Fundamental Sleep Research

Circadian Sleep Regulation in the Absence of Light Perception: Chronic Non-24-Hour Circadian Rhythm Sleep Disorder in a Blind Man With a Regular 24-Hour Sleep–Wake Schedule

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Summary: Sleep disturbances and the failure to entrain circadian rhythms to the 24-hour day have been reported in the majority of totally blind subjects. The present case study of a totally blind man with a well-documented recurring sleep disturbance was designed to investigate the mutual relationship between sleep and the circadian timing system. The 63-year-old subject, a high school teacher with a regular work schedule, had suffered from cyclically recurring insomnia for the past 28 years. Analysis of a sleep log that he had kept for the past 15 years suggested that his circadian rhythms were not entrained to the 24-hour day. During a 3-month inpatient study, the period of the endogenous circadian pacemaker was assessed by analysis of ambulatory core body temperature, urinary excretion and a series of estimates of the phase of core body temperature cycles and plasma cortisol levels during constant routines. All circadian markers revealed periods in the range of 24.22–24.27 hours, with no evidence for a modulation of the observed periods by the sleep–wake cycle. During this 3-month inpatient study, a complete cycle of the subject's sleep disturbance and remission was polysomnographically documented while the subject lived on a regular 24-hour schedule. Because the subject's circadian rhythms were free-running and his sleep times were fixed, sleep occurred at virtually all circadian phases. Analysis of sleep latency, REM sleep latency, sleep duration, wake in sleep episode and REM sleep during sleep episode revealed a strong modulation by circadian phase. These findings in this blind man suggest that: 1) the period of his cyclically recurring sleep disturbance is directly related to the nonentrained period of an endogenous circadian pacemaker that drives circadian variation in core body temperature, urinary excretion, plasma cortisol and sleep propensity; 2) both his sleep structure and the severity of his daily sleep disruption are directly related to circadian phase and 3) his circadian pacemaker, which has an endogenous period that deviates only 0.2–0.3 hours from 24 hours, cannot be entrained by periodic daily exposure to nonphotic time cues, including a very regular 24-hour sleep–wake schedule. Key Words: Circadian rhythms—Blindness—Sleep—Nonentrainment.
in other variables in the blind. More than 40 years ago, Remler (4) recognized that disrupted sleep was associated with abnormalities in the daily temperature rhythm in the blind and suggested diagnostic evaluation of the endogenous component of that rhythm in such patients, free of the masking effects of activity, sleep and meals. More recently, Orth and Island (5) discovered that the endogenous circadian rhythm of cortisol secretion was not synchronized to the 24-hour day in some blind individuals, a finding consistent with the later case study of Miles et al. (2). In 1983, nonentrained melatonin rhythms were reported in a number of blind subjects (6), and Sack and coworkers (7,8) reported that in such subjects the cortisol and melatonin rhythms oscillate with the same non-24-hour period. Thus, it has been established that blindness may lead to nonentrainment of multiple circadian rhythms, including the sleep–wake cycle—a fact consistent with the conclusion that light is the principal synchronizer of the human circadian timing system (9–12).

Many blind subjects nonetheless attempt to maintain socially acceptable sleep times, even if doing so results in desynchronization of their nonentrained endogenous circadian rhythms from their scheduled sleep–wake times. However, despite an earlier attempt to do so (2), the presence of non-24-hour circadian rhythms has not been verified longitudinally in any blind subject who has regularly maintained a 24-hour sleep–wake schedule that has been documented with polysomnographic sleep recording. Furthermore, although it is known that in sighted subjects the structure and duration of sleep strongly depends on circadian phase (13–15), the circadian influence on sleep and sleep structure in nonentrained totally blind subjects has not been quantified.

