

# Sleep and Circadian Rhythms in Humans

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During the past 50 years, converging evidence reveals that the fundamental properties of the human circadian system are shared in common with those of other organisms. Concurrent data from multiple physiological rhythms in humans revealed that under some conditions, rhythms oscillated at different periods within the same individuals and led to the conclusion 30 years ago that the human circadian system was composed of multiple oscillators organized hierarchically; this inference has recently been confirmed using molecular techniques in species ranging from unicellular marine organisms to mammals. Although humans were once thought to be insensitive to the resetting effects of light, light is now recognized as the principal circadian synchronizer in humans, capable of eliciting weak (Type 1) or strong (Type 0) resetting, depending on stimulus strength and timing. Realization that circadian photoreception could be maintained in the absence of sight was first recognized in blind humans, as was the property of adaptation of the sensitivity of circadian photoreception to prior light history. In sighted humans, the intrinsic circadian period is very tightly distributed around approximately 24.2 hours and exhibits aftereffects of prior entrainment. Phase angle of entrainment is dependent on circadian period, at least in young adults. Circadian pacemakers in humans drive daily variations in many physiologic and behavioral variables, including circadian rhythms in alertness and sleep propensity. Under entrained conditions, these rhythms interact with homeostatic regulation of the sleep/wake cycle to determine the ability to sustain vigilance during the day and to sleep at night. Quantitative understanding of the fundamental properties of the multioscillator circadian system in humans and their interaction with sleep/wake homeostasis has many applications to health and disease, including the development of treatments for circadian rhythm and sleep disorders.

## INTRODUCTION

Seventy years ago, Kleitman (1963) was the first to study human circadian rhythms in human subjects shielded from periodic environmental cues. In 1938, he studied two subjects living on non-24-hour sleep/wake, light/dark, and meal schedules while living deep within Kentucky's Mammoth Cave, shielded from the influence of the Earth's 24-hour day. Measurement of the daily rhythm of body temperature in one of the subjects revealed the circadian temperature rhythm to be endogenously generated, persisting for a month with a near-24-hour period despite imposition of a 28-hour rest/activity schedule. That first underground cave study of human circadian rhythms, in the longest known cave on Earth, was far ahead of its time. The fact that a physiological rhythm could oscillate *not only* in the absence of periodic changes in the environment, *but also* at a period different from that of behavioral cyclicality established the endogenous and physiologic nature of human circadian rhythms for the first time. More than two decades later, in a paper on human circadian rhythms that was presented at the first CSHL symposium on circadian rhythmicity, Lobban reported on a series of field studies in which subjects lived on non-24-hour schedules during the continuous light of summer within the Arctic circle (Lewis and Lobban 1957a,b; Lobban 1961). At the time, controversy still persisted as to whether the circadian rhythm of body temperature in humans could be shifted by an inversion of the daily routine, such as is required by night-shift workers—a question that had been hotly debated since the beginning of the 20th century (Benedict 1904; Gibson 1905). The 1960 CSHL symposium on circadian clocks brought together scientists working on circadian rhythms in many

different organisms, and a number of common properties of circadian clocks began to emerge.

Few at the 1960 CSHL symposium on circadian clocks, however, could have imagined that the then-recent discovery by Hastings and Sweeney (1958) of the circadian phase-dependent sensitivity to photic resetting of the circadian pacemaker in the unicellular marine dinoflagellate *Gonyaulax polyedra*, and its codependence on the intensity (Hastings and Sweeney 1958) and wavelength of light (Sweeney et al. 1959; Hastings and Sweeney 1960), would be found to apply to circadian clocks in a remarkably wide array of organisms, from cyanobacteria (Kondo et al. 1993) to humans (Czeisler et al. 1989; Jewett et al. 1992, 2000; Boivin et al. 1996; Zeitzer et al. 2000; Khalsa et al. 2003; Lockley et al. 2003). The purpose of this chapter is to review progress that has been made in understanding the properties of the human circadian pacemaker(s) and the relationship between circadian rhythms and the timing of the sleep/wake cycle. We also review the critical role of sleep and circadian rhythms in clinical and occupational medicine.

## THE HUMAN CIRCADIAN SYSTEM

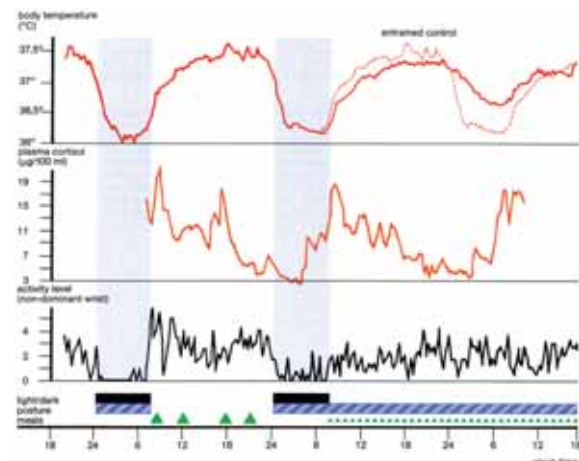
In humans, many aspects of human physiology and behavior vary with circadian phase (Czeisler and Jewett 1990; Johnson et al. 1992; Allan and Czeisler 1994; Waldstreicher et al. 1996; El-Hajj Fuleihan et al. 1997; Cajochen et al. 1999; Czeisler et al. 2000). Thirty-five years ago, the central neuroanatomic structures responsible for both the generation of endogenous circadian rhythms and their synchronization with the 24-hour day were identified (Moore 1972; Moore and Eichler 1972; Moore and Lenn 1972; Stephan and Zucker 1972). Deep

within the brain, two bilaterally paired clusters of hypothalamic neurons comprising the suprachiasmatic nuclei (SCN) act as the central neural pacemaker for the generation and/or synchronization of circadian rhythms in mammals (Ralph et al. 1990; Klein et al. 1991; Edgar et al. 1993; Moore 1994; Welsh et al. 1995; Mumford et al. 1996; Weaver 1998). Evaluation of the impact and the formal properties of the circadian system in humans is aided by the number of variables that can be measured simultaneously but hampered by constraints on the interventions that can ethically be used to study the system, rendering it difficult to characterize the basic properties of the circadian system in humans.

Circadian rhythms are self-sustained and persist in the absence of environmental time cues with remarkable precision. As such, a circadian rhythm represents a cyclic process that can be described by the period (?), phase (?), and amplitude of the oscillation, together with its resetting sensitivity to various circadian synchronizers. These formal properties of the circadian oscillatory system are thought to be determined genetically by a core set of clock genes, which are critical for the generation, maintenance, and synchronization of circadian pacemaker output. Normally, circadian rhythms are entrained to the solar day, ensuring that behavioral, physiologic, and genetic rhythms are timed appropriately with daily changes in the environment. Circadian entrainment is achieved through daily resetting of the circadian pacemaker, such that  $T = ? - \Delta?$ , whereby  $T$  is the imposed period of the environmental synchronizer (e.g., the 24-hour solar day),  $?$  is the intrinsic period of the circadian oscillator, and  $\Delta?$  is the daily phase shift required for stable entrainment. The relationship between the phase of an endogenous circadian rhythm (e.g., the peak of the melatonin rhythm) and the phase of the imposed environmental synchronizer (e.g., the light/dark cycle), termed the phase angle of entrainment (?), is a function of the difference between  $T$  and  $?$  and the resetting sensitivity of the circadian system. Defining the period and resetting properties of the human circadian system is therefore critical for understanding how the timing of diverse behavioral and physiologic processes is established.

### Circadian Phase

The phase of a circadian rhythm is defined with respect to an easily identifiable reference point of the endogenous circadian oscillation, such as the trough of the body temperature rhythm or the onset of the melatonin rhythm. Thus, a circadian phase shift can be determined by measuring the change in timing of the chosen phase marker from one cycle to the next. During ambulatory conditions, changes in environmental stimuli and behavior (e.g., light/dark, rest/activity, and temperature) often obscure the endogenous component of the underlying circadian oscillations that is being measured. Therefore, endogenous circadian phase is best assessed under environmental conditions that minimize exposure to stimuli that evoke response(s) in the physiologic variables being monitored for a minimum of one circadian cycle (Fig. 1). During a constant routine procedure, ambient light is continuously dim, metabolic intake is distributed evenly throughout day



**Figure 1.** The constant routine procedure is used to assess circadian phase and amplitude. During normal entrainment to a 24-hour day, body temperature, cortisol, and activity exhibit a high-amplitude diurnal rhythm. The constant routine procedure allows for assessment of circadian phase and amplitude by reducing the effects of exogenous time cues and rest/activity cycles on the underlying circadian rhythm. During the constant routine procedure, subjects are kept awake continuously in bed in a constant posture, with continuous exposure to dim ambient light, and small meals are spread evenly throughout the protocol. The circadian rhythm of core body temperature during the constant routine procedure shows a decrease in measured amplitude, as compared to the observed amplitude of the rhythm assessed during baseline sleep/wake (red trace). In contrast, the cortisol rhythm shows a similar waveform during entrained conditions and the constant routine procedure (orange trace). The diurnal rhythm of rest/activity, as determined by wrist-actigraphy monitoring, is markedly reduced during the constant routine procedure (black trace). (Gray shading) Sleep episodes in darkness; (blue hatched bars) constant posture; (green triangles) timing of meals. (Reprinted, with permission, from Czeisler 1986 [© Boehringer Ingelheim].)

and night, and constant posture and wakefulness are maintained. The phase and amplitude of endogenous circadian components of daily rhythms in sleep propensity and in thermoregulatory, endocrine, cardiac, renal, respiratory, neurobehavioral, and gastrointestinal functions have been characterized under such constant routine conditions and have been found to be distinct from the profiles of those variables recorded in the presence of periodic stimuli that evoke responses in these functions.

