

primordial germ cells. Alternatively, the MH-3 gene may be expressed and play a role in embryonic cells that are not of the germ cell lineage.

In contrast to the defined functions of *Drosophila* homeo box genes, nothing is known about the functions of the 10–20 homeo box genes in mice. Their relationship to the control of development remains to be determined.

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## Bright Light Resets the Human Circadian Pacemaker Independent of the Timing of the Sleep-Wake Cycle

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Human circadian rhythms were once thought to be insensitive to light, with synchronization to the 24-hour day accomplished either through social contacts or the sleep-wake schedule. Yet the demonstration of an intensity-dependent neuroendocrine response to bright light has led to renewed consideration of light as a possible synchronizer of the human circadian pacemaker. In a laboratory study, the output of the circadian pacemaker of an elderly woman was monitored before and after exposure to 4 hours of bright light for seven consecutive evenings, and before and after a control study in ordinary room light while her sleep-wake schedule and social contacts remained unchanged. The exposure to bright light in the evening induced a 6-hour delay shift of her circadian pacemaker, as indicated by recordings of body temperature and cortisol secretion. The unexpected magnitude, rapidity, and stability of the shift challenge existing concepts regarding circadian phase-resetting capacity in man and suggest that exposure to bright light can indeed reset the human circadian pacemaker, which controls daily variations in physiologic, behavioral, and cognitive function.

IN THE 25 YEARS SINCE DECOURSEY discovered the phase response curve to light in the flying squirrel (1), the resetting of biological clocks by light has been characterized in nearly all species studied except man. Synchronization of the human circadian system, which usually has an intrinsic period greater than 24 hours (2, 3), to a 24-hour day implies that our biological clocks are reset daily. Yet, a specific resetting stimulus that shifts the phase of the human

circadian pacemaker has not been identified. In a controlled case study, we have demonstrated that critically timed exposure to bright indoor light can rapidly reset the human circadian pacemaker by about 6 hours, even when the timing of the sleep-wake cycle is constant.

Despite documentation of human neuroanatomic structures analogous to those subserving circadian rhythmicity and photic entrainment in other mammals (4), attempts

to assess the specific role of light in the synchronization of the human circadian system have been methodologically difficult. In contrast to the results of animal studies, the light-dark cycle was reported to be too weak a synchronizing cue to entrain human circadian rhythms (5); however, these experiments were confounded by the subjects' access to auxiliary lighting. In 1981, we demonstrated that a true light-dark cycle could entrain human circadian rhythms (6). However, studies of light-dark cycle entrainment in humans cannot distinguish whether synchronization occurs (i) directly through an action of light on the endogenous circadian pacemaker or (ii) indirectly by an influence on the behavioral rest-activity cycle (7). Because subjects attempt to sleep when it is dark and are awakened by light, the light-dark cycle influences the timing of the subjects' sleep-wake cycle, which itself may be a synchronizing agent (6, 8).

Having demonstrated that bright light must exceed a minimum threshold (>2500 lux) to suppress melatonin secretion (9), Lewy has suggested that bright light may

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have a more powerful effect on circadian rhythms than ordinary indoor illumination (10). However, it is inherently difficult to demonstrate a direct physiologic synchronizing effect of light beyond its potential indirect influence via behavior because the maximally responsive phase of the circadian

cycle normally occurs during the customary sleep time in diurnal animals (11). Thus, stimulation of the subject by light would intrude on the normal sleep-wake cycle. Hence, we decided to search for individuals with a normal sleep-wake cycle and a markedly advanced endogenous circadian phase

(ECP) position (12), our reason being that the portion of the circadian cycle sensitive to phase-delay shifts by light might be accessible during their usual waking hours in the evening, a time ordinarily free from exposure to bright light.

Because there is an age-related shortening of the internally synchronized free-running period (13), we hypothesized that, on average, the circadian timing system in the elderly would be internally phase advanced with respect to sleep. On screening a group of healthy elderly subjects (14), we identified a woman whose sleep was normal, but who had a marked internal phase advance of her endogenous circadian oscillator, as determined by an extension of the constant routine technique originally proposed by Mills (15) (Fig. 1).

