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CLINICAL REVIEW

Circadian rhythm sleep disorders: lessons from the blind

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KEYWORDS
blindness, melatonin, circadian rhythms, sleep disorders, insomnia

Summary As totally blind people cannot perceive the light–dark cycle (the major synchroniser of the circadian pacemaker) their circadian rhythms often "free run" on a cycle slightly longer than 24 h. When the free-running sleep propensity rhythm passes out of phase with the desired time for sleep, night-time insomnia and daytime sleepiness result. It has recently been shown that daily melatonin administration can entrain the circadian pacemaker, thereby correcting this burdensome circadian sleep disorder. The primary purpose of this review is to elevate awareness of circadian sleep disorders in totally blind people (especially free-running rhythms) and to provide some guidance for clinical management. An additional goal is to show how research on sleep and circadian rhythms in the totally blind can contribute insights into the scientific understanding of the human circadian system.

INTRODUCTION

The occurrence of circadian rhythm abnormalities in totally blind people is not generally appreciated by blind patients nor by the professionals who assist them. Circadian sleep disorders must be discriminated from sleep problems related to depression, poor sleep hygiene and a host of other causes. Thus it is important for sleep specialists, using their understanding of clinical chronobiology, to accurately diagnose sleep disorders in blind patients, to educate family and caregivers regarding their underlying basis, and to provide appropriate treatment. In this review, the mechanisms, clinical features and epidemiological aspects of sleep disturbances in the blind are addressed. There is also some discussion of what research in totally blind people has revealed regarding the human circadian system. Important research questions, such as the role of light on the human circadian system, can be addressed by studying the consequences of its absence in totally blind people. Finally, some suggestions for management and treatment are presented.

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LIGHT AND THE CIRCADIAN SYSTEM

Since the earth began, there have been 10^{14} sunrises and sunsets. Adaptation to the solar light–dark cycle has shaped the evolution of almost all species, so it is not surprising that such a large number of biological processes have a circadian component. By definition, circadian rhythms are not passive responses to the light–dark cycle, but rather are generated by one or more internal clocks. The obvious advantage of an endogenous clock is that an organism can orchestrate physiological changes that lead, rather than lag, the daily changes in the environment. For example, the rise in core body temperature at the end of the night-time sleep period presumably readies an individual for physical activity upon awakening in the morning. The master

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circadian clock in mammals is located in the hypothalamus within two paired, midline structures called the suprachiasmatic nuclei (SCN) [1]. When this tiny area of the brain is destroyed in laboratory animals, circadian rhythms are obliterated and sleep occurs in short bouts evenly distributed over the 24-h day. Remarkably, circadian rhythms can be restored to SCN-lesioned animals by transplanting fetal SCN tissue into the third ventricle of the brain [2]. The SCN generates a rhythm that is approximately, but not exactly, 24 h (hence, *circa* meaning "about" combined with *dian* meaning "day" – about a day). When subjects (human or animal) are placed in a time-isolated environment, rhythms "free run" with a period that is either slightly longer or shorter than 24 h (ranging from about 23 h to about 25 h). Free-running rhythms are an expression of the intrinsic period of the circadian pacemaker, presumably unmodified by external time cues. In order for circadian rhythms to be precisely synchronised (entrained) to a 24-h day, the circadian clock must be regularly adjusted (reset) by exposure to 24-h time cues derived ultimately from the solar light–dark cycle.

The process of entrainment in mammals is primarily mediated by a specific neural pathway, the retinohypothalamic tract (RHT), that conveys photic information directly from the retina to the SCN (see Fig. 1). This pathway is anatomically distinct from the visual imaging system. In animals, very specific experimental lesions of the RHT that block transmission of photic input to the SCN but spare the optic nerves, result in free-running circadian rhythms [3]. In contrast, lesions of the visual system distal to the RHT tract may impair visual perception (for example, produce cortical blindness) but do not affect the circadian time-keeping system. In nature, the transitions in light intensity at dawn and dusk usually provide the critical timing signals for entrainment.

The timing signal from the SCN is distributed widely throughout the brain including the regions that regulate core body temperature, sleep and activity cycles, and hormonal secretion, including an efferent pathway to the pineal gland that stimulates secretion of melatonin during the night-time hours (Fig. 1). In all species, melatonin is normally produced at night, whether an animal is day active or night active; thus, it is ordinarily a concomitant of darkness [4]. Our laboratory has extensively used the timing of melatonin to infer the timing (phase) of the circadian pacemaker.

