Conservation of photoperiod-responsive mechanisms in humans

THOMAS A. WEHR, DOUGLAS E. MOUL, GIUSEPPE BARBATO, HOLLY A. GIESEN, JASON A. SEIDEL, CHARLES BARKER, AND CHARLES BENDER
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Wehr, Thomas A., Douglas E. Moul, Giuseppe Barbato, Holly A. Giesen, Jason A. Seidel, Charles Barker, and Charles Bender. Conservation of photoperiod-responsive mechanisms in humans. *Am. J. Physiol.* 265 (*Regulatory Integrative Comp. Physiol.* 34): R846–R857, 1993.—In animals, circadian pacemakers respond to seasonal changes in day length by making corresponding adjustments in the durations of diurnal and nocturnal periods of circadian rhythms; these adjustments mediate effects of photoperiod on breeding and other seasonally recurring phenomena. Little is known about photoperiod responses of human circadian pacemakers. To investigate this question, we recorded and compared circadian rhythm profiles of 15 individuals after chronic exposures to short (8 h) and long (14 h) nights. As occurs in animals, durations of nocturnal periods of active melatonin secretion (11.9 ± 1.6 vs. 10.3 ± 1.3 h, df = 14, t = 4.583, $P < 0.0005$, paired t test), high prolactin secretion (12.9 ± 2.1 vs. 9.9 ± 2.2 h, df = 11, t = 2.917, $P < 0.01$), and sleep (10.6 ± 0.8 vs. 7.6 ± 0.4 h, df = 14, t = 17.122, $P < 0.0005$) were longer after exposure to long nights than after short ones. Durations of nocturnal periods of low rectal temperature (11.6 ± 2.3 vs. 9.5 ± 1.6 h, df = 12, t = 3.912, $P < 0.001$) and rising cortisol secretion (10.8 ± 1.6 vs. 9.3 ± 1.9 h, df = 14, t = 3.130, $P < 0.005$) were also longer. Some of these differences persisted during 24-h periods of enforced wakefulness in constant dim light, indicating that prior exposure to the two regimes induced abiding changes in the timing of internal processes, such as circadian pacemaker oscillations, that control the durations of nocturnal and diurnal periods of the rhythms.

photoperiodism; seasons; circadian rhythm; light; sleep; melatonin; prolactin; thyrotropin; growth hormone; cortisol; luteinizing hormone; testosterone; body temperature

BECAUSE THE EARTH ROTATES, organisms that live on it are regularly exposed to two different environments: a world of light and a world of darkness. Because adaptations that make animals fit for one of these environments are likely to make them less fit for the other, most animals have specialized in the active engagement of only one of the two environments. They generally withdraw from the other environment, usually by sleeping in a secure refuge, to avoid threats to their survival and minimize inefficient expenditure of energy. Consequently, as day alternates with night, most animals alternate between contrasting behavioral and physiological states, one geared to active engagement of a field environment and one geared to withdrawal into a home environment (28).

Switching between these states is not simply a passive response to changing external light conditions; it is an active process that is triggered internally by circadian pacemakers that are synchronized with dawn and dusk and anticipate the transitions between day and night (28). Furthermore, these pacemakers can detect seasonal variations in the lengths of day and night and make corresponding adjustments in the durations of diurnal and nocturnal periods of the endogenous daily rhythms. Because circadian pacemakers can detect and respond to changes in photoperiod (day length), and because changes in photoperiod correspond to changes in the time of year, animals also use circadian pacemakers as an annual clock to control the timing of seasonal rhythms in their physiology and behavior (25). In some animals, changes in the duration of nocturnal melatonin secretion induced by pacemakers' responses to seasonal changes in photoperiod chemically mediate the latter's effects on breeding and other seasonally recurring phenomena (2).

Although much is known about the capacity of animals to detect and respond to changes in photoperiod, relatively little is known about this capacity in humans. Such a capacity might be masked in modern humans, because we are seldom exposed to the seasonal changes of a purely natural photoperiod. With artificial light, we have created a microenvironment in which we are exposed to long photoperiods year-round.

If, in the course of their evolution, humans have conserved a latent capacity to respond to changes in photoperiod, then it should be possible to unmask this capacity by exposing individuals to artificial photoperiods of different durations and detecting differences in the daily profiles of their circadian rhythms. Specifically, durations of nocturnal periods of circadian rhythms should become longer when individuals are transferred from conventional short nights to long nights. To test this hypothesis, we recorded and compared the circadian-rhythm profiles of 15 healthy volunteers after they were chronically exposed to 8- and 14-h nights on two separate occasions. In each of the two lighting regimes, we measured circadian rhythms in rectal temperature (T_r), electroencephalographically monitored sleep, and plasma levels of melatonin (MT), prolactin (PRL), cortisol, thyrotropin (TSH), and growth hormone (GH).

SUBJECTS AND METHODS

Subjects. Sixteen healthy young individuals (15 men and 1 woman), 20–36 yr old, participated in the experiments. The study protocol was approved by the institutional human research committee of the Intramural Program of the National Institute of Mental Health, and all subjects gave informed consent after the nature and possible consequences of the experiment were fully explained.

Experimental conditions. Subjects adhered to a conventional long-day photoperiod regime (16 h light/activity, 8 h dark/rest) for 1 wk and, after an interval of 2 wk, to a short-day regime (10 h light/activity, 14 h dark/rest) for 4 wk. One week of exposure to the long-day regime was chosen because the 16-h light period approximated the one in which subjects ordinarily were living; therefore it seemed unlikely that a lengthy period of adjustment would be required. Four weeks of exposure to the short-day regime were chosen because this light period differed greatly from the one to which the subjects were usually exposed, and

similar experiments in animals raised the possibility that several weeks of adjustment might be required.

During the dark period of each light/activity regime, the individuals were confined alone in a windowless dark room. They were instructed to remain at bed rest and to sleep whenever possible during the dark period, except when it was necessary to use an adjoining dark bathroom. Activities, such as exercising or listening to music, were not permitted during the dark period. During the daily light period, the individuals went about their normal activities exposed to the ambient artificial and natural light in their normal environment.

Sleep and temperature recordings. During each dark period, vigilance state was recorded electroencephalographically. Electroencephalograph (EEG) records were scored for wakefulness and sleep stages in 30-s epochs according to conventional criteria. T_r was recorded every 6 min, 24 h/day, with an indwelling probe connected to a portable electronic instrument that stored the measurements in electronic memory (Vitalog). At intervals, the data were then transferred via an interface connection to computer files for subsequent analysis.

Blood-sampling procedures. At the end of each of the two photoperiod regimes, blood samples were obtained every 30 min beginning at 1700 h on *day 1* of the blood-sampling period and continuing through the dark/rest/sleep period (either 2400 or 1800 h on *day 1* to 0800 h on *day 2*) and through a 29-h constant-routine protocol from 0800 h on *day 2* to 1300 h on *day 3*. During the constant-routine protocol, individuals remained continuously awake in constant dim (<1 lx) light and consumed small isocaloric meals every 2 h. The purpose of the constant-routine protocol was to minimize or distribute evenly the possible masking effects of sleep, posture, exercise, meals, and light, which might distort the intrinsic patterns of circadian rhythms. Blood samples obtained during the first 24 h (from 1700 h on *day 1* to 1700 h on *day 2*), which encompassed the dark/rest/sleep period, were analyzed by radioimmunoassay for plasma levels of PRL and GH. Blood samples obtained during the last 24 h (from 1300 h on *day 2* to 1300 h on *day 3*), which encompassed the constant-routine period, were analyzed for plasma levels of MT. All blood samples (from 1700 h on *day 1* to 1300 h on *day 3*) were analyzed for plasma levels of cortisol and TSH. Three blood samples (obtained at 1000, 1030, and 1100 h on *day 2*) were analyzed for plasma levels of luteinizing hormone (LH), testosterone, and free 3,5,3′-triiodothyronine (T_3). Plasma levels of TSH, PRL, cortisol, GH, testosterone, LH, and free T_3 were measured in duplicate by radioimmunoassay by Hazelton Laboratories, Vienna, VA, with standard methods (details available on request). Plasma levels of MT were measured in duplicate by radioimmunoassay by StockGrand, Guildford, Surrey, UK (see Ref. 32 for details).

