Editor's Column
This is the premiere issue of The SRS Bulletin. This publication succeeds the APSS Newsletter. In forming this newsletter the SRS Executive Committee is responding to the sentiments of the membership. To have a publication that stresses research, promotes free-flow of ideas and also contains news and comments.

As a research organization, our strength lies in our diversity. We have basic, human and clinical researchers. And the techniques we use range from single-cell recording of brain neurons to epidemiology to clinical intervention. But we all recognize that our commitment is to understand the brain during sleep and wake.

To underscore the strengths associated with such diversity, we launch our new issue by focusing on shiftwork. This theme is appropriate because it embodies the synergism of basic, human and clinical approaches. As researchers we can take pride in the fact that because of our collective efforts there is a growing awareness in industry and in the public about the issues related to shiftwork. The articles in this issue summarize our understanding of the biological clock, what happens when the clock is disturbed, and what intervention(s) can be undertaken to minimize the impact of shiftwork. The cover depicts the passage of time in the form of Dusk and Dawn by Michaelangelo.

The Society’s diversity is also echoed in our new logo, a pair of waves (front cover). The waves symbolize our achievements, and also that we embrace new scientific developments.

As an organization we look forward optimistically to the next century. We welcome your input in this dialogue. Please send your comments, letters, etc to the editor.
Control of Sleep-Wake Cycles by the Mammalian Suprachiasmatic Pacemaker

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Alteration between sleep and wakefulness constitute one of the most pervasive physiological phenomena in the animal kingdom. In mammals, different states of arousal alternate with ultradian period-lengths that are usually measured in minutes; these include transitions between the different stages of nonREM sleep, between nonREM and REM sleep, or between sleep and wakefulness. In most, though not all mammalian species, these higher frequency sleep-wake and sleep-stage alternations have a cyclic temporal distribution across the solar day with an endogenous period of about 24 hours-- the so called circadian sleep-wake cycle. In humans and most non-human primates, the circadian sleep-wake cycle is overtly characterized by a consolidated interval or "bout" of wakefulness (typically 16 hours in duration with relatively little intervening sleep) followed by a consolidated interval of sleep. Many other species, however, show circadian sleep-wake cycles that are much more fragmented in nature. For example, it is not uncommon for a nocturnal rat or hamster to have several hundred transitions between wake and sleep across the 24 hour day, yet remain significantly more awake during the night (Borbely and Neuhaus, 1979; Mistlberger et al., 1983).

Although much is known about the neuroanatomy and physiology of sleep-wake regulation, the circadian control of sleep-wake behavior remains poorly understood. Despite some disagreement as to whether sleep is actively or passively regulated, there is compelling evidence that both arousal and hypnogenic centers exist within the brain (Jones, 1989; Steriade and McCarley, 1990). How these centers interact to produce the precisely timed circadian cycles of sleep and wakefulness is unknown except that the endogenous daily cycles of sleep-wakefulness are somehow controlled by a central neurogenic pacemaker-- the so called circadian clock.

Pacemakers vs. Oscillators.

When we speak of the circadian control of sleep-wakefulness or other physiological functions, we necessarily assume oscillations in the levels of those variables, but sometimes lose sight of the many possible sources of rhythmicity. By virtue of feedback loops and the intrinsic hysteresis in all homeostatic processes, physiological control systems necessarily oscillate. For example, the interplay between complex thermogenic and thermolytic effector mechanisms in thermoregulation produce constant variations in body temperature akin to the hysteresis in a home heating and air-conditioning system. External heat load elevates body temperature above a physiologically defined setpoint, invoking increased gain in heatloss effector mechanisms proportional to the "error" signal (difference between setpoint and actual temperature). This process lowers body temperature below the setpoint level, and invokes increased gain in an "opponent" thermogenic process. Analogous regulatory strategies underlie most physiological control systems including endocrine, cardiovascular, respiratory, thermoregulatory, and perhaps even sleep. Indeed, each can be legitimately viewed as an oscillating sub-system or "oscillator." In oscillators, rhythmic variations dampen out to negligible levels in the absence of external perturbations. By contrast, "pacemakers" exhibit endogenous and sustained oscillations that do not dampen out significantly over time. For the purposes of this discussion, one of the most important neurogenic pacemakers in mammals is located in the suprachiasmatic nuclei of the hypothalamus (SCN) and imposes circadian variations in the setpoints of regulated physiological systems and in organismal behavior (For reviews see: Rusak and Zucker, 1979; Moore-Ede et al., 1982; Mistlberger and Rusak, 1989).

How Many Circadian Clocks Time Sleep and Wakefulness?

Since the discovery of the suprachiasmatic nuclei in 1972 (Moore and Eichler, 1972; Stephan and Zucker, 1972), there has been continuous debate as to whether the mammalian CNS houses more than one circadian pacemaker. There is nonetheless overwhelming evidence that the SCN constitute a central neurogenic pacemaker that modulates most, if not all, rhythmic circadian variables in mammals including sleep-wakefulness (Eastman et al., 1984; Edgar et al., 1993). For example, circadian rhythms in behavior and endocrine function are abolished after local thermal lesions or isolation of the SCN by knife cuts (Reppert et al., 1981; Moore, 1983; Meijer and Rietveld, 1989). The hypothalamic islands produced by such knife cuts exhibit circadian rhythms in electrical activity (Inouye and Kawamura, 1979), as do isolated hypothalamic preparations studied in vitro (Green and Gillette, 1982; Groos and Hendriks, 1982). The SCN also exhibits circadian rhythms in metabolic activity as measured by 2-deoxyglucose uptake in vivo and in vitro (Schwartz and Gainer, 1977; Newman and Hospod, 1986).

In addition, behavioral circadian rhythms and in vitro measures of rhythmic activity within the SCN can be "phase shifted" by the application of either electrophysiological or pharmacological stimuli (Prosser et al., 1990). But the most compelling evidence that the SCN is indeed a circadian pacemaker comes from fetal SCN transplantation studies. Ralph and colleagues (1990) have shown that behavioral circadian rhythms can be restored by placing fetal SCN tissue pieces or SCN cultured cells into the third ventricle of SCN-lesioned animals that otherwise exhibit no circadian oscillations (Ralph and Lehman, 1991). Furthermore, the period of the restored rhythm is defined by the intrinsic period of the donor (Ralph et al., 1990). This landmark study demonstrates that the SCN are in fact necessary and sufficient for the generation of circadian rhythms.
The debate over how many central clocks govern the physiology and behavior of mammals has a long and somewhat tortured history. Some of the earliest debate stemmed from observations in man that, under specific conditions, isolated humans sometimes exhibited what has been coined "spontaneous internal desynchronization" of circadian rhythms (Aschoff and Wever, 1976). This phenomenon is characterized by unique periods in the oscillation of rest-activity (sleep-wake) and body temperature. During internal desynchronization, the daily alternations between sleep and wake can show periods of 26-32 hours—much greater than the body temperature circadian period which is typically only 24.3-25.2 hours. The unique periods of two rhythmic variables was thought to necessarily require two or more circadian clocks (Aschoff and Wever, 1976; Kronauer et al., 1982; Moore-Ede et al., 1982); a concept that was echoed in nonhuman primate studies suggesting that SCN lesions could eliminate behavioral circadian rhythms without eliminating the body temperature rhythm (Fuller et al., 1981). A few rodent studies have claimed persisting body temperature circadian rhythms after SCN-lesions as well (Satinoff and Prosser, 1988).

