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EXPOSURE TO BRIGHT LIGHT AND DARKNESS TO TREAT PHYSIOLOGIC MALADAPTATION TO NIGHT WORK

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Abstract Working at night results in a misalignment between the sleep–wake cycle and the output of the hypothalamic pacemaker that regulates the circadian rhythms of certain physiologic and behavioral variables. We evaluated whether such physiologic maladaptation to nighttime work could be prevented effectively by a treatment regimen of exposure to bright light during the night and darkness during the day. We assessed the functioning of the circadian pacemaker in five control and five treatment studies in order to assess the extent of adaptation in eight normal young men to a week of night work.

In the control studies, on the sixth consecutive night of sedentary work in ordinary light (approximately 150 lux), the mean (±SEM) nadir of the endogenous temperature cycle continued to occur during the night (at 03:31±0:56 hours), indicating a lack of circadian adaptation to the nighttime work schedule. In contrast, the subjects in the treatment studies were exposed to bright light (7000 to 12,000 lux) at night and to nearly complete darkness during the day, and the temperature nadir shifted after four days of treatment to a significantly later, midafternoon hour (14:53±0:32; $P<0.0001$), indicating a successful circadian adaptation to daytime sleep and nighttime work. There were concomitant shifts in the 24-hour patterns of plasma cortisol concentration, urinary excretion rate, subjective assessment of alertness, and cognitive performance in the treatment studies. These shifts resulted in a significant improvement in both alertness and cognitive performance in the treatment group during the night-shift hours.

We conclude that maladaptation of the human circadian system to night work, with its associated decline in alertness, performance, and quality of daytime sleep, can be treated effectively with scheduled exposure to bright light at night and darkness during the day. (N Engl J Med 1990; 322:1253-9.)

APPROXIMATELY 7.3 million Americans work at night, either on permanent shifts or on schedules requiring a rotation of day, evening, and night work.[1] These workers forgo nocturnal sleep and then attempt to sleep during daylight hours. Yet, as Benedict first noted at the turn of the century, a complete physiologic adaptation of endogenous circadian rhythms to such inversion of the daily routine does not occur[2-4] even after years of permanent nighttime work.[5,6] Physiologic maladaptation to an inverted schedule results in diminished alertness and performance during nighttime work, with attendant increases in the number of fatigue-related accidents during nighttime hours.[6-9] Then, despite the nocturnal deprivation of sleep, these workers typically experience daytime insomnia.[10-14] Long-term exposure to variable work schedules that include work at night is also associated with an increased risk of cardiovascular disease, gastrointestinal illness, reproductive dysfunction in women, and sleep disorder.[15-18] Improvements in performance and well-being have been achieved as a result of modifications in work-schedule design,[14] but true physiologic adaptation to night work under field conditions has not previously been demonstrated.

During the past 20 years, considerable progress has been made in understanding the underlying neurophysiologic processes that regulate adaptation to the periodic aspects of the external environment. Studies involving ablation, transplantation, and other procedures have demonstrated that the suprachiasmatic nuclei of the hypothalamus serve as the principal pacemaker of the circadian timing system in mammals.[19-21] A specialized retinohypothalamic tract links the retina to these nuclei, forming a nonvisual photoreceptive system that mediates the synchronization, or entrainment, of the circadian pacemaker with the light–dark cycle.[22] Even though corresponding structures subserving rhythmicity and photic entrain-

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ment in the brain have been identified,[23-25] it was thought that the human circadian pacemaker was uniquely insensitive to light and that it instead relied on "social contacts" to achieve synchrony with the 24-hour day.[26] However, we have demonstrated that the light–dark cycle has a direct synchronizing effect on the human circadian pacemaker.[27,28] Furthermore, we have recently discovered that properly timed exposure to bright light and darkness can reset the pacemaker by as much as 12 hours within two to three days.[29] We found that the pacemaker's resetting response to bright light depends on the timing of the average midpoint of the total daily exposure to light, after weighting for brightness.[29] Therefore, the bright light to which nighttime workers are often exposed during the day (e.g., during the return home from work) may prevent them from adapting to night work. On the basis of these results, we designed a pattern of exposure to bright light and darkness in the work and home environments by which the phase of the pacemaker can be reset rapidly and effectively in persons who work at night, even if they are exposed to natural light on the way home from work each morning.

