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Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia

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STROGATZ, STEVEN H., RICHARD E. KRONAUER, AND CHARLES A. CZEISLER. *Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia.* Am. J. Physiol. 253 (Regulatory Integrative Comp. Physiol. 22): R172–R178, 1987.—The human circadian pacemaker modulates our desire and ability to fall asleep at different times of day. To study this circadian component of sleep tendency, we have analyzed the sleep-wake patterns recorded from 15 free-running subjects in whom the sleep-wake cycle spontaneously desynchronized from the circadian rhythm of body temperature. The analysis indicates that the distribution of sleep onsets during free run is bimodal, with one peak at the temperature trough and, contrary to previous reports, a second peak 9–10 h later. Furthermore, there are two consistent zones in the circadian temperature cycle during which normal subjects rarely fall asleep. We hypothesize that this bimodal rhythm of sleep tendency, revealed under free-running conditions, maintains the same fixed phase relation to the circadian temperature cycle during 24-h entrainment. This would imply that normally entrained individuals should experience a peak of sleep tendency in the midafternoon and a zone of minimal sleep tendency ~1–3 h before habitual bedtime. Our temporal isolation data thereby account quantitatively for the timing of the afternoon siesta and suggest that malfunctions of the phasing of the circadian pacemaker may underlie the insomnia associated with sleep-scheduling disorders.

insomnia; circadian rhythm; sleep-wake cycle; humans; body temperature cycle; internal desynchronization; wake-maintenance zone; napping; shift work

IRREGULAR SLEEP-WAKE SCHEDULES and their attendant insomnia are commonplace in our society (20). For 20–30 million workers in the US, frequent shifts of the sleep-wake schedule are required for adherence to round-the-clock work schedules (15); for others, jet travel across time zones forces adaptation to a new sleep time; but for most of us, it is the conflict between evening social activities and daytime work schedules that leads us to attempt to shift our sleep times, especially during the transitions between weekends and weekdays.

Many researchers (1, 7, 9, 14, 21, 26, 29, 35, 38) have investigated the timing of the sleep-wake cycle by conducting studies of human subjects living alone for weeks in caves, bunkers, or special facilities shielded from environmental time cues. Although those studies have indicated that the duration and internal organization (14, 33, 40) of unrestricted sleep episodes vary with the phase of the hypothalamic (27, 30) circadian pacemaker, less is known about the relation between insomnia and circadian rhythms. We report that the circadian pacemaker modulates our desire and ability to initiate sleep at various times of day. In particular, there is a 2- to 3-h zone, occurring precariously close to but normally just before habitual bedtime, during which it is extremely difficult to fall asleep.

METHODS

Subjects. We have analyzed the sleep-wake and temperature records of 15 internally desynchronized free-running subjects, drawn from long-term studies carried out by our group in the United States (9, 14, 23) as well as by other groups in France (7, 21, 29), the United Kingdom (26), and West Germany (1–3, 38–40) (Table 1). During time isolation totaling more than two subject years, 359 sleep-wake cycles were recorded from sections of the experiments when the sleep-wake cycle spontaneously desynchronized from the ongoing circadian rhythm of body temperature.

The determination of sleep and wake varied across studies. Our group always verified sleep polygraphically, whereas the French, German, and British groups did so only occasionally. Therefore we always used bedrest data when pooling across subjects because these data were available in all cases.

There were some differences in protocol across the experiments. The German group permitted their subjects to drink coffee, tea, and one bottle of beer per wake episode, whereas our group permitted no caffeine or alcoholic drinks. (The French and British groups did not comment on the beverages allowed.) All but one of our subjects (*PR01*, Table 1) had their meals brought to them by laboratory technicians, whereas the German and French subjects prepared their own meals and were isolated from face-to-face interaction with other humans. Finally, our group and the German group instructed the subjects not to take naps, whereas the French and British groups gave no such instructions. The possible effects of such instructions against napping have been discussed recently (39).