### Circadian Amplitude

The measured amplitude of a circadian rhythm refers to the half-distance from the maximum to the minimum of the observed rhythm. As first demonstrated by the late Arthur Winfree (1969, 1974, 1980, 1987), both oscillator phase and oscillator amplitude are required to describe adequately the resetting properties of the circadian system (see below). The absolute value of the measured amplitude of an observed rhythm does not necessarily equate with the endogenous amplitude of the circadian oscillator. Whereas the absolute value of the amplitude of the melatonin rhythm varies by more than tenfold among individuals, the absolute value of the amplitude of the core body

temperature rhythm varies by less than twofold in those same individuals. Suppression of circadian amplitude is associated with a comparable reduction in the amplitude of both parameters, *relative to the initial measured amplitude* of each variable (Shanahan et al. 1997).

### Entrainment to Light

Despite an initial report suggesting that light was an effective circadian synchronizer in humans (Aschoff et al. 1969), based on a subsequent study by that same group (Wever 1970), for many years, it was thought that the human circadian system was insensitive to light and that social interaction was the predominant synchronizer mediating circadian entrainment to the solar day (Wever 1970, 1974, 1979; Aschoff 1976; Aschoff and Wever 1981). This observation led to the belief that humans had evolved beyond the need to rely on periodic exposure to a physical stimulus such as light for circadian entrainment. However appealing this notion may appear, there is now overwhelming evidence that the human circadian pacemaker is in fact exquisitely sensitive to light as a circadian synchronizer—with a phase-response curve and sensitivity to light that are similar to those described in lower organisms such as adult *Drosophila pseudoobscura* and the cockroach *Leucophaea maderae*—and that light is the primary circadian synchronizer in humans (Czeisler 1978, 1995; Czeisler et al. 1981; Shanahan et al. 1997; Czeisler and Wright 1999; Shanahan and Czeisler 2000; Zeitzer et al. 2000; Wright et al. 2001; Gronfier et al. 2004, 2007; Lockley 2007). In mammals, light information is transmitted to the circadian pacemaker in the SCN via the retino-hypothalamic tract, a monosynaptic pathway that originates from a small subset of retinal ganglion cells (Moore 1972; Moore and Lenn 1972). Resetting the SCN, in turn, shifts the timing of diverse behavioral and physiologic functions. To entrain stably to the light/dark cycle, the phase of the circadian pacemaker must be reset daily such that a phase shift is equivalent to the difference between the  $T = 24$  hour cycle and the intrinsic circadian period ( $\Delta\tau = \tau - T$ ). For individuals with a circadian period longer than 24 hours, a daily phase advance of the circadian system is required for stable entrainment to the light/dark cycle. Conversely, individuals with a circadian period shorter than 24 hours require a daily phase delay in order to synchronize to the 24-hour environmental cycle. As discussed below, the resetting effects of light depend on several factors, including the circadian phase at which the light is administered; the pattern, duration, irradiance, and wavelength of the exposure to light; and recent photic history.

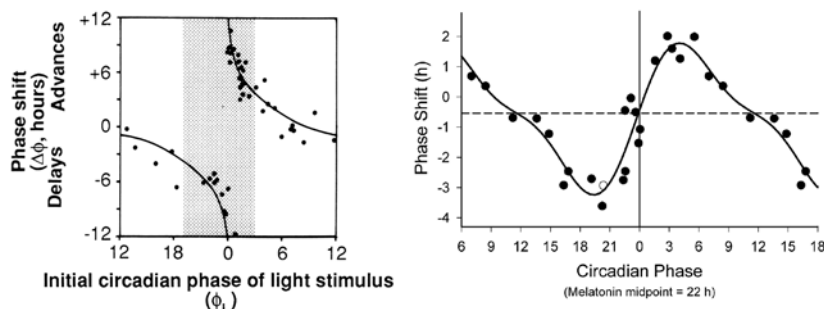
### Circadian Phase-dependent Resetting to Light

The most important functional property of circadian oscillators is phase-dependent resetting; i.e., the magnitude and direction of phase resetting are dependent on the circadian phase at which a synchronizing stimulus occurs. This fundamental property of circadian clocks is summarized by the phase-response curve, a plot of the resetting response versus the circadian phase of the perturbation.

The first phase-response curve was constructed by Hastings and Sweeney (1958) in the single-celled eukaryote *Gonyaulax polyhedra*. Following this pioneering study, phase-dependent resetting of circadian clocks in response to light and other synchronizers has been demonstrated in a diverse array of species, ranging from prokaryotes to humans. A conserved feature in all light-sensitive circadian oscillatory systems is that exposure to light during the early subjective night induces phase-delay shifts, whereas exposure to light in the late subjective night elicits phase-advance shifts.

On the basis of the topology of circadian resetting responses to light, Winfree classified phase resetting as being either Type 1 or Type 0. Weak Type-1 resetting is characterized by small phase shifts of only a few hours and little or no reduction in endogenous circadian pacemaker amplitude. In contrast, strong Type-0 resetting is characterized by large phase shifts of up to 12 hours and occurs via prior reduction of circadian pacemaker amplitude. On the basis of his phase-amplitude resetting model of circadian rhythms in *Drosophila*, Winfree predicted that a critical stimulus of intermediate strength, when administered at a critical circadian phase during the subjective night (the phase at which phase delays transition to phase advances), would drive the circadian oscillatory system to its singularity, characterized by a marked reduction in amplitude such that phase cannot be determined (Winfree 1969, 1980, 1987). Winfree demonstrated the property of critical resetting in *Drosophila*, in which the circadian amplitude of the eclosion rhythm approached zero in response to a carefully titrated light pulse. In summary, Winfree showed that (1) circadian resetting to light cannot be explained by a simple phase-only model and (2) organisms that display Type-0 resetting can also display Type-1 resetting to a stimulus of reduced strength.

Consistent with Winfree's predictions, Type-1 resetting, critical resetting, and Type-0 resetting have been demonstrated in humans (Czeisler et al. 1989; Jewett et al. 1991, 1992; Khalsa et al. 2003). The first human phase-response curve (PRC) to light was constructed in response to a three-cycle bright-light stimulus administered during 3 days (Fig. 2, left). Phase shifts of up to 12 hours were observed, and the Type-0 resetting contour closely matched that described in other organisms, such as the mosquito (Peterson 1980). Consistent with Winfree's phase-amplitude model of resetting, reducing the stimulus to a critical strength administered at a critical phase resulted in critical resetting in which circadian rhythm amplitude approached zero (Jewett et al. 1991). Reducing the stimulus strength further to a single-cycle exposure to bright light (6.5 hours, ~10,000 lux) resulted in Type-1 resetting (Fig. 2, right) (Khalsa et al. 2003). Consistent with Type-1 PRCs in other mammals, maximum phase delays of about -3.5 hours were observed in response to light administered during the early subjective night (before the body temperature rhythm nadir), and maximum phase advances of about +3.0 hours were observed following exposure to light during the late subjective night (after the body temperature minimum). Interestingly, the human PRC does not exhibit a dead zone of sensitivity during the subjective daytime, indicating that the human circadian



**Figure 2.** Circadian phase-dependent resetting of the human circadian system. (*Left*) The human circadian system exhibits Type-0 resetting in response to a three-cycle stimulus of bright light (5 hours,  $\sim 10,000$  lux), characterized by large phase shifts of up to 12 hours. Phase shifts of the body temperature rhythm are plotted with respect to the initial circadian phase at which the light stimulus was given. (*Right*) Type-1 resetting of the melatonin rhythm is observed in response to a single cycle stimulus of bright light (6.5 hours,  $\sim 10,000$  lux). The circadian phase of the light intervention is plotted relative to the nadir of the body temperature rhythm, defined as initial phase zero. (*Left panel*, Reprinted, with permission, from Czeisler et al. 1989 [© AAAS]; *right panel*, reprinted, with permission, from Khalsa et al. 2003 [© Physiological Society].)

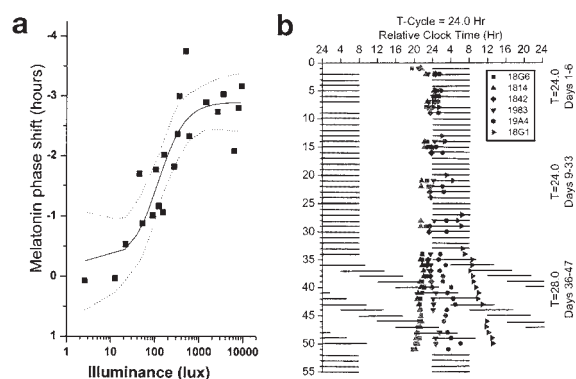
system is sensitive to light across all circadian phases (Jewett et al. 1997; Khalsa et al. 2003).

#### Dose-dependent Resetting to Light

Resetting responses to light can be enhanced by increasing the duration or intensity of the stimulus. In humans, it has been demonstrated that phase resetting of the circadian system exhibits a saturating nonlinear dose-response curve to different levels of illuminance (Fig. 3a) (Boivin et al. 1996; Zeitzer et al. 2000). In the early subjective night, the dose response to 6.5 hours of white light saturates at about 500 lux, when administered on the background of constant dim light. Remarkably, exposure to ordinary indoor room light ( $\sim 100$  lux) elicits a half-maximal phase-shifting response ( $-1.5$  hours) as compared to light that is 100 times brighter, indicating that the human circadian pacemaker is quite sensitive to light encountered in everyday life. These resetting responses

have served as the basis of a mathematical model of the circadian resetting effect of light in humans (Kronauer 1990; Kronauer and Czeisler 1993; Jewett et al. 1999b; Kronauer et al. 1999). Moreover, like circadian rhythms in the mosquito and the tropical *Kalanchoe* plant, exposure to light of critical timing and intensity can drive the oscillator to its region of singularity, effectively “stopping” the circadian clock in humans (Jewett et al. 1991).