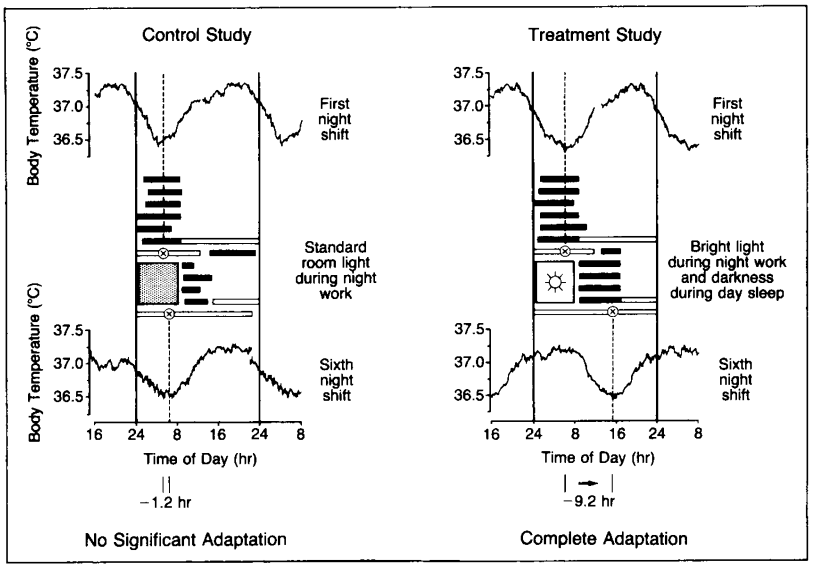

Figure 1. Overall Study Protocol (Middle Panels) and Changes in Temperature Recorded during the First and Sixth Night Shifts (Upper and Lower Panels) in One Man during a Control Study and a Treatment Study.

Solid bars indicate daily sleep episodes, open bars constant routines, and circled x's the initial and final endogenous circadian temperature nadirs as derived from the temperature data (vertical dashed lines) measured during the constant routine. During the second through fifth nights of work (midnight to 08:00 hours), the men were exposed either to ordinary indoor light (approximately 150 lux; stippled box) in the control studies or to bright light (7000 to 12,000 lux; solar symbol in the open box) in the treatment studies. To facilitate visual comparisons, segments of the temperature data have been double-plotted.

Methods

Subjects

Ten two-week studies were carried out in eight healthy men, 22 to 29 years old. The subjects had no medical, psychiatric, or sleep disorders as determined from their medical histories, physical examinations, chest radiographs, electrocardiograms, biochemical screening tests, and psychological screening questionnaires (the Minnesota Multiphasic Personality Inventory). None had worked regularly at night on a permanent or rotating shift within the preceding year, and none had traveled to another time zone during the previous six weeks. They were not taking any medications and were instructed to abstain from the use of alcohol, recreational drugs, and products containing caffeine for the duration of the study. Urinary toxicologic screening was used to verify that they were drug-free at the time of the study.

The first two subjects participated in the control study and then in the treatment study, after an interval of three to five weeks during which they lived at home and maintained a schedule of regular daytime activity and nocturnal sleep. To facilitate recruitment the remaining six men were asked to participate in only one study; each was randomly assigned to either the control study or the treatment study after the successful completion of an initial evaluation of his circadian phase.

All the studies were carried out in the summer, to avoid seasonal variation in exposure to outdoor light during the week of night work. The experimental procedures and the procedure for obtaining informed consent were approved by the Committee for the Protection of Human Subjects from Research Risks of Brigham and Women's Hospital. Written informed consent was obtained from each man before participation in the study.

Overall Study Design

Five control and five treatment studies were performed; each consisted of one week of ambulatory recording of base-line temperature, physical activity, and heart rate, followed by a week of night-shift work. The men lived at home throughout each study, reporting for "work" in the laboratory each night of the second week. To evaluate the extent of physiologic adaptation to nighttime work, the output of the circadian pacemaker was evaluated[30] during the first and sixth consecutive night shifts. On those nights, and during each of the immediately preceding days, the activity of the subjects was restricted to the enforced semirecumbent wakefulness of a laboratory constant routine as described below. Both the control and the treatment protocols are shown in Figure 1.

During the week of base-line recording, the men maintained regular bedtimes and waking times (within a range of ±1 hour). Their subjective sleep–wake logs were verified for accuracy by comparison with the results of continuous ambulatory monitoring of wrist activity, heart rate, and body temperature (PMS-8 Recorder, Vitalog, Redwood City, Calif.) throughout both weeks of the study. In the case of two men (one control and one treatment subject) whose behavior during the study did not conform to the protocol, the results were excluded before the outcome of their experimental trials was determined.

On the second through the fifth nights of work, the men reported to the laboratory at 23:45 hours and spent the eight hours between midnight and 08:00 seated at a desk. On those four nights, the men in the treatment studies were exposed to bright light (7000 to 12,000 lux, an intensity comparable to that of natural sunlight just after dawn) between 00:15 and 07:45 hours, whereas those in the control studies were exposed to ordinary room light (approximately 150 lux). All subjects completed cognitive-performance tasks hourly

during this time and subjective assessments of alertness and mood every 20 minutes. They were otherwise free to do their own work and were given dinner and a snack during each night shift. In all but two trials, the subjects (one in the control study and one in the treatment study) consumed their meals at times of their own choosing. A technician monitored the subjects throughout each night shift to ensure that they remained awake.

After each night shift, the men left the laboratory and traveled home. They were thus exposed to outdoor light each morning during this travel time. The men in the treatment studies were instructed to remain in the dark from 09:00 to 17:00 hours each day, in bedrooms in which the windows were covered with opaque material to exclude sunlight. In contrast, the men in the control studies were not scheduled to remain in the dark at any particular time each day, although most did use their existing window shades or curtains while they slept, at times of their own choosing. No other restrictions were placed on the activities of the subjects in either group during their "nonwork" hours. All were provided with a breakfast and a lunch to take home and eat at will.