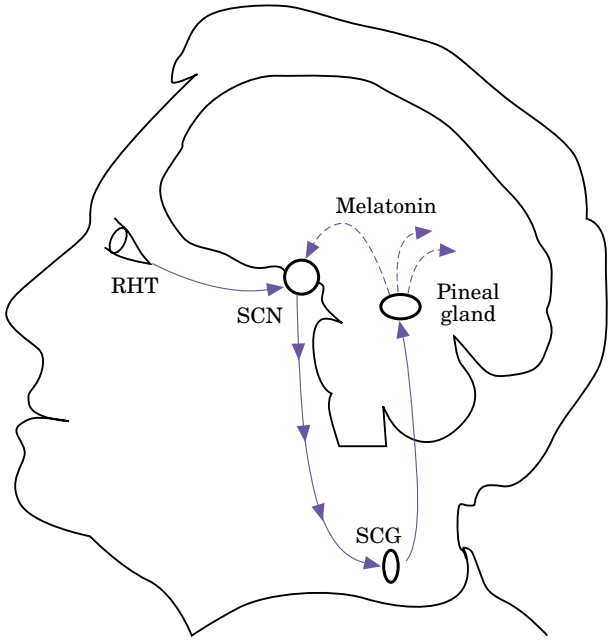

Figure 1 Major components of the circadian system. Photic information travels via the retinohypothalamic tract (RHT) to the suprachiasmatic nucleus (SCN) where it acts to entrain circadian rhythms. The SCN, located in the hypothalamus, is the master clock for the circadian system. From the SCN, the circadian timing signal is broadcast by multiple neuronal circuits. One of the outflow pathways from the SCN travels down a multisynaptic pathway into the thoracic spinal cord and out with sympathetic nerves to the superior cervical ganglion (SCG). Post-ganglionic fibers from the SCG then pass back up into the cranium where they terminate on the pineal gland. Stimulation of the pineal during the night results in the release of melatonin into the circulation which broadcasts a hormonal message for darkness. There are specific melatonin receptors in the SCN that detect circulating melatonin. These receptors complete a feedback loop from the pineal gland to the SCN and presumably mediate the action of exogenous melatonin on the SCN. In totally blind people, the photic input to the pineal gland is absent, and the circadian clock free runs with a rhythm that is slightly different from a 24-h period (approximately 24.5 h).

In addition to entraining the circadian clock, light exposure acutely suppresses melatonin secretion [5]. In nature, the melatonin profile is normally shaped by two factors: (1) the circadian clock which turns pineal secretion on and off; and (2) the timing and intensity of light at dawn and dusk which "gates" the secretion of melatonin [4]. For example, the circadian clock signal for melatonin secretion may

be "on" in the evening, but if bright light is present (for example, it is dusk on a long summer day), secretion will not occur until after dark. The gating effect of light results in a melatonin profile that changes duration through the seasons of the year; the duration signal is an important mediator for annual rhythms in many species. Clinically, the suppressive effect of light has been used to test whether people who are subjectively blind have an intact RHT pathway, the so-called "melatonin suppression test", discussed in more detail below.

CIRCADIAN RHYTHMS IN TOTALLY BLIND PEOPLE

Epidemiology: incidence of sleep problems in the blind

As the circadian system of all species is an adaptation to the light–dark cycle, abnormalities in blind people have been suspected for some time. Several surveys have confirmed a particularly high incidence of insomnia among blind people. For example, Leger and colleagues obtained questionnaires from 794 blind subjects in France (average age = 51.5 ± SD 17.1 years) in which over half of the respondents reported no light perception at all [6]. Thirty-five per cent of the respondents had difficulty initiating sleep, 54% complained of frequent awakening, and 45% awakened too early. Furthermore, 25% were taking hypnotic medications "often" or "always".

In another survey conducted in Great Britain ($n = 388$), sleep disorders were noted in 48.7% of blind subjects; it was rated as "severe" in 7.2%, "moderate" in 13.9% and "mild" in 27.6% [7]. In a control group of normally sighted subjects ($n = 44$), 9.1% reported "mild" disturbances, and none rated their sleep problems as moderate or severe. The incidence was highest (65.5%) and the severity was greatest (12.1%) among the blind with no light perception. The most common problem was interrupted sleep, followed by increased sleep onset latency, reduced total sleep time and daytime naps.

Sleep problems in the blind are not entirely due to circadian rhythm abnormalities. Most people who are considered legally blind have at least some light perception. Indeed, current evidence suggests that even patients who cannot perceive light (are subjectively blind) sometimes have intact photic pathways to the hypothalamus sufficient for entrainment and suppression of melatonin (see below). Perhaps worry, depression, medication side-effects, sleep-related breathing disorders and physical pain are more common in the blind, and account for some portion of the elevated incidence. In order to understand the specific relationship between blindness and sleep disorders, it is necessary to evaluate blind individuals with sleep complaints thoroughly, and not assume that the sleep problem is a product of blindness *per se*.

Free-running rhythms in the totally blind

Early investigations of circadian physiology in blind people reported diminished circadian amplitude [8–11], but this was probably related to inappropriately averaging data from samples drawn at different circadian phases. The exact nature of abnormalities in the totally blind became defined only after longitudinal assessments of circadian phase were made.

Miles *et al.* were the first to use serial measurements of core body temperature and cortisol profiles to document a free-running circadian rhythm in a totally blind person with a severe recurrent sleep disturbance [12]. A second blind person with free-running circadian rhythms was documented by Orth *et al.* [13] using serial measurements of cortisol secretion. In 1983, Lewy and Newsome reported that melatonin rhythms were abnormal in six of 10 subjects [14]. When two of the subjects were sampled serially at weekly intervals for 4 weeks, one was found to have a free-running rhythm and the other was entrained, but at an abnormal phase. Over the next few years, several additional case reports were published confirming free-running rhythms in blind people [15, 16]. In all instances, the circadian period (conventionally designated as the Greek letter "tau") was similar to sighted people living in temporal isolation; in both situations, free-running rhythms are presumed to reflect the period of the endogenous circadian pacemaker. Henceforth, totally blind people with free-running rhythms are abbreviated "BFRs".