Most human subjects are able to maintain stable entrainment to a 24-hour cycle in which ambient room light was about 1.5 lux, suggesting that even candlelight can induce small shifts of the human circadian system (Fig. 3b) (Wright et al. 2001). To date, a systematic evaluation of the duration dependence of circadian resetting responses to light has not been conducted. However, in our preliminary analyses of the human PRC, maximum phase shifts to 1 hour of bright white light ( $\sim 10,000$  lux) were about 40% as effective as phase shifts measured in response to 6.5 hours of white light ( $\sim 10,000$  lux), despite



**Figure 3.** The human circadian system is exquisitely sensitive to light. (*a*) The dose response for phase resetting of the melatonin rhythm to white light (6.5 hours) is nonlinear, with a saturating phase-shift response at  $\sim 500$  lux. Half-maximal phase resetting ( $-1.5$  hours) is observed in response to  $\sim 100$  lux, indicating that ordinary room light is highly effective at resetting the human circadian system. The light exposure was administered during the early biological night, and circadian phase of the melatonin rhythm was assessed during a constant routine procedure, before and after the light intervention. (*b*) Subjects are able to entrain to a 24-hour  $T$  cycle consisting of 16 hours of dim light ( $\sim 1.5$  lux) and 8 hours of sleep in darkness (Days 9–33), provided their intrinsic period is sufficiently close to 24 hours, as determined by forced desynchrony ( $T = 28$  hours, Days 36–47). Symbols indicate the onset of the melatonin rhythm in individual subjects, and the sleep/wake schedule is double-plotted. (*a*, Reprinted, with permission, from Zeitzer et al. 2000 [© Physiological Society]; *b*, reprinted, with permission, from Wright et al. 2001 [© National Academy of Sciences].)

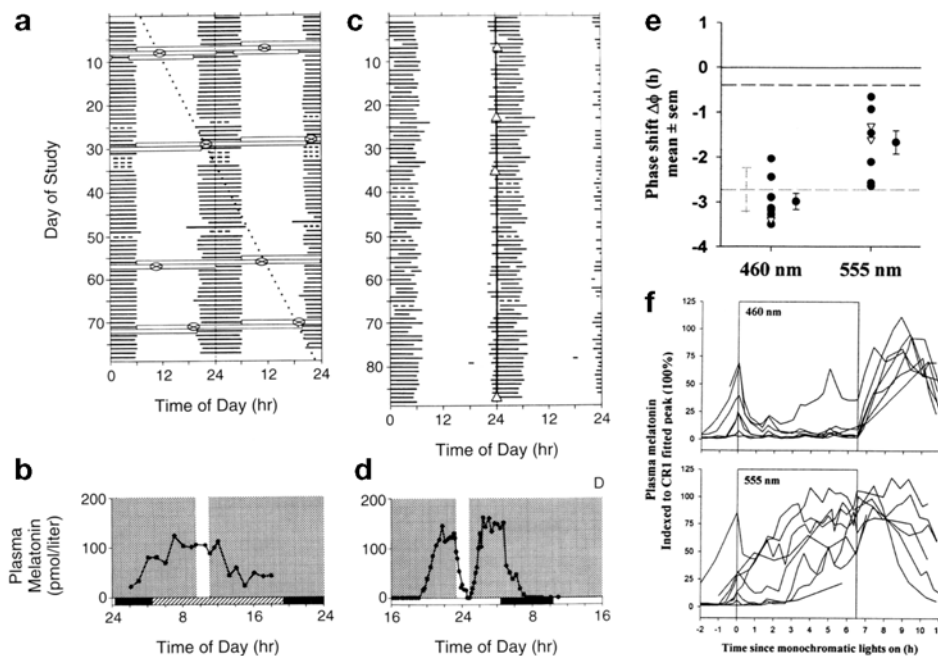


representing only 15% of the stimulus strength (1 hour/6.5 hours) (Khalsa et al. 2003; Lockley et al. 2006a). Hence, for the 6.5-hour light stimulus, the early part of a light stimulus is more effective at resetting the circadian system than the later part, as predicted by Kronauer's dynamic model of the resetting effect of light on the human circadian pacemaker (Kronauer et al. 1999).

### Wavelength Sensitivity of Circadian Responses to Light

The wavelength sensitivity of a circadian system is dependent on the underlying photoreceptors that provide input to the circadian pacemaker. The human visual image-forming system consists of rods and cones that mediate night vision and color vision, respectively. Some blind individuals, with complete loss of conscious visual perception, show intact photic circadian entrainment and melatonin suppression in response to light (Czeisler et al. 1995; Klerman et al. 2002), suggesting that the classical visual photopigments are not required for circadian photoreception (Fig. 4). These results are consistent with findings in lower mammals demonstrating that rods and cones are dispensable for resetting of the circadian pacemaker (Provencio et

al. 1994; Yoshimura and Ebihara 1996; Foster et al. 1998; Foster and Hankins 2002). Recently, it was shown that retinal ganglion cells that project to the SCN contain the blue-light-sensitive photopigment melanopsin (Gooley et al. 2001; Berson et al. 2002; Hannibal et al. 2002, 2004; Hattar et al. 2002). In the absence of rod and cone function, the melanopsin-containing cells mediate circadian entrainment (Yoshimura and Ebihara 1996; Freedman et al. 1999). In animals with intact retinæ, however, the classical visual photopigments and melanopsin contribute to phase resetting of the circadian pacemaker (Hattar et al. 2003; Panda et al. 2003). In blind humans who show intact circadian photoreception, it is likely that the melanopsin cells reset the circadian clock, as evidenced by the short wavelength sensitivity of the circadian system (Czeisler et al. 1995; Zaidi et al. 2007). In normally sighted individuals, circadian phase resetting and melatonin suppression in response to bright monochromatic light is most sensitive to short-wavelength (blue) light (Fig. 4), indicating that melanopsin has a primary role in human circadian photoreception (Brainard et al. 2001; Thapan et al. 2001; Lockley et al. 2003). However, long-wavelength light is also effective at resetting human circadian rhythms, especially in response to lower irradiances, suggesting that the cones can function as



**Figure 4.** Visual photoreceptors are not required for circadian responses to light. (a) In a blind individual who kept a regular sleep/wake pattern for 78 days, the minimum of the body temperature rhythm (crosses) exhibited a free-running period of 24.5 hours (dotted line), indicating that the circadian system did not entrain to the solar day. (b) In the same individual, exposure to bright white light (~10,000 lux, white vertical bar) during the biological night (hatched horizontal bar) did not suppress the rhythm of melatonin. (c) In a different blind individual, the sleep/wake pattern and the peak of the melatonin rhythm (triangles) were synchronized for 88 days, indicating entrainment to the 24-hour day. (d) In this same subject, exposure to bright light during the night inhibited melatonin synthesis, indicating that nonvisual responses to light remained intact in some blind individuals. (Black bars) Sleep in darkness. (e) In normal-sighted subjects, circadian phase resetting of the melatonin rhythm is short-wavelength-sensitive, suggesting that the blue-light-sensitive melanopsin cells are the primary circadian photoreceptors in humans. A 6.5-hour monochromatic light stimulus (460 nm vs. 555 nm) was given during the early biological night. (Upper dashed line) Average drift in phase due to circadian period; (lower dashed line) average phase-shifting response to 6.7 hours of polychromatic white light (~10,000 lux) given at the same circadian phase. (Closed circles) Plasma melatonin; (open triangles) salivary melatonin. (f) In the same set of individuals, the 460-nm light stimulus elicited strong suppression of the melatonin rhythm across the 6.5-hour light intervention, whereas the 555-nm light stimulus elicited weak and transient suppression of melatonin. The boxes enclose the light intervention. (a–d, Reprinted, with permission, from Czeisler et al. 1995 [© Massachusetts Medical Society]; e, f, reprinted, with permission, from Lockley et al. 2003 [© Endocrine Society].)

circadian photoreceptors in humans (Zeitzer et al. 1997; J.J. Gooley et al., unpubl.). To determine the relative contributions of the three-cone photopic visual system and the melanopsin cells to circadian phase resetting, it will be important to characterize fully the spectral sensitivity of the human circadian system.

### Resetting Responses to Intermittent Light

Exposure to intermittent light is highly effective at resetting the human circadian system. The phase-resetting effects of 6.5 hours of continuous bright white light (~10,000 lux) is comparable to a 6.5-hour intermittent exposure consisting of six cycles of 15 minutes of bright light (~10,000 lux) and 60 minutes of dim light (<3 lux) (Rimmer et al. 2000). Despite representing only 23% of continuous bright-light exposure conditions, the intermittent-light regimen elicited comparable phase shifts (Fig. 5a). Thus, a single sequence of intermittent bright-light pulses has a greater resetting efficacy on a per-minute basis than does continuous light exposure. In a subsequent study, exposure to two 45-minute pulses of bright light in the early subjective evening entrained the circadian system to a non-24-hour day (? + 1), indicating that intermittent pulses are highly efficient at resetting human circadian rhythms (Fig. 5b) (Gronfier et al. 2007).

