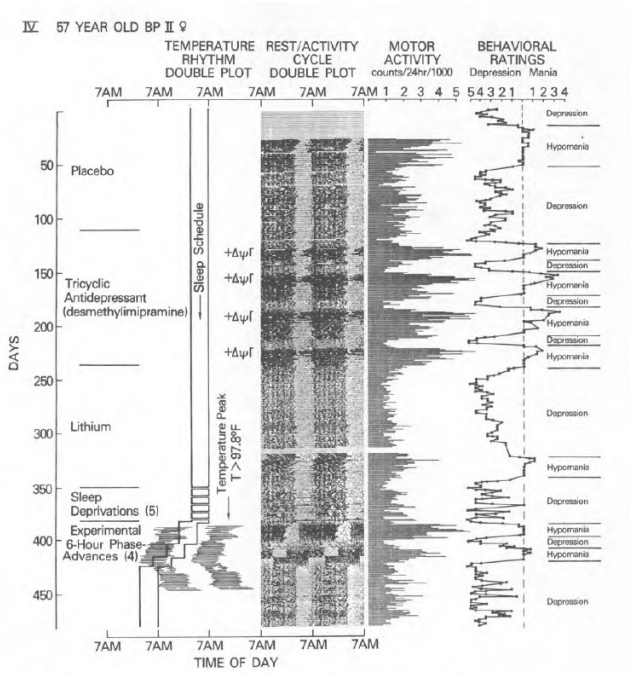


Figure 3-7.
Longitudinal record of drug and sleep schedule, motor activity, and nurses' behavioral ratings during a phase-shift experiment and the year preceding it. Motor activity was recorded with a small electronic accelerometer worn on the wrist. Movement counts per 15-minute sampling interval were recorded in solid-state memory and later retrieved and analyzed by computer. Activity data are displayed here as actograms similar to those used in animal circadian rhythm studies. Each day's data are plotted as a histogram along a horizontal line beginning at 7 A.M.; consecutive days' data are plotted in sequence beneath each other; the entire display is double-plotted to facilitate visual inspection of changes in the rest-activity cycle. Activity is higher (darker) in hypomania or mania and lower (lighter) in day. Total motor activity (counts per 24 hours divided by 1000) paralleled the clinical state (periods of depression (D) are characterized by low activity). Desmethylimipramine induced rapid cycling between depression and hypomania (H). Drug-induced switches into hypomania are associated with increased motor activity as well as advances of its daily onset time (+ Aψ). Clinical remission induced by 6-hour phase advances, reflected in increased activity, mimics the drug effect. The sleep schedule,

which was normal ward routine (11 p.m. to 7 a.m.) for the first year, was interrupted by five weekly deprivations of a single night's sleep (each inducing a day's transient remission), and then followed by the experimental 6-hour phase advances of the sleep schedule. At this time, temperature measurements were taken every 2 hours during waking. The times of day when the longitudinally smoothed temperature curve exceeded 97.8T are indicated by horizontal lines. The temperature maximum advanced with the first two sleep schedule advances (associated with remission) but broke away after the third phase advance and slowed (associated with unremitting depression).

Source: Wehr, T.A., et al., "Phase Advance of the Sleep-Wake Cycle as an Antidepressant," Science, 206 (1979): 710-713.