Assessment of Endogenous Circadian Phase

Previous attempts to evaluate the extent of circadian adaptation to night work have been complicated by the masking effects of activity on the physiologic variables monitored. In this study, the constant-routine method was used to reveal the endogenous component of the body-temperature rhythm, an established marker of the endogenous circadian pacemaker.[31-33] During the constant-routine procedure, we determined the endogenous circadian phase (the particular point at which a regularly recurring event occurs in an intrinsic oscillatory process) at which the nadir of the daily body-temperature cycle occurred. Our method involved an extension and refinement of a technique first proposed by Mills et al.,[34] according to which the subjects are studied under constant environmental and behavioral conditions in order to eliminate (or distribute across the circadian cycle) the physiologic responses evoked by environmental or behavioral stimuli, such as sleeping, eating, changing posture, and changing light levels. During all the constant-routine studies, the men were restricted to absolute, semirecumbent bedrest in a room with constant indoor lighting (approximately 150 lux) and required to remain awake. Wakefulness was monitored by a research technician and verified by continuous polysomnographic recording.[30] During the constant routine, the men's daily nutritional and electrolyte needs were met by identical hourly snacks, with approximately 150 mmol of sodium and approximately 100 mmol of potassium evenly distributed over the 24-hour period. The caloric requirements for weight maintenance were calculated with use of the Wilmore nomogram[35] to determine the basal metabolic rate; they were then adjusted upward by a 10 percent activity factor. Since the constant-routine procedure required that the subjects lose at least one night of sleep, it was carried out concurrently with the first and sixth night shifts. Each constant routine was begun just after the subject awakened on the day of the shift, and it continued for as long as was necessary (at least 21 hours) to determine accurately the endogenous circadian temperature nadir. In two subjects (one in the control study and one in the treatment study), an additional 24 hours was required for this determination during the final constant routine.

Physiologic and Behavioral Measures

Throughout each constant routine, the core body temperature of the subject was recorded at one-minute intervals from a disposable thermistor (Yellow Springs Instrument Company, Yellow Springs, Ohio) inserted 10 cm into the rectum. In addition, blood samples were collected in syringes and transferred to heparin-coated tubes every 15 to 25 minutes on a randomized sampling schedule from an indwelling intravenous catheter with side holes (Deseret Medical, Sandy, Utah) that was placed in a forearm vein[32]; the samples were chilled immediately and centrifuged within two hours, and the plasma was frozen at −20°C. The plasma cortisol concentrations were measured within five months of sample collection by an ^{125}I-coated tube radioimmunoassay procedure (Diagnostic Products, Los Angeles) in the Core Laboratory of Brigham and Women's Hospital General Clinical Research Center (intraassay coefficient of variation [n = 10], 6.2 percent at a mean of 50 nmol per liter and 3.9 percent at a mean of 494 nmol per liter; interassay coefficient of variation [n = 150], 13.2 percent at a mean of 47 nmol per liter and 7.3 percent at a mean of 502 nmol per liter). The urinary volume was measured at three-hour intervals.

Subjective alertness was assessed three times per hour with use of a linear, nonnumeric, 100-mm bipolar visual-analogue scale.[32] Cognitive performance was measured hourly by a test involving calculation that included 125 randomly generated pairs of two-digit numbers.[36] The men were given four minutes to sum as many pairs as possible, and their tests were scored according to the number of calculations completed in the time allowed.

Exposure to Bright Light

The subjects participating in the treatment studies were seated at a desk and exposed to bright light (7000 to 12,000 lux) from one of two sources: either a wall-mounted bank of 80 2.4-m (8-ft), 96-watt "ion-gard" F96TH12 Vitalite wide-spectrum fluorescent lamps (Duro-test, North Bergen, N.J.), separated from the subject by floor-to-ceiling panels made of two sheets of clear glass 3.175 mm thick, separated by a layer of polyvinylbutyl plastic (laminated safety glass); or a portable bank of 16 1.2-m (4-ft) "cool-white" 40-watt lamps (North American Philips Lighting, Bloomfield, N.J.), separated from the subject by a wire-mesh screen. Each subject's daily exposure to ultraviolet light during the trials was well within the guidelines for safety of such exposure established by the American Conference of Governmental Industrial Hygienists and the U.S. Army and recommended by the National Institute for Occupational Safety and Health.[37-39] The men participating in the last four bright-light trials wore clear, ultraviolet-excluding polycarbonate Ultra-Spec 2000 safety glasses with 4C coating (Uvex Winter Optical, Smithfield, R.I.) throughout the exposure to bright light. Illuminance was measured at five-minute intervals with research photometers (International Light, Newburyport, Mass.), each equipped with a detector with a photopic spectral bias and a cosine angular response; the detectors were placed at the subjects' foreheads and directed toward the line of gaze. Fifteen minutes of transitional illumination preceded and followed each exposure to bright light.