The aim of the present case study was thus to test the hypotheses that in a nonentrained blind individual: 1) endogenous circadian rhythms in a number of physiological variables oscillate with a non-24-hour circadian period that can be predicted from the infradian period of the cyclic sleep disturbance, such that:

\[ \tau_i = \tau_c \cdot T / |T_c - T|, \]  

(1)

where \( \tau_i \) = infradian period of the cyclic sleep–wake disturbance, \( T = \) period of the daily sleep–wake schedule, and \( \tau_c \) = circadian period of the nonentrained rhythm(s). Algebraic manipulation of (1) allows estimation of the endogenous circadian period from the infradian rhythm, as follows:

\[ \tau_c = \tau_i \cdot T / (\tau_i \pm T), \]  

(II)

2) sleep propensity, sleep duration and sleep structure depend on the endogenous circadian phase at which sleep occurs.

**METHODS**

**Subject**

A 63-year-old blind man (K.B.) from Germany, who had experienced cyclic sleep disturbances since age 35, was referred to one of us (H.M.) for evaluation. K.B. was married, with two children, and had retired from teaching in June 1987. He suffered from glaucoma since birth and had corrective surgery on both eyes at the age of 10 months. At age 5, the cornea, lens and corpus vitreum of his left eye were destroyed in an accident leaving only residual vision. At age 10, his right eye was enucleated after a series of accidents. At age 15, the residual light/dark vision of his left eye disappeared.

K.B.'s sleep disturbance began at the age of 35 after a transatlantic flight. Periodically, he was not able to sleep at night and felt tired during the day, a situation leading to extended daytime napping despite his very regular schedule as a teacher. This sleep disturbance continued to recur approximately every 3–4 months, prompting K.B. to begin maintaining a sleep–wake log in 1975. Several attempts to treat his disrupted sleep with hypnotics were unsuccessful. He had, however, not taken any sleep medication within the last 2 years. His family history was unremarkable.

Due to the disruptive effects of this sleep disturbance, K.B. contacted one of us (H.M.) in 1984 and participated in an initial evaluation study at the University of Marburg (16). Following that study, K.B. provided informed consent to be studied more extensively in a protocol that was approved by the Brigham and Women's Hospital Committee for the Protection of Human Subjects from Research Risks. A general physical examination and chest radiograph revealed no acute or chronic diseases. He had no allergies and did not take any medications. He reported having nocturia twice per night during periods of disturbed sleep. Noncircadian sleep disorders, such as nocturnal myoclonus and sleep apnea syndrome, were excluded by sleep polysomnogram including nasal/oral airflow and electromyogram (EMG).

**General study design**

The study contained four components: 1) evaluation of subjective sleeplog data collected over the last 15 years; 2) measurements of circadian markers (sleep recording, urine collection, activity recording and ambulatory temperature recording) on a daily basis during a 3-month inpatient study (the approximate length of a complete cycle of sleep disturbance); 3) constant routine assessments of the phases of the endogenous circadian rhythms of cortisol and body temperature.
throughout the 3-month hospitalization and 4) assessment of circadian phase after 3 weeks of exposure to a 7-hour shift of environmental synchronizers.

Assessment of the infradian period of the cyclic sleep disturbance using sleep-wake log data

Since 1975, K.B. kept a log of his nightly sleep duration and daily nap duration, which he estimated and recorded in braille immediately after awakening. These data were translated from the braille by one of us (H.M.), then smoothed with a 30-day moving average. These smoothed data were analyzed by: 1) estimating sequential phases of maximal sleep disruptions using a curve fitting model (17); 2) plotting these estimates cumulatively against time and 3) deriving the best estimate of the infradian period of the cyclic sleep disturbance by linear regression analysis of the estimated phases of maximal sleep disruption.