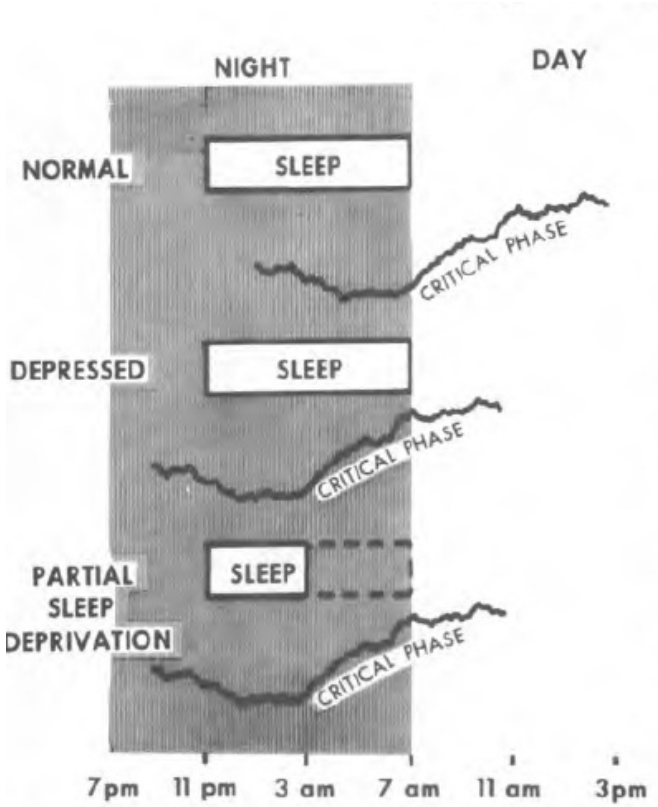


Figure 3-8.
Hypothesis: Depression occurs in susceptible individuals when sleep interacts with a sleep-sensitive phase of the circadian temperature rhythm that is normally associated with the first hours of waking but becomes advanced into the last hours of sleep. Partial sleep deprivation in the second, but not the first, half of the night induces transient depressive remission. Depression severity is worst just after the sleep-sensitive phase (the classical pattern of diurnal variation in depressive mood) and switches into depression tend to occur during the sensitive phase.

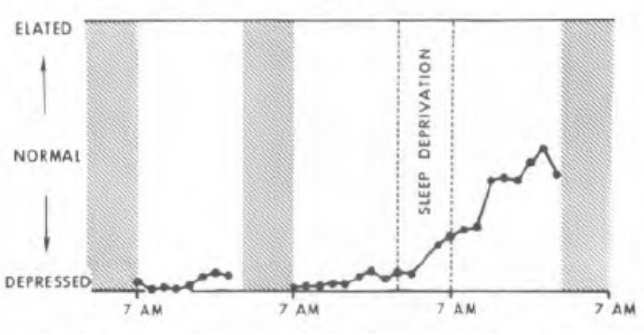


Figure 3-9.
A depressed woman's mood self-ratings show the typical pattern of depressed patients response to total sleep-deprivation therapy. Switch out of depression occurs during the middle of the night.

Advancing the time of the sleep period relative to the REM-temperature-cortisol circadian rhythm is one of two possible ways of correcting the depressive phase disorder. The other approach would be to delay the phase-position of the REM-temperature-cortisol circadian rhythm relative to the sleep period. The controlling oscillator of this rhythm, it will be recalled, is by far the stronger oscillator and is therefore less easily phase-shifted than the controlling oscillator of the sleep-wake cycle (this difference is the basis of jet lag). As with jet lag, correction of the phase-position of the REM-temperature-cortisol rhythm might require one or two weeks or longer.

The authors' group and others have conducted several types of animal experiments that indicate that antidepressants such as monoamine oxidase inhibitors, tricyclic antidepressants, and lithium delay the phase-position of

various circadian rhythms and may do so by lengthening the intrinsic period of their driving oscillator. All of these experiments are preliminary; they may not be specific for antidepressant drugs and could be interpreted in other ways. The authors are unaware of any convincing findings about the effects of psychoactive drugs on the human circadian system. Nevertheless, the results of animal studies nearly all point in the direction required of an antidepressant drug by a phase-advance hypothesis of depression.

Selective REM-sleep deprivation has been reported by Vogel to be as effective an antidepressant as imipramine; onset of its therapeutic effects also has a similar time course to that of the drug. In responders, REM sleep deprivation tends to correct their abnormally early temporal distribution of REM sleep. If this normalization of the temporal distribution of REM sleep is due to a phase-delay in the circadian rhythm of REM sleep propensity, then REM sleep deprivation may act on some phase-control mechanism in the circadian system. Since REM sleep is ordinarily maximal near dawn (see figure 3-1), and involves rapid scanning-like movements of the eye, and since light is an important *zeitgeber* (even in humans), it is interesting to speculate about a possible dawn “light sampling” function for REM. In fact, there is some experimental evidence that entrainment of certain circadian rhythms is impaired in animals that are deprived of REM by sectioning of the extra-ocular muscles."

Animal Models of the Depressive Circadian Phase-Disturbance

Under certain conditions there are similarities between circadian rhythms in SCN-lesioned animals and depressed patients. Halberg and associates studied the effects of bilateral lesions of the SCN on the temperature rhythm in rodents living on a standard 24-hour light-dark cycle. An apparent circadian rhythm in temperature persisted in spite of the lesions, although the amplitude was lower. As in depression, the phase-position of the rhythm in lesioned animals was considerably earlier than in controls.