Statistical Analysis

The endogenous circadian phase was assessed by nonlinear least-squares analysis to fit a two-harmonic regression model to the data on core body temperature collected during the constant routines.[40] Temperature data gathered during the first five hours of the constant routine, when the thermoregulatory system was not yet in a steady state, were excluded from the analysis. The endogenous circadian temperature nadir was defined as the average of the fitted minimums from the single-harmonic and composite wave forms of the model and was used as a reference marker for the phase of the endogenous circadian temperature cycle. In the two studies in which the final constant routine was extended an additional 24 hours, the temperature data used in the analyses were those from the second half of the constant routine, since the estimates of phase derived from the first and second half of the temperature data during similarly extended constant routines were highly correlated (Pearson's correlation coefficient = 0.998; $P<0.001$) (unpublished data).

Paired comparisons between the values obtained for the phase and amplitude of endogenous circadian temperature initially (during the first night shift) and at the end of the study (during the sixth night shift) were made for both the control and the treatment studies by the paired Student t-test (parametric analysis),[41] with confirmation of significant results by the Wilcoxon signed-rank test (nonparametric analysis). Comparisons between the control and treatment studies with respect to the initial endogenous circadian phase, the final endogenous circadian phase, the shift in phase between the first and sixth nights, the values for alertness and performance obtained during these nights, and the amplitude of vari-

ation in the endogenous circadian temperature cycle were made with use of Student's unpaired t-test (parametric analysis), with confirmation of significant results by the Wilcoxon rank-sum test. All statistical analyses were two-tailed.

Finally, in both groups the body temperatures, subjective-alertness and cognitive-performance scores, urinary excretion rates, and plasma cortisol concentrations were averaged according to the time of day during the initial constant routines and compared with the averages for the same times of day during the final constant routines. For the less frequently sampled among these variables (subjective alertness, cognitive performance, and urinary excretion rate), the mean value of the data for each man was calculated every two hours, and an average for all subjects was obtained; for the remaining variables (body temperature and plasma cortisol concentration), the mean (±SEM) value for all subjects was calculated at regular intervals (every 100 minutes).

Results

Sleep–Wake Schedules

During the week of base-line recording, each man maintained a regular sleep–wake schedule consistent with that required for regular daytime work. There were no significant differences between the control and the treatment studies with respect to either the average (±SEM) bedtime (00:22±0:18 vs. 00:04± 0:21 hours) or the average waking time (07:48±0:19 vs. 07:33±0:29 hours) during the week of base-line recording.

During the scheduled night shifts the men in both studies slept during daytime hours, as shown in Figure 1. However, the men in the treatment studies slept an average of two hours longer per day than the men in the control studies after each of the second through the fifth nights of work (7.7±0.1 vs. 5.7±0.5 hours per day; $P = 0.0103$), as reported in their sleep–wake logs and independently verified on the basis of the monitoring data.

Assessments of Endogenous Circadian Phase

The mean initial nadir of the endogenous circadian temperature cycle occurred at 04:59 hours, 2.7 hours before the men's habitual waking time in the week before each study. There was no significant difference between control and treatment studies with respect to the timing of this nadir ($P = 0.1564$) (Fig. 2). In the control studies, the mean times of the initial and final nadirs of the endogenous circadian temperature cycle (04:38±0:11 vs. 03:31±0:56 hours) were similar. In contrast, in the treatment studies, the mean final temperature nadir occurred 9.6 hours later than the mean initial temperature nadir (14:53±0:32 vs. 05:19±0:23 hours; $P<0.0001$) (Fig. 2). The mean shift in the endogenous circadian temperature nadir between the first and sixth nights in the treatment group (−9.6±0.7 hours) was significantly greater than that in the control group (1.1±0.9 hours) ($P<0.0001$). Finally, the mean endogenous circadian temperature nadir on the sixth night occurred significantly later in the treatment studies than in the control studies (14:53± 0:32 vs. 03:31±0:56 hours; $P<0.0001$).

These differences between the control and treatment groups were also statistically significant even when the data for one control trial and one treatment

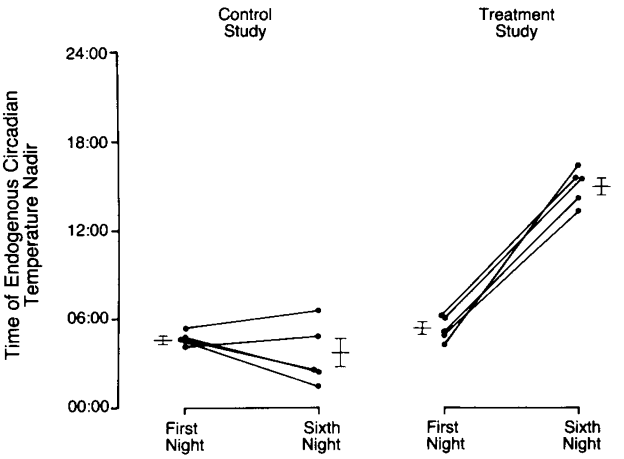

Figure 2. Shifts in Endogenous Circadian Temperature Nadirs between the First and Sixth Nights of Work in the Subjects in the Control and Treatment Studies.