We found that the differences in protocol mentioned above had no detectable influence on the results reported here; when the data from the French, German, British,

TABLE 1. *Published records of internally desynchronized human subjects*

Ref./Fig.	Subject	Age/Sex	Free-Run Study Length, days	Desynchronized Sleep Episodes
38/54	*HN*	27/M	18	7
9/14	*FR03*	25/M	10	8
26/4	*G6*	19/M	12	8
9/14	*FR04*	22/M	12	9
2/5			17	11
9/14	*FR10*	51/M	19	12
38/27	*EvS*	24/F	32	15
3/4	*F*		17	16
1/7			21	17
38/36	*KD*	26/M	44	17
31/3–8	*426F*	23/M	28	18
14/1	*PR01*	23/M	78	40
29/10	*MS*	33/M	177	40
21/2	*JC*	23/M	135	58
23/2	*LD03*	24/M	179	83

Total study length days, 799; total desynchronized sleep episodes, 359. M, male; F, female.

and American groups were analyzed separately, the results agreed with one another.

Estimating circadian period and phase. We estimated the period and average waveform of each subject's temperature rhythm by a nonparametric form of spectral analysis using waveform eduction (9), which is related to periodogram analysis (16). The midtrough of the subject's averaged temperature rhythm was defined as *phase 0* in a cycle of 360°. When temperature data were unavailable, periods and phases were derived from sleep data alone (9, 31). The methods used in this procedure were validated by testing them against records for which temperature data were available (31).

Because our waveform eduction procedure may be unfamiliar, we elaborate on the difference between our methods and those used by others to estimate circadian phase.

Other groups have adopted the actual minimum of the body temperature rhythm as the phase reference (38–40). The problem with the method is that it ignores masking effects on temperature. The temperature rhythm contains a masking component due to sleep and posture in addition to the endogenous component that presumably reflects the output of the circadian pacemaker. This masking component must be filtered out somehow; otherwise it contaminates the estimate of the endogenous phase (see DISCUSSION).

Waveform eduction is the filtering procedure that we have adopted. The temperature time-series data are "folded" at different trial periods and averaged to compute an educed waveform. The period selected is the one that minimizes the variance of the residuals about the average waveform. For internally desynchronized subjects the resulting educed waveform reflects the endogenous component of the temperature cycle. It is relatively free of the masking effects of sleep on temperature because during internal desynchronization, sleep is more evenly distributed at all phases of the circadian cycle than it is during entrainment or internally synchronized free run. Thus, when applied to internally desynchronized subjects, the eduction procedure "averages out" the masking components evoked by sleep.

Normalized raster plot. Each sleep-wake record was double plotted in a raster format folded at the period of the temperature rhythm. Mid-low temperature was aligned with the vertical midline of the raster plot. These conventions normalize sleep-wake records relative to the circadian temperature cycle, which is the physiologically important periodicity (14), rather than the 24-h clock cycle, which is irrelevant during time isolation.

Conversion of free-running circadian phase to 24-h clock time. We now describe a way to connect the phase of the circadian temperature cycle during free run to that observed during 24-h entrainment. During desynchronized free run, events are referenced to the minimum of the educed temperature cycle. To determine how this measure is related to entrained data, we need an estimate of the time of day when the minimum of the endogenous component of the circadian temperature cycle occurs. Estimation of circadian phase is inherently problematic during entrainment precisely because the masking effects of sleep occur at a consistent phase of the temperature cycle and are thus difficult to average out. It is for this reason that the endogenous circadian phase (ECP) estimation protocol was devised (10, 11, 13). It distributes wakefulness evenly across more than one circadian cycle in the same way that internal desynchrony distributes sleep evenly. The method allows the phase of the endogenous component of the temperature cycle to be estimated accurately during conditions of 24-h entrainment.

Using the ECP protocol, we have found recently that in healthy college-age men with an average waketime of 8:25 A.M. ± 12 min, the endogenous temperature minimum occurs at 6:42 A.M. ± 15 min (mean ± SE, $n = 29$ subjects) (11, 13). Hence, in these college students, entrained circadian *phase 0* corresponds to 6:30–7:00 A.M.