These early multiple pacemaker claims have not, however, held up to the scrutiny of more recent studies. For example, Zulley and Campbell (1985) have shown that spontaneous internal desynchronization may be an unusual artifact of subject volition. If subjects are specifically told not to nap while studied in isolation from time cues, many show spontaneous desynchronization. But if told to sleep anytime they feel like sleeping, subjects do not exhibit desynchronization. Studies of unrestrained squirrel monkeys (designed in part to replicate earlier work; Fuller et al., 1981) failed to show persisting body temperature, sleep-wake or behavioral circadian rhythms after complete SCN-lesions (Edgar, 1986; Edgar et al., 1993). These findings, and recent work in SCN-lesioned rats (c.f. Edgar, 1994) support a growing consensus that complete SCN lesions effectively and consistently eliminate circadian rhythms in sleep-wakefulness (including component stages of sleep), body temperature and consummatory behavior (Eastman et al., 1984; Kittrell, 1991; Edgar, 1994).

Perhaps the most compelling evidence that body temperature and sleep-wakefulness are controlled by the same circadian pacemaker has recently been obtained from SCN-transplant studies. Fetal (E16-E17) SCN tissue transplants restore circadian rhythms to all sleep stages (including REM sleep), consummatory behavior (drinking), and body temperature in rats that had previously received complete SCN lesions (Edgar et al., 1992). That SCN transplants permanently restore circadian rhythms to all of these variables, obviates the need for a second pacemaker.

Having now argued that SCN are both necessary and sufficient for generating circadian rhythms in sleep-wake and body temperature, it should be noted that the majority of circadian rhythms researchers view complex multicellular organisms as multioscillatory systems. Some of these "oscillators" could have weak pacemaker properties that, when coupled to the SCN, have important roles in circadian timekeeping mechanisms. An example is the food anticipatory rhythm observed in SCN-lesioned rats (Stephan et al., 1979). If food-restricted SCN lesioned rats are presented with food access for a limited duration at the same time each day, they will ultimately exhibit anticipatory motor behavior prior to food access—a behavior that persists for many days even if the food restriction schedule is terminated. Other examples of persisting rhythms in isolated tissues and cellular systems have been offered as well (c.f. Moore-Ede et al., 1982; Mistlberger and Rusak, 1989).

**Functional Role of the SCN in Sleep-Wake Regulation**

Although it seems obvious that the SCN produces rhythms in the daily timing of wakefulness and sleep, surprisingly little attention has been given to how this is achieved functionally (and by extension, physiologically). It is clear that the SCN are not essential for the manifestation of sleep and wakefulness per se; SCN-lesioned animals continue to awaken and sleep spontaneously (Mistlberger et al., 1983; Tobler et al., 1983; Eastman et al., 1984; Edgar et al., 1993), suggesting that the circadian system modulates brain regions important in arousal state control. To predict which of these regions are the targets of circadian control, a better understanding of how the SCN influences sleep and/or wake is essential. For example, it is possible that the SCN could invoke hypnogenic brain centers to actively promote sleep, invoke cortical activating centers that promote wakefulness, or differentially affect both systems during the respective halves of the circadian cycle. Previous studies limited almost exclusively to nocturnal rodents (rats) have offered limited insight into these possibilities, especially as they relate to man. Compensatory sleep mechanisms (e.g., recovery sleep after sleep deprivation) and other homeostatic functions (e.g., thermoregulation) remain intact after SCN lesions (Mistlberger et al., 1983; Tobler et al., 1983; Edgar, 1986). Furthermore, total sleep time in rats is not changed substantially after SCN lesions (Mistlberger et al., 1983). Such observations initially led researchers to conclude that the SCN plays no active role in the regulation of daily total sleep time. However this is not the case in primates which, in contrast to rats, exhibit highly consolidated sleep-wake patterns. After SCN lesions, squirrel monkeys (a diurnal new-world primate), exhibit a 4 hour increase in total sleep time when studied in constant conditions (Edgar, 1986; Edgar et al., 1993). Instead of 15-16 hours of uninterrupted wake SCNx monkeys are no longer able to spontaneously maintain prolonged intervals of wakefulness at any time of day, and on an hourly basis, they spend about 50% of the time sleeping, thus accounting for the 4-hour increase in total sleep time.

Even stronger evidence that the SCN participate in the regulation of total wake and sleep time comes from examination of sleep and wake bout length. The percent of the circadian day occupied by slow wave activity and REM sleep does not change appreciably in the absence of circadian control, nor does the duration of sleep bout-lengths during the subjective night (rest-phase of the circadian cycle). But SCN-lesions have a profound
impact on a monkey's ability to remain awake during the subjective day. SCN-lesioned monkeys show, on average, a 15-fold reduction in wake bout lengths when compared to subjective day wake bout lengths in intact animals (Edgar et al., 1993; Edgar, 1994). Thus, the primate SCN appear to actively invoke and/or facilitate central mechanisms responsible for promoting cortical and behavioral arousal, but do not appear to strongly drive nonREM sleep at any time in the circadian day (Edgar et al., 1993).

The notion that the primate SCN actively promotes and maintains alertness at particular phases of the circadian cycle is consistent with numerous observations in man (indeed too numerous to adequately review here). One of the earliest hints of SCN-dependent waking came from work by Czeisler and colleagues who demonstrated that the duration of human sleep was a function of the phase of sleep onset relative to the body temperature circadian rhythm (Czeisler et al., 1980a). Though not explicitly stated in those studies, an implied conclusion was that regardless of the time of sleep onset, spontaneous wakeings are highly regular and largely limited to a relatively narrow portion of the circadian cycle. These findings have since been echoed in forced desynchrony studies where subjects are required to conform to sleep-wake schedules with periods significantly different from the endogenous period of the circadian system. Under these conditions, Dijk and colleagues have demonstrated potent alerting effects of the circadian system that increase across the circadian day, and are present even after extended prior waking (Dijk and Czeisler, 1994). These data are consistent with ordinary experience with jet-lag and shift work, where it is nearly impossible to sleep at circadian phases corresponding with the later half of the subjective day. Forced desynchrony findings are also consistent with the SCN-lesioned monkey data, suggesting the existence of an SCN-dependent alerting mechanism that permits diurnal primates to remain awake for 16 hours or more across the subjective day.

Are Sleepiness/Alertness Rhythms Controlled by Opponent Processes?

In light of the aforementioned discoveries, we have proposed an alternative conceptual model of sleep-wake regulation called the "Opponent Process Model" (Edgar and Dement, 1992; Edgar et al., 1993). The purpose of this model is not to simply predict human sleep-wake behavior, but rather, to serve as a conceptual launch pad for the design of new basic and clinical research. Unlike existing models, the Opponent Process Model offers a specific and testable hypothesis about the physiological function of the suprachiasmatic nuclei in day-active primates— that the SCN serve to promote and maintain wakefulness at specific times in the circadian cycle, and in doing so, contribute actively to circadian variations in physiological sleepiness/alertness by "opposing" the homeostatic elements arising from prior wakefulness (e.g. the consequence of SCN-dependent alerting).