Assessment of nonentrainment of circadian rhythms

To assess nonentrainment of circadian rhythms, the subject was studied during a 4-month period, which started upon his arrival from Germany to Boston. K.B. was admitted to the Brigham and Women's Hospital, Boston, from 4 September until 19 December 1990. During this 3-month period he lived on a 24-hour schedule similar to his habitual one in Germany with his activities scheduled with reference to Middle European Summer Time (MEST). Throughout the text, clock times are given in MEST (MEST = Eastern Standard Time + 7 hours) in a 24-hour scale. Durations are indicated as a number of hours. Attended walks were allowed in the afternoon and visitors were permitted at all times, except during the scheduled sleep episodes. No other shielding from temporal cues was maintained, except during constant routines, when the subject was kept in temporal isolation. He was scheduled to sleep in total darkness between 2300 and 0700 hours MEST, but he was allowed to get up earlier if he desired. He was scheduled to nap after lunch (1300 hours) each day, although he was permitted to forgo the opportunity if desired. From 20 December to 10 January, he visited relatives in the United States and, thus, was exposed to U.S. Eastern Standard Time (EST), a sudden 7-hour shift of time cues. He returned to the Brigham and Women's Hospital on 10 January 1991 for a final 3-day phase assessment.

Ambulatory recording

K.B. wore an ambulatory monitor (Vitalog PMS-8) from 7 September 1990 to 19 December 1990, except during constant routines (see below). In addition to wrist activity and heart rate monitoring, the Vitalog recorded core body temperature (CBT) in 1-minute intervals using a probe inserted 10 cm into the rectum.

Constant routine recordings

In order to assess the phase (and amplitude) of the subject's circadian pacemaker, we unmasked the circadian rhythms of CBT and plasma cortisol using the constant routine method (18). K.B. completed four full-length 40-hour constant routines, each requiring him to miss 1 night of sleep, and five shorter 16-hour constant routines, which did not require disturbance of his sleep-wake cycle. During these constant routines, K.B. remained in a semirecumbent position. His food and fluid requirements were met by an isocaloric diet, consisting of hourly meals providing 130-150 mEq Na+, 80-120 mEq K+, and 2.5 liters of fluid per day. He was also attended constantly by a technician, who was instructed to prevent him from falling asleep. CBT was recorded on-line on a VAX 11/750 in 1-minute intervals, and subjective assessments of alertness and mood were administered every 20 minutes. Saliva samples were collected every 30 minutes. Blood samples were collected hourly beginning 12 hours before and continuing until 14 hours after the short (16-hour) constant routines and every 20 minutes for the last 35 hours of the 40-hour constant routines through an intravenous catheter inserted in a forearm vein. The blood samples were then centrifuged, and plasma was frozen immediately at -20°C.

Urinary variables

During the entire inpatient study period, urine was collected at the subject's request, and total volume and specific gravity were measured. Urine samples were frozen immediately and later assayed for free cortisol, sodium and potassium. The total number of urine samples was 589, on average 5.6 (range 3-9) samples per day, 14.9% collected during the sleep episodes.

Polysomnographic assessment of one 3-month cycle of sleep disruption and remission

During K.B.'s admission to the Brigham and Women's Hospital, all sleep episodes were polysomnographically recorded, with the exception of 13 spontaneous 1- to 2-hour naps that occurred without notification of the polysomnographic technologist. Because satisfactory signals were not obtained with the standard electrooculograph (EOG) montage (19), EOG was performed by two 6-mm gold-disc electrodes placed directly on the eyelids. With this montage, eye movements could be detected. The records were scored in

Sleep, Vol. 16, No. 4, 1993
TABLE 1. Estimates of endogenous circadian period (and 95% confidence intervals) derived from subjective and objective variables. For the estimates assessed with the minimum variance technique, both the evoked (A) and endogenous (B) component are presented. NK = not known.