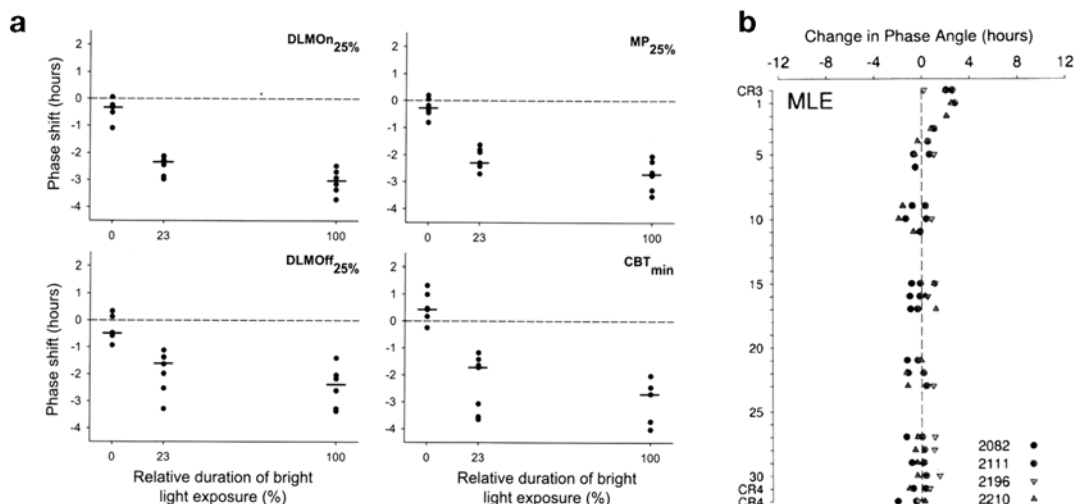
### Effects of Photic History on Resetting Responses to Light

Not surprisingly, most studies that have examined the resetting capacity of the human circadian pacemaker have focused on the light stimulus (i.e., duration, intensity, and

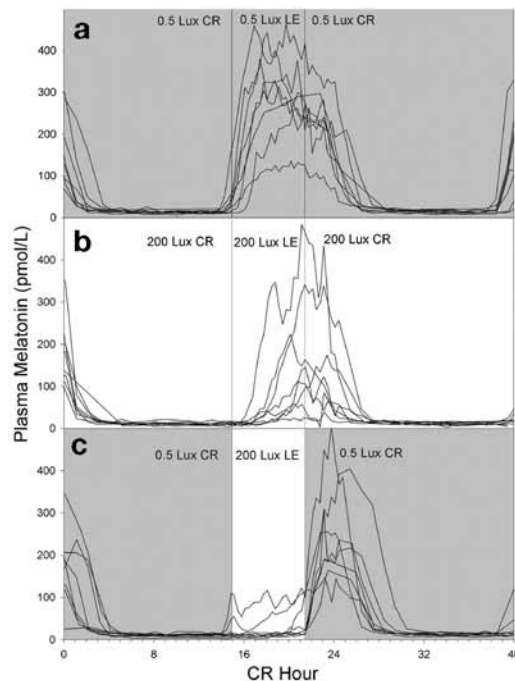
wavelength) and the circadian phase at which the stimulus was administered. However, the effects of background lighting and photic history on the light resetting of the circadian pacemaker are largely unknown. Prior exposure to 3 days of indoor room light (~200 lux) attenuates suppression of the melatonin rhythm in response to 200 lux of light, as compared to prior exposure to 3 days of dim light (<3 lux) (Fig. 6) (Smith et al. 2004). It is currently being investigated whether preexposure to room light desensitizes circadian phase resetting. In future studies, it will be important to determine the time course and dose dependence of desensitization of circadian responses to light.

### Period of the Human Circadian System

As noted above, Kleitman demonstrated in 1938 that one of his subjects exhibited a near-24-hour rhythm of body temperature, despite being scheduled on an imposed sleep/wake schedule of 28 hours (a forced desynchrony protocol), revealing that circadian rhythms could be separated from the influence of the timing of sleep/wake and light/dark schedules. Subsequently, Jürgen Aschoff and Rütger Wever attempted to determine the average period of the human circadian system by conducting a series of month-long studies of human subjects living in underground bunkers in Germany, beginning in 1960 and continuing for more than 25 years. In contrast to the finding from Kleitman's first cave study, they reported that under such conditions, human subjects exhibited rhythms of body temperature, urine volume, and sleep/wake with an average period of about 25 hours. Their studies of humans exposed to a self-selected, periodic light/dark cycle sug-



**Figure 5.** The human circadian system is highly sensitive to intermittent light. (a) Exposure to intermittent bright light (~9500 lux) is nearly as effective as continuous exposure to 6.7 hours of bright light at resetting the circadian rhythms of melatonin and body temperature, despite representing only 23% of the duration of the continuous-light exposure condition. Light intervention was administered during the early biological night. The intermittent bright-light stimulus consisted of six 15-minute pulses of light separated by 60 minutes of dim light (<1 lux). (CBT) Core body temperature minimum; (DLMOn<sub>25%</sub>) dim-light melatonin onset; (DLMOff<sub>25%</sub>) dim-light melatonin offset; (MP<sub>25%</sub>) melatonin midpoint. (b) Intermittent light is highly efficient at entraining the circadian system to a non-24-hour day (? + 1 hour). Subjects were exposed to two 45-minute pulses of bright light in the early subjective evening. The melatonin offset during the ? + 1-hour *T* cycle is plotted with respect to the phase measured on Day 3 of the protocol. Symbols correspond to the melatonin offset measured in different subjects. (a, Reprinted, with permission, from Gronfier et al. 2004 [© American Physiological Society]; b, reprinted, with permission, from Gronfier et al. 2007 [© National Academy of Sciences].)



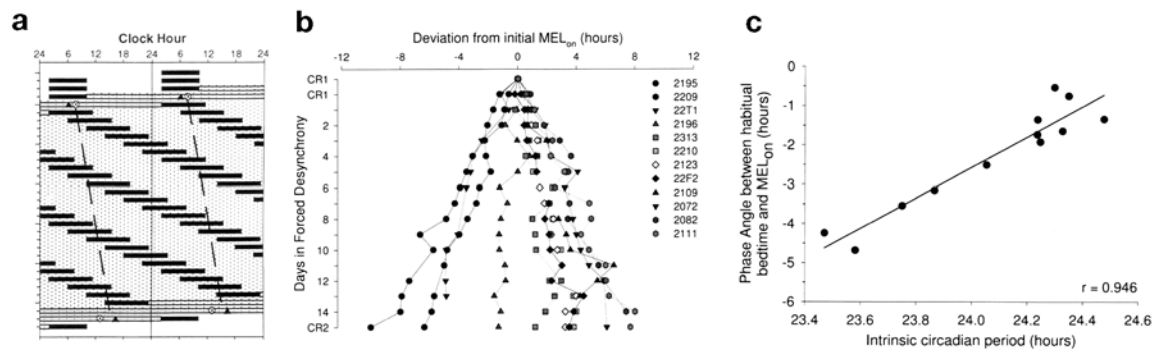
**Figure 6.** Adaptation of melatonin suppression in response to prior exposure to room light. (a) The baseline rhythm of melatonin is shown in eight subjects, as assessed during a constant routine procedure in dim ambient light. (b) Following exposure to room light (~200 lux) for 3 consecutive days during scheduled wake, the melatonin rhythm showed only minor suppression and a delayed onset in response to exposure to room light during the biological night. (c) In contrast, following exposure to dim light (<1 lux) for 3 consecutive days during scheduled wake, an acute exposure to room light (6.5 hours) resulted in strong suppression of the melatonin rhythm. (Reprinted, with permission, from Smith et al. 2004 [© Endocrine Society].)

gested that—unlike that of other mammals—the period of the activity rhythm in humans was highly variable, ranging from 13 to 65 hours (median 25.2 hours) and that the circadian period of the body temperature cycle averaged nearly 25 hours. These findings from Aschoff and Wever were consistent with similar reports that subsequently emerged from cave studies in France (Siffre 1964; Chouvet et al. 1974; Jouvet et al. 1974), England (Mills 1964), the United States (Siffre 1975), and from similar laboratory studies of humans shielded from external time cues conducted in Baltimore (Findley 1966), Gainesville, Florida (Webb and Agnew 1974a, b), and New York (Weitzman et al. 1981). However, in all of these studies, human subjects were given free access to artificial lighting and were therefore allowed to self-select their exposure to the light/dark cycle. Under these experimental conditions, human subjects self-selecting their bedtimes and wake times most commonly choose to retire near the nadir of the endogenous circadian temperature cycle and awaken on the rising slope of the temperature rhythm (Czeisler 1978; Czeisler et al. 1980a,b). Thus, they do not expose themselves to light equally across the circadian cycle (Klerman et al. 1996). Unrestricted exposure to ordinary indoor room light was permitted in those studies because, at that time, it had been incorrectly concluded

that the human circadian system was not sensitive to the resetting effects of ordinary indoor room light intensity (Wever 1970, 1974; Aschoff 1976). Once it was demonstrated that human circadian pacemakers were exquisitely sensitive to the resetting effects of light, we realized that it was necessary to reassess circadian period in humans under conditions in which exposure to light was controlled (Czeisler et al. 1999). Subjects in prior studies designed to assess circadian period in humans had self-selected their exposure to light, the most powerful stimulus known to reset the circadian pacemaker. Moreover, analysis of those data revealed that subjects in those experiments had preferentially selected exposure to light during the phase-delay portion of the daily light sensitivity rhythm (Klerman et al. 1996; Khalsa et al. 2003). Mathematical modeling revealed that this would result in a net phase delay of the circadian system each day, leading the observed circadian period measured under such conditions to be longer than the actual intrinsic circadian period of the individuals at that time (Fig. 7a) (Klerman et al. 1996).