One may ask how the concepts of Opponent Process regulation differ from the "Two-Process model" of sleep-wake regulation as presented in its various forms over the last decade by BORBELY and colleagues (BorBely, 1982; Daan et al., 1984; BorBely et al., 1989). This has proven a challenging question to answer for various reasons. First, in its fundamental rendition, the Two Process model suggests that the manifestation of sleepiness is the singular function of a "homeostatic" process called "S." The level of Process-S (sleepiness) interacts with arbitrarily defined thresholds modulated by a circadian process "C." These thresholds (which are not physiologically defined) somehow impose control over manifest sleep-wake behavior. With this said, it should be noted that the model has been revised in attempts to address discrepancies with empirical data, creating something of a moving target. Indeed, the most recent version (Achermann and BorBely, 1994) actually embraces elements of the opponent interaction hypotheses originally evidenced by SCN-lesion studies in monkeys (Edgar, 1986, 1994; Edgar and Dement, 1992; Edgar et al., 1993) and forced desynchrony studies in humans (Dijk and Czeisler, 1994). Second, the concept of Opponent Process regulation was inspired by the Two Process model. Though lacking a suitable explanation for threshold-based circadian determinants of manifest arousal state (which seems much more likely to be graded and probabilistic in nature), the Two Process model has offered superb characterization of the compensatory (a.k.a. homeostatic) sleep response to prior wakefulness. In a simplistic way, one could conceive of Opponent Process regulation as the assignment of physiological hypotheses to what were previously only harmonic functions in a Two-Process mathematical equation. In its absolute simplest form, Opponent Process regulation (by definition) has at least two functional control elements (e.g. processes). But unlike the conventional Two-Process model, in which physiological sleepiness is determined only by the level of Process-S (a product of prior wake duration alone), the Opponent Process model hypothesizes that physiological sleepiness results from the combined influences of the SCN on cortical and behavioral activation and the as yet undefined determinants that inhibit such activation (e.g. BorBely's Process-S). Furthermore, sleepiness/alertness is predicted to result from multiple convergent elements in arousal state control. For example, alertness can be influenced directly by the SCN, and indirectly by SCN modulation of motivated behaviors that serve to further reinforce arousal (c.f. Welsh et al., 1988; Edgar et al., 1991a). Finally, in Opponent Process regulation, the SCN is thought to actively participate in the regulation of total sleep time, and predicts increased total sleep time after SCN-lesions in diurnal primates (or in humans with neuropathology of the basal hypothalamus that disrupt circadian timekeeping function).

Speciation, Sleep and the SCN. Should we assume that rats are the best model for understanding human sleep physiology and pathophysiology? Certainly rodents serve a useful purpose in basic sleep research; especially with the introduction of molecular genetics techniques. But the polyphasic nature of
nocturnal rodent sleep can be a two-edged sword. Polyphasic sleep patterns have allowed reliable assessment of pharmacological action on sleep infrastructure and to some extent, circadian timing. But highly fragmented sleep-wake patterns also confound interpretations of compensatory sleep responses and their interactions with the circadian system. Consider the following paradox: "One could ask how sleepy can a rat get if it naps all the time? Alternatively, one could ask how can a rat ever become sleep satiated if sleep continuity (sleepbout length) is the most reliable determinant of sleep quality (c.f. Levine et al., 1987; Roehrs et al., 1994). Obviously, polyphasic sleep-wake patterns offer the rat some selective advantage in addition to those afforded by the circadian system. These questions may be crucial toward fully understanding the functional role of the SCN in sleep-wake regulation.

It seems plausible that a major function of the circadian timekeeping system is to assure that an organism is awake, alert, and motivated at times of day that offer the greatest competitive advantage; the organism must gather food, find mates, and complete a plethora of rituals associated with each behavior to maximize fecundity. Indeed, fecundity is the "Darwinian bottom-line" to survival of the species. It is not surprising, then, that lesions of the suprachiasmatic nuclei produce reductions in the intensity of some motivated behaviors (Johnson et al., 1988), and selectively decrease an animal's ability to remain awake for extended periods of time across its usual activity phase of the circadian day (Edgar, 1986, 1994; Edgar et al., 1993). Are animals less alert following SCN-lesions? The answer to this question is not as simple as one might think. Objective measures of sleep latency in diurnal monkeys measured at different times of day (akin to the multiple sleep latency test) suggest that SCN-lesioned monkeys have short sleep latencies, approximating that seen in intact animals during the night (Edgar, 1994). But subjectively, monkeys appear more readily aroused at all times of day as if they are more sleep satiated. Similar observations have been noted in SCN-lesioned rats that show greatly attenuated soporific responses to benzodiazepines (Edgar et al., 1991b) except when the animals are sleep deprived prior to treatment (Trachsel et al., 1992). Collectively these observations suggest that SCN lesions reduce an animal's ability to spontaneously sustain wakefulness for extended periods of time. As a result, small accumulations of sleepiness due to prior waking are compensated by a rapid return to sleep. In monkeys, which normally have highly consolidated sleep and waking halves of the circadian cycle, SCN lesions produce ultradian patterns that in many ways most closely approximate that of rodent sleep-wake patterns.

The Circadian Control of REM Sleep: Although much of the present discussion has focused on the concept of SCN-dependent alerting and rhythms of sleepiness/alertness, it should be noted that circadian timing of REM sleep offers compelling evidence of strong circadian control. There is a clear temporal relationship between REM sleep and the circadian rhythm in body temperature (the latter thought to best reflect the temporal position of the circadian pacemaker itself), that remains even under conditions where the sleep-wake cycle spontaneously dissociates from the period of the temperature circadian rhythm (Czeisler et al., 1980b). Although studies in monkeys reveal little or no active facilitation of nonREM sleep at night (Edgar et al., 1993), REM sleep is remarkably resistant to temporal displacement (Edgar, 1986), consistent with studies in humans. Does this reflect active control of a sleep stage by the circadian system, or is REM sleep timing the expression of SCN-dependent cortical activation preceding normal day-time wakefulness? In mice, the circadian rhythm of REM sleep and theta-dominated wakefulness (highly activated waking), when plotted together, appear as two halves of the same circadian rhythm, leading Welsh and colleagues (1985) to posit this notion. The physiological mechanisms governing the circadian timing of REM sleep is a fertile and virtually unexplored area awaiting discovery.

Future Directions

How the SCN signal other brain regions to initiate and maintain daily intervals of arousal and oppose the process underlying homeostatic sleep drive is not known. Effort projections from the SCN are well documented (Watts, 1991) offering numerous testable possibilities. Owing to the framework of our Opponent Process model, we favor the possibility that the SCN directly or indirectly influence centers that mediate cortical and behavioral activation. The subparaventricular zone (located dorsal to the SCN) and the retrochiasmatic area (immediately caudal to the SCN) receive dense projections from the SCN and project to such areas as the basal forebrain, septal nuclei, medial preoptic hypothalamus, posterior hypothalamus, midepine and paraventricular thalamus, and rostral brain stem (Watts et al., 1987; Watts, 1991), each of which could have important functional relevance to rhythms in sleepiness/alertness. Determining the mechanisms underlying SCN-dependent alertness will prove an important and challenging venture for investigators in the years ahead. Indeed, much more effort is needed in this frontier of basic sleep research. The advent of sophisticated automated sleep scoring technology has greatly accelerated progress in these endeavors (Van Gelder et al., 1991); but studies into the circadian control of sleep and wakefulness are technically difficult and can still take many months or sometimes even years to complete. Such are the challenges from which opportunity springs, new ideas are born, and new careers in basic sleep research are made.