The men in the control studies were exposed to ordinary indoor light on the second through fifth nights, and they slept at home on a free schedule during the day, whereas the subjects in the treatment studies were exposed to bright light during night work and to darkness during daytime sleep, which was scheduled for the period between 09:00 and 17:00 hours. Horizontal lines and vertical bars denote mean ±SEM values.

trial for each of the first two men (who participated in both the treatment and control studies) were excluded from the analysis. Finally, there was no significant difference between the mean amplitudes of the initial and final temperature wave forms in either the control or the treatment studies. However, for one man in the treatment study the amplitude of the cycles for temperature and plasma cortisol concentration was attenuated during the first 24 hours of the final constant routine; when the constant-routine study was extended for an additional 24 hours, both the amplitude and phase shift of these variables were comparable with those of the other subjects in the treatment studies.

24-Hour Patterns of Physiologic and Behavioral Variables

The mean 24-hour patterns of core body temperature, subjective alertness assessments, cognitive performance, urinary excretion rate, and plasma cortisol concentrations during the initial constant routine in both the control and treatment studies had prominent circadian variations. The mean wave forms and timing for each of these variables during the initial constant routine were similar in the men who subsequently participated in the control and treatment studies and also resembled those reported previously[30,31,33,42] (Fig. 3). During the final constant routines, a persistent circadian rhythm was apparent in the average wave form for each variable in both groups. Furthermore, the internal temporal relation between these rhythms did not change during the final constant routine of the control and treatment studies. The relation of each of these average rhythms to the time of day did not change from the initial to the final constant

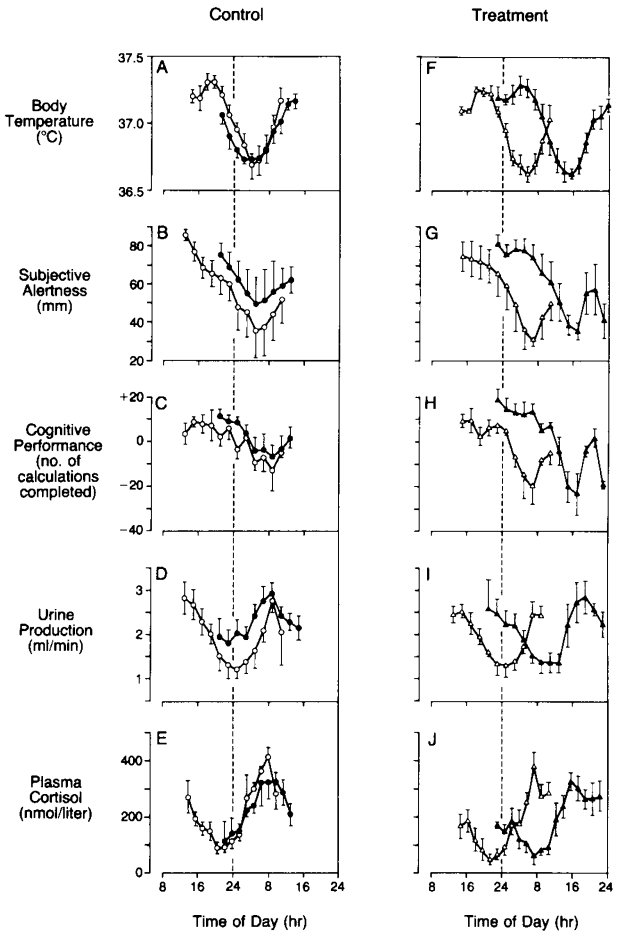

Figure 3. Shifts in Physiologic and Behavioral Measures during the First and Sixth Nights of Work in the Subjects in the Control and Treatment Studies.

Each point shows the mean ±SEM for each variable at a given hour during the initial (open symbols) and final (solid symbols) constant routines in the control subjects (left-hand panels) and the subjects in the treatment group (right-hand panels). Vertical dashed lines indicate the beginning of the night shift (midnight). Conditions during the control and treatment studies were as described in Figure 2. The values for cognitive performance are expressed as the deviation from the 24-hour mean.

routine in the control studies, but in the treatment studies the average curves were displaced to a later hour (Fig. 3). The average curves for the final constant routines of the treatment studies also occurred later than those of the control studies. The magnitude of the displacement was consistent with quantitative estimates of the shift of the endogenous circadian phase as derived from the temperature data.