We initially tested whether this subject's markedly advanced internal phase position during entrainment was associated with a shortened intrinsic period of the circadian pacemaker. We scheduled her to a 27-hour day, thereby forcing desynchrony between the rhythm of body temperature and the behavioral rest-activity cycle. Two independent assessment techniques validated that her circadian pacemaker did have an exceptionally short intrinsic period of 23.7 hours (Fig. 2).

We then compared circadian phase assessments before and after laboratory entrainment to a 24-hour day, with and without 4 hours of exposure to bright indoor light every evening (Fig. 3). The intensity of the artificial light stimulus (7,000 to 12,000 lux) was equivalent to ambient outdoor light intensity just after dawn (see cover), which is an order of magnitude less than the intensity of sunlight at midday (>100,000 lux) (16). During laboratory entrainment, the subject lived on a fully scheduled regimen [scheduled bed rest (dark), activity (light), mealtimes, and social interactions; with a period of 24 hours], in an environ-

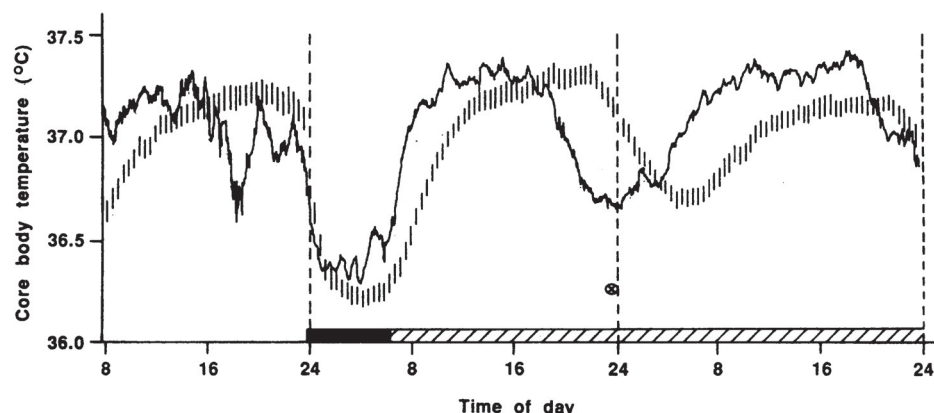


Fig. 1. The core body temperature (solid line) of a healthy, 66-year-old woman (subject 505) under baseline (first 24 hours) and constant routine (remaining 40 hours) conditions. The subject was free from dementia or other central nervous system pathology, psychopathology, and medications. These data are superimposed upon average ( $\pm$  SEM) temperature data collected from 29 young, normal subjects on the same protocol (vertical hatch marks). Data from the controls are averaged with respect to their habitual bedtimes, normalized to her bedtime of 24:00 (12 midnight). Black bar represents the bed rest episode of subject 505, which was scheduled at its regular time. Hatched bar represents the period of constant routine [40-hour regimen of enforced supine wakefulness in constant indoor light (about 150 lux), with the daily nutritional intake equally partitioned into hourly liquid aliquots]. This regimen is designed to expose the endogenous component of the circadian rhythm of core body temperature by minimizing the masking effects of sleep-wake and light-dark transitions and exogenous environmental and behavioral stimuli (15). The encircled cross marks the minimum of a harmonic regression model fitted to the temperature data with the method of Brown *et al.* (33). Note that the ECP minimum of subject 505 occurred at 23:35 (11:35 p.m.), advanced 6.7 hours earlier than her regular waketime of 06:15 (6:15 a.m.); however, this advanced internal phase was not revealed during the day preceding the constant routine because of masking effects. The rhythm of cortisol secretion was similarly phase advanced during her constant routine. Her marked phase advance was confirmed on two subsequent repetitions of this constant routine protocol.