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SRS Bulletin Vol 1, 1995, page 5
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SRS Bulletin Vol 1, 1995, page 6


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**Health-Risk Factors in Shift-workers**

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When one considers the many millions of people affected, the state of our knowledge regarding the impact of shiftwork on health is woefully inadequate. Many of the conclusions described in this article are based on single studies involving but a few hundred people (or fewer). Not only is there no agreed animal model which can be used to provide the sort of information routinely available to toxicologists, for example, but also many of the clinical studies that are available have lacked the epidemiological sophistication needed for the results to be considered definitive. Much of the information presented in this review should therefore be considered preliminary.

Not surprisingly, the major health consequence of shiftwork appears in the domain of sleep. Most shift-workers rate sleep as a major problem area in their lives, with documented evidence from the United States, Japan and Germany indicating that shift-workers get significantly less sleep per "night" than their day-working counterparts (Kogi, 1985, Tepas and Carvalhais, 1990). This is particularly true of jobs involving either night-work or extremely early morning start times. Complaints usually concern sleep maintenance insomnia, as one would expect from patterns of sleep which are disrupted both by circadian rhythm dysfunction and by the noise and demands of a day-oriented society. As Tepas and colleagues have pointed out, however, often this truncation of sleep is also a function of choices made by the shift-worker and his or her family, which inevitably limit the time available for sleep. Education of shift-workers and
their families can often be of benefit in avoiding these maladaptive practices.

One area of sleep disorders medicine which we need to know much more about is the interaction of shiftwork sleep disruption with pathologies such as sleep apnea. This may be particularly common in sedentary occupations such as truck drivers and train engineers. Only recently have preliminary studies started to address this issue, which has major implications for public safety, particularly in view of the additional hours many people are being asked to work, and the aging of the "baby-boom" generation.

Also related to the sleep disruption is the use and abuse of hypnotic drugs, and the mistaken use of alcohol as a hypnotic. As Gordon et al (1985) have documented, this can be quite widespread, particularly in rotating shift workers. Again, education of the work-force can be of benefit, since many lay people do not know the sleep-disrupting properties of alcohol, or the issues of tolerance and withdrawal relating to hypnotics. A similar argument applies to the use of stimulants such as caffeine. Although more evidence needs to be gathered, it seems likely that "substance abuse" of one form or another may be a significant health risk of shiftwork.

Probably the next most frequent health complaint in shift-workers after that of sleep disorders is "stomach trouble". Gastrointestinal disorders relating to shiftwork are reviewed by Scott and Ladou (1990). Several studies have found increased incidence of constipation, stomach medicine use, and ulcers, particularly in non-tolerant shift-workers who switch to day-work, and in rotating shift-workers. The etiology of these disorders is unclear, because it is often true that shift-workers make (through either choice or necessity) rather unwise dietary choices. However, the current link between the stomach and the biological clock does make it likely that at least some of the gastrointestinal distress is due to circadian dysfunction. It is also true that many shift-workers are under occupational and/or domestic stress which may itself lead to gastrointestinal problems.

While few experts would dispute that shiftwork is a risk factor for sleep disruption and gastrointestinal disorders, there is less consensus in its role as a risk factor for cardiovascular disease. Rutenfranz et al. in their influential 1977 review, for example, discount cardiovascular risk, citing previous failures to demonstrate any effect. More recently, though, as Scott and Ladou (1990) remark, evidence in favor of such a link is increasingly mounting. Probably the best study is that of Knutsson and colleagues (1986) who followed more than 500 male Swedish paper mill workers in a longitudinal study. The risk of ischemic heart disease (IHD) rose linearly as a function of years of shiftwork exposure to reach a peak at 20 years which represented more than two and one half times the baseline level of day-workers matched for age. Thereafter, the rate declined, presumably as shift-workers either retired or died. There is, moreover, circumstantial evidence, such as that of the study which showed serum triglycerides (a known risk factor for IHD) to decline when the direction of rotation was changed to a phase delay, a change better tolerated by the circadian system. Whether or not the link between shiftwork and IHD is ever definitively proven, it would certainly seem prudent to warn shift-workers of the possible link, and to educate them into lifestyle changes regarding diet, smoking and exercise which may lessen the risk of IHD from other factors.

In view of the link between depression and circadian dysfunction established in the psychiatric literature (Wehr and Goodwin, 1981), it is certainly plausible to hypothesize that the circadian disruptions of shiftwork may themselves lead (in vulnerable individuals) to depressive disorders. However, again we find that the literature is sparse. As Cole, Loving and Kripke (1990) remark in their review, while there is some evidence for depressive symptomatology (often poorly defined), there is no evidence that diagnostically defined depression is more common in shift-workers, or former shift-workers, than in appropriately matched day-workers. At best, the evidence is mixed. Again, a large scale prospective study is needed using research diagnostic criteria.

In conclusion, the main message of this paper is that much more research needs to be done in the area of health consequences of shiftwork. It is rather chastening to be unable, even, to answer the heartfelt question posed to us by many shift-workers: "Is this shortening my life?". In the meantime, it seems prudent to warn shift-workers that "Shiftwork is probably bad for the heart and the head, and definitely bad for the gut", to educate them in lifestyle changes that might ameliorate some of those risks, and to educate them in the sleep hygiene and chronohygiene needed to cope more successfully with the stresses of shiftwork.

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Timing of Fatalities and Industrial Accidents

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Disease related fatalities and human error accidents do not occur at random throughout the 24-hour day. Rather, they show a two-peak pattern with a prominent peak in the early morning and a smaller peak in the midafternoon. The two-peak pattern seen in large group data is not always consistent with circadian and constant routine data from individual subjects. Round-the-clock measures in groups readily demonstrate diurnal rhythms for parameters such as body temperature, grip strength, cognitive function, etc. However, for parameters such as sleep tendency, disease-related deaths and human error accidents, there is second peak in the midafternoon. Many well-publicized human error catastrophes have occurred in the early morning or mid-afternoon and involved sleep-deprived workers. Thus, risk managers and designers of round-the-clock work schedules are increasingly concerned with the physiology that gives rise to early morning and midafternoon peaks in human error and its interaction with sleep deprivation.

An exemplary set of sleep tendency data comes from Mary Carskadon and her colleagues who asked a group of people to stay awake for 24 hours and documented 278 episodes of unintentional sleep. Figure 1 shows the temporal distribution of the unwanted naps. The numbers on the vertical axis refer to the number of naps that occurred in each of the 2-hour intervals.

This general distribution is in accordance with data from the laboratories of Weitzman, Lavie and others on the temporal distribution of the biological tendency for humans to fall asleep. Moreover, this siesta effect or afternoon dip has been recognized nonscientifically for centuries and is institutionalized by certain cultures in the form of a large afternoon meal followed by a nap.