Figure 2 provides an example of melatonin and cortisol rhythms in a BFR (unpublished data). Blood samples were drawn hourly for 24 h on three occasions spaced about 2 weeks apart. The melatonin onset (MO), the time when melatonin rose

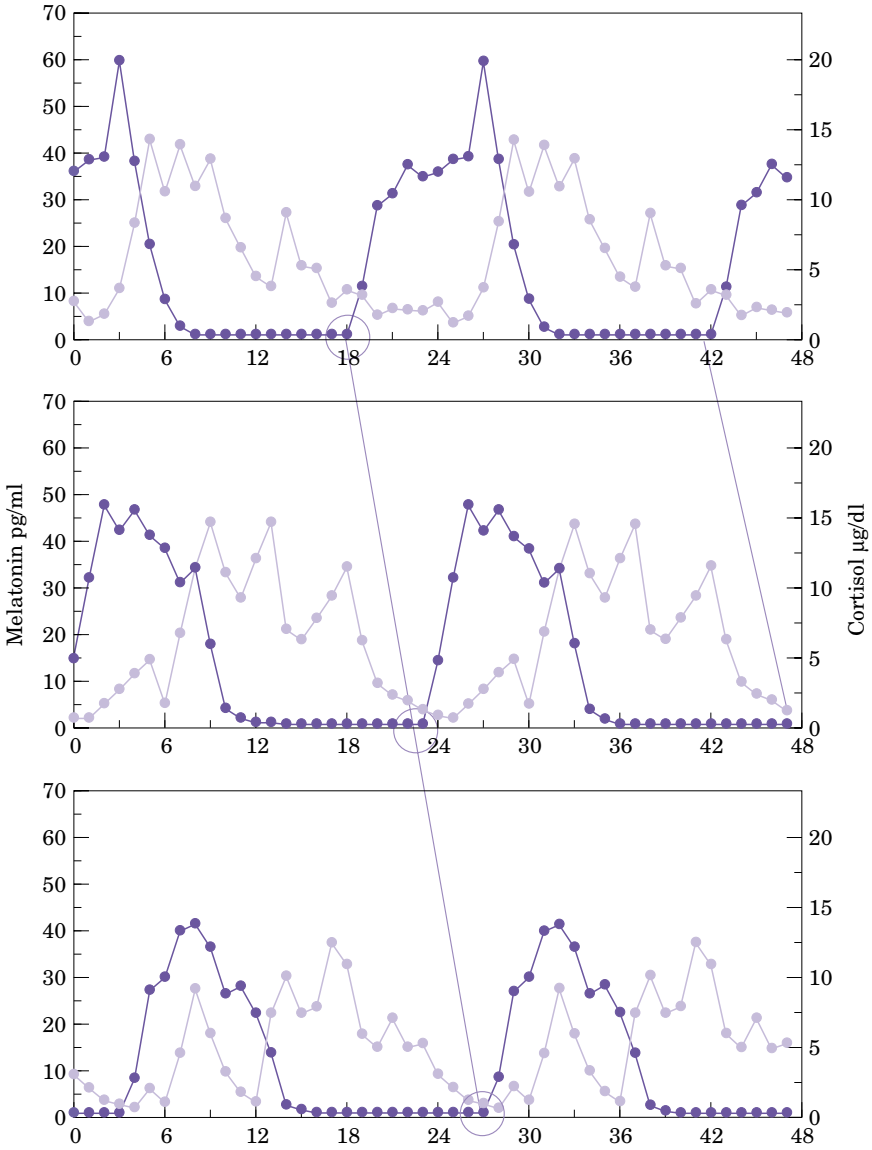

Figure 2 Melatonin and cortisol profiles in a totally blind person with free-running rhythms. Melatonin (dark circles) and cortisol (light circles) data from a blind person studied approximately every 2 weeks are presented. On each of the 3 study days, data are plotted on a repeated 24-h interval scale. A straight line is drawn through the melatonin onsets. The phase of melatonin production delayed an average of 0.3 h each day, thus we concluded that this subject had a free-running rhythm with tau = 24.3 h. Although the plasma cortisol rhythm also free ran with a similar tau, and appeared to be phase-locked with the melatonin rhythm, phase was more obviously discernible in the melatonin rhythm.

above 10 pg/ml, shifted 0.3 h per day; therefore, the circadian period was determined to be 24.3 h. The cortisol rhythm also shifted at the same rate, but simple inspection illustrates that the melatonin onset provides a much more precise estimate of circadian phase.

In 1992, we reported on a series of 20 newly recruited totally blind people, living in normal society [17]. The causes and duration of blindness varied greatly. Circadian rhythms were assessed primarily by serial assessments of the MO at 2–3-week intervals. When analysing the results, we classified the rhythms as suggested by Lewy and Newsome [14]: if the MOs consistently occurred at a normal phase, subjects were classified as "entrained, normal phase" ($n = 3$). (One of these subjects had a pupillary reflex and thus had some intact photic input to the brain stem even though he was