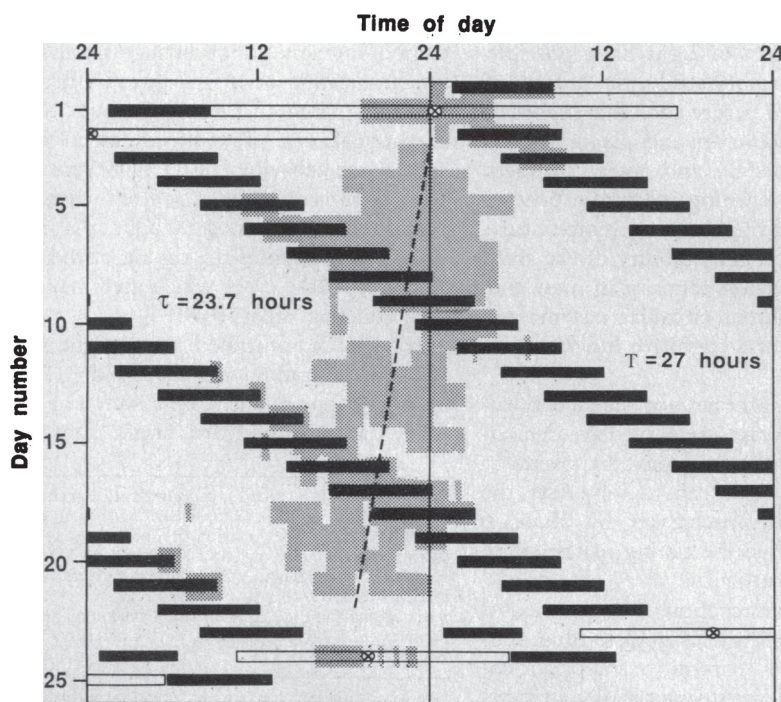


Fig. 2. A 27-hour sleep-wake schedule was imposed in subject 505 to force internal desynchronization between the behavioral rest-activity cycle and the output of the circadian pacemaker, as reflected by the endogenous component of the body temperature rhythm. The rest-activity pattern is double plotted in raster format, with successive days plotted both next to and beneath each other. Solid bars represent episodes of scheduled bed rest. Open horizontal bars represent constant routines (15). The encircled crosses represent ECP minima obtained as in Fig. 1, and provide an estimate of the intrinsic circadian period of 23.73 hours. A single plot of the times that the body temperature was below the normal entrained mean (36.83°C) is overlaid with stippling. A second independent estimate of the intrinsic circadian period was obtained by applying nonparametric spectral analysis-waveform education (34) to parts of the data set disjoint from those used in the ECP estimates. The dashed line indicates the midtrough of the body temperature cycle thus determined, which indicated a period of 23.79 hours. There is a significant correlation between the results of these two period estimation techniques ( $P < 0.01$ ) (35).



mental scheduling facility free of external time cues (6). The subject's bedtimes and waking times were scheduled to correspond with her habitual ones, as calculated from a prior sleep-wake log. Social contact was limited to members of the staff. The ECP evaluations (Fig. 3A) and spectral analysis-waveform education of the temperature data (Fig. 3B) before and after laboratory entrainment with ordinary room light suggest a small cumulative advance of the ECP minimum (Fig. 3A), consistent with the subject's intrinsic circadian period of less than 24 hours (17) (Fig. 2).

In contrast, the intervention with bright light caused a phase-delay shift of the endogenous component of the body temperature rhythm of nearly 6 hours (Fig. 3C). The shift was unexpectedly large, but three independent estimates corroborate the occurrence of an approximately 6-hour delay. First, as estimated by phase evaluation before and after the intervention, the ECP minimum was shifted by  $-5.7$  hours (that is, to a later hour). Second, spectral analysis-waveform education of the temperature data during the intervention indicated a shift of  $-7.1$  hours, which was evident by the second day (Fig. 3D). Third, the secretory patterns of cortisol monitored during constant routines before and after the intervention also demonstrated a 6-hour phase-delay shift (Fig. 4). This resulted in a 90-degree change in the relationship between the timing of the sleep-wake cycle and the cortisol secretory pattern. Subsequent ambulatory temperature monitoring of the subject indicated that the temperature cycle drifted back to its original, advanced phase position over the course of 7 to 10 days after the light pulses were discontinued and the subject returned to her home environment. Measurement of her ECP 1 month after discharge confirmed that it had returned to its markedly advanced position.

Although appropriate caution must be exercised in drawing conclusions based on data from an individual case, the results of this study challenge previous understanding of the temporal organization of the human circadian system. First, the phase shift of the thermoregulatory and neuroendocrine markers of the endogenous circadian oscillator was induced by light and occurred despite the fact that the timing of the sleep-wake cycle remained constant. Second, the 6-hour, light-induced shift was uncharacteristically large since mammals typically have weak phase response curves to light compared to insects and plants. Third, the shift took place with unexpected rapidity. Although the large magnitude of the phase-delay shift observed in this subject could be associated with the short period of her en-

dogenous circadian oscillator, there is also evidence of a diminution of phase-resetting capacity with advancing age (18).