Etiology of the Depressive Circadian Phase-Disturbance

The cause of the abnormally early phase-position of circadian rhythms in depression is presently unknown. One possibility is that the intrinsic period of the circadian rhythms is abnormally short. As indicated, a circadian rhythm that exhibits an unusually short period in free-running conditions will adopt an unusually early phase-position when entrained to the day-night cycle. This abnormality could only be demonstrated by placing depressives in temporal isolation conditions. In the only study of this type known to the authors, a patient with a 48-hour depressive cycle exhibited a free-running period in the cortisol and temperature rhythm that was not significantly different from 24 hours. Either his intrinsic period was unusually short (as predicted by the hypothesis) or he was entrained to a subtle 24-hour *zeitgeber* that somehow was not excluded from the experiment. In another experiment, which may be

relevant to the problem, Jenner, together with a 48-hour cycling patient, lived in a special isolation facility on a 21-hour "day." He found that the patient was able to adapt to the short days more easily than he could. This would be the predicted result if the patient's intrinsic period was shorter than that of the experimenter's. Clearly, more free-running studies of depressed patients are required to shed light on this problem.

If future research demonstrates that depressives' intrinsic circadian period is short, what could be the cause? An organism's intrinsic circadian period is partly genetically determined; therefore it might be possible to selectively breed long or short intrinsic circadian periods into certain experimental animals. Of course, a genetic factor is known to be of major importance in affective illness. Another possibility is that endocrine disturbances alter the intrinsic period. For example, estrogen shortens the intrinsic circadian period of certain experimental animals. In this case more fundamental abnormalities in endocrine regulation could cause perturbations in the circadian system that, in the model already described, could then trigger depressive symptoms.

If the intrinsic period of depressives' circadian rhythms is normal, another possible explanation for their abnormally early phase-position could lie in their sensitivity to *zeitgebers,* such as light. The perceived strength of a *zeitgeber* can alter the phase-position of a circadian rhythm entrained to it. In

the case of an organism whose intrinsic circadian period is longer than 24 hours, the stronger the *zeitgeber* is, the earlier is the phase-position of the circadian rhythm entrained to it. In a hypersensitive organism the perceived strength of the *zeitgeber* would be abnormally great and the phase-position of circadian rhythms entrained to it would be abnormally early. This hypersensitivity hypothesis could be investigated by testing depressives' responses to stimuli that have the properties of time cues (for example, light).

In summary, a reasonably large number of clinical studies have established that a group of circadian rhythms, especially those controlled by the strong circadian oscillator, are abnormally phase-advanced relative to the day-night cycle and the sleep-wake cycle in depressives. A small amount of experimental evidence supports the hypothesis that the phase-disturbance plays a causal role in depressive pathophysiology, and that it may act through a pathogenic mechanism involving the interaction of sleep and waking with a critical circadian phase associated with early morning. The cause of the phase-disturbance is unknown; experiments that might shed light on the problem have been outlined.

Uncoupling of Circadian Oscillators in Mania

Severe disruption of sleep is as characteristic of mania as it is of depression. In contrast to the depressive, however, the manic actually seems

to require less sleep. Some nights, manics sleep not at all and yet remain alert and energetic. The authors' group has longitudinally monitored the rest-activity (sleep-wake) cycle in sixteen patients who frequently switched into and out of the manic phase of their illness. With this type of patient it was possible to study manic episodes prospectively. The principal finding was that the majority of patients experienced one or more alternate nights of total insomnia when they switched into mania. When many of these same patients were sleep-deprived for one night during depressive episodes, they experienced transient, or in a few cases sustained, switches into mania or hypomania. Their responses to sleep-deprivation suggest that their nights of spontaneous total insomnia may be causally important in the process responsible for spontaneous switches into mania. In fact, the switch process may depend on the interaction of sleep and wakefulness with a critical circadian phase, as previously discussed in relation to depression.

When patients experienced alternate nights of total insomnia at the beginning of mania, the period of their sleep-wake cycle was, in effect, lengthened to approximately 48 hours (see figure 3-2). These double length sleep-wake cycles may reflect a corresponding lengthening of the period of their controlling oscillator, a lengthening sufficient to cause it temporarily to escape from its normal one-to-one mode of entrainment to the 24-hour day-night cycle into a one-to-two mode (the secondary mode of entrainment). In the discussion of the normal human circadian system, it was noted that the

controlling oscillator of the sleep-wake cycle is a weak oscillator whose period is labile and may lengthen in free-running conditions, escaping from one-to-one coupling with the stronger oscillator, which controls the REM-temperature-cortisol circadian rhythm. In some subjects the period of the sleep-wake cycle may lengthen to such an extent (fifty hours) that it can temporarily recouple with the stronger oscillator in a one-to-two mode (see figure 3-2). These subjects, like manics, remain energetic and alert without sleep for thirty to forty hours during each sleep-wake cycle. On the basis of these known characteristics of the human circadian system in free-running conditions, it is proposed that the period of the controlling oscillator of the sleep-wake cycle in mania is abnormally long, so that it escapes from its normal mode of entrainment.