Performance and Alertness Measures during the Night Shift

As shown in Figure 3H, the shift in the endogenous circadian phase observed during the final constant routine in the treatment studies was associated with significantly higher normalized levels of performance during the hours of the night shift (midnight to 08:00) after treatment than before treatment ($P = 0.041$). In the control studies, there was no significant difference in performance during the night-shift hours between the initial and the final constant routines (Fig. 3C). Similarly, the mean values for alertness were significantly higher during the night shift after the bright-light intervention in the treatment studies than they were before treatment ($P = 0.0009$) (Fig. 3G). Although the mean values for alertness during the night shift were also significantly higher in the control studies at the time of the final constant routine than at the time of the initial constant routine ($P = 0.009$) (Fig. 3B), the improvement was significantly greater in the treatment studies than in the control studies (31.5± 7.8 vs. 13.4±6.3 mm, respectively; $P = 0.004$).

Discussion

Despite the high prevalence of night work in modern society, the physiologic response of the circadian timing system to the reversal it occasions in the sleep–wake schedule is poorly understood. This is largely because night workers are exposed to conflicting synchronizing cues: their work schedule demands activity at night and sleep during the day, whereas all other periodic environmental cues (in particular the light–dark cycle) are oriented toward activity during the day and sleep at night. Although some laboratory experiments have indicated considerable adaptation to a week of simulated nighttime work,[12] those experiments were conducted in laboratories shielded from the environmental light–dark cycle to which shift workers are ordinarily exposed. Studies of shift workers exposed to normal periodic environmental cues have suggested that an incomplete adaptation to nighttime work occurs in persons who live at home and travel daily to work.[2-6,43,44]

In this study, we attempted to resolve the dilemma by evaluating endogenous circadian rhythms under controlled laboratory conditions on the first and sixth night shifts in men otherwise living at home. The physiologic and behavioral data that we collected in the control studies demonstrate that under field conditions the circadian timing system fails to adapt to an inversion of the daily routine even after a week of night work. In fact, three of the five men had small maladaptive advances of the endogenous circadian phase on the sixth night shift as compared with the first. The failure of the circadian timing system to adapt to night-shift work in persons working in ordinary room light at night and sporadically exposed to bright outdoor light during the day is probably a consequence of the direct and powerful biologic effect of light on the human circadian pacemaker.[28,29]

In contrast, in the treatment studies we found that four cycles of exposure to a properly designed regimen of bright light and darkness induced a complete physiologic adaptation to night work in the men living at home and traveling to and from work. The physiologic and behavioral adaptation to the night shift was evident with respect to all measured variables. The success of this experimental paradigm in inducing an ad-

aptation to an inversion of the sleep–wake schedule is consistent with the finding that travelers adapt more rapidly to a time-zone shift if they remain outdoors on arrival rather than in their hotel rooms[45,46] and with recent studies suggesting that bright light is an effective synchronizer of circadian rhythmicity in human subjects.[29,47-53] Our findings are comparable with the results of experiments conducted under conditions of 24-hour daylight in the Arctic, in which adaptation of the body-temperature cycle to a reversal of the activity–sleep schedule was achieved after only three to four days among subjects who concurrently reversed their exposure to the natural light–dark cycle by using blindfolds during daytime sleep.[54] However, it should be noted that the resetting effect of light on the circadian pacemaker is critically dependent on the timing, intensity, and duration of the light exposure. The desired phase shift may not be achieved even with the same amount of exposure to bright light[55] unless it is administered at appropriate times.[29]

The use of the constant-routine procedure allowed the extent of adaptation of both physiologic and behavioral variables to be evaluated in the control and treatment studies. The endogenous circadian rhythms of body temperature, plasma cortisol concentration, and urinary excretion rate all failed to adjust to the schedule of night work in the control studies, yet in the treatment studies they were all effectively synchronized with the night-work schedule. The indexes of alertness and performance remained at their lowest daily levels from midnight to 08:00 hours in the control studies, even after a week of nighttime work. In the treatment studies, these same indexes during the night were significantly improved, and there was a marked decline in alertness (or an increase in sleepiness) during the daytime, when night workers must attempt to sleep. This increase in daytime sleepiness is consistent with the shift in phase of the physiologic variables and may account for the significantly increased sleep time among the men in the treatment studies. Taken together, these data suggest that the schedule of light and darkness to which these men were exposed shifted a master circadian pacemaker that drives all these physiologic and behavioral rhythms.

Misalignment of the circadian phase and sleep deprivation are the principal factors contributing to the decrements in performance and increased accident rates associated with night-shift work.[9] Therefore, the ability of exposure to light and darkness to adjust the circadian phase and improve the sleep of night-shift workers could have important implications for both industrial productivity and safety. Furthermore, since circadian-phase misalignment, sleep deprivation, or both may add to the deleterious consequences for health that are associated with nighttime work (such as digestive, cardiovascular, and sleep disorders), the ability to induce physiologic adaptation to such a schedule could also have important consequences for the health of night workers.

Although this study is a step toward the development of a practical treatment for maladaptation to nighttime work, a number of important questions remain to be answered. They concern the relative importance of exposure to bright light during nighttime work as compared with darkness during daytime sleep, variability both between individuals and according to age and sex in the phase-shifting response to bright light, and the number, duration, and intensity of light exposures needed to induce and maintain optimal physiologic adaptation to nighttime work.