Even when all environmental and behavioral synchronizing cues are shifted simultaneously, as in jet lag, the human circadian pacemaker is thought to require about a day of adaptation for every one to two time

zones crossed, depending on the direction of travel (19). Although our protocol design did not allow us to determine precisely the length of time required to achieve a complete phase shift, the temperature data in Fig. 3D suggest that critically timed exposure to bright light may induce more rapid phase shifts than the more haphazard expo-

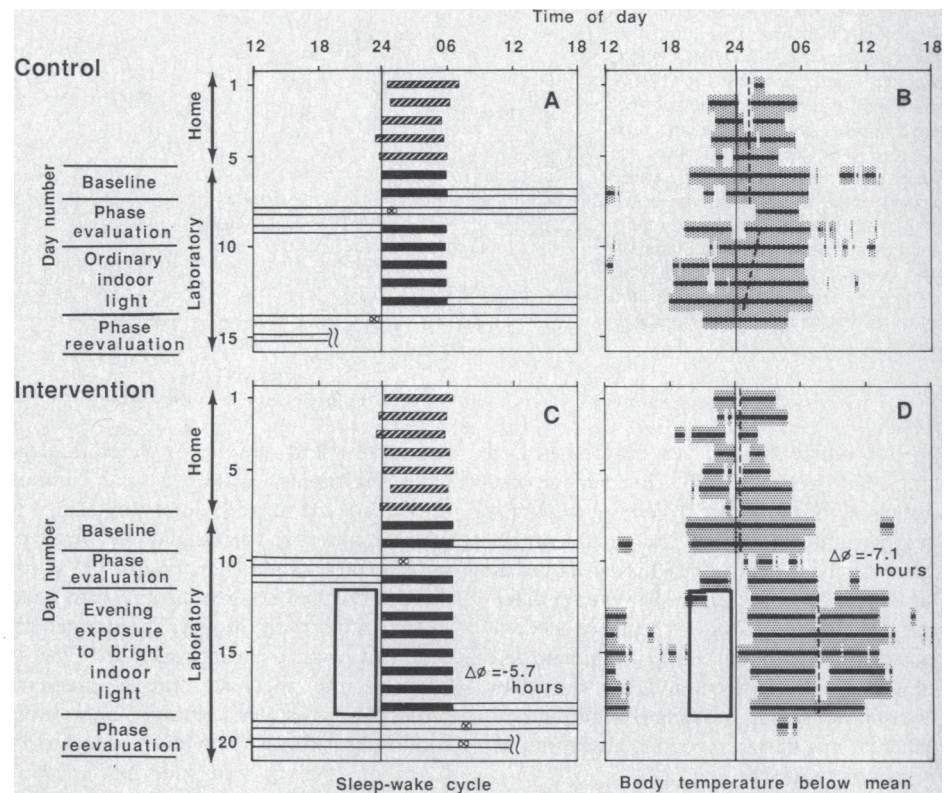
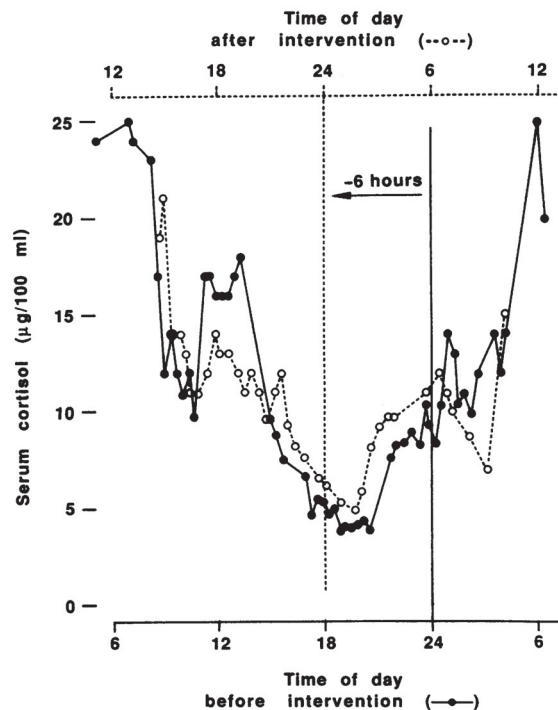