<table>
<thead>
<tr>
<th>Subjective and Objective Variables</th>
<th>( \tau )</th>
<th>95% CI</th>
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<tbody>
<tr>
<td><strong>Sleep log</strong></td>
<td></td>
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<tr>
<td><strong>Ambulatory CBT</strong></td>
<td></td>
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<tr>
<td>Minimum variance</td>
<td>23.98 hours (component A)</td>
<td>NK</td>
</tr>
<tr>
<td></td>
<td>24.27 hours (component B)</td>
<td>NK</td>
</tr>
<tr>
<td><strong>Nonorthogonal Fourier analysis</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>24.22 hours</td>
<td>NK</td>
</tr>
<tr>
<td><strong>Constant routine phase estimates</strong></td>
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<td></td>
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<tr>
<td>CBT</td>
<td>24.25 hours</td>
<td>24.17-24.33 hours</td>
</tr>
<tr>
<td>Cortisol</td>
<td>24.24 hours</td>
<td>24.22-24.26 hours</td>
</tr>
<tr>
<td><strong>Urinary variables (minimum variance)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary volume</td>
<td>23.98 hours (component A)</td>
<td>NK</td>
</tr>
<tr>
<td></td>
<td>24.25 hours (component B)</td>
<td>NK</td>
</tr>
<tr>
<td>Urine cortisol</td>
<td>not detected (component A)</td>
<td>NK</td>
</tr>
<tr>
<td></td>
<td>24.25 hours (component B)</td>
<td>NK</td>
</tr>
</tbody>
</table>

randomized order by one of us (T.K.), according to standard criteria. Sleep latency (SL) was defined as the time from lights off to the first epoch of stage 1 and REM latency (RL) as the time from sleep onset to first-stage REM. Two nights were excluded from the analysis because of the technical recording problems. Nocturnal sleep episodes and naps following 40-hour constant routines were also excluded from the analysis because of the confounding effect of sleep deprivation on those recordings.

**Data analysis**

**Core body temperature**

The period of the CBT rhythm throughout the 3-month experiment was estimated using the minimum variance technique, which is a nonparametric spectral analysis procedure (20). The temperature data during the 40-hour constant routines were fitted with a dual harmonic regression model (17) to assess the endogenous phase of the temperature minimum (\( T_{\text{min}} \)) as well as the endogenous temperature rhythm amplitude. The period of the CBT rhythm was then also estimated using linear regression through the sequence of the estimated temperature minima derived from the constant routines.

**Hormonal assays**

The plasma cortisol concentrations were measured within 4 weeks of sample collection by an \(^{125}\)I-coated tube radioimmunoassay procedure at the Core Laboratory of the Brigham and Women's Hospital General Clinical Research Center (21). The phase of the minimum of the cortisol rhythm (\( C_{\text{min}} \)) was estimated using a single-harmonic regression model (17). To assess the circadian period of the plasma cortisol rhythm, the times of the estimated minima were plotted against day number and subjected to linear regression.

Plasma melatonin levels were measured by radioimmunoassay according to the method of Fraser et al. (22).

**Urinary variables**

For all urinary variables, the average amount excreted per minute for the period between two urine samples was calculated by dividing the total excretion by the duration of the interval between samples. The urinary data were then subjected to nonparametric spectral analysis, as described below.

**Assessment of circadian waveforms and phase relations**

The circadian waveforms of the CBT rhythm, sleep and urinary variables were derived by the educed waveform technique (20), in which the data train of 104 days was divided into segments with a length equal to the period of the endogenous (nonentrained) component of the temperature rhythm (\( \tau = 24.27 \) hours) derived using the minimum variance technique (see Results below). For analysis of the urinary data, all of the 102 segments were then averaged in bins of 1-minute duration. For analysis of the sleep data, the segments were divided into either eight bins, each of 182 minutes duration (45 degrees), or 12 bins, of 121.3 minutes (30 degrees) duration each. The average waveform was then calculated by averaging by bin. In all...
waveforms, the phase of the fitted minimum of the endogenous temperature cycle is arbitrarily assigned a reference value of 0 degrees.

RESULTS

Infradian period of the patient's recurring cycle of sleep disturbance

The patient’s self-assessed durations of nighttime sleep and naps showed a repetitive pattern of variation, with 49 cycles occurring over the past 15 years (Fig. 1a). The duration of daytime naps was inversely correlated with nocturnal sleep duration (Pearson’s correlation coefficient $-0.266; p < 0.0001$). The period of this recurring sleep disturbance was remarkably stable over this 15-year period, as illustrated in Fig. 1b. Visual inspection suggested a small change in period upon the patient’s retirement from his full-time job as a high school teacher in 1987.