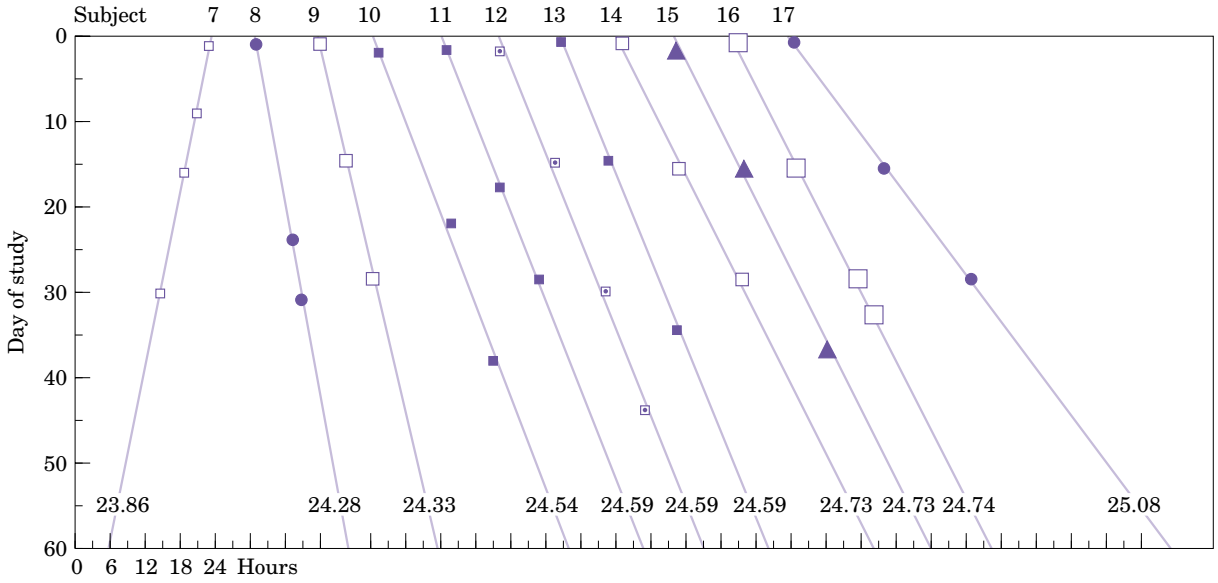

Figure 3 Melatonin onsets and circadian periods in 11 totally blind subjects with free-running rhythms (Reprinted with permission [17]). In this group of totally blind subjects, the melatonin onsets and regressions derived for each subject are shown. (The intercepts are evenly spaced so that the data could be displayed more clearly.) The calculated circadian period for each subject is listed with each regression. The slope of the line is proportional to the circadian period; a vertical slope would indicate a period of 24 h (normal entrainment).

subjectively blind.) If MOs occurred consistently at the same time but at an atypical phase, they were classified as "entrained, atypical phase" ($n = 3$). If MOs did not seem to follow a discernable pattern, they were classified as "unstable" ($n = 3$). If the MO shifted in linear proportion to the time between sampling, subjects were classified as "free running". This was the most common pattern ($n = 11$).

In Figure 3, the MO data for each of the 11 subjects with free-running rhythms are plotted separately. A regression line that describes the free-running circadian period [circadian period (tau) = 24 $\pm$ the slope] is drawn through the MOs for each subject. The intrinsic circadian period appears to be a stable trait for each individual but varies between individuals [mean = 24.55 (SD) $\pm$ 0.31 h; range 23.86–25.08 h]. One of the subjects had a tau less than 24 h; it is interesting that she was the oldest subject tested (see discussion below regarding the effects of age on circadian period). We were unable to discern any relationship between age of onset, duration of blindness, cause of blindness or regularity of daily habits, and the pattern of melatonin rhythms in these free-running subjects.

Klerman *et al.* recently reported that a smaller proportion of their subjects were free running – just six of 15 totally blind subjects [18]. The circadian period in their sample ranged from 24.1 to 24.5. In a much larger sample, Lockley *et al.* assessed circadian rhythms in 49 blind individuals in England by measuring the urinary metabolite of melatonin, 6-sulfatoxymelatonin at regular intervals [19]. The sample contained a mixture of subjects ranging from limited vision and light perception ($n = 19$) to no light perception (NLP) ($n = 30$). Among the NLP subjects, about one-third had both eyes, one-third had one eye present and one-third was bilaterally enucleated. The majority of the subjects with some visual perception had normal circadian rhythms. Conversely, most NLP subjects had abnormal rhythms; of these, over half were free running. The incidence of abnormal rhythms increased in subjects with either one or both eyes absent.

In summary, although insomnia and sleep complaints are common in the blind, circadian rhythm abnormalities are seen mainly in totally blind people. Several patterns have been described, but the most common pattern in the totally blind is a free-running rhythm.

CLINICAL SYMPTOMATOLOGY

Among BFRs, not everyone suffers sleep symptoms to the same degree. For some, it is the most disabling aspect of blindness; they dread the days

and weeks of sleeplessness and daytime fatigue. It is like having severe and prolonged jet lag that inexorably recurs. On the other hand, some individuals with comparable circadian desynchrony have minimal complaints; their abnormal rhythms may be appreciated only because they volunteered for a research study. Recurrent bouts of daytime napping (as the endogenous sleepiness rhythms passes through the daytime hours) is a striking feature in BFRs [19–21] and having the freedom to nap may ameliorate the symptoms.

Some blind people with free-running rhythms give up trying to sleep at night; instead, they sleep "in tune" with their body clock on a non-24-h sleep–wake schedule. Because they synchronise their sleep with other body rhythms, they presumably have less insomnia and sleep deprivation, but their social and occupational life obviously suffers. Very rarely, non-24-h sleep–wake cycles are also seen in sighted people [22–24]. The clinical features are quite similar to blind people on a non-24-h sleep–wake schedule; however, sighted people often have a reclusive lifestyle and personality idiosyncrasies that may contribute to the behavior.