Psychometric assessments. Twice each day, just before and just after the dark/rest/sleep period, subjects assessed their mood states with the Profile of Mood States and their levels of energy and mood with 100-mm-line rating scales (13). Every hour during the constant routine, from 1300 h on *day 2* to 1300 h on *day 3*, subjects assessed their level of sleepiness with the Stanford Sleepiness Scale (12).

Data analysis. Based on published information about animals' responses to a change in photoperiod, we predicted that durations of nocturnal periods of circadian rhythms would be longer after exposure to long nights than after exposure to short nights. Therefore, one-tailed paired *t* tests were used to assess the statistical significance of differences between the durations of nocturnal periods of circadian rhythms in the two photoperiod regimes. For each individual, durations of nocturnal periods of circadian rhythms were defined as follows. *1*) Nocturnal period of low T_r: interval between downward and upward midrange crossings of five-point moving average of levels (for constant-routine data) or of mean 24-h profiles of last 6 days of each photoperiod regime (for non-constant-routine data). *2*) Nocturnal period of rising cortisol secretion: interval between minimum and maximum values of five-point moving average of plasma levels. *3*) Nocturnal period of high TSH secretion: interval between upward and downward midrange crossings of five-point moving average of plasma levels. *4*) Nocturnal period of high PRL secretion: cumulative time that 24-h profiles of plasma levels were above their mean. *5*) Nocturnal period of active MT secretion: interval between appearance and disappearance of sustained detectable plasma levels. *6*) Nocturnal sleep period: mean interval between first and last occurrences of sleep during last six nights of each photoperiod regime. *7*) Nocturnal period of rising sleepiness: interval between last minimum and first maximum values of scores on the Stanford Sleepiness Scale.

The degree to which photoperiod-induced changes in the durations of nocturnal periods of different circadian rhythms were correlated with one another was assessed by calculating Spearman correlation coefficients of all possible pairwise comparisons of these changes.

Using phase markers that we used to define the onsets of nocturnal periods of circadian rhythms (described above), we examined whether transfer from short nights to long nights altered the internal phase relationships among the four circadian rhythms that were measured in the constant-routine protocol, namely, the rhythms in MT, cortisol, TSH, and T_r. Paired *t* tests (2 tailed) with Bonferroni corrections for multiple comparisons were used to assess the statistical significance of differences between these internal phase relationships in the two photoperiod regimes.

To assess possible effects of the change in photoperiod on mental state and sleep characteristics, weekly means of daily mood and sleep variables from the 1 wk of short nights and 4 wk of long nights were analyzed with one-way analysis of variance (ANOVA) with repeated measures with Greenhouse-Geisser corrections. When there was a statistically significant effect of week, differences between weeks were explored with post hoc Tukey tests. For the sake of brevity, only post hoc test results pertaining to differences between the fourth week of long nights and the week of short nights are presented in RESULTS. Sleep variables included minutes of total sleep, minutes of *stages 1–4* and rapid-eye-movement (REM) sleep, minutes of wakefulness in the dark period before, during, and after the sleep period (sleep latency, wakefulness after sleep onset, and early morning awakening, respectively), and REM density.

To explore effects of long-term exposure to long nights, 2 of the 16 individuals, a 34-yr-old man and a 35-yr-old woman, were exposed to 14-h nights for 15 wk. For both subjects, high-resolution magnetic resonance images of the head were obtained with a 4.5-T scanner just before the period of exposure to long nights (November 1991), just before the end of the period of exposure to long nights (February 1992), and after several months of reexposure to short nights (July 1992). Measurements of these images were used to estimate changes in pituitary volume over the course of the experiment.

RESULTS

Fifteen individuals completed the experiment. The 16th individual progressively became severely depressed and suicidal during the first 5 days of exposure to long nights and was removed from the experiment. He gradually recovered during the first week of his return to a normal schedule. Although he had no prior history of affective disorder, his second-degree relatives did. Since terminating the experiment 2 years ago, he has remained well.

For MT, total sleep, and sleepiness, preliminary data from seven of the individuals who participated in the experiment were published previously (32). The present results confirm and extend the earlier findings for MT and sleep. All other findings are new.

Changes in durations of nocturnal periods of circadian rhythms after transfer from short nights to long nights. After transfer from short nights to long nights, the group exhibited lengthening of the nocturnal periods of the following (Table 1 and Fig. 1): *1*) high pituitary PRL secretion (Fig. 2), *2*) low T_r (Figs. 3 and 5), *3*) rising adrenal cortisol secretion (Fig. 4), *4*) active pineal MT secretion (Fig. 5), and *5*) sleep (Figs. 6–10). Ipso facto, they exhibited a corresponding shortening of the diurnal periods of these rhythms.

In addition, the group exhibited lengthening of the nocturnal interval between the peak of slow-wave sleep at the beginning of sleep (Fig. 2) and the peak of REM sleep at the end of sleep (Fig. 9) and lengthening of the interval between the peak of pituitary GH secretion at the beginning of sleep and the midpoint of the dark period (Fig. 2 and Table 1). The rhythm of pituitary TSH secretion was uniquely unaffected by the change in photoperiod (Fig. 4 and Table 1).

Correlations between changes in durations of nocturnal periods of different rhythms. After transfer from short nights to long nights, we could find no relationship between changes in the duration of the nocturnal period of one circadian rhythm and that of another. There was no pair of rhythms for which the Spearman correlation between changes in durations of nocturnal periods of the rhythms was statistically significant.

Changes in internal phase relationships between rhythms. After transfer from short nights to long nights, the time of the nightly decline of T_r advanced relative to the time of the nightly onset of MT secretion [mean 1.2 ± 1.0 (SD) h, df = 12, $t = 4.132$, $P = 0.001$, paired t test with Bonferroni correction] and to the time of the nightly rise of TSH secretion (mean 2.1 ± 1.1 h, df = 10, $t = 6.211$, $P < 0.001$; Fig. 5). The time of the nightly minimum of cortisol secretion also advanced relative to the time of the nightly rise of TSH secretion (mean 1.6 ± 1.3 h, df = 11, $t = 4.255$, $P = 0.001$).

Changes in sleep patterns. After transfer from short nights to long nights, sleep typically separated into two fragments with an interval of wakefulness between them (Fig. 6). Consequently, the temporal distribution of sleep became symmetrically bimodal (Fig. 9).

In long nights compared with short nights, subjects had more total sleep, REM sleep, and *stages 1* and *2* sleep but approximately equal amounts of *stages 3* and *4* sleep. ANOVAs of weekly means of sleep variables revealed that there were statistically significant effects of week on minutes of total sleep (df = 4,14, $F = 52.796$, $P < 0.0001$), REM sleep (df = 4,14, $F = 18.690$, $P < 0.0001$), *stage 1* sleep (df = 4,14, $F = 43.268$, $P < 0.0001$), and *stage 2* sleep (df = 4,14, $F = 41.280$, $P < 0.0001$) but not on minutes of *stage 3* sleep [df = 4,14, $F = 0.727$, not significant (NS)], *stage 4* sleep (df = 4,14, $F = 1.592$, NS), and delta (*stage 3* + *stage 4*) sleep (df = 4,14, $F = 0.535$, NS). Post hoc Tukey tests indicated that in the fourth week of long nights compared with the week of short nights, there was significantly more total sleep (493.9 ± 50.7 vs. 430.5 ± 15.8 min), REM sleep (112.3 ± 14.1 vs. 94.9 ± 13.3 min), *stage 1* sleep (32.4 ± 8.6 vs. 18.2 ± 8.3 min), and *stage 2* sleep (312.9 ± 42.2 vs. 276.9 ± 31.1 min). In the fourth week of long nights and the week of short nights, time in *stage 3* sleep was 23.8 ± 16.3 and 22.1 ± 14.4 min, time in *stage 4* sleep was 16.7 ± 19.9 and 13.9 ± 17.4 min, and time in delta (*stage 3* + *stage 4*) sleep was 40.4 ± 32.4 and 36.0 ± 29.0 min, respectively.