An average schedule that is perhaps more relevant for much of the labor force involves sleep from 11:00 P.M. to 7:00 A.M.; on this schedule, which is 1.5 h earlier than that of the college students above, circadian *phase 0* would occur at 5:00–5:30 A.M.

RESULTS

When sleep-wake records from internally desynchronized subjects are replotted in a normalized raster (see METHODS), they reveal two consistent zones of the circadian cycle (Fig. 1, stippled bands) in which sleep seldom begins spontaneously. Notice that, in the four subjects shown in Fig. 1, no black bars ever begin in the stippled zones. In other words, the subjects all avoided bedtime at those phases in the circadian cycle. However, sleep episodes begun earlier were able to continue through the zones. Hence, they are "wake-maintenance" zones, in that subjects who are already awake tend to maintain their wakefulness through the zones (32). The zones occur ~8 h before and ~5 h after the temperature minimum (Fig. 1) and are ~2–3 h wide. Although the zones could be wider in some of the cases shown, the same minimal zones are drawn for all, to emphasize their universality across subjects. The invariant timing of the zones is impressive when one observes how different the four subjects are in other respects: sleep fractions range

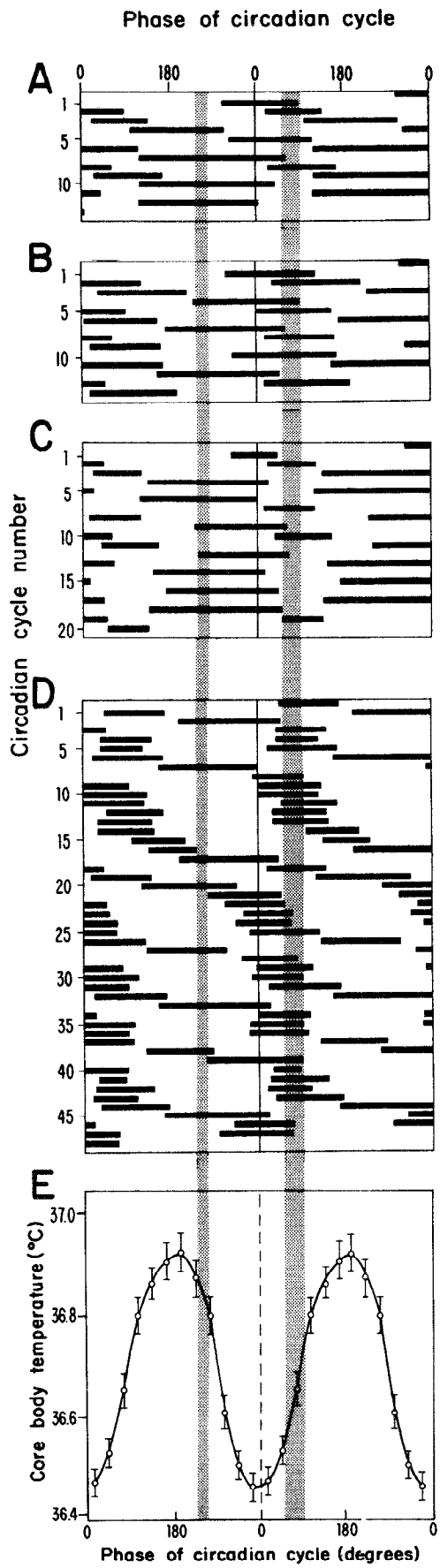

FIG. 1. *A–D*: sleep-wake records of internally desynchronized human subjects. *Subjects FR03, FR04, FR10,* and *PR01,* respectively (see Table 1). *Black bars* represent sleep and are plotted twice (*below* and to *right* of previous sleep episode) to emphasize continuity in data. *Stippled vertical bands* represent wake-maintenance zones in circadian cycle. *E*: rhythm of body temperature (means ± SE) averaged across subjects in *A–D*.

from 0.30 to 0.36 and average sleep-wake cycles range from 29 to 40 h.