The following are excerpts from a letter from a totally blind person with free-running circadian rhythms (reprinted with permission [25]). At the time, she was 44 years old and had a history of visual problems beginning in childhood, with the development of total blindness at age 24:

"Late in my pregnancy I had two or three eye hemorrhages. The last one occurred the day I went into labor. I lost all my light perception and never got it back. A few months later, I had the eye surgically removed because it had always given me pain and headaches and had now become completely useless for vision.

I also began to have trouble sleeping late in my pregnancy, and I assumed the pregnancy was the cause. However, even after the baby was born, I had terrible bouts of insomnia. It took me several years to figure out and admit that these bouts were cyclical and that, when they went away, they would always come back. Without calendaring my pattern, I figured out that I could sleep more or less normally for about 2 months. The insomnia came then and lasted about 4 weeks. Sometimes it was shorter or longer, apparently exacerbated by stress.

The first sign of insomnia is that I cannot get to sleep at a reasonable hour of the night. I need to stay up later, or I will not be able to sleep. It reaches a point where I cannot sleep all night and must then get up and go to work. I would be able however to sleep all morning (fall asleep at 06:00 and sleep till 12:00 or 13:00).

The cycle works its way around the clock. In a little while, I need a late morning nap if I can get it (10:00 to 13:00 or 14:00, ideally). Later, I sleep beginning early in the afternoon. Next, I am desperate to take a few hours nap as soon as I get home from work (17:00 or 18:00). After that phase, I just need to go to bed early. I begin to snap out of it when I can sleep 21:00 to 02:00 or 03:00. . . .

When I first developed this condition, I went to doctors for help. They did not understand it and gave me bad advice. I was treated as a neurotic housewife, given strong sedatives and told to give up my afternoon naps. I tried one or two sedatives before throwing them away, since they turned my brain to jelly. I tried giving up naps, but after a few sleepless nights, I began to hallucinate. . . . Being blind is OK although something of an inconvenience. Having a free-running sleep cycle can be awful."

DIAGNOSIS

Formal diagnostic criteria

There is no specific category in the nomenclature for sleep problems in the blind, but BFRs will often meet criteria for the formal diagnosis of a non-24-h sleep–wake pattern (see Table 1) [26].

These criteria need some elaboration. For one thing, symptoms are expected to vary as underlying circadian rhythms beat in and out of synchrony with the 24-h solar and social day. As described in the ASDA manual [26]:

". . . In the long run, their sleep phase periodically travels in and out of phase with the conventional social hours for sleep. When 'in phase', there may be no sleep complaint and daytime alertness is normal. As incremental phase delays in sleep occur, the complaint will consist of difficulty initiating sleep at night coupled with over-sleeping into the daytime hours or inability to remain awake in the daytime. Over long periods of time, the patient therefore alternates between being symptomatic and asymptomatic, depending on the degree of synchrony between his (sic) internal biological rhythms and the 24-h world.

Most patients . . . attempt to sleep and arise at

Table 1

International Classification of Sleep Disorders for Non-24-Hour Sleep–Wake Syndrome (780.55-2)

A. Primary complaint of either difficulty initiating sleep or difficulty in awakening.
B. Progressive delays of sleep onset and offset with the inability to maintain stable entrainment to a 24-h sleep–wake pattern.
C. Presence of the sleep pattern for at least 6 weeks.
D. Evidence of a progressive sequential delay of the sleep period by:
   1. Polysomnography performed over several consecutive days on a fixed 24-h bedtime and wake-time schedule,
   2. Continuous 24-h temperature monitoring over at least 5 days that shows a progressive delay of the temperature nadir.
E. Does not meet criteria for any other sleep disorder causing inability to initiate sleep or excessive sleepiness.

conventional social times. This produces progressively less sleep, with secondary daytime sleepiness interfering with functioning at work or at school. In addition, sleep may be skipped for 24–40 h, followed by sleeping for 14–24 h without awakening. . . ."

Using both daily diaries and wrist actigraphy monitoring, Lockley *et al.* have shown that the most sensitive indicator of a circadian rhythm desynchrony in BFRs was daytime napping [20, 21, 27]. In addition, there were transient advances and delays in sleep timing that paralleled the timing of melatonin secretion.

The formal diagnostic criteria call for documentation of the non-24-h rhythm using either laboratory sleep or temperature monitoring (Criteria D, Table 1). This is a rather difficult criterion to meet outside of a research setting. In the future, there may be simpler ways to document a free-running rhythm (for example, periodic measurements of salivary melatonin levels). Currently, the diagnosis can be presumed on the basis of periodic insomnia (obtained by history or sleep diary) associated with daytime napping in the context of total blindness.

Sleep and total blindness in children

Anecdotally, people who were blind from birth relate stories of "driving their parents crazy" with irregular sleep habits, but surprisingly little is written about this problem in the medical literature. Perhaps it is discounted by pediatricians as a variant of common childhood sleep difficulties. It may be unfairly perceived as a lack of discipline by parents. Likewise, school performance in totally blind children may suffer because of classroom sleepiness. Moreover, some children manifest sleepiness, not by taking naps, but by becoming hyperactive.

As totally blind children mature, their ability to maintain a more regular schedule can be expected to improve, but the symptoms of an underlying circadian disorder may become more subtle, with periodic fluctuations in mood, alertness and bedtime preferences. Some degree of flexibility on schedules remains appropriate.

CIRCADIAN RHYTHM SCIENCE: LESSONS FROM THE BLIND

What have we learned, and what might we learn about the human circadian system by studying circadian rhythms and sleep in blind people? Below are listed some of the conceptual issues on the circadian science research agenda in which research in blind people has already or could, with further investigation, influence knowledge and understanding. These issues are as relevant to sighted people as to the blind.