Figure 2 presents the temporal distribution of 437,511 disease-related deaths dating to the late 1800's. Numbers on the vertical axis refer to thousands of deaths. It appears that the peaks for fatalities coincide with the peaks for sleep. There is a 60% increase from a trough at about 2 AM to a peak at about 8 AM. There is also a smaller peak at about 2 PM. There is a similar two-peak pattern in non-lethal heart ECG abnormalities and medically documented heart attacks.

Figure 3 shows the timing of 6,052 unexplained traffic accidents and appears to have some relationship to sleep tendency as shown in Figure 1. The numbers on the vertical axis refer to hundreds of accidents. These accidents were randomly selected from around the world and are the kind in which investigators could find no drug, alcohol or mechanical problems. The shape of this curve is typical of those found for such diverse events as

![Image of Figure 1](image1)

![Image of Figure 2](image2)
Schedules. Rethinking the sleep needs of workers is difficult, because there are few established guidelines. Concerns about our economy and international competitiveness must be weighed against the hard-to-budget costs of human error and unintentional injury. Historically, societies have been able to ignore the consequences of sleep related errors on the road and in the workplace, because, like the stagecoach driver of a hundred years ago, workers rarely controlled more than one or two horsepower. Nowadays, a single worker may control enough energy to run New York City. While this worker’s sleep needs and tendency to fall asleep on the job are probably the same as those of workers a hundred years ago, the potential consequences of his errors are without historical precedent. In modern times, entire continents may be threatened by a key worker falling asleep on the job.

Suggested Readings:


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**Light Treatment for Shift Work**

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In 1980, Al Lewy and colleagues discovered that although ordinary indoor room light (about 500 lux) did not suppress the nocturnal secretion of melatonin by the human pineal gland, light of increasing intensity could suppress this hormone more and more, with maximal suppression at about 2500 lux. Therefore, they suggested that humans may also require bright light for the entrainment of circadian rhythms. This report triggered the current era of research on the use of high intensity ("bright") light to phase shift and entrain human circadian rhythms. Before that it was believed that "social cues" were more important zeitgebers for humans. Several researchers have shown that in humans, as in animals, light can phase shift circadian rhythms according to a phase response curve (PRC). However, the human studies differ from most animal studies in that higher intensities and longer durations of light were used.

The human PRC studies, and most other studies of the phase-shifting effect of bright light, were performed in laboratories where subjects can be shielded from sunlight and other potential 24-hr zeitgebers. However, in field studies (as in real shift work), subjects are exposed to the natural LD cycle and other potential zeitgebers which will oppose large phase shifts of their circadian rhythms. After all, the "job" of the 24-hour zeitgebers is to keep circadian rhythms entrained with a phase conducive to a diurnal lifestyle. Thus, in order to produce circadian adaptation in night shift workers, their circadian rhythms must
be phase-shifted to re-align with the daytime sleep period, despite the conflicting zeitgebers. Studies have shown that such re-alignment decreases fatigue during the night shift and produces better daytime sleep.

Charles Czeisler and colleagues performed a field study in which subjects were exposed to bright light (7000-12,000 lux) throughout almost all of their 8-hr simulated night shift, and remained in the dark for a fixed 8-hr daytime sleep period after each night shift. Four nights of bright light and 4 daytime sleep/dark periods produced circadian adaptation; the circadian temperature rhythm was phase shifted 9.6 hrs, matching the sleep period phase delay shift of about 9 hrs. In contrast, in control trials in which subjects spent the night shift in dim light and then slept at times of their own choosing, the circadian temperature rhythm remained entrained with a normal phase relative to the 24-hr day. This illustrates the typical situation for real night shift workers who do not have access to bright light during the night shift, and usually have erratic daytime sleep schedules determined primarily by social constraints.

Charmaine Eastman and colleagues conducted a series of 3 field studies in which the sleep period was inverted (shifted 12 hrs). Shift workers who rotate from the day to the night shift often experience such a large displacement of sleep. Workers on permanent night shifts also experience a disruptive shift in the timing of their sleep between days off and work days, but it is usually a little less than 12 hrs. In these 3 field studies, there were 8 or more consecutive, simulated night shift and day sleep periods, and subjects were required to remain in bed in the dark during the scheduled sleep periods. The first study investigated the timing of nocturnal bright light. The light (about 5000 lux) was 6 hrs in duration for the first 4 nights and 3 hrs thereafter. Subjects wore dark welder's goggles whenever they went outside during the daytime, in order to attenuate sunlight that might inhibit the desired circadian rhythm phase shift. The combination of nocturnal bright light, a fixed daytime sleep/dark period and dark welder's goggles resulted in successful circadian rhythm adaptation in most subjects. The circadian temperature rhythm phase shifted by about 2 hrs/day, with cumulative phase shifts of 10-12 hrs. The rhythms either gradually delayed or gradually advanced to re-align with sleep, with the direction determined by the timing of the bright light relative to the baseline temperature rhythm, in agreement with the PRCs. When most of the bright light occurred before the temperature minimum, the rhythm usually delayed, when most occurred after the minimum, the rhythm usually advanced.

In the second study, the relative contributions of the bright light and goggles were assessed. With dim light during the night shift and no goggles to wear outside, the circadian temperature rhythm usually remained entrained to the 24-hr zeitgebers. Bright light (6 hrs of about 5000 lux around the temperature minimum during the first 2 night shifts) and goggles were each important for facilitating temperature rhythm phase shifts. However, the combination of bright light plus goggles was the most successful for producing circadian adaptation. When subjects wore goggles, the direction of phase shift depended on the timing of the bright light, as in the previous study. However, when subjects did not have goggles, the temperature rhythm phase advanced, but did not phase delay, to re-align with sleep. Apparently, sunlight exposure during the time between the end of the night shift and bedtime was enough to prevent the temperature rhythm from phase delaying, since light at this time is expected to coincide with the phase advance portion of the PRC. However, goggles appeared to attenuate daylight enough to permit phase delays.

In the third experiment, the duration of nocturnal bright light (about 5000 lux around the temperature minimum) was studied. There were 3 groups of subjects, exposed to either 6 hrs, 3 hrs or 0 hrs of bright light (i.e., dim light) during all 8 simulated night shifts. Substantial circadian adaptation (large cumulative temperature rhythm phase shifts) were produced in most subjects in the bright light groups, but not in the dim light group. There was no significant difference between the 6 and 3-hr groups, showing that durations longer than 3 hrs are not necessary for circadian adaptation. This means that light treatment can be more convenient and more feasible for real shift workers.

So far, practical applications of bright light treatment have been implemented and studied primarily by Karen Stewart at NASA. Schedules of bright light and dark sleep are designed to shift the circadian rhythms of astronauts and ground crew before the launch of space shuttles, to match the shifted sleep schedules required during the missions. Despite the success of the NASA programs, there is still much basic research needed on the use of bright light to shift human circadian rhythms in the field. Other intensities, durations and patterns of light need to be tested using various shifts of the sleep schedule. We need to determine when dark goggles are useful, and when we can obtain the desired results without them. Ultimately, successful implementation of bright light programs for ordinary shift workers will require the education not only of the workers themselves, but also of managers who design work schedules.