To assess the period of the human circadian pacemaker more precisely, Kleitman's forced desynchrony protocol was used to distribute circadian resetting stimuli more uniformly across the circadian cycle, and the strength of those synchronizers was minimized (Czeisler et al. 1990a, 1999). In the forced desynchrony method for assessment of circadian period, the imposed sleep/wake cycle is scheduled outside of the range of entrainment of the human circadian system (Fig. 7b). Importantly, subjects are only exposed to dim light during each scheduled wake episode, thereby minimizing the phase-resetting effects of light and ensuring that stable entrainment does not occur (i.e.,  $T = \tau - \phi$  is not satisfied). As a result, the output of the endogenous circadian pacemaker becomes desynchronized from the imposed sleep/wake schedule. Because the forced desynchrony protocol is conducted over many circadian cycles, the timing of the sleep/wake and light/dark cycles is distributed much more uniformly across circadian phases, allowing for assessment of intrinsic circadian period.

Reevaluation of the circadian period under these controlled conditions has revealed that the intrinsic circadian period in sighted humans averages between 24.1 and 24.2 hours, with low interindividual variability as seen in other mammals, and that the intrinsic period remains stable with age in healthy adults. About 25% of human subjects exhibit a circadian period of less than 24 hours. The percent coefficient of circadian period variation in human subjects is about 0.55%, rather than 30% as previously estimated for free-running activity patterns (Czeisler et al. 1999). This tighter distribution is consistent with circadian period variability observed in other animals, such as the hamster, mouse, and gila monster (Czeisler et al. 1999). It has been argued that the circadian period estimated in forced desynchrony experiments may not be a better measure of the intrinsic period of the circadian oscillator, reflecting merely differences in experimental conditions. To test directly whether the average period of the human circadian pacemaker is closer to 24 hours (as measured on the forced desynchrony protocol) or to the classic value of 25 hours previously estimated in humans (as measured in



**Figure 7.** Assessment of circadian period by forced desynchrony. (a) The intrinsic period of a human subject was determined by exposure to a  $T = 28$ -hour cycle (18.67 hours wake, 9.33 hours sleep), which was outside the range of entrainment. The circadian period of this individual was 24.28 hours, as determined by the drift in phase of the melatonin peak (*closed triangles*) and the body temperature rhythm (*crosses*), assessed before and after the imposed forced desynchrony. During wake episodes, the light intensity was  $\sim 15$  lux. (*Black bars*) Scheduled sleep episodes; data are double-plotted. (b) Daily melatonin phase estimates are shown for a group of subjects exposed to a  $T = 28$ -hour forced desynchrony protocol for 2 weeks. A quarter of subjects exhibited a circadian period of less than 24 hours. Data are plotted with respect to the timing of the dim-light melatonin onset at the beginning of the imposed forced desynchrony. (c) Phase angle of entrainment correlates strongly with intrinsic circadian period. The phase angle was determined as the difference in time between habitual bedtime (lights off) and the daily onset of melatonin secretion. Circadian period was determined by forced desynchrony. (a, Reprinted, with permission, from Czeisler et al. 1999 [© AAAS]; b,c, reprinted, with permission, from Gronfier et al. 2007 [© National Academy of Sciences].)

a self-selected light/dark cycle in the absence of external synchronizers), the range of entrainment in response to a weak resetting stimulus ( $\sim 1.5$  lux) was examined. It was found that in a dim light/dark cycle, most subjects were able to stably entrain to a 24.0-hour  $T$  cycle, whereas none were able to entrain to a 24.6-hour  $T$  cycle (Wright et al. 2001). These results indicate that the average circadian period in humans is much closer to 24 hours than to 25 hours, as predicted from the forced desynchrony studies. Moreover, small interindividual variations in intrinsic circadian period as measured in the forced desynchrony protocol are associated with remarkable differences in the phase angle of entrainment to the 24-hour day, as illustrated in Figure 7c (Gronfier et al. 2007). Thus, the conclusion that circadian period is very close to 24 hours in humans is both supported by and accounts for the ability of a very weak photic synchronizer (i.e., candlelight) to entrain circadian rhythms in most humans to a 24-hour day but not to a 24.65- or 23.5-hour day. Recently, it was discovered that the intrinsic period of the human circadian pacemaker was significantly longer in sighted subjects entrained to a 24.65-hour light/dark cycle than it was in those same subjects after entrainment to a 23.5-hour light/dark cycle (Scheer et al. 2007). Such aftereffects of prior entrainment, which have been observed in other species (Pittendrigh and Daan 1976), reveal the plasticity of the period of the human circadian system.

In blind individuals, whose circadian rhythms are not synchronized to the 24-hour day, the average circadian period is closer to 24.5 hours (Lockley et al. 1997), in both field and laboratory studies (Sack et al. 1992; Dijk and Lockley 2002; J.T. Hull et al., unpubl.). The somewhat shorter intrinsic period observed in sighted subjects may reflect aftereffects of prior entrainment in the sighted subjects (Scheer et al. 2007) and/or inclusion of only those blind subjects with longer than average circadian periods, who are therefore unable to maintain entrainment via weaker non-photic synchronizers (Czeisler et al. 1999). Collectively,

these findings indicate that the period of the human circadian pacemaker, as measured immediately upon release from long-standing entrainment to the 24-hour day, is very close to 24 hours, with a tight distribution in the general population ranging from about 23.5 hours to 24.7 hours. Thus, in most individuals, daily phase shifts of less than 1 hour are required for stable entrainment to the 24-hour day.

## REGULATION OF THE SLEEP/WAKE RHYTHM

The sleep/wake cycle is perhaps the most overt manifestation of circadian rhythms in humans. Because the rest/activity cycle is commonly used as an output variable in studies of circadian rhythms in vertebrates (Ralph et al. 1990), the timing of the sleep/wake cycle in humans is often presumed to be a simple reflection of the output of the circadian pacemaker. In actuality, many other factors affect sleep propensity in humans. This is because, like nutrition, sleep is an independent biological need in all animals. Without sleep, animals are unable to sustain life (Rechtschaffen et al. 1989). Therefore, sleep propensity is dependent not only circadian rhythmicity, but also on sleep satiety—also known as the level of homeostatic sleep drive (Dijk and Czeisler 1995). Acute sleep loss, sleep interruptions, sleep disorders, and chronic under-sleeping—i.e., sleeping less each day than the amount needed—increase homeostatic sleep drive. Increased homeostatic sleep drive due to any of these factors increases sleep propensity and impairs neurobehavioral performance (Jewett 1997). There is an interaction between the circadian and homeostatic systems, such that the amplitude of circadian oscillations in neurobehavioral performance is increased disproportionately when homeostatic sleep pressure is elevated (Jewett 1997; Jewett et al. 1999c). In particular, reaction time slows and the frequency of attentional failures increases when sleep propensity is elevated, regardless of whether that elevation is a result of acute sleep deprivation, chronic sleep



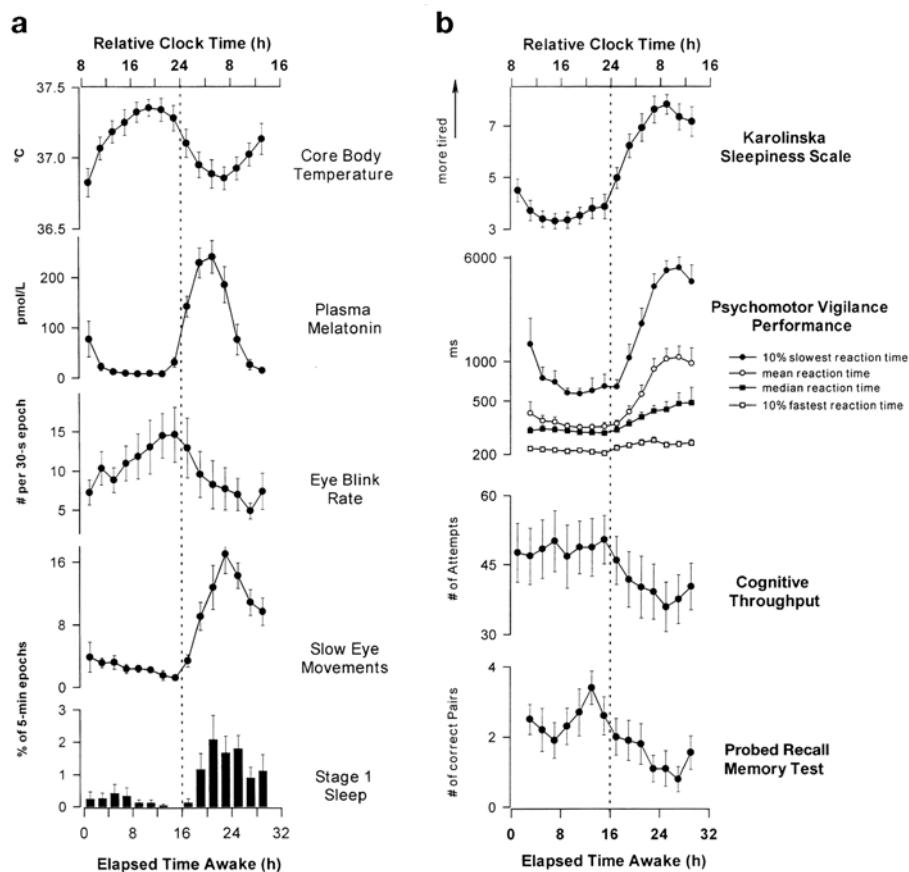
loss, or misalignment of circadian phase (Cockley et al. 2004). Some exogenous agents, such as hypnotics, increase sleep propensity, whereas others, such as stimulants, decrease sleep propensity.