How important is light for entrainment human circadian system?

For some time it was thought that the human pacemaker was quite different from other species; that is, more sensitive to social cues or to the timing of sleep, than to light. The tide of scientific opinion has shifted as the potent phase-resetting effects of bright-light exposure have become appreciated [28, 29].

It is quite remarkable that many (possibly most) totally blind people cannot entrain their circadian rhythms to a 24-h day, despite abundant access to informational time cues such as clocks, radios, social interactions, regular sleep schedules or exercise. This failure to entrain despite access to temporal information is a strong argument for the paramount importance of light as a circadian time cue in humans. As discussed below, the timing of sleep and activity may have some direct influence on the pacemaker, but it is possible that sleep exerts its main effect

on the circadian system by gating the timing of light exposure (people turn out the lights and close their eyes when they sleep).

Although the occurrence of free-running rhythms in totally blind people has underscored the importance of light, how can normal entrainment in totally blind people be explained? One possible explanation may involve a residually intact RHT. Czeisler *et al.* [30] found bright light induced suppression of endogenous melatonin in three blind people, and concluded that photic information was still conveyed to the circadian system in these patients, even though there was no conscious light perception. None of these subjects were free running at the time of the study, nor did they have a history of sleep disorders. A small series of patients who were consciously blind from ceroid-lipofuscinoses were also shown to have normal melatonin suppression tests [31].

What is the role of non-photic time cues on the circadian system?

Although many (perhaps most) totally blind individuals have free-running rhythms, how is it that some appear to be normally entrained? Are some especially sensitive to non-photic cues? Which of the non-photic cues are important: sleep schedule, activity or social interactions [32]?

Klerman *et al.* recently conducted a detailed study of 15 blind subjects who lacked subjective light perception and had no suppression of melatonin secretion following bright-light exposure [18]. Nevertheless, nine out of 15 were able to maintain entrainment to the 24-h day, although the timing of entrainment was atypical in four of the subjects. To explore the possible mechanisms of entrainment in this series, two of the subjects were exposed to bright light that would have produced major phase shifts in sighted people. Eight-hour exposures centered on the core body temperature minimum did not shift rhythms in these subjects, ruling out photoreception (ocular or non-ocular) as the mechanism of entrainment.

One subject with a circadian period very close to 24 (24.1) was then tested in a time-isolated environment in which sleep and activity were scheduled to a 23.8-h day. This protocol advanced both temperature and melatonin rhythms, suggesting that non-photic time cues were having an effect on this blind subject. A second subject with a similar intrinsic period of 24.1 h was placed on a 24.8-h rest/activity schedule, but this failed to alter the circadian period which continued at 24.1 h. In summary, Klerman *et al.* have generated evidence that non-photic cues may influence free-running rhythms in some totally blind people [18]. More research is needed on this question.

Are some blind people "pseudo-entrained"?

In some totally blind people, the intrinsic circadian period may be so close to 24 h that they appear to be entrained, but are, in fact, free running. Such individuals might be termed "pseudo-entrained". However, if the intrinsic period were even slightly different from 24 h, they would eventually drift to a new circadian phase. Testing this hypothesis requires repeated monitoring of circadian phases over a long period of time. Recently we studied a blind subject

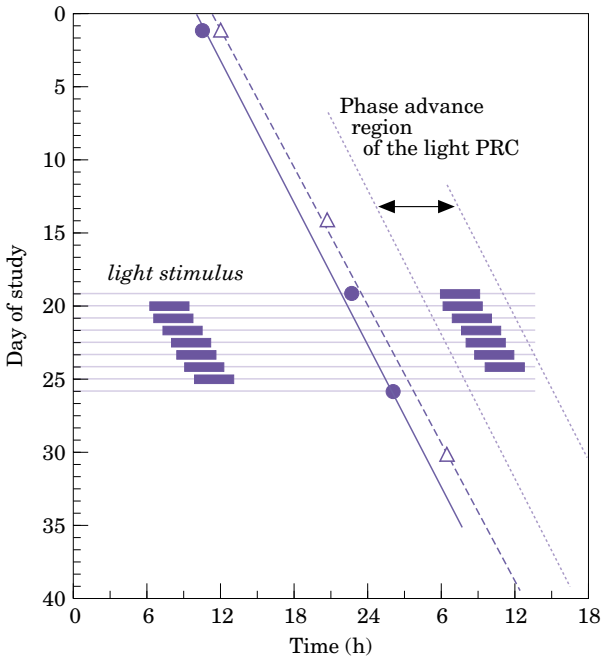

Figure 4 Extraocular light treatment given to a totally blind subject with free-running melatonin rhythms. The circadian rhythms of a 57-year-old totally blind man were assessed by measuring the melatonin onsets (MOs) during a pre-treatment baseline (triangles) and then during a 7-day, 3 h per day, treatment with extraocular light exposure (closed circles). The light stimuli are shown as rectangles and are double-plotted; light exposure was delayed 30–45 min per day so that it would coincide with the phase advance portion of the light phase response curve. Extraocular light exposure did not appear to produce a significant change in this subject's free-running rhythm.

whose MO was found to be at about 14:00 (7 h earlier than normal) on the three times it was measured at bi-weekly intervals (unpublished data). When we measured it again 6 months later, it remained at 14:00. We concluded that his circadian rhythms were truly entrained at an atypical phase. Entrainment at an atypical phase remains unexplained.