Fig. 3. Evening exposure to bright indoor light reset the circadian pacemaker of subject 505 by about 6 hours, even while her rest-activity cycle was held fixed. (A) ECP evaluations before and after entrainment schedule ( $T = 24$  hours) involving exposure to ordinary room light (50 to 250 lux) suggest a small cumulative advance of the ECP minimum consistent with her 23.7 hour intrinsic circadian period established in Fig. 2 and the observation that subjects tend to drift in the direction of their intrinsic period while in the laboratory environment, presumably because it offers weaker synchronizing cues than those of the home environment (17). Symbols as in Fig. 2; hatched bars indicate bed rest episodes reported from home sleep-wake diaries during ambulatory monitoring. (B) Raster plot of body temperature troughs during control study. Symbols as in Fig. 2, with the addition of horizontal black bars highlighting the specific times and days when body temperature was below the baseline-entrained mean ( $36.83^{\circ}\text{C}$ ), from which the stippled area is derived. Although there is no phase shift, there is an apparent transient shortening of her average temperature-cycle period during entrainment to a light-dark cycle with ordinary room light in the laboratory. (C) ECP evaluations 10 months later in the same subject before and after entrainment schedule as described in (A), with the addition of an intervention stimulus consisting of evening exposure to bright indoor light. This caused a 5.7-hour phase-delay shift of the circadian

pacemaker. Symbols as in (A). The subject was exposed to bright indoor light of 7,000 to 12,000 lux, comparable in intensity to natural outdoor sunlight around twilight (16) (see cover). She was exposed to the light while seated in front of a bank of 16 4-foot, 40-watt Vitalite wide spectrum fluorescent lamps (Durotest Corp., North Bergen, NJ) between 19:40 and 23:40 (7:40 p.m. and 11:40 p.m.) each day for 7 days (open vertical box). Light intensity was measured at her forehead by a digital photometer (Model TL1350, International Light, Inc., Newburyport, MA), with the sensor directed toward the line of gaze. Fifteen minutes of intermediate level light (3000 to 6000 lux) preceded and followed each 4-hour exposure. (D) Raster plot of body temperature troughs (body temperature below baseline-entrained mean of  $36.69^{\circ}\text{C}$ ) before and during the intervention study. This plot confirms the magnitude of the phase-delay shift shown in (C) and demonstrates the unexpected rapidity of the shift, which is evident 1 to 2 days after the start of the intervention. Although the disappearance of the trough between 19:00 and 24:00 (7:00 p.m. and 12 midnight) could be due to a masking effect of light, the extension of the trough into the 08:00 to 14:00 (8:00 a.m. to 2:00 p.m.) period cannot be so readily explained. Symbols as in (B). Estimates of the phase shift were based on spectral analysis of data sets disjoint from those used to derive the estimates of the ECP minima shown in (C).



Fig. 4. Superposition of the serum cortisol concentrations of subject 505 before (filled circles and solid line) and after (open circles and dashed line) intervention with bright indoor light. To align the secretory patterns the horizontal time scale for the data after the intervention has been shifted to the left by 6 hours. Blood samples were collected while the subject was in ordinary room light (50 to 250 lux) during constant routines performed immediately before and after the intervention (Fig. 3). The subject's habitual bedtime (24:00; 12:00 midnight) for the week before the intervention (solid vertical line) and for the week after the intervention (dashed vertical line) are therefore separated by 6 hours on the horizontal time scale. Thus, the intervention did not change the shape of the cortisol secretory pattern but caused a phase delay of 6 hours with respect to both clock time and sleep.



sure to synchronizing cues characteristic of transmeridian travel (20). Our data are consistent with the report by Wever *et al.* that bright light extends the range of entrainment of the synchronized human circadian system to 29 hours (21). However, a different experimental design is required to demonstrate the true range of entrainment, free of the masking effects and the systematic error in estimating the range of entrainment inherent in a design involving a continuously lengthening schedule (22).

Our results have theoretical significance for models of human circadian rhythms. Most important, the phase shift obtained through the intervention was consistent with the phase response model derived from animal studies (1) in that there was a phase-delay shift in response to a stimulus in the early half of the subjective night. After the abrupt phase shift, continued presentation of the stimulus at the same clock hour but at an earlier relative phase produced a much smaller response that was sufficient to maintain stable entrainment, as expected of a phase response curve to light.