In long nights, unlike short nights, subjects spent much time in a state of quiet wakefulness characterized by a prominent and sustained alpha rhythm in the EEG (unpublished observations). ANOVAs of weekly means of sleep variables indicated that there were statistically significant effects of week on the duration of the interval of wakefulness from the beginning of the dark period to the beginning of sleep (sleep latency; df = 4,14, $F = 55.248$, $P < 0.0001$), the cumulative duration of wakefulness

Table 1. *Nocturnal periods of daily rhythms: durations in short nights vs. long nights*

	Duration, h			df	t	P
	Short nights	Long nights	Difference			
	Regular routine					
Low temperature	9.2±1.8	12.1±1.5	2.9±2.5	13	4.327	0.001
Rising cortisol	7.0±1.9	9.0±1.0	2.0±1.7	11	4.069	0.001
High thyrotropin	10.0±2.5	10.4±1.9	0.4±2.3	11	0.636	NS
High prolactin	9.9±2.2	12.9±2.1	3.0±3.6	11	2.917	0.007
Interval between sleep-related GH peak and middle of dark period	2.7±0.6	4.3±0.8	1.6±0.8	10	6.980	0.000
Sleep	7.6±0.4	10.6±0.8	3.0±0.7	14	17.122	0.000
Interval between peak of slow-wave sleep and peak of REM sleep	5.4±1.4	7.3±1.4	1.8±1.5	14	4.705	0.000
	Constant routine					
Low temperature	9.5±1.6	11.6±2.3	2.1±2.0	12	3.912	0.001
Rising cortisol	9.3±1.9	10.8±1.6	1.5±1.8	14	3.130	0.004
High thyrotropin	11.6±1.1	11.8±1.6	0.2±1.6	11	0.693	NS
High melatonin	10.3±1.3	11.9±1.6	1.7±1.4	14	4.583	0.000
Rising sleepiness	7.9±3.3	9.1±3.6	1.2±4.5	14	1.038	NS

Values are means ± SD of nocturnal period durations. GH, growth hormone; REM, rapid eye movement. Statistical tests were paired (t values) and 1 tailed (P values).

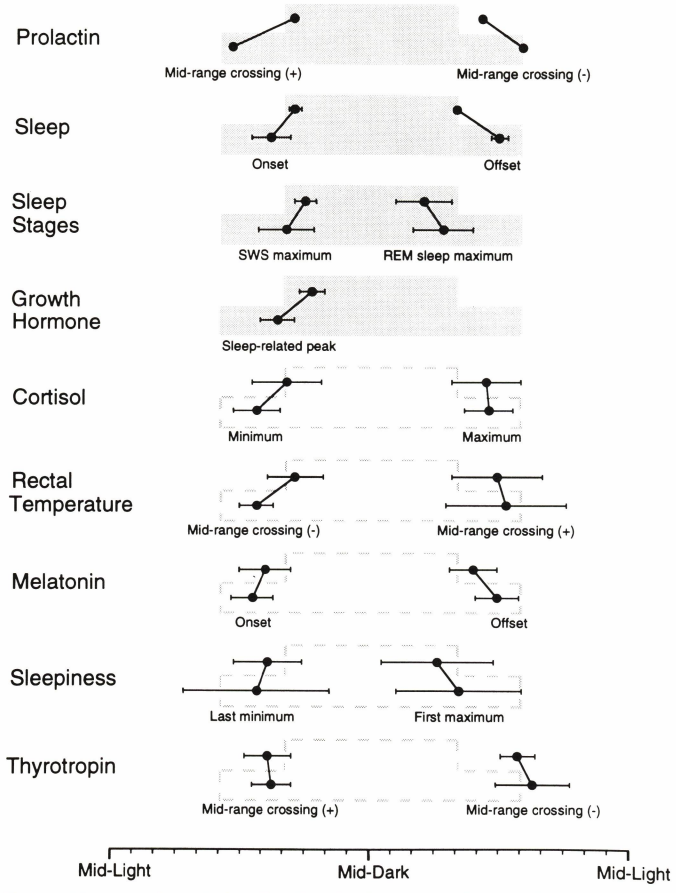

Fig. 1. Nocturnal periods of daily rhythms were longer during or after exposure to long (14 h) nights compared with exposure to short (8 h) nights. For each of the 2 conditions, mean times of onsets and offsets of nocturnal periods of daily rhythms are shown (see text for definitions). Prolactin, sleep, sleep stages, and growth hormone were measured during last day of each photoperiod schedule. For these variables, shaded areas indicate durations and times of occurrence of dark periods in each of the 2 schedules (in each pair: *top*, short nights; *bottom*, long nights). Cortisol, rectal temperature, melatonin, sleepiness, and thyrotropin were measured after end of each photoperiod schedule, in a constant-routine protocol in which individuals remained continually awake in constant dim (<1 lx) light. For these variables, broken lines indicate durations and times of occurrence of dark periods to which individuals had been exposed during week(s) preceding constant routine. REM, rapid eye movement; SWS, slow-wave sleep.

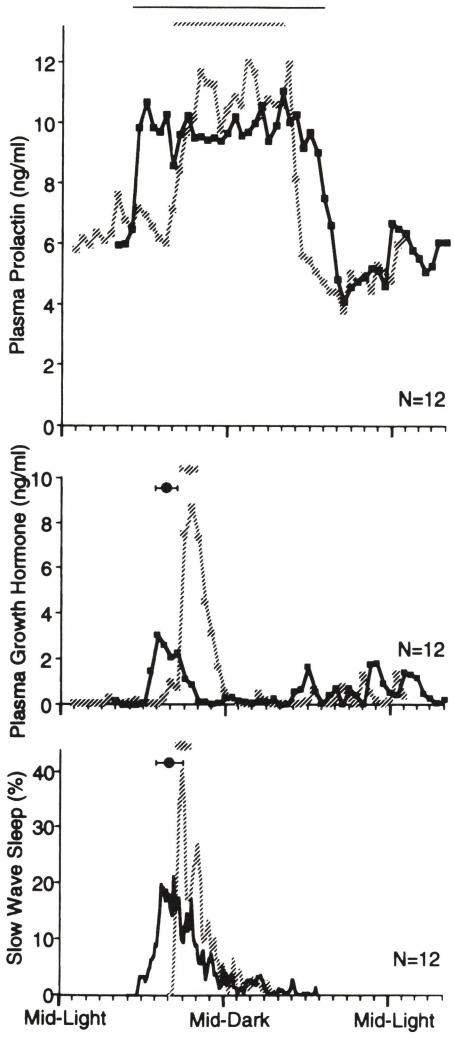

Fig. 2. Mean 24-h profiles of 30-min plasma levels of prolactin (*top*) and growth hormone (*middle*) and mean 24-h profiles of 6-min percentages of slow-wave sleep (*bottom*) in short (8 h) nights (hatched lines) and long (14 h) nights (solid lines). Horizontal lines above data indicate times of respective dark periods. Data are referenced to midpoints of dark periods, and hourly intervals are marked along abscissa. For each photoperiod schedule, mean times of nightly peaks of sleep-related growth hormone secretion and slow-wave sleep are shown above corresponding data.

within sleep (wake after sleep onset; df = 4,14, $F = 33.881$, $P < 0.0001$), and the duration of the interval of wakefulness from the end of sleep to the end of the dark period (early morning awakening; df = 4,14, $F = 49.471$, $P < 0.0001$). Post hoc Tukey tests indicated that in the fourth week of long nights compared with the week of short nights, there were significant increases in these measures of wakefulness (144.1 ± 52.7 vs. 25.1 ± 16.3 min, 128.5 ± 56.6 vs. 17.5 ± 10.0 min, and 62.6 ± 24.4 vs. 1.4 ± 1.9 min, respectively; Fig. 11).