If this interpretation is correct and is causally important, then any procedure or agent that lengthens the intrinsic period of circadian rhythms would tend to precipitate mania in susceptible individuals. As noted, evidence from animal studies indicates that some antidepressant drugs may act by lengthening the intrinsic circadian period. By the same mechanism these drugs might be expected to precipitate mania. In fact, antidepressants do tend to precipitate mania in depressed manic-depressives.

In experimental animals, estrogen withdrawal also lengthens the intrinsic circadian period. In this regard, it may be relevant that affective

episodes, especially manias, occur more frequently in the postpartum period.

Animal Models of Circadian Rhythm Disturbances in Mania

Using behavioral stress with primates, Stroebel was able to induce dramatic changes in the pattern of their circadian temperature rhythm. In a subgroup of animals a prominent 48-hour rhythmic component emerged and was superimposed on the basic 24-hour rhythm. This alteration in the temperature rhythm is not unlike that which occurs in free-running human subjects whose sleep-wake cycles reach double length; because of masking effects alternate temperature peaks are blunted by sleep and the intervening peaks are reinforced by wakefulness. The result of this interaction is a waveform with a fundamental near 24-hour component combined with a near 48-hour component. It is not stated whether the 48-hour component was associated with double length sleep-wake cycles in the primates. The animals developed these patterns while living on a normal light-dark cycle after they were deprived of an important object in their environment. From a psychiatric point of view, the experiment is interesting because it indicates that mania-like circadian rhythm disturbances can be precipitated by loss-related stresses.

Rapid Manic-Depressive Cycles as a Beat Phenomenon of Dissociated Circadian Rhythms

In a subgroup of manic-depressive patients who were studied longitudinally, it was found that circadian rhythms in temperature and other physiological and behavioral variables were no longer strictly entrained to external time cues, but were free-running with a period *shorter* than 24 hours, and gradually beat in and out of phase with the day-night cycle in such a way, apparently, as to generate the long-term manic-depressive cycles. It is unknown whether Kripke's patients exhibited double-length sleep-wake cycles when they switched into the manic phase of their mood cycles. His data were the first to directly support Halberg's hypothesis that periodic psychiatric disorders might arise as a beat phenomenon of two internally desynchronized circadian subsystems.

In one study, most of the patients who had rapid (one-to six-week) manic-depressive cycles experienced one or more of the double-length sleep-wake cycles at the onset of each manic phase of their mood cycle. It is conceivable that these recurring escapes of the sleep-wake cycle from its primary (one to one) mode to its secondary (one to two) mode of coupling into the day-night cycle and to other circadian rhythms could result from its driving oscillator having an overly long intrinsic period. In this case the manic-depressive cycles could be regarded as a kind of beat phenomenon between the driving oscillator of the sleep-wake cycle and the day-night cycle and other circadian rhythms. Because this oscillator is relatively weak, its oscillations remain relatively well coordinated with the day-night cycle and

other circadian rhythms, so that the dissociation of its oscillations is expressed only in the periodic 24-hour phase-jumps associated with the double-length sleep-wake cycles.

It was proposed earlier that antidepressant drugs promote a slowing of the intrinsic rhythm of circadian oscillators, which leads to lengthening of the period of the sleep-wake cycle and its temporary escape from the primary mode of entrainment in mania. A possible endpoint of this drug effect could be a process of frequently recurring escapes and double-length sleep-wake cycles. In this regard, it was observed in a subgroup of manic-depressive patients (all women) that maintenance treatment with antidepressant drugs does in fact induce rapid (three-to six-week) cycling between mania and depression. When the drugs are withdrawn, Conclusion the rapid-cycling stops. Most of these patients experience 48-hour sleep-wake cycles at the beginning of each manic phase. Thus, a drug-induced slowing of the intrinsic rhythm of circadian oscillators, leading to more frequent escapes from the primary mode of entrainment, could be a mechanism underlying the drug-induced rapid manic-depressive cycles. An analogous phenomenon was observed in experimental animals chronically treated with antidepressants. In some cases, the drugs appear to promote dissociation and relative coordination of two oscillatory components of the activity-rest cycle. Although the two components remain synchronized with one another most of the time, the slower component periodically lengthens dramatically and

temporarily escapes from one-to-one coupling into the other component. In this way the two components beat in and out of phase every three weeks or so, in a manner similar to the rapidly cycling manic-depressives (see figure 3-10).