Our data also support a hierarchical model in which the external light-dark cycle ordinarily synchronizes the endogenous circadian oscillator (6), which in turn governs the internal organization and spontaneous duration of sleep (3, 23). These data are incompatible with alternate models in which sleep must play either a primary or an essential intermediate role in the entrainment of physiologic rhythms. This conclusion is consistent with recent findings in depressed patients suggesting that prior light exposure affects the time of onset of the

nocturnal rise in melatonin secretion, even when the timing of sleep is held constant (24). Also, the magnitude of the change in internal phase relations that we observed implies that bright light must be acting directly on the endogenous circadian pacemaker, rather than through an intermediary process as we had earlier concluded (25). In addition, the apparent drift of phase to earlier hours under entrained laboratory conditions is consistent with the conclusion, based on analysis with our mathematical model, that the laboratory is a weaker synchronizer than the external environment (26).

Demonstration that light can have a direct effect on the human circadian oscillator also has important practical implications. Sleep-wake disorders such as delayed sleep phase insomnia (27), jet lag (28), and shiftwork insomnia (29) may respond to manipulation of circadian phase with therapeutic exposure to light. Since Lewy *et al.* discovered the enhanced biologic effects of bright light as compared to ordinary room light (9), phototherapy with bright light has been used clinically in the treatment of affective illness; however, there is disagreement as to whether its mechanism of action has a circadian basis (30). Evaluation of the use of phototherapy in such conditions has relied on either subjective measures of clinical response or biologic markers with no established relationship to the endogenous oscillator. We have now demonstrated an effective protocol for objectively quantifying changes in the phase position of the circadian pacemaker before and after a therapeutic intervention. This protocol could be used to

correlate changes in internal phase relations with clinical response to treatments aimed at correcting hypothesized abnormalities of circadian phase orientation. This would provide important corroborative evidence for the hypothesized role of circadian dysfunction in affective illness.

Finally, although it is possible that these results are found only in those individuals who have a stably advanced circadian phase, this is an unlikely interpretation of the data for several reasons. First, the advanced phase position in our subject is a predicted consequence of the short intrinsic period of her circadian pacemaker. An analogous range of circadian period is seen among individuals of a given animal species without attendant alteration in the nature of the phase response mechanism (31). Second, the phase orientation of our subject is commonly expressed by otherwise normal subjects upon exposure to free-running conditions (2, 3). Third, the nature of the response to light, a finite delay produced by stimulation during that phase typically associated with the first half of the subjective night, is consistent with the response in virtually all other species tested, both diurnal and nocturnal (27). Although it would be useful to confirm these results on subjects with more standard circadian phase orientations, studies in subjects with a stable internal phase advance provide important evidence to resolve the heretofore inseparable link between the physiologic and behavioral components of the light-dark cycle as a synchronizer of the human circadian system.

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7. Various authors modeling the complex interaction between the output of the endogenous circadian pacemaker and the periodic, behavioral rest-activity cycle have referred to this pair of oscillatory processes, respectively, as the deep ( $x$ ) oscillator and the labile ( $y$ ) oscillator (32); the strong (Type I) oscillator and the weak (Type II) oscillator (2); and the C (circadian) oscillator and process S (sleep regulating variable) [S. Daan, D. G. M. Beersma, A. A. Borbély, *Am. J. Physiol.* 246, R161 (1984)]. The endogenous component of the body temperature cycle is the generally accepted marker of the output of the circadian pacemaker, which also drives the endogenous components of the daily cycles in cortisol release, REM sleep propensity, urinary potassium excretion, alertness, and cognitive performance (2, 3). The other independent periodic process observed is marked by the timing of the sleep-wake-rest-activity cycle and the many physiologic responses that are associated with the changes in posture,