After transfer from short nights to long nights, average REM density, a measure of the intensity of phasic eye movements during REM sleep, increased. An ANOVA of weekly mean values of REM density revealed statistically significant effects of week (df = 4,14, $F = 14.119$, $P < 0.0001$), and post hoc Tukey tests indicated that in the fourth week of long nights compared with the week of short nights, there were significant increases in REM density (2.5 ± 0.7 vs. 2.0 ± 0.7 units).

Changes in longitudinal self-ratings. After transfer from short nights to long nights, the individuals felt less fatigue, according to their Profile of Mood States subscale scores for this symptom. An ANOVA revealed a statistically significant effect of week (df = 4,11, $F = 13.56$, $P < 0.0001$), and post hoc Tukey tests indicated that in the fourth week of long nights compared with the week of short nights, there was a statistically significant decrease in fatigue scores (5.2 ± 4.1 vs. 0.7 ± 1.0). They also felt happier and more energetic. ANOVAS of weekly mean values of 100-mm-line self-rating scores for these items revealed statistically significant effects of week (df = 4,11, $F = 16.5$, $P < 0.0001$; and df = 4,11, $F = 13.18$, $P < 0.0001$), and post hoc Tukey tests indicated that in the fourth week of long nights compared with the week of

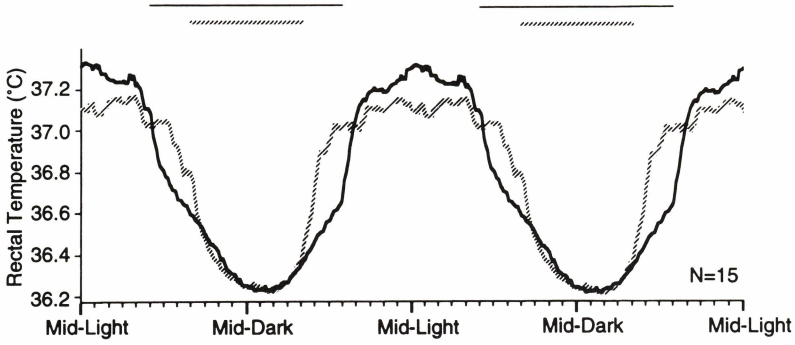

Fig. 3. Mean 24-h profiles of 6-min levels of rectal temperature in short (8 h) nights (hatched lines) and long (14 h) nights (solid lines). Data are taken from last 6 days of each photoperiod schedule. See Fig. 2 for indications.

short nights, there were statistically significant increases in these scores (69.1 ± 7.4 vs. 57.8 ± 7.2 and 67.8 ± 10.6 vs. 52.3 ± 10.2; Fig. 12).

Changes in LH, testosterone, and free T_3. When the results for long days and short days were compared, there were no statistically significant differences in plasma levels (means of 1000, 1030, and 1100h samples) of LH (8.4 ± 2.6 vs. 9.4 ± 3.0 mIU/ml, df = 12, t = 1.207, NS, paired t test), testosterone (551.8 ± 209.8 vs. 569.1 ± 212.4 ng/dl, df = 12, t = 0.427, NS), and free T_3 (2.1 ± 0.5 vs. 2.1 ± 0.5, df = 11, t = 0.32, NS).

Post hoc findings. During the light period, T_r was higher in short days than in long days (Figs. 3 and 7). A post hoc ANOVA of temperature levels referenced to the middle of the dark period (based on individuals' means for each time of day calculated from data from the last 6 days of each photoperiod regime) showed a statistically significant interaction between type of photoperiod and time of day (df = 48,672, F = 10.87, $P < 0.0001$). Post hoc Tukey tests showed that most daytime temperature values in the 10:14-h light-dark cycle were higher than the corresponding values in the 16:8-h light-dark cycle (Fig. 3).

An exploratory post hoc analysis revealed that levels of sleep-related peaks in GH secretion were lower in long nights than in short nights (5.7 ± 4.4 vs. 11.2 ± 6.9 ng/ml, df = 11, t = 2.987, P = 0.012, 2-tailed paired t test; Fig. 2).

After a man and a woman were exposed to long nights for 15 wk, their pituitary volumes decreased; after they were chronically reexposed to short nights, their pituitary volumes increased again to baseline values. The respective volumes were 0.483, 0.398, and 0.504 ml in the man and 0.737, 0.637, and 0.770 ml in the woman. After their long-term exposure to long nights, both subjects found it extremely difficult to adjust to the return to short nights. They experienced a sustained and profound decrease in energy and increase in fatigue.

DISCUSSION

Striking homologies between humans and animals emerged from our investigation of the effects of photoperiod on sleep and circadian rhythms.

Nocturnal periods of daily rhythms were longer in long nights. The individuals in this experiment responded to changes in photoperiod duration as animals do, by making corresponding adjustments in the durations of diurnal and nocturnal periods of their daily rhythms. When night was lengthened, the nocturnal periods of daily rhythms in MT, PRL, cortisol, T_r, and sleep also lengthened. In addition, the interval between the peak of slow-wave sleep

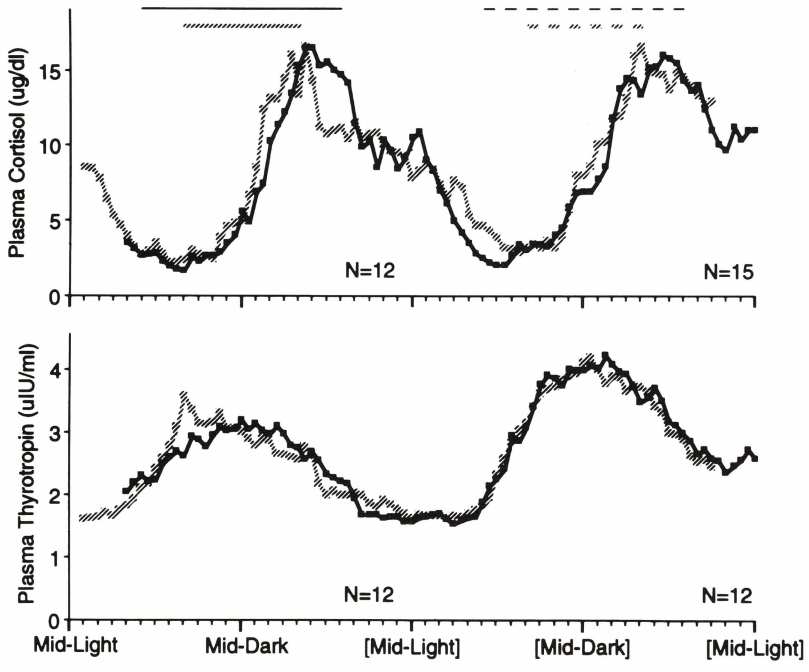

Fig. 4. Mean profiles of 30-min plasma levels of cortisol (*top*) and thyrotropin (*bottom*) during last day of exposure to short (8 h) nights (hatched lines) and long (14 h) nights (solid lines) and during constant-routine measurement periods that followed last short and long nights. See Fig. 2 for indications. During constant-routine portion of study, individuals remained continuously awake in constant dim light, and no light-dark cycle was applied. For constant-routine data, times corresponding to midpoints of light and dark periods in previous days' light cycles are shown in brackets along abscissa, and extents of previous days' dark periods are indicated by broken horizontal lines above data.