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References

1. Mellor EF. Shift work and flexitime: how prevalent are they? Mon Labor Rev 1986; November:14-21.
2. Åkerstedt T, Pátkai P, Dahlgren K. Field studies of shiftwork. II. Temporal patterns in psychophysiological activation in workers alternating between night and day work. Ergonomics 1977; 20:621-31.
3. Knauth P, Emde E, Rutenfranz J, Kiesswetter E, Smith P. Re-entrainment of body temperature in field studies of shiftwork. Int Arch Occup Environ Health 1981; 49:137-49.
4. Smith PA. Oral temperature rhythms in two groups of industrial shiftworkers. In: Proceedings of the 2nd International Symposium on Night and Shift Work, Slanchev Bryag, Studia Laboris et Salutis. Vol. 11. 1972:66-78.
5. Benedict FG. Studies in body-temperature I. Influence of the inversion of the daily routine: the temperature of night-workers. Am J Physiol 1904; 11:145-69.
6. Folkard S, Monk TH, Lobban MC. Short and long-term adjustment of circadian rhythms in 'permanent' night nurses. Ergonomics 1978; 21:785-99.
7. Harris W. Fatigue, circadian rhythm, and truck accidents. In: Mackie RR, ed. Vigilance: theory, operational performance, and physiological correlates. Vol. 3 of NATO conference series. III. Human factors. New York: Plenum Press, 1977:133-46.
8. Åkerstedt T. Sleepiness as a consequence of shift work. Sleep 1988; 11:17-34.
9. Mitler MM, Carskadon MA, Czeisler CA, Dement WC, Dinges DF, Graeber RC. Catastrophes, sleep, and public policy: consensus report. Sleep 1988; 11:100-9.
10. Foret J, Lantin G. The sleep of train drivers: an example of the effects of irregular work schedules on sleep. In: Colquhoun WP, ed. Aspects of human efficiency diurnal rhythm and loss of sleep. Cambridge: English Universities Press, 1972:273-82.
11. Åkerstedt T, Gillberg M. Sleep disturbances and shift work. In: Reinberg A, Vieux N, Andlauer P, eds. Night and shift work: biological and social aspects. Oxford: Pergamon Press, 1981:127-37.
12. Rutenfranz J, Knauth P, Angersbach D. Shift work research issues. In: Johnson LC, Tepas DI, Colquhoun WP, Colligan MJ, eds. The twenty-four hour workday: Proceedings of a Symposium on Variations in Work-Sleep Schedules. Cincinnati: Department of Health and Human Services, 1981: 221-59.
13. Vokac Z, Lund L. Patterns and duration of sleep in permanent security night guards. J Hum Ergol (Tokyo) 1982; 11:Suppl:311-6.
14. Czeisler CA, Moore-Ede MC, Coleman RM. Rotating shift work schedules that disrupt sleep are improved by applying circadian principles. Science 1982; 217;460-3.
15. Åkerstedt T, Knutsson A, Alfredsson L, Theorell T. Shift work and cardiovascular disease. Scand J Work Environ Health 1984; 10:409-14.
16. Shift Work Committee, Japan Association of Industrial Health. Opinion on night work and shift work. J Sci Labour (Jap) 1979; 55:1-37.
17. Kogi K. Sleep problems in night and shift work. J Hum Ergol (Tokyo) 1982; 11:Suppl:217-31.
18. Czeisler CA, Moore-Ede MC, Coleman RM. Resetting circadian clocks: applications to sleep disorders medicine and occupational health. In: Guilleminault C, Lugaresi E, eds. Sleep/wake disorders: natural history, epidemiology, and long-term evolution. New York: Raven Press, 1983:243-60.
19. Moore RY. Organization and function of a central nervous system circadian oscillator: the suprachiasmatic hypothalamic nucleus. Fed Proc 1983; 42:2783-9.