Linear regression analysis of the data before and after his retirement revealed a period of 118.48 days ($t$ test: 95% confidence interval (CI), 117.75–119.22 days) between 1975 and 1987 and 99.75 days ($t$ test: 95% CI, 98.05–101.45) between 1987 and 1991. The circadian periods derived from these infradian cycles, according to equation (II) correspond to $24.204$ hours (95% CI derived from infradian period analysis: $24.203–24.206$ hours) and $24.243$ hours (95% CI: $24.239–24.247$ hours) for the first and last segments, respectively. These data are summarized in Table 1.

Core body temperature throughout a 3-month inpatient study

Figure 2a illustrates the change in the daily pattern of ambulatory core body temperature (CBT) and its relation to scheduled sleep episodes throughout a 3-month inpatient study corresponding to the last cycle of recurring sleep disturbance of Fig. 1. At the beginning of this cycle, when wakefulness within the scheduled sleep episode was at low levels, CBT below the mean occurred mainly during the scheduled sleep episode. When K.B.’s night sleep was disturbed, temperature values below the mean also occurred outside the main sleep episodes. At first, these below-mean values outside the sleep episodes occurred shortly after night sleep and then over the weeks progressively drifted to later hours. Analysis of the CBT data by non-parametric spectral analysis revealed a strong component at 23.98 hours and a weaker component at 24.27 hours (Fig. 2b).

Core body temperature and plasma cortisol data during constant routines

The minimum of the CBT rhythm during the first constant routine, which was carried out in the undisturbed phase of the last 3-month cycle of sleep disturbance, occurred at 0513 hours, near the end of the habitual sleep episode. On successive constant routines, the minimum drifted to progressively later clock times. Estimates of the period of the CBT rhythm by linear regression analysis on the 40-hour constant routines revealed a period of $24.249 ± 0.019$ (SEM) hours (Figs. 2a, 3).

The minima of the plasma cortisol rhythm during both 40-hour and 16-hour constant routines drifted to
later clock hours at the same rate, consistent with an estimated period of $24.242 \pm 0.007$ (SEM) hours (Fig. 3). In the course of the experiment, no obvious changes in the phase relation between CBT minima and plasma cortisol minima occurred. On average, the minima of the CBT rhythm lagged 9.6 hours behind the minima of plasma cortisol levels, a phase angle comparable to that in internally desynchronized sighted subjects. There were no detectable levels of plasma melatonin.

**Urinary excretion**

Nonparametric spectral analysis of urine production and urine cortisol revealed periods very close to the period derived from the ambulatory CBT rhythm (Table I). Figure 4 shows the waveforms that were deduced by using a 24.27-hour period. A prominent rhythm was observed in all of these variables. Urine flow was maximal at 100 degrees and minimal at approximately 300 degrees. The pattern for the excretion of sodium and potassium per minute was similar to that for urine volume. The peak of the rhythm of plasma cortisol concentration preceded that of urine cortisol concentration by approximately 4 hours.
CIRCADIAN SLEEP REGULATION IN A BLIND MAN

FIG. 2. Linear regression analysis of the fitted minima of the endogenous circadian temperature cycle (filled circles, referenced to ordinal scale on left) recorded during standard 40-hour constant routines and linear regression through the fitted minima of the plasma cortisol cycles (open squares, referenced to ordinate scale on right), assessed during both short (16-hour) and standard (40-hour) constant routines. The phases of the CBT minima (T_m;n) and the plasma cortisol minima (C_m;n) obtained during constant routines are plotted against time, beginning on 7 September 1990. Middle European Summer Time (MEST) was employed as the reference clock hour. Note that the period of the temperature cycle was nearly identical with that of the plasma cortisol rhythm and that their phase relationship remains stable throughout the study, notwithstanding their mutual desynchrony from the subject’s sleep–wake cycle.