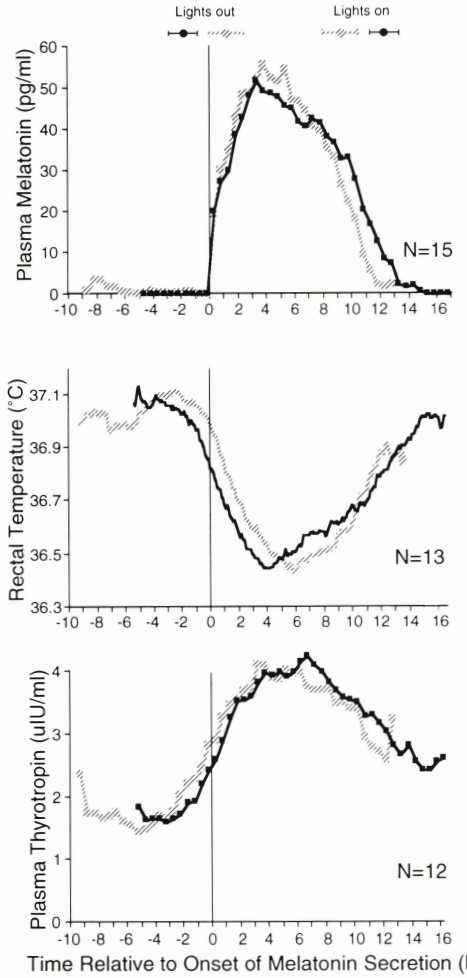

Fig. 5. Mean profiles of 6-min levels of rectal temperature (*middle*) and 30-min plasma levels of melatonin (*top*) and thyrotropin (*bottom*) were measured while individuals remained continuously awake in constant dim light after they had been chronically exposed to short (8 h) nights (hatched lines) and long (14 h) nights (solid lines). For each photoperiod schedule, data for all 3 variables are referenced to individuals' times of onset of nocturnal melatonin secretion. Mean times of onsets (lights-out) and offsets (lights-on) of dark periods to which individuals had been exposed are shown (*top*; light-dark cycle was suspended during constant-routine measurement period). Nightly decline in rectal temperature occurred earlier, relative to onset of melatonin secretion and rise of thyrotropin secretion, after exposure to long nights than after exposure to short nights.

at the beginning of the night and the peak of REM sleep at the end of the night increased. For MT, PRL, and sleep, similar responses have been described in animals (2, 14, 21, 31), but for cortisol and T_r they have not.

The MT finding is potentially important because changes in the duration of nocturnal MT secretion in animals have been shown to chemically mediate effects of seasonal changes in the photoperiod on breeding, thermoregulation, metabolism, and other functions that vary with the seasons (2). Whether the photoperiod-induced changes in MT secretion that we observed could modify such functions in humans needs to be investigated. In this regard, there were no changes in LH or testosterone levels after 4 wk of exposure to long nights, and the results of an experiment in which we assessed the effects on two individuals' reproductive function of 15 wk of exposure to long nights were inconclusive (unpublished observations). The preliminary finding that chronic exposure to long nights reversibly decreased the size of these individuals' pituitary glands, however, is a potentially important finding that needs to be confirmed in additional subjects.

The PRL finding is of special interest because changes in photoperiod have been shown to modify PRL secretion in many animals, and changes in PRL secretion have been shown to chemically mediate seasonal effects of the photoperiod on skin and its appendages (10). Although a parallel to the human PRL response to photoperiod can be found in domestic cats (21), the responses of other animals are opposite, in that they secrete less PRL in long nights (31).

In humans, the nocturnal rise in PRL secretion is thought to be sleep dependent (24). If so, then it is not surprising that the cumulative duration of high PRL secretion increased when the cumulative duration of sleep increased in long nights. However, the pattern of PRL secretion in long nights suggests that PRL secretion is not strictly sleep dependent. In long nights, the onset of the nightly surge in PRL secretion was detected in samples obtained 30 min after the beginning of the dark period (Fig. 2), even though none of the subjects had fallen asleep at this time (average sleep latency ~2 h; Fig. 11). An alternative possibility is that darkness stimulates human PRL secretion. Results of a subsequent experiment, however, failed to support this hypothesis (unpublished data). Another possibility is that quiet rest stimulates human PRL secretion. A previously published report that meditation stimulates human PRL secretion seems consistent with this hypothesis (16). Indeed, our subjects, when lying awake in long nights, resembled meditating individuals in displaying prominent and sustained alpha rhythms in their EEGs.

Change in photoperiod modified timing of internal processes that control daily rhythms. The findings that the durations of nocturnal periods of MT and sleep were longer in long nights extend and confirm previously published preliminary findings in 7 of the 15 subjects who participated in the experiment (32). These results are also consistent with data of Beck-Friis et al. (3), Burefsová et al. (5), and Kauppila et al. (17), who found seasonal changes in the duration of nocturnal MT secretion in individuals who were studied naturalistically in their normal routines [using similar methods, however, Illnerová et al. (15), Broadway et al. (4), and Matthews et al. (22) did not find such differences]. The unique feature of our observations is that differences in profiles of the MT, cortisol, and T_r rhythms that were observed after exposure to the two photoperiod schedules were detected during the constant-routine period, when the light-dark cycle was suspended, and the individuals remained continuously awake in constant dim light. In this situation, differences in the rhythm profiles cannot be ascribed to merely passive responses evoked by the immediate presence or absence of light [for example, light can directly suppress human MT secretion (20)]. The detection of these differences in the conditions of the constant routine

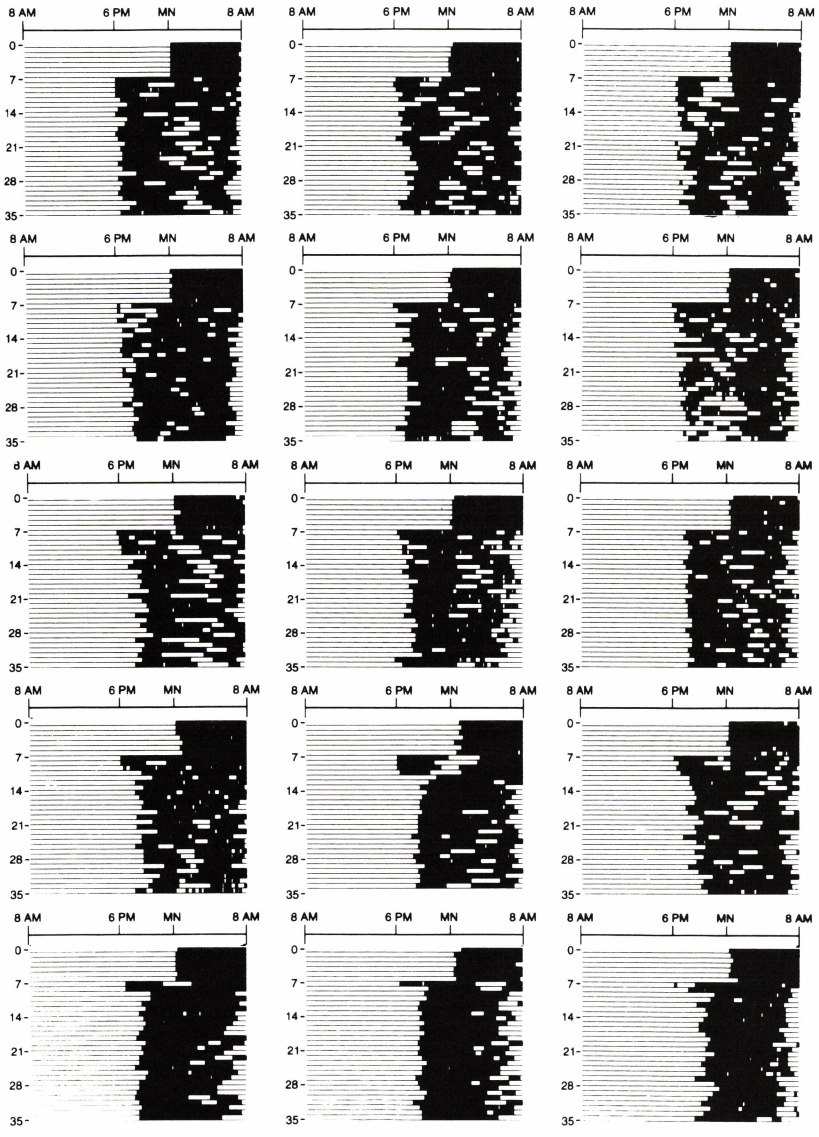

Fig. 6. Raster plots of all individuals' sleep patterns in short nights (2400–0800 h) and long nights (1800–0800 h). In each raster plot, periods of sleep are represented by horizontal black bars, and 24-h sections of data (0800–0800 h) are shown successively beneath one another. A 2-wk interval between short-night schedule (1st wk) and long-night schedule (last 4 wk), during which individuals returned to their habitual routines (i.e., ~16 h light, ~8 h dark), is not shown in raster plots. Order of raster plots [in horizontal rows (*left* to *right* and *top* to *bottom*)] ranks degree to which individuals' sleep periods (interval between first and last occurrence of sleep) increased in duration during long nights. In long nights, sleep generally separated into ≥2 fragments and often exhibited a symmetrical bimodal pattern of distribution.

means that chronic exposure to each photoperiod schedule must have induced abiding history-dependent changes in the timing of internal processes, such as pacemaker oscillations, that control the duration of nocturnal and diurnal periods of the individuals' T_r, MT, and cortisol circadian rhythms.