### Homeostatic and Circadian Interaction

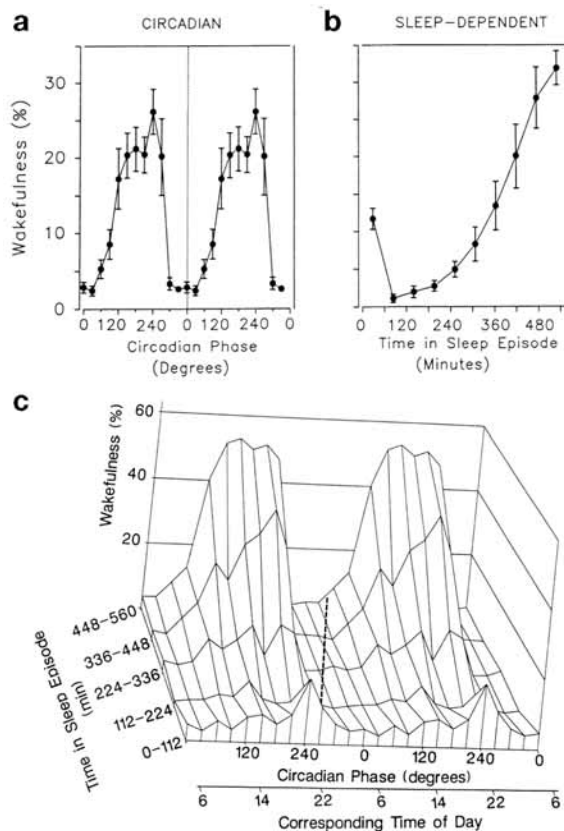
Just 25 years ago, Kronauer revealed that the interaction of two oscillatory processes with very different properties best explained the timing of human sleep/wake behavior in human subjects living for many months in the absence of time cues (Kronauer et al. 1982). Remarkably, that same year, Borbély (1982) hypothesized that each and every day in humans, the timing of sleep and wakefulness is governed by a subtle interplay between two such cyclic processes—one reflecting homeostatic sleep drive and the other the output of the circadian pacemaker. Homeostatic sleep drive accumulates with each waking hour and is only dissipated by sleep itself. This appetitive oscillatory process has properties very different from those of the circadian oscillator, which opposes the

increasing homeostatic drive for sleep that builds near the end of our habitual waking day, leading Edgar et al. (1993) to propose an opponent process model of sleep regulation in primates.

Daily variations in alertness and neurobehavioral performance reflect the output of the circadian pacemaker(s) in humans (Czeisler et al. 1990b, 1994; Dijk et al. 1992; Johnson et al. 1992; Cajochen et al. 1999; Wyatt et al. 1999; Durmer and Dinges 2005). Sleepiness, vigilance, short-term memory, and attention or ability to concentrate are most impaired just after the body temperature nadir, near our regular wake time (Fig. 8) (Cajochen et al. 1999). Ironically, the circadian drive for wakefulness peaks just before habitual bedtime in humans entrained to the 24-hour day. This paradoxical phase relationship between the timing of the circadian sleep propensity rhythm and the timing of sleep and wakefulness during entrainment to the 24-hour day is postulated to facilitate consolidation of sleep and wakefulness in humans (Fig. 9) (Dijk and Czeisler 1994). During entrainment to the 24-hour day, the circadian pacemaker opposes this increasing drive for



**Figure 8.** Alertness and performance are dependent on the elapsed time since sleep. (a) The time course of body temperature, melatonin, eye-blink rate, slow eye movements, and stage-1 sleep are shown for ten subjects during a constant routine procedure. Eye movements and sleep were assessed during the Karolinska drowsiness test, which was administered hourly. (b) In the same group of subjects, the time course is shown for sleepiness as assessed by the Karolinska sleepiness scale (KSS; highest possible score = 9, lowest possible score = 1), psychomotor vigilance (a 10-minute reaction time test), cognitive throughput (number of attempts in a 4-minute addition task), and memory performance (number of correct word pairs in a probed recall memory task). The mean  $\pm$  S.E.M. is shown for each measure. All data were binned in 2-hour intervals and expressed with respect to elapsed time since scheduled wake time. (Vertical dashed line [16 hours]) Time at which each subject would normally go to bed. (Reprinted, with permission, from Cajochen et al. 1999 [©American Physiological Society].)



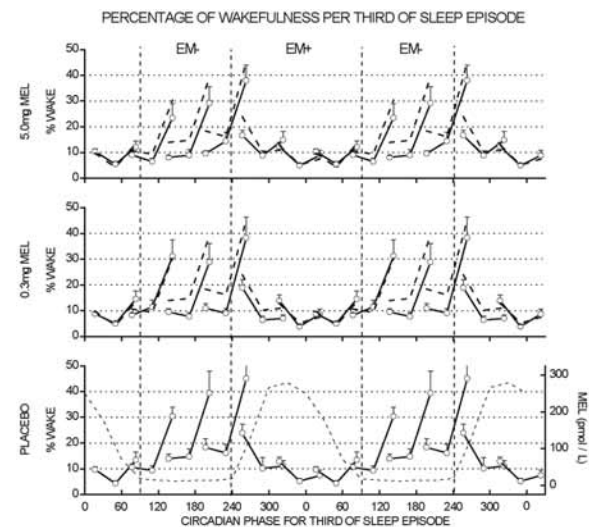
**Figure 9.** Percent wakefulness during scheduled sleep is determined by the interaction of circadian and homeostatic processes. The percentage of wakefulness during scheduled sleep was assessed in eight subjects during a forced desynchrony protocol ( $T = 28$ -hour cycle; 18.67 hours wake, 9.33 hours sleep). (a) Percent wakefulness shows a high-amplitude circadian rhythm that peaks just before normal bedtime. (b) After the first hour of scheduled sleep, percent wakefulness shows a nonlinear increase with respect to the elapsed time of the sleep episode. (c) Percent wakefulness during scheduled sleep is determined by interaction of the circadian rhythm in the drive for waking and the homeostatic drive for waking, which is dependent on the time elapsed since the start of the sleep episode. Circadian phase zero is defined as the phase of the body temperature minimum. For reference, clock times are shown that would correspond to the circadian phase of the body temperature rhythm under entrained conditions. (Dashed line) Trajectory of circadian phase and time elapsed since the start of scheduled sleep, corresponding to a nocturnal sleep episode under entrained conditions. (Reprinted, with permission, from Dijk and Czeisler 1994 [© Elsevier Science].)

sleep in the latter half of the usual waking day by sending out an increasingly stronger drive for waking. A couple of hours before bedtime, the pineal gland releases the sleep-promoting hormone melatonin into the bloodstream. Melatonin receptors on the SCN then suppress the firing of SCN neurons (Liu et al. 1997). This action of melatonin, which should not interfere with the ability of SCN to oscillate with a near-24-hour period (Schwartz et al. 1987), may serve to quiet the wake-promoting signal emanating from the SCN, thereby facilitating sleep just after the peak of the circadian drive for wakefulness (Barinaga 1997). The SCN, in turn, promotes sleep most strongly just before the habitual wake time, after many

hours of sleep have dissipated homeostatic sleep pressure. The peak in the circadian rhythm of REM (rapid eye movement) sleep propensity is just before wake time, concurrent with the peak in the circadian rhythm of sleep propensity (Czeisler et al. 1980b).

### Melatonin, Sleep, and Alertness

Forced desynchrony studies have revealed that sleep efficiency is greatest when subjects sleep at the circadian phase during which endogenous melatonin is released (Dijk et al. 1997). In contrast, wakefulness during the sleep episode is greatest when the sleep episode is scheduled to occur at a circadian phase during which endogenous melatonin secretion is absent (Dijk et al. 1997; Wyatt et al. 1999). This observation led us to hypothesize that exogenous administration of melatonin might improve sleep efficiency at such times. In a double-blind, placebo-controlled trial, it was found that melatonin administration 30 minutes before the scheduled sleep episode enabled volunteers to obtain about 30 minutes more sleep when they slept at a circadian phase at which they did not release endogenous melatonin (Fig. 10) (Wyatt et al. 2006). It was found that both 0.3 mg of melatonin, which raised plasma melatonin levels two to three times higher than endogenous secretion, and 5.0 mg of melatonin, which raised plasma melatonin



**Figure 10.** Exogenous melatonin improves sleep quality during the biological daytime but not during the biological night. The percentage of wakefulness during scheduled sleep was assessed in eight subjects during a 27-day forced desynchrony protocol ( $T = 20$ -hour cycle; 13.33 hours wake, 6.67 hours sleep). Melatonin (5.0 mg or 0.3 mg) or placebo was given 30 minutes before each scheduled sleep episode. The percentage of wakefulness during scheduled sleep was reduced during the biological daytime in subjects who were given melatonin before the sleep episode. In contrast, during the biological night, when melatonin levels are normally high, exogenous melatonin did not reduce percent wakefulness during scheduled sleep, as compared to subjects who were given the placebo. For reference, the percentage of wakefulness under the placebo condition (lower panel) is replotted in the upper two panels with a dashed line. (Dashed trace) Mean level of endogenous melatonin is plotted for the placebo group. Circadian phase zero is defined as the phase of the body temperature minimum. (Reprinted, with permission, from Wyatt et al. 2006 [© American Academy of Sleep Medicine].)

levels much higher, to be effective. In these healthy young adult subjects, no difference in efficacy between the two doses was found, although the study was not powered to detect such a difference. There was no effect of melatonin administration on sleep efficiency when the melatonin was administered at the circadian phase of endogenous melatonin production (Wyatt et al. 2006). Thus, the efficacy of melatonin as a hypnotic is dependent on circadian phase.