What about extraocular light exposure?

Another possibility is that entrainment might occur via extraocular photoreceptors. Recently Murphy and Campbell have reported that a light pad placed behind the knee can shift the rhythms of sighted people who were kept in complete darkness [33]. If this mode of light exposure can also shift rhythms in blind people, it would provide strong evidence for an influence of extraocular light on the circadian system, and would be a practical treatment for blind people with free-running rhythms. We attempted to replicate this finding by having a 57-year-old male BFR wear light pads (Biliblanket Plus® [Ohmeda]) behind the knees 3 h per day (as was done by Campbell and Murphy [33]) at home for 7 days. The timing of the exposure was shifted 30–45 min each day so that the light exposure would remain (assuming no immediate shifts) on the phase advance region of the light phase response curve (PRC). As seen in Figure 4, the baseline circadian period for this subject was 24.63 h and the post-treatment period was 24.61 h; i.e. there was no apparent phase shifting effect of the extraocular light exposure (unpublished observation). Blind subjects are ideal candidates for studies of extraocular light exposure experiments and more subjects should be tested.

How much light is needed for entrainment in partially blind people?

As described above, Lockley *et al.* studied melatonin rhythms in 49 blind subjects [19]. Fourteen out of 19 subjects with light perception had normal rhythms; none of the remaining five with abnormal rhythms had free-running rhythms. Seventeen out of 30 with no light perception had free-running rhythms. It appears that even a small amount of photic input is sufficient for entrainment, and that free-running rhythms are observed primarily in totally blind people. These data do not support the concept that low light levels (as may occur in institutional settings) produce circadian rhythm abnormalities.

Is there a separate and distinct retinal photosensor that mediates RHT signaling?

At one time it was assumed that rods were the photoreceptors because sensitivity to suppression of melatonin occurred in the blue-green spectrum (509 nanometers) [34]. However, this finding has been called into question on several counts. First, scotopic vision is saturated (non-functional) at high light levels, while bright light is necessary for melatonin suppression. Furthermore, studies of mice strains with hereditary retinal degeneration that destroys all of the rods suggest the circadian phase-shifting effects of light may be mediated by the residual cones or even by some, as yet, unidentified retinal photoreceptive element [35]. More research is needed on the question of which photoreceptive element is critical for the RHT.

What is the intrinsic circadian period of the human circadian pacemaker?

It is difficult to design experiments that unequivocally reveal the intrinsic period of the human circadian pacemaker. The original estimate was about 24.5 and was obtained from the observations of spontaneous desynchrony reported by Ashoff and Wever in their classical studies of temporal isolation in underground bunkers [36]. Recently, estimates of tau of about 24.2 h were obtained using "forced desynchrony" protocols [37]. It has been argued that the forced desynchrony method provides a more accurate estimate of tau because subjects are not free to choose bedtimes, which could structure the light–dark exposure and shift rhythms. The average free-running circadian period in blind people is remarkably similar to the tau observed in the early bunker experiments; in our series the average tau was 24.5. In the Lockley *et al.* series [19] the average tau in the free-running subjects was also 24.5 (range 24.13–24.79). Further research is needed to resolve the differences in tau estimated by these different approaches.

Does the circadian period change with age?

Teenagers and young adults tend to be "owls" (preferring later bedtimes and tending to awaken later), while older people tend to be "larks" (preferring early bedtimes and tending to awaken early).

It has been suggested that this tendency is the result of a circadian clock that speeds up with age (has a shorter tau).

We had the opportunity to monitor melatonin rhythms in six totally blind men twice after an intervening interval of about a decade [38]. All six subjects exhibited a slightly longer circadian period in the second assessment (mean increase $\pm$SD of 0.13 ± 0.08 h; $P<0.01$). In four subjects, 95% confidence intervals of the differences in the circadian period were non-overlapping. These findings do not support the commonly held view that the circadian period gets shorter during human aging. In fact, the period appears to lengthen slightly during at least one decade in mid-life. Furthermore, the effects of age seem to be quite small in comparison to the differences between subjects which may be a reflection of genetic factors.

Is there more than one circadian pacemaker?

If one master clock drives all the circadian rhythms, the timing of the body temperature, cortisol and sleep-propensity rhythms can be inferred from the melatonin rhythm. To investigate this hypothesis, we measured several circadian rhythms concomitantly in one totally blind individual [39]. Melatonin and cortisol were measured from serial blood samples, and body temperature from a continuous rectal thermometer. In addition, we measured the endogenous sleep-propensity rhythm using an ultra-short ("7/13") sleep–wake schedule [40]; the results are shown in Figure 5. This experiment documented that a person who maintained a conventional 24-h schedule nevertheless had melatonin, cortisol, temperature and sleep-propensity rhythms that were free running in concert with a period of 24.5 h.

At one time it was suggested that different circadian rhythms may under certain circumstances develop different and distinct periods (a form of "internal desynchrony"). This concept requires that each rhythm has its own slave oscillator that becomes uncoupled from the master oscillator. Our data from blind people appear to support the concept of a single oscillator that generates all the rhythms; rhythms can appear to be dissociated because they are differentially evoked by uncontrolled sleep and activity (masking effects). Skene *et al.* have also shown that melatonin and cortisol secretion are phase locked in BFRs [41].

What is the relative contribution of circadian and homeostatic influences to overt sleep and are there individual differences?