Evidence for a complex circadian system with multiple-component oscillators or output pathways. The response of each type of circadian rhythm to the change in photoperiod was independent of the responses of every other type of rhythm. Thus, for example, after transfer from short nights to long nights, the sleep period could lengthen several hours while the duration of nocturnal MT secretion remained virtually unchanged, and vice versa (see examples in Fig. 8). Some of the rhythms also responded independently in another important respect: the timing (phase position) of rhythms in certain variables, such as T_r and cortisol, relative to the timing of rhythms in other variables, such as MT and TSH, systematically changed when the photoperiod was changed (Fig. 5). The independence of the responses of different rhythms to the photoperiod adds to mounting evidence that the circadian system is a complex system composed of multiple subsystems whose rhythmic outputs are controlled by separate processes that can be dissociated from one another (27).

Like our human subjects, some animals respond to changes in photoperiod by altering the internal phase relationships between their circadian rhythms. According to one theory of photoperiodic time measurement (the internal coincidence theory), changes in internal phase relationships induced by the photoperiod mediate its seasonal effects on animals' behavior and physiology (11, 29).

Recently, Cagnacci et al. (6) showed that infusions of MT lower body temperature in humans and that suppression of nocturnal MT secretion with a β-adrenergic antagonist drug greatly diminishes the nocturnal decline in body temperature. These investigators suggest that the characteristic nightly decline in the T_r circadian rhythm is largely induced by the nightly onset of MT secretion acting in concert with the nightly onset of sleep. Our data, however, do not support this hypothesis. If the onset of MT secretion played a significant role in the induction of

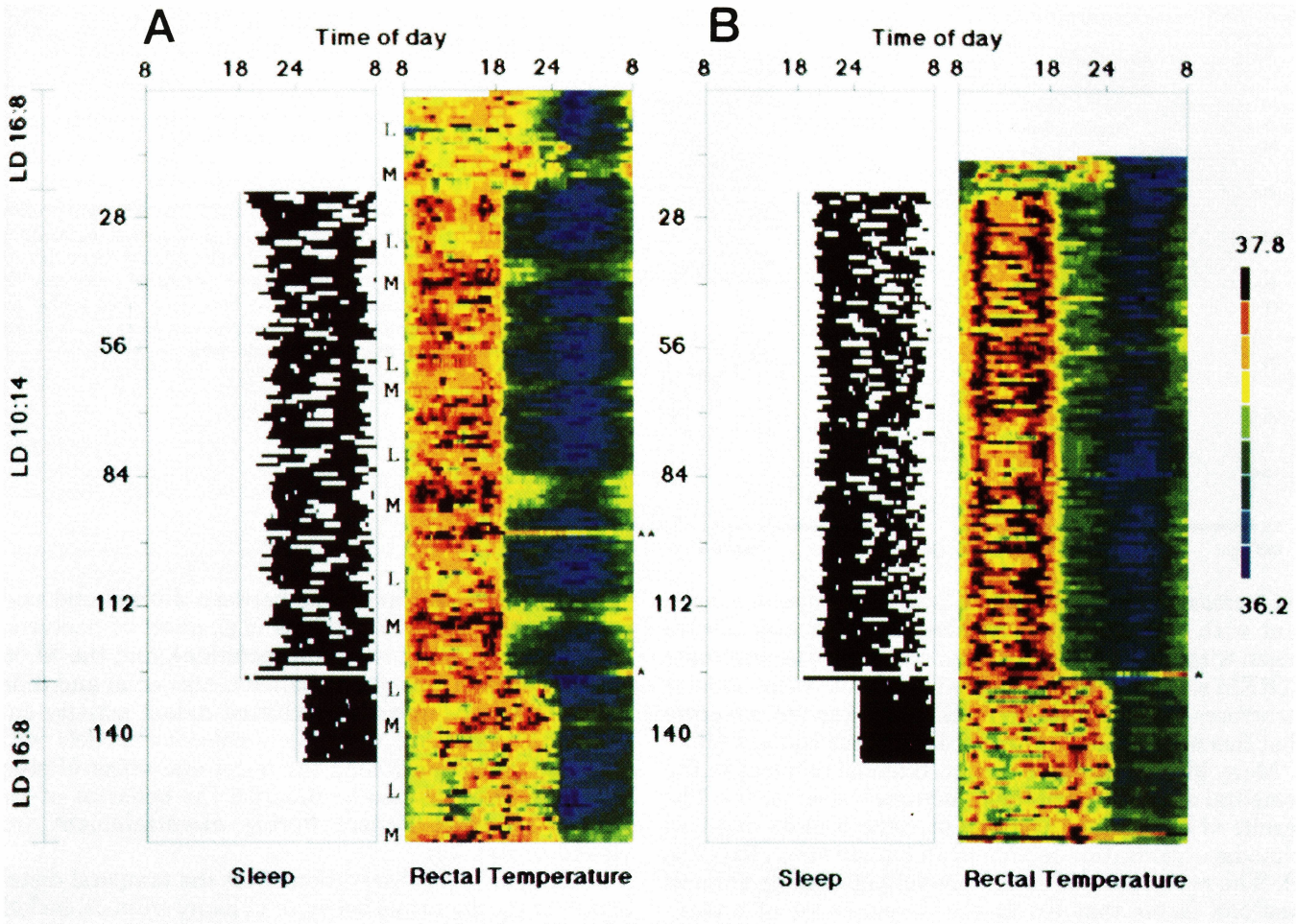

Fig. 7. Raster plots (see Fig. 5) of electroencephalographically monitored sleep and rectal temperature of a 35-yr-old woman (*left*) and a 34-yr-old man (*right*) who were transferred to short days (LD 10:14) for 15 wk and then transferred back to long days (LD 16:8). In long nights, sleep separated into ≥2 fragments. Woman's sleep fragments exhibited symmetrical bimodal pattern of distribution characteristic of most other individuals who participated in experiment. Both individuals' daytime temperatures were consistently higher in short days. Elevations of rectal temperature can be seen during each luteal phase of woman's menstrual cycle, which persisted throughout period of observation. L, midcycle LH surge; M, onset of menses. *Elevation of nocturnal temperature during constant-routine measurement period, when individuals remained continuously awake in constant dim light. **Elevation of nocturnal temperature during flu-like illness.

the nightly decline in T_r, then the timing of the former relative to the latter should have remained constant in the constant-routine conditions after exposure to the two photoperiods, but this was not the case. Relative to the onset of MT secretion, T_r declined earlier after exposure to long nights than after exposure to short nights (Fig. 5). Moreover, T_r clearly began to decline before MT began to be secreted in each of the two conditions (Fig. 5). Taken together, the results of the two studies suggest that the T_r rhythm is generated by a process that is separate from the MT rhythm, but, as Cagnacci et al. (6) suggest, its amplitude is reinforced by the MT rhythm and by the sleep-wake cycle.