When the data for all 15 internally desynchronized subjects are pooled, we obtain the distribution of sleep onsets selected at different phases of the body temperature cycle (Fig. 2*A*). The wake-maintenance zones appear as local minima in the histogram and are statistically significant. Their statistical significance was established by the following Monte Carlo test. We generated 2,000 random histograms, each based on 350 random real numbers uniformly distributed between 0 and 24. For each histogram, these numbers were sorted into 24 bins. Only 9 of the 2,000 random histograms had two consecutive bins with fewer events than observed in the "morning" zone (Fig. 2), implying $P < 0.005$. For the "evening" zone, $P < 0.001$.

To relate the timing of these wake-maintenance zones in the free-run data to clinical findings obtained during ordinary 24-h schedules, we convert circadian phases to approximate times of day (see METHODS and DISCUSSION). Circadian *phase 0* corresponds to 6:30–7:00 A.M. for college students with an average waketime of ~8:30 A.M., and to 5:00–5:30 A.M. for much of the labor force with an average waketime of 7:00 A.M. (see METHODS). As shown in the free-run data of Fig. 2, the wake-maintenance zones are observed to occur ~5 h after and ~8 h before the time of minimum temperature. Hence, for the entrained college students, a morning wake-maintenance zone is predicted to be centered near noon and an evening zone is predicted to be centered near 10:30–11:00 P.M. Figure 2 illustrates the approximate conversion from circadian phases to clock hours for people who sleep from 11:00 P.M. to 7:00 A.M. The morning wake-maintenance zone would then occur near 10:00–11:00 A.M., and the evening zone would occur near 9:00–10:00 P.M., just before entrained bedtime.

DISCUSSION

Hypothesis about sleep propensity. The findings reported here concern the rhythm of sleep propensity as manifested during internally desynchronized free run. We wish to use these results to shed light on some previous findings regarding sleep propensity in the 24-h world, when the circadian cycle is not free running but is instead phase locked to the light-dark cycle and other daily synchronizers.

To extrapolate from free-run to 24-h entrainment, we reason as follows: our results show that during internally desynchronized free-run there is a component of sleep propensity that is linked to the circadian temperature cycle; we hypothesize that during 24-h entrainment this component of sleep propensity remains linked to the circadian temperature cycle and does so with the same phase relation as during free run. Thus the peaks and troughs of Fig. 2*A* are expected to have counterparts during entrainment, occurring at the approximate times of day indicated at the top of Fig. 2 (see METHODS for

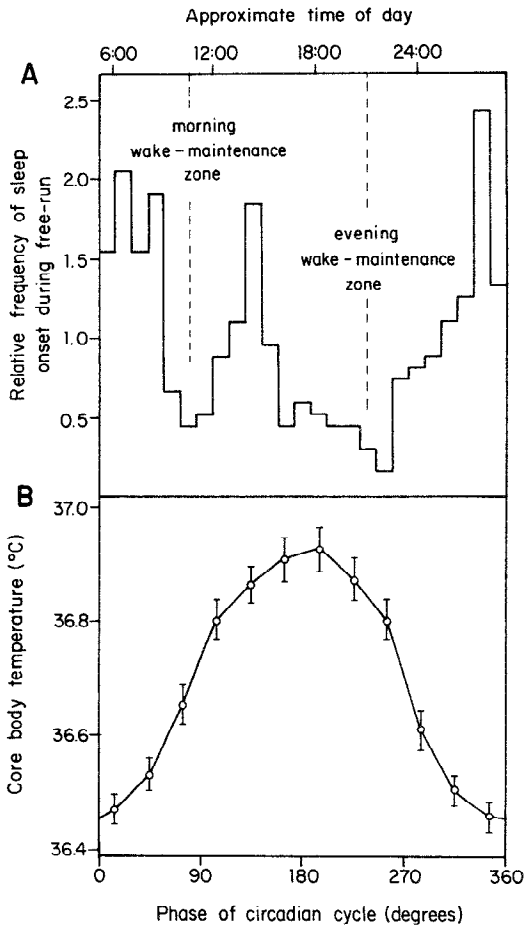

FIG. 2. *A*: distribution of bedtimes selected by internally desynchronized free-running subjects. Frequency of 1 represents average across all phases in circadian cycle ($n = 15$ subjects; 359 sleep onsets.) Habitual waketime of 7:00 A. M. is assumed in converting circadian phases (*lower horizontal axis*) to approximate times of day (*upper horizontal axis*) (see METHODS). *B*: rhythm of body temperature (means ± SE) averaged across subjects of Fig. 1.

conversion of circadian phase to clock time). In particular the wake-maintenance zones in the free-running circadian cycle are expected to be present during 24-h entrainment.