Further Reading


Melatonin Treatment for Shiftwork

Robert L. Sack
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Melatonin administration may be a useful treatment for shiftwork-related insomnia for several reasons. It can facilitate circadian phase-shifting and thus help to realign endogenous circadian rhythms with daytime sleep. Melatonin may also have a direct sedative effect, or possibly an indirect sleep-promoting effect (discussed below), particularly for sleep that is initiated at an atypical phase of the circadian cycle; i.e., the daytime hours.

**Melatonin -induced phase shifts:**

Symptoms of insomnia and diminished alertness in night-shiftworkers may be alleviated by "resetting the body clock;" that is, by shifting the phase of the circadian pacemaker to promote greater congruence between daytime sleep and the endogenous sleep propensity rhythm. In recent years, both bright light exposure and melatonin administration have been shown to facilitate phase shifts (1, 2). Moreover, for both light and melatonin, the direction of the phase shift is critically dependent on the timing of treatment; that is, both treatments are based on a phase response curve (PRC). We have shown that the melatonin PRC is inversely related to the light PRC, consistent with the concept of melatonin as a "darkness signal" (3).

Our use of melatonin as a phase-shifting agent began with the treatment of totally blind people who had free-running rhythms and periodic insomnia. We were inspired by the work of Redmond and Armstrong who showed that daily injections of melatonin would entrain rats who were free-running in dim light conditions (4). In blind subjects, we gave melatonin (5 mg) at bedtime for three weeks and observed cumulative phase advances of up to 16 hours by the end of the treatment trial; however, complete entrainment of free-running rhythms was difficult to achieve (5).

We next administered melatonin to normally sighted subjects and were able to construct a melatonin PRC (3). Melatonin administration around circadian time (CT) 8 (afternoon and the early evening) produced phase advances, while administration around CT 0 (early morning) produced phase delays. The magnitude of the shifts was modest (rarely more than 1.5 h), but the effects were consistent. Presumably the degree of phase-shifting was limited by competing time cues from the light dark cycle. A melatonin PRC of a similar configuration has also been recently reported by Zaidan and colleagues (6).

Because melatonin was shown to phase shift circadian rhythms both in blind and sighted individuals, we embarked on a clinical trial of melatonin administration to improve adaptation to night shift work. To date, we have treated 15 workers who were on a "7-70 schedule;" that is, seven consecutive ten-hour night shifts followed by seven days off duty and a return to a conventional day-active schedule; thus the subjects alternated between a diurnal and nocturnal orientation on a weekly basis. We measured their endogenous melatonin profile at the end of each week to assess whether their underlying rhythms adapted to this schedule. Without treatment, there was substantial variability in the degree of phase-shifting (7): one third of the subjects made large (up to 12 hour) shifts in their endogenous melatonin rhythms during the work week so that their underlying rhythms coincided with their daytime sleep; on the other hand, the eight out of 15 had no shift in their underlying rhythms and maintained melatonin in secretion during the nighttime hours. The remainder made small shifts to an intermediate phase.

**Melatonin treatment (0.5 mg at bedtime) resulted in significant phase shifts in six of eight subjects who did not shift on their own. The magnitude of the phase shifts with melatonin treatment were much larger than the shifts observed in our previous studies of normal subjects who maintained conventional sleep schedules and were exposed to a typical light-dark cycle (3). These differences might be explained by hypothesizing that melatonin treatment in shiftworkers has a modest phase-shifting effect by itself, but that it delayed the phase of the light PRC so that sunlight exposure (as might occur during the morning commute) hit the sensitive delay region, producing large phase shifts.**

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One could also speculate that in subjects who did not shift with placebo or melatonin, morning sunlight hit the advance region of the light PRC and constrained any phase-shifting tendency. In the future it will be important to determine the specific phase-shifting potency of melatonin under conditions that control for any potential contribution from light exposure. In addition, there needs to be further consideration of the interaction of melatonin treatment with different night work schedules. For example, for workers on a rapid rotation, phase shifting would be undesirable and treatment might be designed (using the melatonin PRC) which is aimed at counteracting a tendency to shift, thus stabilizing circadian phase.

**Melatonin as a sleep-promoting agent:**
A treatment strategy different from circadian realignment is to increase tolerance for sleeping and working out of phase with the endogenous sleep-wake propensity rhythm. Melatonin may have a direct sedative action analogous to the classical sedative-hypnotic drugs. On the other hand, melatonin may promote sleep by more indirect mechanisms; for example, by its hypothermic action (8, 9). Thus, melatonin administration during the day may act as a "night signal" and induce a nocturnal physiological profile. In this way, melatonin administration could indirectly promote sleep at an atypical circadian phase. What is the evidence that melatonin has sleep-promoting properties? Its nocturnal pattern of secretion provides circumstantial evidence for a role in sleep, although melatonin is elevated at night in nocturnal as well as diurnal species. Bright light exposure during the nighttime hours, which suppresses melatonin production but it remains uncertain whether this is due to melatonin suppression or an activating effect of light itself. Our own pilot study found that melatonin administration at night could reverse the alerting effect of light, suggesting that the effects of light were the result of melatonin suppression (9). Early clinical trials in normal volunteers indicated that melatonin administration may indeed have some sleep-promoting effects; however, more recent double-blind, one-night trials conducted by James and colleagues looking at the acute effects of 1 and 5 mg doses were unable to show sleep promoting effects in healthy young subjects (10); however the lack of response may have been related to a "ceiling effect." James et al. also found no response when melatonin (5 mg) was administered to a group of patients with "subjective" insomnia (11). On the other hand, MacFarlane et al. (12) reported an increase in total sleep time (subjective assessment) in insomniacs treated with higher doses of melatonin (75 mg at bedtime for two weeks). This dose produced peak circulating concentrations of 60,000 pg/ml (about 1,000 times normal nocturnal peak concentrations). Waldhauser et al., (13) recently reported improvement in polygraphically-monitored sleep during a one-night trial of melatonin (80 mg) while the subjects were exposed to recorded traffic noise designed to produce "artificial insomnia." Recently, melatonin has been reported to be of benefit to elderly insomniacs who have low melatonin secretion (14).

All of the studies just mentioned tested melatonin administration prior to nighttime sleep; however, melatonin administered prior to daytime sleep would be more relevant for shiftworkers. In this regard, Hughes et al. (15) recently reported a placebo-controlled, double-blind, crossover study to assess the hypnotic efficacy of 3 doses of melatonin (1 mg, 10 mg & 40 mg) administered at 10 am. Subjects were then put to bed from 1200 hr until 1600 hr. All doses of melatonin shortened sleep latency and the higher doses, significantly increased sleep duration. Also, Dollins et al. (16) reported the effects of four relatively small doses of melatonin (0 mg, 0.1 mg, 0.3 mg, 1 mg and 10 mg) taken orally at 11:45 am. Subjects were allowed a 30 min. nap at 13:00 and the sedative effects of melatonin were assessed with a behavioral measure of sleep onset (release of a microswitch). All but the smallest dose of melatonin shortened sleep latency in this paradigm. Folkard et al. found that melatonin (5 mg) given to night-shift workers prior to their daytime sleep improved wake-time subjective alertness although the effects on performance measures were mixed (17). Dawson et al. (personal communication) found that melatonin improved daytime sleep in a simulated shift work protocol, but had little effect on phase; however, the timing of administration may not have been optimal for producing phase shifts. Questions regarding the dose-response curve for the sleep-promoting effects of melatonin need to be resolved. The Hughes study (15) found a linear dose-response curve for daytime sedation up to about 10 mg, with flattening at higher doses. However, the Dollins study (16) found sleep-promoting effects with doses as little as 0.3 mg, much lower than any previously reported. There are also insufficient data on the dose response relationship for phase-shifting effects. It is possible that phase-shifts will occur with doses of melatonin that produce physiological plasma levels, but that sleep-promoting effects will occur only at pharmacological blood levels. Whether the sleep-promoting effects of melatonin are considered a therapeutic advantage (if taken just prior to sleep) or a side effect (if taken in the morning to promote a phase delay) obviously depends on the clinical context.