- the timing of meals, and sleep-wake state inherent in the rest-activity cycle. It is now accepted by each of these groups that their models employ, at least in a mathematical sense, two oscillatory processes to model the observed data, although there is no consensus as to the physiologic basis of these oscillatory processes.
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  12. Free-running subjects typically develop a marked, stable internal phase advance of the endogenous component of the body temperature cycle relative to the sleep-wake cycle, and yet they are able to maintain normal consolidated sleep episodes (2, 3). In contrast, individuals with delayed circadian phase position often have difficulty initiating sleep, when the evening wake-maintenance zone impinges upon the bedtime hour [S. H. Strogatz, R. E. Kronauer, C. A. Czeisler, *Sleep Res.* **14**, 219 (1985)]. Thus, to avoid the confounding influence of sleep disruption, an attempt was made to identify individuals with a marked internal phase advance rather than an internal phase delay of the ECP position with respect to sleep.
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  14. All subjects had consistent sleep-wake patterns by history, with no transmeridian travel in the preceding 3 months or shiftwork in the preceding 3 years. Subjects had no evidence of medical, psychiatric, or sleep disorders, as determined by clinical history, physical examination, chest radiograph, electrocardiogram, clinical biochemical screening tests, a psychological screening questionnaire (Minnesota Multiphasic Personality Inventory), and a dementia rating scale. Informed consent was obtained from all subjects after the nature and possible consequences of the studies had been explained.
  15. The constant routine procedure is a regimen designed to unmask the endogenous component of the core body temperature rhythm to allow ECP determination by fitting a harmonic regression model to the data (33). This technique minimizes the masking effects [J. Aschoff, *Cold Spring Harbor Symp. Quant. Biol.* **25**, 11 (1960)] that otherwise obscure or distort the observed rhythm [J. N. Mills, D. S. Minors, J. M. Waterhouse, *J. Physiol. (London)* **285**, 455 (1978); D. S. Minors and J. M. Waterhouse, *Chronobiol. Int.* **1**, 205 (1985)]. Our extended version of the regimen is 40 hours in duration, which is certain to expose at least one core body temperature trough [C. A. Czeisler, E. N. Brown, J. M. Ronda, R. E. Kronauer, G. S. Richardson, W. O. Freitag, *Sleep Res.* **14**, 295 (1985)].
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  17. We have observed ECP minima of subjects drift by a small amount (–35 to +24 degrees) after entrainment ( $T = 24$  hours) in the laboratory compared to home environment, presumably because the laboratory offers weaker synchronizing cues than does the home environment. The direction of the drift appears to depend on the period of the endogenous circadian oscillator, with phase advances being associated with intrinsic periods shorter than 24 hours and phase delays occurring in those subjects with intrinsic periods longer than 24 hours.
  18. It has been reported that rodent species with short free-running periods tend to have a greater phase-delay shifting ability than species with long periods [S. Daan and C. S. Pittendrigh, *J. Comp. Physiol.* **106**, 253 (1976)]. However, when chemical and environmental interventions are used to change the free-running period within individuals, there is no consistent relationship between free-running period and delay shifting capacity. Furthermore, although animal studies have demonstrated a decrease in circadian period with age (31), both animal and human studies indicate that older individuals require a greater number of days to resynchronize circadian rhythms following a phase shift of environmental synchronizers [W. C. Dement, G. Richardson, P. Prinz, M. A. Carskadon, D. Kripke, C. A. Czeisler, in *Handbook of the Biology of Aging*, C. E. Finch and E. L. Schneider, Eds. (Van Nostrand Reinhold, New York, 1985), pp. 707–708], suggesting that phase resetting capacity decreases with age. It is thus unclear whether the shortening of circadian period seen within individuals with advancing age is associated with an increased or a decreased capacity for delay shifting.
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  25. On the basis of results of laboratory studies of free-running subjects, we have proposed a mathematical model of the human circadian timing system that has two interacting oscillators (32). The model indicates that, for experiments conducted in ordinary room light, the primary synchronizing drive from the environment ( $z$ ) acts on the endogenous circadian pacemaker ( $x$ ) via the behavioral rest-activity cycle ( $y$ ). However, simulations with this model indicate that even with marked increases in the strength of  $z$ , there is a limit to the strength of its drive onto  $x$  via  $y$  due to saturation of  $y$  amplitude (26). This saturation of  $y$  predicts that any effects of  $z$  on  $x$  via  $y$  are limited to about 1.5 hours per day [P. H. Gander, R. E. Kronauer, R. C. Graeber, *Am. J. Physiol.* **249**, R704 (1985)]. This is inadequate to explain the rate and magnitude of the phase shift reported here. We thus conclude that bright light must act directly on the endogenous circadian pacemaker—a direct action of  $z$  onto  $x$ .
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