Estimation of endogenous circadian period during 3-month inpatient study

All of the observed variables showed a frequency component in the non-24-hour range (Table 1) that could not be attributed to the influence of the subject’s regular 24-hour rest/activity and social schedule and his 24-hour schedule of exposure to environmental time cues. In fact, a 24-hour component was observed only for ambulatory CBT and urinary volume. Urinary cortisol excretion did not exhibit a pronounced 24-hour component. For all variables, throughout the 3-month study the estimates of the non-24-hour frequency component were within the range of 24.22–24.27 hours.

For those variables for which an estimate of the 95% confidence interval was available, it overlapped with the 95% confidence interval of the period predicted from the subject’s recurring sleep disturbance.

FIG. 4. Comparison of educed waveforms of (A) urine volume, (B) urine sodium, (C) urine potassium, (D) urine free cortisol, (E) plasma cortisol and (F) core body temperature. The data trains of each figure were divided into segments of 24.27 hours (obtained from Fig. 2b) and averaged. The minimum of the educed temperature wave (F) was defined as circadian phase 0 and used as a reference marker for Fig. 4A–E. Each vertical bar represents ±1 standard error of the mean.

Sleep, Vol. 16, No. 4, 1993
FIG. 5. The dependency of objective and subjective sleep parameters on the phase of the endogenous circadian temperature rhythm at the start of nocturnal sleep episodes. (A) Total sleep time (TST) as assessed by polysomnographic recording (black bars) and as estimated by the subject (open bars), plotted with respect to the bedrest onset; (B) latency to sleep onset; (C) latency from sleep onset to REM sleep; (D) elicited waveform of core body temperature. Vertical bars represent ±1 standard error from the mean in all panels. ANOVA revealed a significant variation with circadian phase for subjective TST [F(7,85) = 9.03; p < 0.001], objective TST [F(7,85) = 12.30; p < 0.001], sleep latency [F(7,86) = 5.89; p < 0.001] and REM sleep latency [F(7,86) = 7.42; p < 0.001].

Sleep

ANOVA revealed that sleep latency, REM sleep latency and total sleep time varied significantly with circadian phase of the CBT rhythm at which the nocturnal sleep episodes began (in all cases p < 0.0001). Maximum sleep durations were observed when sleep began at approximately 300 degrees (0 degrees is defined by the minimum of the elicited waveform of the CBT rhythm), whereas minimum sleep durations occurred at approximately 150 degrees, which is shortly before the maximum of the CBT rhythm. Although the patterns of the subjective and objective data were similar, the subject tended to overestimate his sleep duration, thereby underestimating his sleep disruption (Fig. 5, panel A).

Sleep latency was shortest around the minimum of the CBT rhythm, whereas K.B.'s maximum sleep latencies were present just before the falling limb of the CBT cycle (Fig. 5, panel B). When analyzed by 30-degree bins, a similar pattern was found for wakefulness within the scheduled sleep episode: wakefulness showed a minimum at the trough of the CBT cycle and gradually increased, reaching a peak just before the...
CBT began to fall, then dropping sharply to minimum levels (Fig. 6, panel C). The interval between sleep onset and the first occurrence of REM sleep was, on average, only 20 minutes per bin (bin = 121.3 minutes = 30 degrees) when sleep was initiated at the CBT minimum. When sleep was initiated at the maximum of the CBT cycle, REM latency averaged 75 minutes (Fig. 5, panel C).

This dependency of REM sleep on circadian phase is further illustrated in Fig. 6, panel B. At the crest of the CBT cycle (90–240 degrees), REM sleep during sleep episode averaged ~10 minutes per bin, thus reaching minimum levels. At the temperature trough (phase 0), REM sleep reached its maximum level of ~20 minutes per bin.