In summary, melatonin administration is an intriguing potential treatment for shiftwork adaptation which builds on a growing understanding of the biology of the circadian system.

**Bibliography**


NEWS AND COMMENTS

"Student's Perspective"

Gina Poe, 1994 SRS Student Representative and Member at Large

All of us are well aware that the field of sleep research is "wide open" to a variety of studies that must be done to provide a basic understanding of the sleep process. Unfortunately, however, the otherwise healthy field of sleep research must suffer the ills of the burgeoning neuroscience superstructure, as we must compete for grants in the larger neuroscience context. I saw a chart just last week that indicated the number of RO1 (the primary research grant that most researchers must apply for, and receive to even be considered for a research position at a university) submissions has doubled since 1991. Fewer than 15% of reviewed RO1 applications were funded in 1993. So what is a sleep trainee to do? The answer is short and sweet.

1. Make sure your training puts you a cut above the rest.

2. Identify and seriously consider ALL of your post-training career options.
Here are a few ways you can accomplish task number 1.

A. Coerce your mentor or your graduate program curriculum committee to offer specific training in grant writing, manuscript writing and presentation skills (e.g. slide talks and poster preparation). One way you can encourage the generation of such a course is to disseminate to the faculty the following information on the first national workshop on "Teaching Survival Skills and Ethics to Emerging Scientists", to be held May 18-21, 1995 at Ogelbay Resort in West Virginia. This will be an NSF-subsidized workshop, costing participants only $375 (includes round trip airfare, housing, food and materials). Participants must agree to improve an existing course, or establish a new course in survival skills by no later than the Fall of 1996. Application deadline for the course is January 15, 1995. Write to Michael Zigmond, Project Director, (email: zigmond@bns.pitt.edu) or Beth Fischer, Project Coordinator (email:fischer@bns.pitt.edu) at: Department of Neuroscience, 570 Crawford Hall, Pittsburgh, PA 15260. FAX: 412-624-7327.

B. If you are a graduate student, write your thesis proposal in grant proposal format. Use a funded grant of your advisor as an example of the format. If you are a postdoc, submit your own grant proposal. Though you may be currently funded on a training grant, an individual grant (such as an NRSA, or better yet, a K21) will bring in more money to your lab, look great on your CV, and give you invaluable training on the grant writing/submission process.

The above suggestions are ways to ensure that you stand out above the rest. Now, let us consider possible next steps. Unfortunately, the academic environment, in which we spend most of our time as graduate students, generally discourages us from pursuing any career save academic science. Those interested, on any level, in pursuing alternative careers feel strong social pressures to hide such leanings from faculty members and sometimes colleagues. Fortunately, with the increasing difficulty in obtaining faculty positions, more trainees are getting bold about pursuing other options. Here is a very partial list of our options:

**Research and Teaching:**

1. Tenure track position at an institution with undergraduate, graduate and post doctoral students.

2. Tenure-track positions in undergraduate institutions that support academic research, such as Smith college and many more.

3. Non tenure-track research positions at the above two institution types. Though job security is compromised, increasing numbers of these positions are becoming available as tenure positions fade, yet demand for persons qualified for both teaching and research continues.

4. The eternal post-doc. Though this option is certainly possible, it is not recommended due to the inherent dependence on someone else to write the grants on which your salary depends.

**Research:**

1. Junior and Senior research positions (dependent on the number of years of post-graduate experience and grantsperson-ship) at a private research institution (non-profit), such as Scripps, Salk, and the Neurosciences Institute. Your salary usually depends directly on grants (soft-money), so job security is low, but so are your administrative and teaching duties.

2. Research positions in privately owned for-profit companies, such as a pharmaceutical company. While you are relieved of depending on grants for your salary, you may sacrifice intellectual freedom to pursue scientific areas that look interesting in favor of research that promises a profitable result. These positions traditionally pay higher than academia, but you usually have to stick to company designated vacation leaves and more standardized work hours. Opportunities to teach may sometimes be arranged.

3. Government research institutions such as the Veteran's Administration or the Los Alamos research labs. If you want to teach, often a deal with a local university can be struck. The salary varies (it can be quite high) and the only downside I can think of is that you are somewhat subject to the whims of D.C. politics.

**Teaching:**

1. Four-year and two-year colleges that do not require research for tenure. The pay isn't great (fair-to-middling), but if you love to teach and just want to dabble in research on the side or abandon it altogether, this is the place for you. Be sure to get some T.A. experience in graduate school and save your student evaluations.

2. High school/ Elementary school teacher or science department coordinator. The dearth of good science teaching in our public (and private) institutions puts science teachers and program coordinators in demand. Though this doesn't always translate to a decent salary, the potential to influence youngster's lives is high. Consider putting your teaching and research skills to work in creating a science program that will be envied nation-wide. Private as well as public funding institutes are increasingly aware of the need for early science training, so don't overlook the funds that are becoming available in this arena.
Further training in clinical fields:

1. Sleep disorders medicine (as a Licensed Clinical Polysomnographer). This allows you to feed your family, do some direct good to others, and even allows for the possibility of clinical research.

2. Clinical psychology, specializing in areas related to sleep, such as sleep and mood disorders, etc. This is a highly competitive Ph.D. program, however, your Ph.D. in Neuroscience may help. If you are willing to put in the extra years training, the payoffs again, are job stability, direct benefit to others, and clinical research.

3. Becoming a physician. Though medical schools relying on the AMCAS application process may not adequately weight the advantage a Ph.D. gives the potential physician, there are an increasing number of schools (such as Harvard and Duke) that look at the applicant as a unique individual and purport a thoughtful, problem-solving medical school atmosphere rather than the typical, cram-the-information-in philosophy of medical education. These types of environments should work better for people with Ph.D. backgrounds. Same benefits as 1 and 2.

One final word to the wise:

Don't be an ostrich, burying your head in research and hoping for the best. Face the facts, chart your course, and be proactive and prepared.

The National Center for Sleep Disorders Research

The National Center for Sleep Disorders Research was created in 1993 by the United States Congress to conduct and support research, training, health information dissemination, and other activities with respect to sleep disorders. In addition to clinical sleep disorders, the center included research in biological and circadian rhythms, the basic understanding of sleep, and other sleep-related research. The Center was also instructed to coordinate its projects with sleep-related activities of other Federal agencies, including other organizations within the National Institutes of Health, the Centers for Disease Control and Prevention, the Department of Transportation, Defense, Education, Labor and Commerce, and other public and nonprofit entities.