This hypothesis will be shown to unify, in a quantitative fashion, such seemingly disparate findings as the nap tendency in the midafternoon (4, 5, 17, 28, 34), the bimodal distribution of sleep-related traffic accidents (25), the ~10:00 P. M. time of minimum sleep ability found in ultradian sleep studies (6, 24, 36, 37), and the induction of sleep-onset insomnia caused by entrainment to a 23.5-h day (18). The hypothesis also suggests that a malfunction of the phasing of the circadian pacemaker may underlie the insomnia associated with sleep-scheduling disorders.

Bimodality of circadian sleep tendency. Our results indicate that, in internally desynchronized subjects, the timing of self-selected sleep onset is distributed bimodally in the circadian cycle (Fig. 2). The major peak occurs at the trough of body temperature, a phase when subjective alertness (9, 14) and psychomotor performance (8) are lowest, and the propensity for rapid-eye-movement sleep is highest (6, 9, 14).

The second peak of sleep onset frequency occurs ~9 h after the temperature minimum (Fig. 2). When this circadian phase is converted to clock time (see hypothesis above) the second peak corresponds to a clock time near 3:00 P.M., coincident with the afternoon siesta practiced in many cultures (5), the timing of naps in young adults (17), and the "midday dip" in performance measures (8) and in sleep latency (28). Others (4, 34) have speculated that our endogenous rhythm of sleep tendency is bimodal and hence that afternoon napping is biologically, as well as culturally, based. Figure 2 is to our knowledge the first demonstration in internally desynchronized humans of a peak corresponding to entrained nap phase.

Nevertheless the second peak is not due to naps in the usual sense; the sleep episodes begin after ~25 h of prior wake and may last for over 20 h (33). Most of the free-running subjects studied here were instructed to "avoid naps." Without this injunction, true naps might have been observed more often (39).

Previous studies of sleep propensity during free run. Zulley and Wever (40) have also reported a bimodal distribution of sleep onsets in free-running desynchronized subjects. However, there are several important differences between their study and ours. Zulley and Wever (40) referenced their sleep onsets to the cycle-by-cycle minimum of temperature, rather than to the mid-trough of the averaged temperature cycle, as we have done. They found one peak of sleep onsets near the temperature minimum, but their second peak was centered on the falling limb of the temperature cycle, ~7 h before the temperature minimum, whereas our second peak (Fig. 2) occurs much earlier, on the rising limb of the cycle, ~15 h before the minimum. By conversion of these circadian phases to approximate clock times (METHODS and DISCUSSION above), their second peak would occur in the hours just before midnight, whereas ours would occur in the midafternoon. This is the sense in which our results represent the first demonstration in free-running subjects of a peak in sleep propensity at the phase of entrained afternoon napping.

The discrepancies between our results and those of Zulley and Wever (40) regarding the phase of the second peak are due to systematic errors resulting from their choice of circadian phase reference. The cycle-by-cycle minimum of temperature adopted by Zulley and Wever (40) is more heavily confounded by the masking effects of sleep on body temperature. Consider the masking effects of those sleep episodes responsible for the second peak, which begin well before the average temperature trough. For such sleeps the minimum of temperature observed on that cycle will appear earlier than the average midtrough, because the inactivity and reclining posture during sleep depress the observed temperature below its phase-adjusted mean value (10, 11, 13, 40). In other words, a consideration of masking effects explains why sleep episodes beginning near nap phase occur much earlier relative to our reference phase than they do relative to the reference phase of Zulley and Wever (40).