**DISCUSSION**

The present data demonstrate that in this blind subject the cyclic occurrence of severe subjective and objective sleep disturbances are associated with nonentrainment of endogenous circadian rhythms of a variety of physiological variables. In the absence of light input, exposure to strong social cues and a regular 24-hour sleep-wake schedule over a 28-year period could not entrain the circadian pacemaker in this blind subject, even though its intrinsic period deviated only 12–16 minutes from 24 hours during that time. The lack of evidence for relative coordination (23) (i.e. periodic modulation of the observed period of the output of the pacemaker caused by phase control of insufficient strength for entrainment) during this 104-day inpatient study indicates that neither social cues nor a regular sleep-wake cycle had a substantial entraining influence on his circadian pacemaker. Furthermore, even after the subject abruptly shifted his sleep-wake cycle and his exposure to social and other environmental time cues by 7 hours, no evidence was found for an entraining effect of these periodic stimuli on K.B.'s circadian pacemaker, because the phase of the CBT cycle and the plasma cortisol rhythm equaled the phase extrapolated from the free-running period before this shift.

The only change in the intrinsic period of the endogenous circadian pacemaker derived from his 15 years of diary records was observed shortly after K.B.'s retirement in 1987, which was associated with a lengthening of the intrinsic period of his circadian pacemaker by 0.14% (2 minutes). Whether this slight slowing of the circadian clock is due to aging or to the feedback effect of the other factors altered by retirement (such as activity) cannot be determined from this single case.

As we hypothesized, the period of K.B.'s nonentrained circadian rhythms was predicted by the average time interval between phases of maximally disrupted sleep. All circadian variables were free running with a period very close to the period predicted from the infradian period of his sleep disturbance. The 95% confidence interval for the intrinsic period of the subject's circadian pacemaker derived from the infradian sleep disturbance overlapped those derived from both the cortisol and temperature data collected during the inpatient constant routines. Furthermore, although 95% confidence intervals cannot presently be obtained for the period estimates using the minimum variance technique and nonorthogonal Fourier analysis of the ambulatory temperature data, both estimates of the period derived from these procedures were indeed very close to the circadian period derived from the sleep log data.

The mutual phase relationships between the endogenous circadian rhythms of CBT, plasma and urinary cortisol, and urinary volume and electrolytes (as assessed directly during the constant routines and as extracted by waveform eduction during the 3-monthlong inpatient study) matched that found in free-running sighted subjects whenever the period of the sleep-wake cycle was different from the endogenous circadian period of the body temperature cycle [i.e. internal desynchronization (24)]. This strongly suggests that the circadian rhythms in all of these variables are driven by a single circadian pacemaker. However, the relative magnitude of the endogenous and evoked components differed between the physiological variables. In this subject, for instance, urinary volume showed a small 24-hour component but a strong component of 24.25 hours, whereas the opposite was observed for ambulatory CBT. This probably reflects differences in the magnitude of the evoked effects of sleep and activity versus the endogenous circadian component (25). Surprisingly, urinary cortisol was almost free from masking effects of the rest-activity cycle. However, we have observed striking interindividual differ-

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<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SE</th>
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<tbody>
<tr>
<td>SL</td>
<td>1.5</td>
<td>32.2</td>
<td>8.8</td>
</tr>
<tr>
<td>RL</td>
<td>7.4</td>
<td>226.3</td>
<td>42.7</td>
</tr>
<tr>
<td>REM</td>
<td>9.4</td>
<td>88.2</td>
<td>50.3</td>
</tr>
<tr>
<td>TST</td>
<td>120.6</td>
<td>405.2</td>
<td>283.3</td>
</tr>
<tr>
<td>ONE%</td>
<td>5.05</td>
<td>21.8</td>
<td>13.1</td>
</tr>
<tr>
<td>TWO%</td>
<td>45.7</td>
<td>70.6</td>
<td>57.7</td>
</tr>
<tr>
<td>THREE%</td>
<td>0.6</td>
<td>27.8</td>
<td>11.2</td>
</tr>
<tr>
<td>FOUR%</td>
<td>0.0</td>
<td>7.2</td>
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</tr>
<tr>
<td>SW%</td>
<td>0.6</td>
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</tr>
<tr>
<td>REM%</td>
<td>5.7</td>
<td>27.7</td>
<td>17.5</td>
</tr>
<tr>
<td>WISST%</td>
<td>13.8</td>
<td>73.7</td>
<td>39.4</td>
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</table>