As part of its responsibilities, the Center was directed to advise the Director of the National Institutes in the development of a comprehensive plan for the conduct and support of sleep disorders research, to identify and periodically update research priorities, and to coordinate research supported by the National Institutes of Health.

In order to develop a Research Plan, the Advisory Board to NCSDR wishes to identify important unexplored research areas and promising new research opportunities relevant to sleep research. Areas of interest include but are not limited to the preclinical and clinical sciences related to sleep disorders medicine and pertinent areas of other clinical disciplines, chronobiology, neurobiology, molecular biology and biochemistry, physiology, pharmacology, psychology and behavior, aging and development, alcoholism and substance abuse, epidemiology, public health, operations research, mathematical modelling, and bioengineering.

Interested members of the public and scientific community are invited to submit written recommendations for future research directions in sleep and related fields. These suggestions should be forwarded by January 15, 1995 to:

Dr. J. Christian Gillin
Chairman
Research Subcommittee of the Advisory Board to the NCSDR
Professor of Psychiatry
University of California, San Diego
VAMC (116A)
3350 La Jolla Village Drive
La Jolla, CA 92161
619 534 2137

Annual Meeting News

Our 1995 APSS meeting will be in Nashville, a truly unique American city. For those who want to take advantage of the meeting for a family vacation, we have negotiated a special pre-meeting room rate of only $79 at the spectacular Opryland Hotel. Reduced rates will also be available for the many attractions of Opryland, immediately adjacent to the hotel. Room rates during the meeting will be only $99.

The scientific program is already shaping up as one of the more memorable in the history of our societies. 1995 marks the 100th
birthday of Nathaniel Kleitman, the father of modern sleep research. To mark this milestone and celebrate the life of Dr. Kleitman, we have arranged a special symposium on the discovery of REM sleep. Dr. Kleitman, Dr. Eugene Aserinsky, Dr. William Dement and Dr. Michel Jouvet have agreed to participate in this first ever gathering of the men who discovered this third state of existence and created our field.

Another giant of sleep research, Dr. Alan Rechtschaffen will be giving the keynote scientific talk. Dr. Rechtschaffen will summarize his landmark research on the effects of sleep deprivation.

Several outstanding scientists have agreed to give invited one hour lectures:
- Dr. Barry Jacobs: Serotonin and motor activity
- Dr. John Remmers: Obstructive sleep apnea: separating neural from anatomic factors
- Dr. Terry Young: Epidemiology of sleep apnea
- Dr. Peter Reiner: Reticular Activating Systems

A special invited one hour lecture will be given by Dr. Julius Axelrod. Dr. Axelrod, who won the Nobel Prize for his studies of monoamine metabolism, will talk on "Neurotransmitters, second messengers and psychoactive drugs."

A symposium analyzing recent controversies and claims about the hypnotic effects of melatonin will be chaired by Dr. W. Mendelson. Dr. Axelrod will review his seminal work on the neural regulation of melatonin synthesis, as part of the symposium.

Other Symposium, Discussion Group and speaker slots will be decided at the January meeting of the Program Committee.

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**The World Federation Of Sleep Research Societies**

**2nd International Congress: The Mystery Of Sleep**

Under the leadership of Chairperson Tom Roth and Honorary President Allan Rechtschaffen, the World Federation of Sleep Research Societies will be having its 2nd International Congress on September 12-16, 1995, at the Crystal Palace in Nassau, the Bahamas.

Aimed towards bringing together a broad spectrum of the sleep community worldwide including researchers, clinicians, students, technicians and suppliers, the program itself will emphasize critical issues of current scientific thought and will promote international exchange, collaboration and the cross-fertilization of ideas with leaders in related scientific fields.

The Scientific Program Committee includes such distinguished scientists as Joelle Adrien (France), Torbjoern Akerstedt (Sweden), Michel M. Billiard (France), Alexander A. Borbely (Switzerland), Roger J. Broughton (Canada), Rene Drucker-Colin (Mexico), Carlo Franzini (Italy), James A. Horne (United Kingdom), Shojiro Inoue (Japan), Barbara E. Jones (Canada), Michel Jouvet (France), Meir Kryger (Canada), Peretz Lavie (Israel), Elio Lugaresi (Italy), V. Mohan Kumar (India), Teruo Okuma (Japan), Allan I. Pack (USA), Eliot A. Phillipson (Canada), Mark H. Sanders (USA), Hartmut Schulz (Germany), Jerome Siegel (USA), Mircea Steriade (Canada), Colin E. Sullivan (Australia) and David P. White (USA).

The Call for Abstracts will be sent out in January and the deadline for the submission of abstracts will be April 15, 1994.

For further information, please contact:

**Global Events**

710 North Trenton Drive

Beverly Hills, CA 90210-3105

Tel: 1-310-247-8004

Fax: 1-310-247-8457

e-mail: 74117.65@compuserve.com

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**Student Essay Contest**

The application forms for the high school students essay contest have already been mailed to all SRS members. We urge you to encourage your local high school science teachers to get involved. The essay contest has been going well and it
represents an important way for us to reach out to the community. However, students from only a few schools are entering the contest. We need greater participation from all the States and Canada. **Deadline is March 15, 1995**

For more information contact: **Dr. Tom Kilduff,**
Stanford Sleep Lab, 415 723-9380
415 725 5356 (FAX)
MS.TSK@FORSYTHE.EDU (e-mail)

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**SRS Young Investigator Award**

This award recognizes outstanding research effort by a new investigator in the field of sleep research. The basis for evaluation of candidates will be a single publication in a refereed journal on which the candidate is the first author and which has been published or is officially accepted for publication by the application deadline. To be eligible, candidates must be 35 years old or younger on the application deadline. Exceptions to the age rule will be considered for those applicants who feel that extenuating circumstances warrant such consideration. A letter detailing these considerations should be included with the application.

The award consists of a plaque and a travel honorarium of $750 that may be applied towards travel to the 1994 APSS meeting. The plaque will be presented at a ceremony at the 1995 Annual Meeting.

To apply, candidates should submit 20 copies of the paper, a single copy of CV, and documentation of age. If a paper is in press at the time of application, a copy of the written notification of the paper's acceptance for publication should also be included. In addition, applicants should provide a letter of recommendation from a senior investigator familiar with the applicant's research. It is the candidate's responsibility to insure that the letter of recommendation reaches the Award Committee by the closing deadline. Finally, candidates must be in good standing in the SRS or must include a completed application for membership and fee with their award application. Repeat applications from unsuccessful applicants from previous years are encouraged.

**Application receipt deadline is April 1, 1995.**

Send applications to:
Adrian Morrison, DVM
Animal Biology School of Veterinary Medicine
University of Pennsylvania
3800 Spruce St
Philadelphia, PA 19104
215-898 8891
215 573 2004 (fax)

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**SRS Travel Awards**

SRS has a limited number of travel awards for trainees to attend the annual meeting in Nashville. Trainees eligible for these awards include predoctoral fellows and other fellowship trainees currently engaged in sleep research. Applications will be judged by the SRS Travel Awards Committee.

**Application receipt deadline is March 15, 1995.**

For more information contact:

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