Another problem with Zulley and Wever's (40) use of the actual temperature minimum as a phase reference is that it includes too much cycle-to-cycle variability. Because of random effects in addition to the systematic

masking errors mentioned above, this measure, if taken literally, would suggest the unrealistic result that the circadian period fluctuates by a few hours from day to day. The true stability and phase of the circadian cycle would have been captured better by waveform eduction (see METHODS) or by fitting a regression line through the temperature minima, as Wever (38) has done in other contexts.

As a direct check on the explanations above, we replotted in our format several of Wever's (38) records of desynchronized subjects, and the results (31) then agreed with those reported here.

Finally, Zulley and Wever (40) made no attempt to relate the rhythm of sleep propensity observed in free run to that observed during 24-h entrainment. We will now show that the results from free-run experiments are intimately related to various findings about sleep propensity in the 24-h world.

Bimodal distribution of sleep-related traffic accidents. The bimodality of circadian sleep tendency has some surprising and important consequences for everyday life. Lavie et al. (25) have reported a bimodal distribution in the occurrence of sleep-related traffic accidents as a function of the time of day. Most sleep-related traffic accidents occurred in the night (11:00 P.M.–5:00 A.M.) or the midafternoon nap phase (1:00 P.M.–4:00 P.M.), whereas the fewest occurred near 10:00 A.M. and 9:00 P.M., exactly corresponding to the predicted times of the morning and evening wake-maintenance zones of Fig. 2. In other words the wake-maintenance zones are the times when one is least likely to fall asleep at the wheel. The close agreement between the distributions of sleep-related traffic accidents (25) and spontaneous sleep onsets during free-run (Fig. 2) suggests that both distributions reflect the same intrinsic bimodality in the circadian control of sleepiness and vigilance.

Interpretation of morning wake-maintenance zone. Before devoting our attention to the relation between insomnia and the evening wake-maintenance zone, we pause to dispel a common misconception about the morning wake-maintenance zone (Fig. 2). One might think that it arises merely because subjects are unlikely to fall asleep immediately after waking up. In fact, the free-running subjects studied here had been awake for an average of 22 h by the time they reached the morning zone, yet their sleep onset frequency is only half the overall average. Moreover, the fractional rate of sleep onset (% of subjects currently awake who fall asleep in the next hour) is also a minimum in the morning zone (31). Thus the low sleep tendency in the morning wake-maintenance zone is not simply ascribable to the subjects' having just awakened.

Insomnia and wake-maintenance zones. The evening wake-maintenance zone normally occurs just before entrained bedtime (Fig. 2) and thus raises an intriguing question: is the evening zone implicated in some sleep-onset insomnias? Our results (Figs. 1 and 2) show only that free-running subjects rarely select bedtimes in the zones; but would they find it difficult to fall asleep then, were they to try?

Ultradian sleep studies indicate that it is indeed difficult to fall asleep in the evening wake-maintenance zone but not particularly difficult to fall asleep in the morning zone. Several researchers (6, 24, 36, 37) have placed subjects on dramatically shortened sleep-wake schedules to measure their ability to fall asleep at many times of day and night. For example, in the studies of a "90-min day" by Carskadon and Dement (6), 10 subjects lived on a high-frequency cycle of 30 min of bedrest and 60 min of enforced wakefulness for over 5 calendar days. When averaged across all subjects, the amount of sleep obtained during the 30-min bedrest opportunities was highly dependent on the phase in the body temperature cycle at the time sleep was attempted (6). On average, the least sleep was obtained at 10:30 P.M., ~8 h before the average temperature minimum, precisely as expected from the free-run data (see METHODS and Fig. 2). Very similar results were obtained by Czeisler (9) in his reanalysis of the studies of a "180-min day" conducted by Weitzman et al. (37). Webb and Agnew (36) studied the sleep latencies of subjects living on a cycle of 3 h rest and 6 h enforced activity for 6 calendar days. The 9-h cycle resulted in bedrest onset times at eight different hours of the day. The average sleep latencies varied unimodally with time of day, rising steadily from <5 min at 7:00 A.M. to a peak of 55 min at 10:00 P.M. Although temperature data were not reported, the clock times of these minimum and maximum sleep latencies agree with those estimated from the free-run data (see METHODS). Webb and Agnew (36) describe their results as "surprising" in view of the rise of sleep latency to a "high point at the normal sleep onset time."