Nights after 40-hour constant routines were excluded. SL: sleep latency, RL: REM-latency, REM: time in REM sleep in minutes, TST: total sleep time within a night, ONE%: percentage of stage 1 within a night, TWO%: percentage of stage 2 within a night, THREE%: percentage of stage 3 within a night, FOUR%: percentage of stage 4 within a night, SW%: percentage of slow wave sleep (stage 3 + 4) within a night, REM%: percentage of REM sleep within a night, WISST%: percentage of wake within 480 minutes of scheduled sleep.
ences in the relative strength of the endogenous versus the evoked component of the temperature rhythm among sighted subjects, thus limiting the generality of this finding.

Because the subject kept a regular 24-hour schedule and his circadian rhythms were free-running, this case offered the unique opportunity to study the circadian modulation of sleep in considerable detail. The polysomnographic recording of sleep confirmed the cyclic variation in sleep duration as reported by the subject over a 15-year period. Although sleep data collected during spontaneous desynchrony between the sleep–wake and body temperature cycles in sighted subjects have suggested that the structure and duration of sleep depends on circadian phase, those findings have been confounded by the unequal distribution of sleep onsets with respect to circadian phase and by the large variation in the duration of wakefulness preceding sleep. Nevertheless, the observed variation in the duration of nighttime sleep and its structure as a function of circadian phase was similar to that observed in sighted subjects during spontaneous desynchronization of the sleep–wake cycle and the CBT cycle (14,15). Specifically, nighttime sleep duration was shortest when sleep was initiated at the rising limb of the CBT cycle and longest when initiated just after its maximum. These data support the notion that nonentrainment of the circadian pacemaker is a primary cause of the cyclic sleep disturbance in this subject. The inverse relationship between nighttime sleep duration and the length of daytime nap sleep may be the reflection of a compensatory mechanism offsetting nighttime sleep loss. This suggests that a homeostatic process contributes to the regulation of sleep duration, in addition to the circadian process (26).

Averaged per 2-hour bin, sleep latencies for the nocturnal sleep episodes varied between 6 and 16 minutes. This result indicates that although circadian phase modulates sleep latency, sleep could be initiated at all circadian phases, arguing that a standard duration of prior wakefulness (i.e. ~16 hours) can overcome the effect of the “forbidden zone” for sleep that has been observed in studies of ultrashort sleep–wake schedules (i.e. the 20-minute “day”) (27). The sudden increase of wakefulness within sleep just before the fall of body temperature suggests, however, a strong drive for waking at this circadian phase, as has been reported for sighted subjects during spontaneous desynchrony of the sleep–wake cycle from the body temperature rhythm (28). However, neither the data on sleep latency nor the dependency of wakefulness within the scheduled sleep episodes on circadian phase confirmed the peak in sleep propensity just before the maximum of the core body temperature rhythm, which has been observed in temporal isolation studies (29).

The present case demonstrates that the endogenous circadian rhythms of many variables can free-run with a period slightly different from 24 hours, despite scheduled exposure to social cues and strict maintenance of a 24-hour sleep–wake schedule. Thus, the attempts of such blind persons to keep a socially acceptable schedule can have severe repercussions on the quality of their sleep and wakefulness. These and other recent findings (30,31), together with our recent observation (Martens et al. in preparation) that photic input was capable of suppressing melatonin secretion in a blind patient whose sleep showed no evidence of disturbance, underscore the significance of research aimed at a better understanding of the mechanism involved in synchronization of the human circadian pacemaker to the 24-hour environment.

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