Similarly, exogenous melatonin acts as a soporific agent when it is administered during the daytime, when melatonin is usually absent from the bloodstream (Dollins et al. 1994; Cajochen et al. 1996, 1997). Photic suppression of endogenous melatonin levels at night results in an immediate improvement in alertness and performance (Campbell and Dawson 1990; Cajochen et al. 2005; Lockley et al. 2006c). Melatonin suppression appears to be critical to this immediate alerting effect of light, because retinal exposure to bright monochromatic green light (~555 nm) at the peak of the photopic sensitivity function is less effective in eliciting both melatonin suppression and improvements in alertness and performance than is exposure to shorter-wavelength blue light (~460 nm) near the peak of sensitivity of the novel photopigment melanopsin (Cajochen et al. 2005; Lockley et al. 2006c).

#### APPLICATIONS TO CLINICAL AND OCCUPATIONAL MEDICINE

Unlike most other diurnal animals, humans frequently attempt to forego sleep during nighttime hours for work or pleasure. The difficulty humans have in remaining alert while working at night is chronicled in ancient literature. There are many reasons why it is so difficult to do so. First of all, working at night requires individuals to perform when their circadian sleep propensity rhythm is misaligned with respect to the timing of wakefulness. Alertness and sleep propensity vary markedly with circadian phase (Czeisler et al. 1980a,b; Dijk and Czeisler 1994, 1995; Dijk et al. 1997, 1999; Wyatt et al. 1999; Czeisler and Khalsa 2000; Czeisler and Dijk 2001). Night work requires individuals to remain awake and alert at the peak of the circadian sleep propensity rhythm. In the absence of sleep, in the latter half of the night near the habitual wake time, elevated homeostatic drive for sleep interacts with the circadian peak of sleep propensity to create a critical zone of vulnerability. On the basis of laboratory studies that have quantified the contribution of the circadian pacemaker and the sleep homeostat to sleep duration and consolidation, subjective alertness, neurocognitive performance, and mood (Czeisler et al. 1980a,b; Dijk and Czeisler 1994, 1995; Dijk et al. 1997, 1999; Wyatt et al. 1999), the interaction of these two processes in determining alertness and performance has been successfully modeled mathematically (Jewett 1997; Jewett et al. 1999a,c; Jewett and Kronauer 1999). During extended durations of wakefulness, sleepiness generally increases and neurobehavioral performance deteriorates; at the same time, there is a circadian rhythm in these parameters (Dijk et al. 1992, 1999, 2000; Johnson et al. 1992; Klein et al. 1993; Czeisler et al. 1994; Dijk and Czeisler 1994, 1995; Boivin et al. 1997; Jewett 1997;

Jewett et al. 1999a,d; Wyatt et al. 1999; Czeisler and Khalsa 2000; Czeisler and Dijk 2001; Cajochen et al. 2002; Wright et al. 2002). During sustained wakefulness coupled with circadian phase misalignment, 24 hours of sleep deprivation has been shown to impair neurobehavioral performance to an extent that is comparable to a level of 0.10% blood alcohol content (Dawson and Reid 1997; Lamond and Dawson 1999; Williamson and Feyer 2000; Powell et al. 2001; Falletti et al. 2003). Positron emission tomography (PET) imaging has revealed that such acute sleep deprivation is associated with decreased metabolism in the thalamus, prefrontal cortex, and parietal cortex (Thomas et al. 2000). In fact, the amount of time it takes to react to a visual stimulus (simple reaction time) averages three times larger after 24 hours of wakefulness at an adverse circadian phase than before an individual has stayed up all night (see Fig. 8) (Cajochen et al. 1999). Extended durations of wakefulness also increase the risk of attentional failures—in which the eyes begin rolling around in their sockets—heralding an involuntary transition from wakefulness to sleep, despite efforts to remain awake (Cajochen et al. 1999; Lockley et al. 2004).

#### Impact of Marathon Shifts on Safety

Despite advances in understanding the impact of sleep deprivation on performance, there are very few industries in the United States for which work hours are limited by law. Thus, individuals in many safety-sensitive industries routinely work marathon shifts, often as a consequence of direct or indirect monetary incentives. Firefighters in Los Angeles, for example, are routinely scheduled to work shifts that last 96 consecutive hours. The 100,000+ physicians-in-training in the United States are routinely required to work shifts of  $\geq 30$  consecutive hours, often twice per week (Czeisler 2006). Yet, physicians scheduled to work more than 24-hour shifts during their training experience twice as many attentional failures working at night (Lockley et al. 2004), and they make 36% more serious medical errors, including more than five times as many serious diagnostic mistakes while caring for patients in intensive care units, as those same interns when scheduled to work no more than 16 consecutive hours (Landrigan et al. 2004, 2007; Czeisler 2006; Lockley et al. 2006b, 2007). Despite averaging 2.6 hours of sleep during >24-hour marathon shifts, such physicians also have more than twice the risk of a motor vehicle crash driving home from such >24-hour shifts than from shifts averaging 12 hours in duration (Barger et al. 2005). When performing procedures during the daytime, these young physicians have a 73% increased risk of a percutaneous injury after a night on duty than after a night of sleep (Ayas et al. 2006). During the course of 1 year, one in five of these physicians reported making a fatigue-related mistake that seriously injured a patient and one in 20 of these physicians reported making a fatigue-related mistake that resulted in the death of a patient (Barger et al. 2006). These mistakes were, respectively, 600% and 300% more likely to occur during months in which those interns were scheduled to work extended duration (>24 hours) shifts more than once per week (Barger et al. 2006).

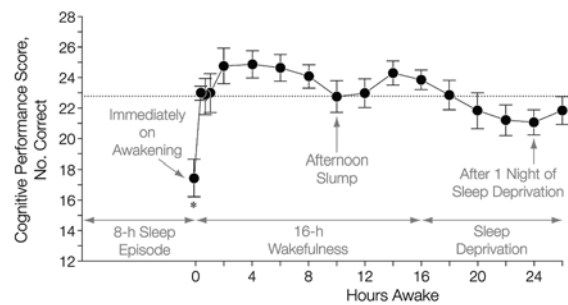


### First Night Shift

The impairments associated with 24 consecutive hours of wakefulness are not limited to those scheduled to work for 24 consecutive hours. In fact, many employees scheduled to work a standard 8-hour night shift remain awake for 24 consecutive hours when they make the transition from the day shift to the night shift, because they are often awake all day (i.e., for 16 hours) before they even begin their first night shift. Thus, vigilance performance and attention are at their worst on the first night of a shift rotation sequence (Santhi et al. 2007).

### Chronic Sleep Restriction

Ironically, after having struggled to stay awake throughout the night, those same night workers have difficulty sleeping during the day—again due to circadian misalignment, this time between the timing of the sleep opportunity and the timing of the sleep propensity rhythm. The resulting chronic sleep loss can itself have an adverse impact on performance. A number of consecutive nights of inadequate sleep have been shown to have detrimental effects on alertness, vigilance, psychomotor skills, and mood (Belenky et al. 2003; Czeisler 2003; Van Dongen and Dinges 2003; Van Dongen et al. 2003; Durmer and Dinges 2005). Objective measures of performance, including reaction time and memory, worsen. Within a week, loss of as little as 2 hours of sleep per day can impair performance—as measured by the ability to sustain vigilance on a reaction time task—by an amount equivalent to 24 consecutive hours of wakefulness (Belenky et al. 2003; Van Dongen et al. 2003). Such chronic sleep deprivation leads to an increased probability of experiencing lapses of attention, episodes of automatic behavior, and/or falling asleep while attempting to remain awake. Chronic sleep loss adversely affects neurobehavioral performance, even in individuals sleeping at night and attempting to perform during the daytime. In a condition of chronic sleep deprivation, even when wakefulness is scheduled during an appropriate circadian phase, the probability of a sleep-related attentional failure or neurocognitive performance failure while waking is markedly increased (Belenky et al. 2003; Van Dongen et al. 2003; Durmer and Dinges 2005). Six hours of time in bed per night for a week or two brings the average young adult to the same level of impairment as 24 hours of wakefulness, whereas 4 hours of time in bed per night rapidly induces a level of impairment comparable with 48 hours of wakefulness (i.e., two consecutive days and nights without sleep). Metabolic studies have demonstrated that such sleep curtailment has adverse effects on the metabolic and immune systems as well (Spiegel et al. 2000, 2001, 2002, 2004a,b, 2005; Mander et al. 2001; Van Cauter et al. 2007). Moreover, sleep loss interferes with memory consolidation and learning (Stickgold et al. 2000; Walker et al. 2002; Huber et al. 2004; Walker and Stickgold 2004; Stickgold 2005). As with alcohol intoxication, chronically sleep-deprived individuals tend to underestimate the extent to which their performance is impaired, despite increasing impairment evident in objective recordings of the rate of lapses of attention (Van Dongen et al. 2003). Importantly, the



**Figure 11.** Cognitive performance is severely impaired by sleep inertia. Performance on a 2-minute addition task (2-digit numbers) was assessed in nine subjects during a 26-hour wake episode following 8 hours of sleep. Immediately upon awakening, cognitive performance was much worse than that observed following a night of sleep deprivation. (Dotted line) Group mean across the 26-hour period. Error bars indicate the S.E.M. and the asterisk indicates a significant difference from all subsequent time points ( $P < 0.01$ ). (Reprinted, with permission, from Wertz et al. 2006 [© American Medical Association].)

effects of recurrent nights of sleep restriction are not overcome with a single night of sleep (Belenky et al. 2003).