The results of these ultradian studies may seem paradoxical, but they are consistent; it is most difficult to fall asleep a few hours before our regular bedtime, precisely at that circadian phase when the fewest bedtimes were selected during internally desynchronized free run (Figs. 1 and 2).

The ultradian studies also reveal an important difference between the two wake-maintenance zones: it is much more difficult to fall asleep in the evening zone than in the morning zone. The subjects in the ultradian studies fell asleep rapidly in the morning zone occurring ~5 h after the temperature minimum. Taken together, the results from free-run (Fig. 2) and ultradian studies suggest that, in the morning zone, people seldom choose to go to bed but can fall asleep readily when instructed to do so, whereas, in the evening zone, they find it difficult as well as undesirable to fall asleep.

Another line of evidence links the evening wake-maintenance zone to sleep-onset insomnia. Fookson et al. (18) induced sleep-onset insomnia in a healthy 21-yr-old male by entraining him to a 23.5-h schedule. Both sleep and temperature rhythms entrained to the short day length but with altered internal phase relations; his circadian temperature rhythm was retarded relative to his imposed bedrest time. Our interpretation (31, 32) of the observed insomnia is as follows: because the evening wake-maintenance zone is tied to the circadian cycle, it too was retarded relative to bedrest. Circadian phase estimates based on temperature data indicate that the zone impinged on the scheduled bedtime and thereby interfered

with sleep onset. Later in the experiment (18), the schedule was shortened to 23.0 h. The subject's sleep-onset insomnia vanished, and his temperature rhythm desynchronized from the 23.0-h schedule. In our interpretation, the disappearance of the insomnia is consistent with the observed desynchronization of the temperature rhythm; the loss of circadian entrainment unlocked the evening zone from the scheduled bedtime and allowed sleep onset to occur after a normal latency.

Clinical implications. Our findings suggest that a malfunction of the phasing of the circadian pacemaker to the 24-h day may underlie the insomnia associated with sleep-scheduling disorders. A small delay in circadian phase would cause the evening wake-maintenance zone to impinge on the bedtime hour, likely resulting in an increased sleep latency. In contrast, only a large phase advance would lead to an overlap of the weaker morning zone with the later hours of sleep. This asymmetry between the zones may account for the rarity of advanced compared with delayed sleep-phase syndrome (12).

Give the proximity of the evening wake-maintenance zone to habitual bedtime, even people without sleep disorders may occasionally select a bedtime during this zone when it is most difficult to fall asleep. For example, many people experience difficulty falling asleep on Sunday night. Presumably they have allowed their sleep-wake schedule (and hence the circadian system with its evening zone) to drift to later hours over the preceding weekend and have thereby inadvertently allowed the evening zone to intrude on their habitual weekday bedtime hour.

Many other factors can precipitate conflicts between bedtime and the evening wake-maintenance zone. First, jet lag acutely alters circadian phasing and often results in a temporary overlap of the evening zone with the new bedtime hour, particularly after eastward travel, until adaptation reestablishes normal phase relations. Second, rotating shift-work schedules result in a similar misalignment of phases that persists chronically because of changing work hours and conflicting cues from environmental and social synchronizers. Third, endogenous factors that may have a genetic basis (19, 22), such as abnormalities in circadian period or a reduced capacity of the pacemaker to be reset by environmental synchronizers, have been hypothesized (12) to underlie the symptoms of patients with chronic sleep-scheduling disorders. In each of these three conditions the circadian phase disorder and its attendant insomnia may be amenable to treatment involving strategically timed exposure to bright light, which was recently indicated (10) to be a phase-resetting stimulus in humans. Thus our findings linking circadian phase dysfunction with insomnia provide a framework for unifying the study and treatment of each of these seemingly disparate conditions.

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