20. Turek FW. Circadian neural rhythms in mammals. Annu Rev Physiol 1985; 47:49-64.
21. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. Science 1990; 247:975-8.
22. Takahashi JS, DeCoursey PJ, Bauman L, Menaker M. Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. Nature 1984; 308:186-8.
23. Lydic R, Schoene WC, Czeisler CA, Moore-Ede MC. Suprachiasmatic region of the human hypothalamus: homolog to the primate circadian pacemaker? Sleep 1980; 2:355-61.
24. Sadun AA, Schaechter JD, Smith LE. A retinohypothalamic pathway in man: light mediation of circadian rhythms. Brain Res 1984; 302:371-7.
25. Stopa EG, King JC, Lydic R, Schoene WC. Human brain contains vasopressin and vasoactive intestinal polypeptide neuronal subpopulations in the suprachiasmatic region. Brain Res 1984; 297:159-63.
26. Wever R. Zur zeitgeber-staerke eines licht-dunkel-wechels fuer die circadiane periodik des menschen. Eur J Physiol 1970; 321:133-42.
27. Czeisler CA, Richardson GS, Zimmerman JC, Moore-Ede MC, Weitzman ED. Entrainment of human circadian rhythms by light-dark cycles: a reassessment. Photochem Photobiol 1981; 34:239-47.
28. Czeisler CA, Allan JS, Strogatz SH, et al. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science 1986; 233:667-71.
29. Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (Type 0) resetting of the human circadian pacemaker. Science 1989; 244:1328-33.
30. Czeisler CA, Brown EN, Ronda JM, Kronauer RE, Richardson GS, Freitag WO. A clinical method to assess the endogenous circadian phase (ECP) of the deep circadian oscillator in man. Sleep Res 1985; 14:295.
31. Wever RA. The circadian system of man: results of experiments under temporal isolation. New York: Springer-Verlag, 1979.
32. Czeisler CA. Internal organization of temperature, sleep-wake, and neuroendocrine rhythms monitored in an environment free of time cues. (Ph.D. thesis. Stanford, Calif.: Stanford University, 1978.)
33. Minors DS, Waterhouse JM. The use of constant routines in unmasking the endogenous component of human circadian rhythms. Chronobiol Int 1984; 1:205-16.
34. Mills JN, Minors DS, Waterhouse JM. Adaptation to abrupt time shifts of the oscillator[s] controlling human circadian rhythms. J Physiol (Lond) 1978; 285:455-70.
35. Wilmore DW. The metabolic management of the critically ill. New York: Plenum Press, 1977.
36. Klein KE, Wegmann HM, Athanassenas G, Hohlweck H, Kuklinski P. Air operations and circadian performance rhythms. Aviat Space Environ Med 1976; 47:221-30.
37. Documentation of the threshold limit values and biological exposure indices. 5th ed. Cincinnati: American Conference of Governmental Industrial Hygienists, 1986:672-3.
38. Sliney DH. Standards for use of visible and nonvisible radiation on the eye. Am J Optom Physiol Opt 1983; 60:278-86.
39. National Institute for Occupational Safety and Health. Occupational exposure to ultraviolet radiation: criteria for a recommended standard. Cincinnati: Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, 1972. (DHEW publication no. (HSM) 73-11009.)
40. Brown EN. Estimating circadian phase. (M.D. honors thesis. Boston: Harvard Medical School, 1987.)
41. Brown BW Jr, Hollander M. Statistics: a biomedical introduction. New York: John Wiley, 1977.
42. Czeisler CA, Weitzman ED, Moore-Ede MC, Zimmerman JC, Knauer RS. Human sleep: its duration and organization depend on its circadian phase. Science 1980; 210:1264-7.
43. Reinberg A, Andlauer P, De Prins J, Malbecq W, Vieux N, Bourdeleau P. Desynchronization of the oral temperature circadian rhythm and intolerance to shift work. Nature 1984; 308:272-4.
44. Monk TH. Advantages and disadvantages of rapidly rotating shift schedules — a circadian viewpoint. Hum Factors 1986; 28:553-7.
45. Gerritzen F. The diurnal rhythm in water, chloride, sodium and potassium excretion during a rapid displacement from East to West and vice versa. Aviat Space Environ Med 1962; 33:697-701.
46. Klein KE, Wegmann HM. The resynchronization of human circadian rhythms after transmeridian flights as a result of flight direction and mode of activity. In: Scheving LE, Halberg F, Pauly JE, eds. Chronobiology. Tokyo: Igaku Shoin, 1974:564-70.
47. Wever RA, Polasek J, Wildgruber CM. Bright light affects human circadian rhythms. Pflugers Arch 1983; 396:85-7.
48. Dijk DJ, Beersma DG, Daan S, Lewy AJ. Bright morning light advances the human circadian system without affecting NREM sleep homeostasis. Am J Physiol 1989; 256:R106-R111.
49. Van Cauter E, Van Onderbergen A, Bosson D, et al. Effect of triazolam on the adaptation of the circadian rhythms of cortisol, melatonin and REM propensity to an 8-h delay of the sleep-wake cycle in man. Presented at the First Meeting of Society for Research on Biological Rhythms, 1988. abstract.
50. Eastman CI. Bright light in work-sleep schedules for shift workers: application of circadian rhythm principles. In: Rensing L, an der Heiden U, Mackey MC, eds. Temporal disorder in human oscillatory systems. New York: Springer-Verlag, 1987:176-85.
51. Honma K, Honma S, Wada T. Phase-dependent shift of free-running human circadian rhythms in response to a single bright light pulse. Experientia 1987; 43:1205-7.
52. Drennan M, Kripke DF, Gillin JC. Bright light can delay human temperature rhythm independent of sleep. Am J Physiol 1989; 257:R136-R141.
53. Broadway J, Arendt J, Folkard S. Bright light phase shifts the human melatonin rhythm during the Antarctic winter. Neurosci Lett 1987; 79:185-9.
54. Sharp GWG. Reversal of diurnal temperature rhythms in man. Nature 1961; 190:146-8.
55. Moline ML, Pollak CP, Wagner DR, Lester LS, Salter CA, Hirsch E. Effects of bright light on sleep following an acute phase advance. Sleep Res 1989; 18:432.