### Sleep Inertia

Performance is markedly degraded during the transition from wakefulness to sleep (Langdon and Hartman 1961; Hartman and Langdon 1965; Hartman et al. 1965; Koulack and Schultz 1974; Dinges et al. 1985; Balkin and Badia 1988; Dinges 1993; Naitoh et al. 1993; Achermann et al. 1995; Bruck and Pisani 1997; Ferrara and De Gennaro 2000; Balkin et al. 2002; Wertz et al. 2006). The extent to which this phenomenon, called sleep inertia, interferes with neurobehavioral performance is related to the depth of the prior sleep episode (Dinges 1993). Thus, agents that interfere with sleep, such as caffeine, can mute the effect of sleep inertia (Van Dongen et al. 2001). The adverse impact of sleep inertia on performance can exceed the impact of total sleep deprivation (Fig. 11) (Wertz et al. 2006). Individuals who are subjected to acute total sleep deprivation or chronic sleep restriction often experience very deep sleep, which will increase the effects of sleep inertia (Dinges 1993).

### Sleep Disorders

Some medical conditions and medications increase homeostatic sleep drive indirectly by disrupting sleep; others increase sleep tendency directly. Either can increase the risk of attentional failures, sleep-related errors, and accidents (Carter et al. 2003; Colten and Altevogt 2006). These include primary sleep disorders, such as narcolepsy and sleep apnea. Patients with obstructive sleep apnea have a 6- to 13-fold increased risk of motor vehicle crashes (Teran-Santos et al. 1999). Repeated interruptions of sleep, such as is experienced by physicians when they are on call, degrade the restorative quality of sleep, compared to an equal amount of consolidated sleep. This is thought to be a primary basis for the excessive daytime sleepiness associated with sleep-disordered breathing, which induces many brief arousals during the night. Interestingly, just being on call



itself disturbs sleep, even when the individual is not called (Torsvall and Åkerstedt 1988; Richardson et al. 1996). Age decreases the risk of sleep-related lapses of attention at night; in fact, young people are at the greatest risk of the hazards of sleep loss (Åkerstedt et al. 1994). However, as individuals age, it becomes increasingly more difficult to obtain the recovery sleep that is needed following sleep deprivation. Even when sleep deprived, older people have a great deal of difficulty sleeping at an adverse circadian phase (Dijk and Duffy 1999; Dijk et al. 1999, 2000).

### Drowsy Driving

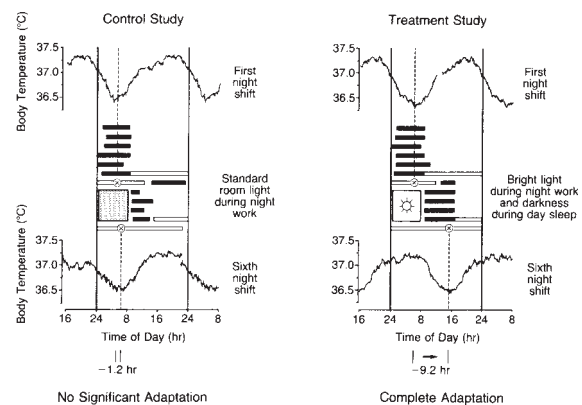
The United States is a drowsy nation. Individuals struggling to stay awake in the face of elevated sleep pressure—whether due to acute total sleep deprivation, chronic sleep restriction, or repeated interruption of sleep (due to external interruptions or the presence of a sleep disorder)—are not always able to do so. This is reflected by our performance on the single most safety-sensitive task that is shared in common by most American adults: driving motor vehicles on the nation's highways. This routine highly over-learned task performed in a moving vehicle, the motion of which stimulates the neurovestibular input to the ventrolateral preoptic (VLPO) area (Fuller et al. 2002), provides a setting that can unmask elevated homeostatic sleep drive. Sleep loss and misalignment of circadian phase increase the likelihood that the VLPO area of the hypothalamus will initiate an involuntary transition from wakefulness to sleep (Saper et al. 2005). The nonlinear interaction of the SCN and the sleep homeostat results in two times of day at which such sleep attacks are most probable: in the wee hours of the morning near the habitual wake time and in the mid afternoon. Once a sleep attack occurs, driving performance of an unresponsive drowsy driver is of course even worse than that of a drunk driver. Sometimes drowsy individuals linger in the transitional state between sleep and wakefulness, in which part of the brain is asleep while part of the brain remains awake. This transitional state of *automatic behavior* or *sleep drunkenness* is characterized by the ability to continue performing routine highly overlearned tasks such as driving—even providing semiautomatic responses to stimuli—without appropriate situational awareness or judgment (Guilleminault et al. 1975a,b).

The scope of the problem of drowsy driving in the United States is staggering. Data collected by the National Highway Transportation Safety Administration (NHTSA) indicate that at least 15 million drivers nationwide have nodded off or fallen asleep while driving in the past 6 months (Royal 2003). Data collected by NHTSA reveal that 250,000 drivers in the nation fall asleep at the wheel every day, or about three drivers every second throughout day and night, endangering themselves, their families, and their fellow citizens (Royal 2003). The outcome of these fall-asleep episodes is sobering. More than half of these drowsy drivers wandered into another lane, drifted onto the shoulder, or drove across the centerline during the incident. In another 10% of these incidents, the driver ran off the road. In fact, an estimated 1,350,000 drivers nationwide were involved in a drowsy-driving-related crash in the past 5 years—that is 30 drowsy driver crashes per hour or one

every 2 minutes. NHTSA also sponsored a 100-car study in which drivers were video-monitored while driving in their cars for a year. Analysis of the data revealed that 22% of actual and near-miss crashes were caused by drowsiness—equal to the fraction of actual and near-miss crashes caused by all other sources of driver distraction combined (Klauer et al. 2006). Drowsy driving accounts for an estimated 20% of all motor vehicle crashes and injuries (Colten and Altevogt 2006). That means that there are more than 200,000 motor vehicle injuries every year due to drowsy driving crashes, 60,000 of which are debilitating injuries and more than 8000 motor vehicle fatalities every year.

### FUTURE INITIATIVES

Twenty-five years ago, it was demonstrated that simple changes to the scheduling of night shift work designed to facilitate circadian adaptation could significantly improve both work schedule satisfaction and productivity (Czeisler et al. 1982). However, it has been recognized since the turn of the 20th century that the circadian rhythms of night shift workers often fail to adjust to the inversion of their sleep/wake schedules, even after years of permanent night shift work (Benedict 1904). Therefore, after the discovery that light could rapidly reset the human circadian pacemaker, the efficacy of its use in night shift workers was studied. Exposure to bright light and darkness was then found to be effective in resetting the circadian rhythms of night shift workers (Fig. 12) (Czeisler et al. 1990b), such that the sleep-promoting hormone melatonin was released during their scheduled daytime sleep episode, rather than during their scheduled nighttime shift (Czeisler et al. 1991). This circadian rhythm realignment improved performance during night shift hours and increased the dura-



**Figure 12.** Adaptation to shift work with exposure to bright light and darkness. Exposure to room light (<150 lux; stippled box) during 5 nights of night work resulted in small shifts of the circadian rhythm of the body temperature rhythm, as assessed on the first and sixth nights of shift work. In contrast, exposure to bright light (7,000–12,000 lux; solar symbol in the open box) resulted in strong resetting and adaptation to the night shift schedule. The protocol is shown in the middle panels: (Black bars) Sleep; (crosses) body temperature minimum (also shown in the vertical dashed lines). Shift work was scheduled from midnight to 8:00 a.m. The temperature data are double-plotted. (Reprinted, with permission, from Czeisler et al. 1990b [© Massachusetts Medical Society].)

tion of sleep during the daytime hours by nearly 2 hours per day (Czeisler et al. 1990b).

This lighting technology was first applied to facilitate circadian adaptation of NASA astronauts to night launches of the space shuttle (Czeisler et al. 1991). NASA has installed bright-light facilities in its astronaut crew quarters at both the Johnson Space Center and the Kennedy Space Center. Since its introduction nearly 20 years ago, NASA has used bright-light shifting of crew members during the prelaunch quarantine period for all space shuttle flights requiring a shift of three or more hours in the timing of sleep. Bright-light shifting of circadian rhythms has also been used successfully to facilitate adaptation to the night shift on off-shore oil platforms in the North Sea and in other specific locations (Bjorvatn et al. 1999). High-fidelity simulations of the transition from day shift work to night shift work have revealed the extent to which exposure to bright light during night work, exposure to darkness during day sleep, or regularity in the timing of sleep contributed to the overall improvement that was observed when all three were optimized. Exposure to bright light and a fixed daytime sleep episode in darkness each contributed approximately equally to the resulting circadian adaptation (Horowitz et al. 2001).

Given recent discoveries that exposure to shorter-wavelength light is more effective than other wavelengths in resetting circadian rhythms (Lockley et al. 2003), future countermeasures for shift workers will likely involve timed exposure to light of specific wavelengths and intensities in order to facilitate most effectively adaptation to night shift work. In addition, it is critical that corporations develop appropriate policies regarding the maximum work episode duration, minimum time off between shifts, and maximum weekly work hours, along with policies regarding travel across time zones (Czeisler and Fryer 2006).

It is also very important for our society to establish work-hour limits to protect workers in our 24/7 culture. The European Union has led the way on this front with its adoption of the European Working Time Directive, which limits—in all occupations—the number of consecutive hours to which employees can be scheduled. In principle, all EU employees are limited to 13 consecutive hours of work, with a minimum of 11 hours of rest between work shifts, although there are a number of exceptions and opt-out policies that impact these rules. Given the toll that sleep deprivation is taking on the health, productivity, and safety of American workers, it is time that U.S. policy makers evaluate the evidence and implement comprehensive legislation on this issue in the United States. However, as the Institute of Medicine highlighted in its recent report on sleep deprivation and sleep disorders (Colten and Altevogt 2006), education is the most pressing hurdle that must be overcome to address this under-recognized public health problem.

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