This chapter has described the physiology and neuroanatomy of the human circadian system. It has presented evidence from many different sources that disturbances in the circadian system may play an important role in the pathophysiology of affective illness. It is hypothesized that a driving oscillator of the circadian rhythms of REM sleep, body temperature, and cortisol secretion is abnormally phase-advanced in depression, and that in mania the driving oscillator of the sleep-wake cycle is abnormally slow and escapes from its primary mode of entrainment to the day-night cycle. Animal experiments provide only preliminary evidence that antidepressant drugs, by slowing the intrinsic rhythm of circadian oscillators, may counteract depressives' abnormal phase-advance and promote escape from entrainment in mania. Many questions await further study. For example, lithium slows circadian oscillators and treats depression, but unlike tricydies and monoamine oxidase inhibitors it does not precipitate mania. The possible circadian basis of antidepressant drug action must be further investigated in order to determine whether the circadian rhythm effects are specific for clinically active drugs. Several arguments have been given supporting a hypothesis that the interaction of sleep with a critical circadian phase is a

pathogenic mechanism in depression. This hypothesis simply integrates the depressive circadian rhythm phase-advance with the observation that sleep deprivation is an antidepressant. In future depression research, it may be desirable to focus on endocrine (or other) changes that occur during the last hours of sleep (or sleep deprivation) as well as on photoperiodic mechanisms related to the perception of dawn light. The relevance of sleep-deprivation experiments to the pathophysiology of manic-depressive illness is underscored by the fact that 48-hour sleep-wake cycles often occur at the switch out of depression into mania and may result in a kind of spontaneous, endogenous sleep-deprivation "therapy."

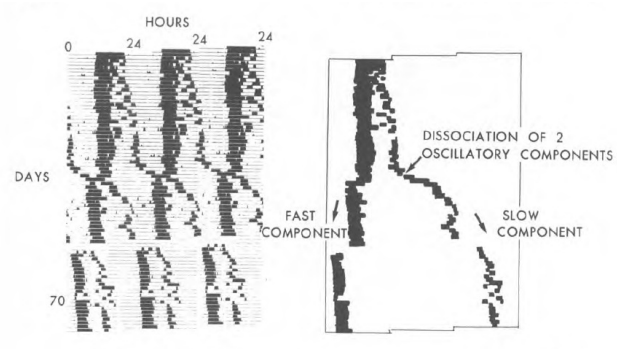


Figure 3-10.
Uncoupling and relative coordination of the oscillations of two components of a hamster's activity-rest cycle during free-running in isolation from external time cues and after treatment with imipramine. Note three-week cycle of uncouplings. Imipramine sometimes induces three-week manic-depressive cycles in depressed bipolar patients.

In the studies of mania and manic-depressive cycles, patients were

compared with normal subjects whose circadian oscillators spontaneously dissociate during free-running experiments in caves. Like the patients, some of these normal subjects periodically exhibit double-length sleep-wake cycles as well as cyclic fluctuations in REM sleep patterns, urinary free-cortisol, performance, and mood. However, there are important differences in the experimental conditions and the responses of these subjects. The normals seldom experience severe affective changes such as mania or depression. And the patients are entrained (albeit abnormally) to the 24-hour day-night cycle. If circadian rhythm disturbances are essential for the expression of affective symptoms, there must still be some other predisposing factor that distinguishes patients from normals. Perhaps the relative chronicity of the rhythm disturbances in patients is important. Or perhaps the interaction of the external day-night cycle with the rhythm disturbances is the critical factor altering their behavior. Although circadian rhythm disturbances may prove to be important pathogenic mechanisms in affective illness, their fundamental cause may lie outside of the circadian system. For example, endocrine disturbances could alter the behavior of an otherwise normal circadian pacemaker.

A circadian theory of affective illness is attractive because it can integrate clinical symptoms (such as early awakening and diurnal variation in mood), epidemiological features (such as seasonality and cyclicity), disturbances in REM sleep, and endocrine function. It also provides a possible

way of understanding the effects of psychotropic drugs and procedures such as sleep deprivation. It suggests new animal models of depression, mania, and manic-depressive cycles. Most important, it could point the way to new treatment approaches designed to manipulate the circadian system directly.

For the present, the authors hope that the emerging findings in this area will stimulate clinicians to attend to patients' reports of the patterns in the recurrences of their illness and to the changes in the daily rhythms that may accompany them. It is also hoped that more experimental evidence bearing on the role of the circadian system in affective illness will be forthcoming.

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