Sleep is organized in multiple modular bouts with bimodal distribution. The results of the present experiment reveal that the nocturnal sleep of humans is homologous to the nocturnal behavior of other animals to a greater extent than is generally appreciated.

The sleep of most kinds of animals is not consolidated but occurs in multiple bouts throughout the night (or day) (30, 33). It is commonly believed that humans are an exception to this rule, because their sleep is usually consolidated into a single uninterrupted nocturnal bout. In long nights, however, human sleep is quite similar to that of other animals. Our subjects' sleep usually separated into two or more fragments with intervals of wakefulness between them (Figs. 6 and 7). This finding is consistent with reports of similar polyphasic sleep patterns in human infants and in human adults during enforced bed rest (reviewed in Ref. 33). These observations raise the possibility that consolidation of sleep in humans is an artifact of modern lighting technology.

As has been reported previously in both humans and animals (19), our subjects' spontaneous awakenings occurred more often during REM sleep than would have been expected on the basis of chance (unpublished observations). Because of this association, an arousal function has been ascribed to REM sleep, especially to the phasic component of REM sleep that is measured as REM density. The fact that REM density and spontaneous arous-

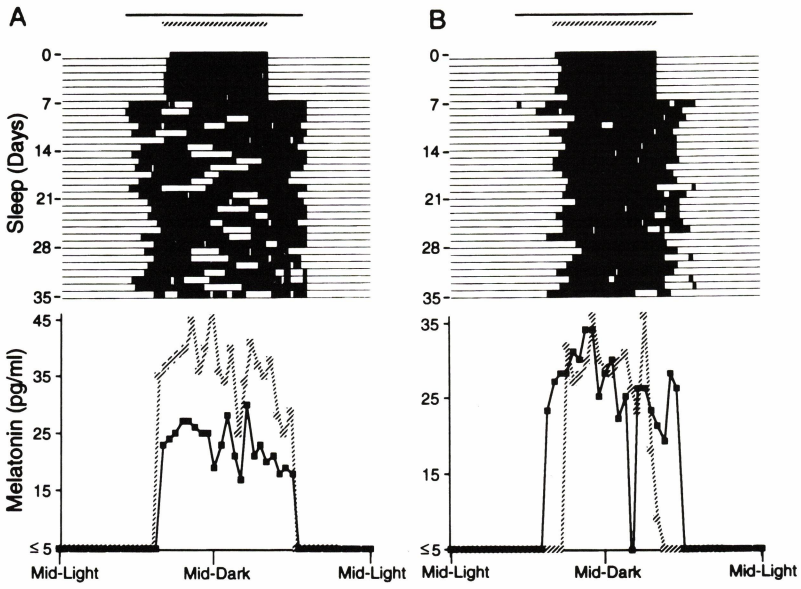

Fig. 8. Sleep raster plots (*top*) and 24-h melatonin profiles (*bottom*) in an individual whose sleep period increased in duration but whose nocturnal melatonin secretion did not (*A*) and in an individual whose nocturnal melatonin secretion increased in duration but whose sleep period did not (*B*). Indications for raster plots are as in Fig. 6, except that sleep is referenced to mid-dark.

als increased concomitantly in long nights seems consistent with this idea. Because sleep bouts almost always began with non-REM sleep, their propensity to terminate in REM sleep tended to produce sleep bouts with modular structures of *n* complete non-REM-REM cycles, a feature that has been noted previously in another context (19).

Many kinds of animals exhibit bimodal patterns in the temporal distribution of their nocturnal behavior (1). The results of the present experiment make it clear that this bimodal organization is present in human sleep, too (Fig. 6). The occurrence of such bimodal patterns in animals was one factor that led to the development of a dual-oscillator model of the circadian system, which is discussed below.

Models of a photoperiod-responsive circadian system. According to the classic Pittendrigh-Daan (25) model of the circadian system, animals respond to changes in photoperiod by means of a compound circadian pacemaker that employs two separate oscillators, one synchronized with dawn [the morning (M) oscillator] and the other with dusk [the evening (E) oscillator], to track the changing boundaries of the photoperiod. In this model, the E oscillator controls transitions between diurnal and nocturnal periods of daily rhythms (e.g., onset of nocturnal rodent activity and melatonin secretion), and the M oscillator controls transitions between nocturnal and diurnal periods (e.g., offset of nocturnal rodent activity and melatonin secretion) (14, 25). Analogous models with dual oscillators controlling the onset and offset of sleep have also been devised to describe the behavior of the human circadian system during disentrainment (reviewed in Ref. 33).

Such models fit observations that the temporal distribution of the nocturnal behavior of many animals, including the human subjects in this experiment, is bimodal and that the internal phase relationship between the two modes can be modified by changing the duration of the photoperiod (Fig. 9). The best evidence supporting a dual-oscillator model is the phenomenon of splitting of rodent activity rhythms during disentrainment in constant light. During splitting, E and M activity bouts separate from one another and recouple in an alternate antiphase coupling mode (reviewed in Ref. 33). In the split mode, the circadian system free runs with a period that is

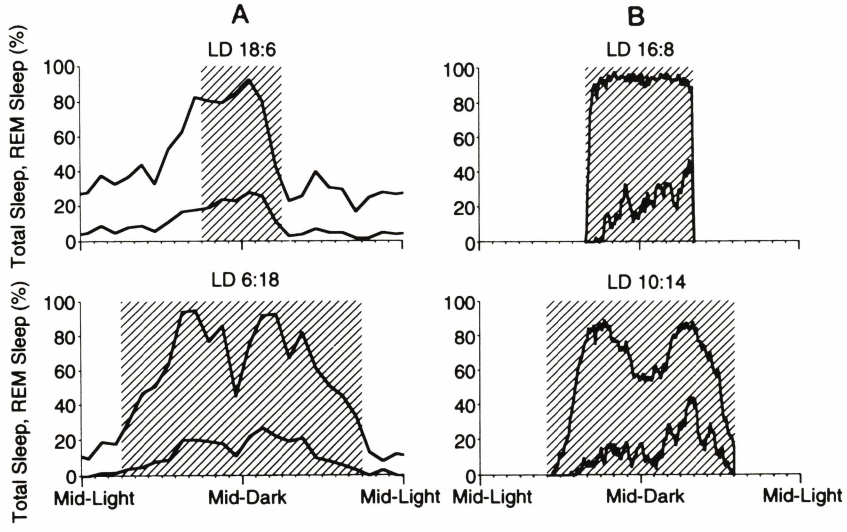

Fig. 9. Mean 24-h profiles of EEG-monitored sleep and REM sleep in Siberian chipmunks (*Eutamias sibiricus*; *A*) and humans (*B*) in short (*top*) and long nights (*bottom*). In both species, a symmetrical bimodal pattern of distribution of sleep emerges in long nights. Human data are from 12 individuals whose sleep periods expanded in long nights. Chipmunk data adapted, with permission, from Dijk and Daan (9).

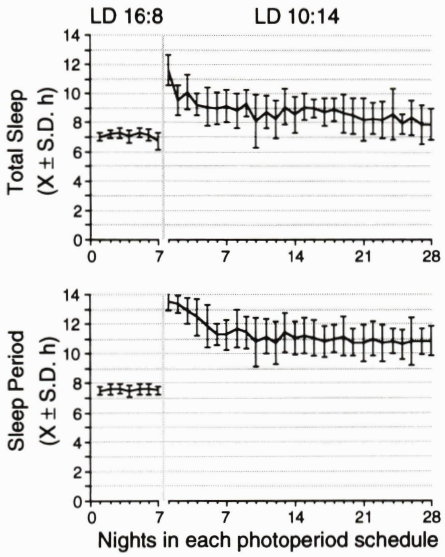

Fig. 10. *Top*: mean cumulative duration of sleep for each night of each photoperiod schedule. *Bottom*: mean duration of interval between first and last occurrence of sleep (sleep period) for each night of each photoperiod schedule. For each graph, data were taken from 12 individuals whose sleep increased in duration and separated into ≥2 fragments after transfer from short nights (LD 16:8) to long nights (LD 10:14; see Fig. 9).

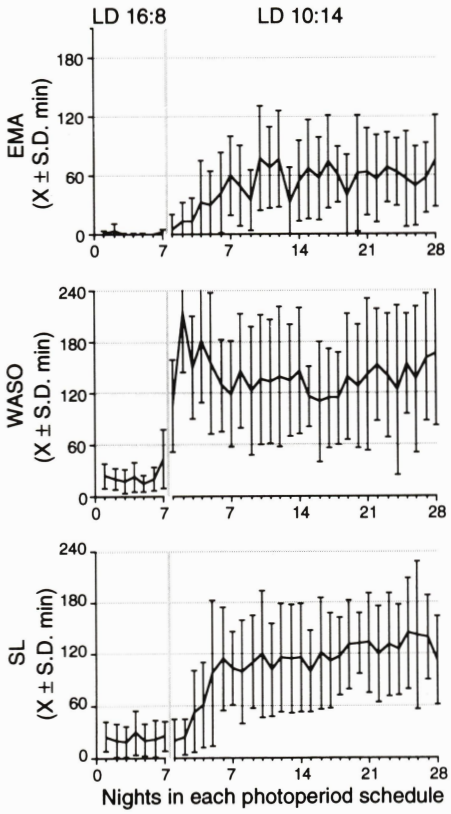

Fig. 11. For each night of each photoperiod schedule, mean durations of intervals between last occurrence of sleep and end of dark period [early morning awakening (EMA); *top*], cumulative time awake between first and last occurrence of sleep [wakefulness after sleep onset (WASO); *middle*], and durations of intervals between beginning of dark period and first occurrence of sleep [sleep latency (SL); *bottom*]. Data from same individuals as in Fig. 10.

shorter than in the unsplit mode. Previously, we described behavior in disentrained humans that, in each of these respects, resembles splitting in animals, and we suggested that a dual-oscillator model like that of Pittendrigh and Daan (25) might be used to describe the human circadian system (33). However, the independence of the responses of different rhythms to the change in photoperiod in the present experiment might have to be accommodated in such a model by postulating that different rhythms are controlled by separate dual-oscillator pacemakers or by separate slave oscillators or separate output pathways coupled to one or more dual-oscillator pacemakers. In that same study, we also suggested that the bimodal pattern of human sleep in long nights could be simulated with Borbély and Daan's two-process model of sleep regulation by lowering the model's circadian threshold for sleep onset (33). However, the circadian process in the two-process model might have to be modified further, possibly by introducing multiple dual oscillators, slaves, or output pathways to simulate the wave-form alterations that photoperiod changes induced in the constant-routine profiles of T_r and MT and cortisol secretion and to accommodate the independence of the responses of different rhythms to the change in photoperiod in the present experiment.

Individuals were warmer in short days than in long days. A curious post hoc finding was that subjects' daytime temperatures were 0.2–0.3°C higher in short days than in long days (Figs. 3 and 7). In contrast, minimum nighttime temperatures did not change. However, nighttime temperatures were low for longer periods in long nights than in short nights. This latter difference, in effect, compensated for the increase in daytime temperatures, so that the 24-h average temperature remained more or less constant across photoperiods. This reciprocal relationship between the level of temperature in the daytime and time spent at low temperatures at night might reflect the activity of homeostatic mechanisms that stabilize the amount of energy expended on heat production. It is also conceivable that elevation of daytime temperature in short days is a photoperiod-induced preadaptation to the cold environment to which humans would be exposed in the daytime in winter.

Confounding of darkness, enforced bed rest, and boredom. Further research will be necessary to determine whether, and to what extent, darkness per se or factors associated with the dark condition, such as instructions to rest or confinement in a boring environment, were responsible for the differences that we observed in the subjects' sleep and circadian rhythm profiles in short and long nights. Whatever the answer to this question, the conditions and results of the experiment are still likely to be relevant to the behavior of photoperiod-responsive mechanisms in natural environments. In natural environments, darkness, enforced rest, and confinement tend to occur together and act in concert, because darkness inhibits arousal and restricts movement of day-active animals, including humans (7). In fact, in animals, changes in level of arousal evoked by the immediate presence of light and darkness have been shown to help mediate the phase-resetting effects of light and darkness on circadian oscillators (23). Until recently, this possibility was ignored in the interpretation of the responses of animals to

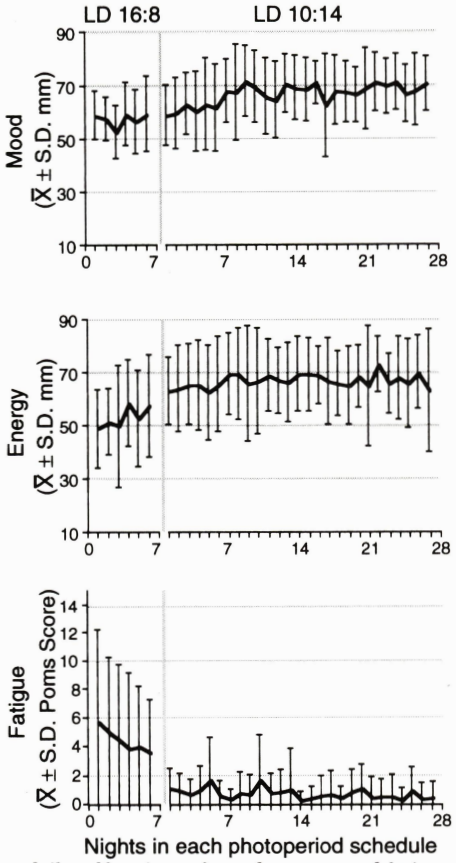

Fig. 12. Mean daily self-ratings of mood, energy, and fatigue during 1 wk of 8-h nights and during 4 wk of 14-h nights. After transfer from short nights to long nights, mood, energy, and fatigue improved.

manipulations of the light-dark cycle. In light of these findings in animals, it would be surprising if the de-arousing properties of enforced bed rest did not contribute significantly to the results of the present experiment.

Nonresponsive individuals. A few individuals failed to exhibit photoperiod responses that were characteristic of the group as a whole. For example, 12 individuals' sleep periods expanded and broke up into two or more fragments in long nights, but 3 individuals' sleep periods remained compressed and consolidated, as though no change in photoperiod had occurred (Figs. 6 and 8). In other photoperiod-responsive species, such as the Djungarian hamster (*Phodopus sungorus*), individuals of certain strains are similarly unresponsive to shortening of the photoperiod. Their nocturnal activity periods remain compressed and consolidated after transfer to long nights (26).

Implications for human health and disease. Identification in humans of mechanisms that respond to changes in photoperiod may prove relevant to health and disease. For example, such mechanisms might play a role in the pathophysiology of manic-depressive illness, which, like the photoperiod responses of some animals, is characterized by long-term cyclic changes in sleep duration, body weight, locomotor activity, aggressiveness, and sexual drive, by seasonal patterns of recurrence, and, in some cases, by responsiveness to light (18, 34). The fact that one of our experimental subjects, who may have been genetically predisposed to affective illness, became profoundly depressed and suicidal when he was exposed to short days and long nights and recovered when he was reexposed to long days and short nights lends some credence to this idea.

Of more general relevance, our experimental results suggest that humans' practice of using artificial light to maintain long summer-type photoperiods year-round has significantly altered the autochthonous daily patterns of behavior and physiology that are controlled by photoperiod-responsive mechanisms. Specifically, it can be inferred from our results that this practice of extending the natural photoperiod with artificial light has reduced and consolidated sleep, decreased rest and quiet wakefulness, decreased the duration of nightly exposure to high levels of pineal MT, pituitary PRL, and REM sleep and to low levels of body temperature, decreased daytime body temperature and vigor, increased daytime fatigue, and (possibly) increased sleep-related GH secretion and pituitary size. The impact on human health and disease of this "experiment," which began in prehistoric times and has been increasingly intensified by progress in the technology of artificial lighting, remains to be explored more fully.

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