According to the prevalent models of sleep regulation, sleep propensity is mainly dependent on a build up of sleep drive related to prior wakefulness (process "S", the homeostatic mechanism) and on the modulation of alertness, which is generated by the circadian pacemaker (process "C", the circadian mechanism). It is likely that the relative importance of the circadian and homeostatic processes may be different between individuals, and within an individual at different times of their life. Currently, one of the most elegant ways to differentiate circadian from sleep-dependent processes is to have subjects live in temporal isolation on a sleep–wake schedule that is beyond the range of entrainment; the so-called "forced desynchrony" protocol [37]. In this way, subjects sleep at every phase of the circadian cycle, and the relative contributions of circadian and homeostatic influences can be mathematically parsed. These experiments have been very useful for documenting certain characteristics of the circadian system, but they are labor intensive and expensive.

Similar data can be obtained in BFRs without the necessity of employing a temporal isolation facility. For example, Figure 6 shows cortisol data obtained from a group of BFRs plotted on "circadian time" (with reference to the MO) versus clock time. Like subjects on a forced desynchrony protocol, BFRs sleep at every phase of the circadian cycle; when plotted on circadian time (with reference to the MO), the effects of sleep and activity are cancelled out as they are equally distributed over all time points. Also, in this example, the large number of samples smooth out any pulsatile secretion. The resulting profile shows that the circadian rhythm for cortisol secretion is a linear function, increasing for 12 h and then decreasing for 12 h. This is an example of demasking; that is, removing any distorting influence of sleep and activity on a circadian rhythm, and could be applied in principle to any circadian rhythm. The study of sleep in BFRs could in principle tease apart the homeostatic and circadian

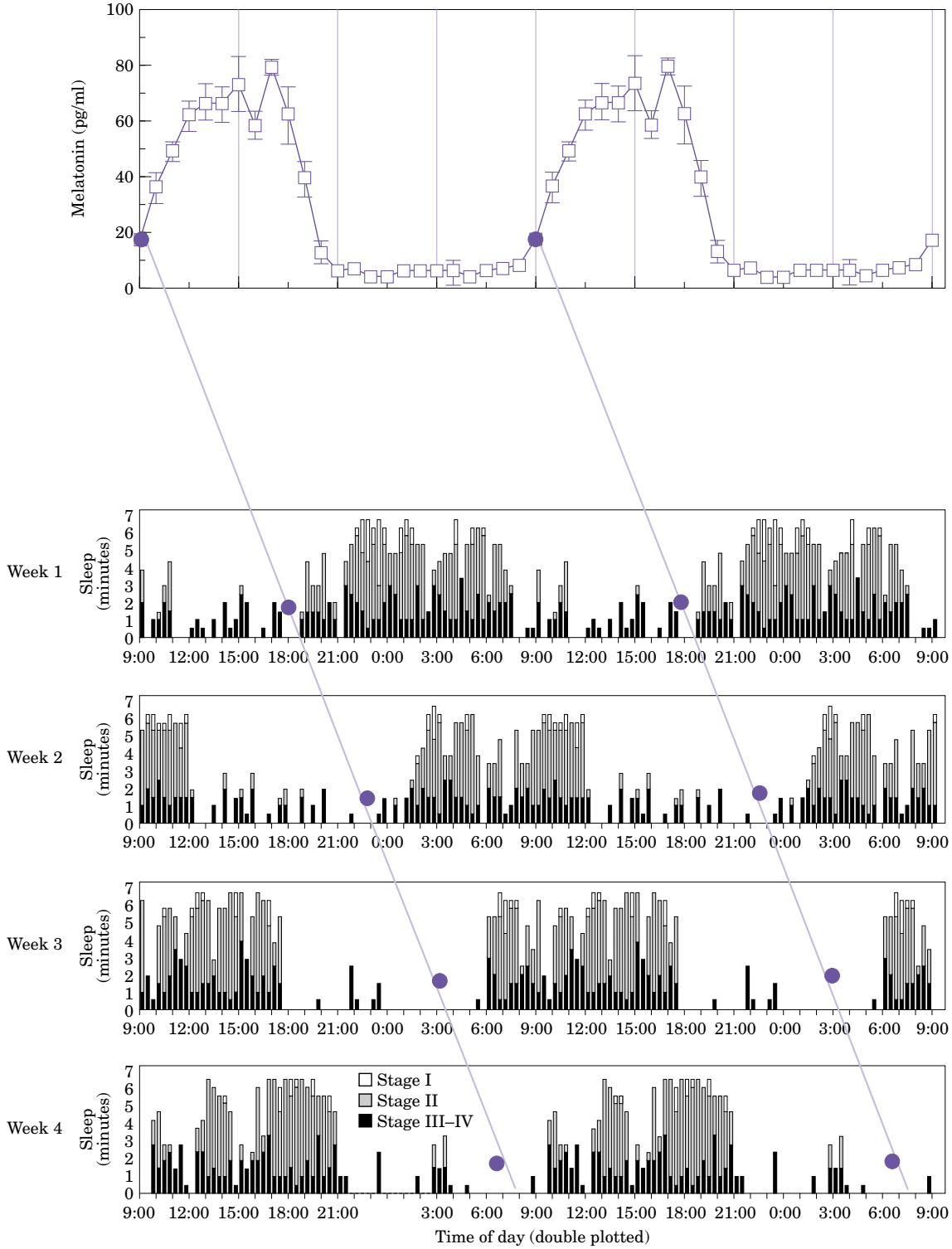

Figure 5 Sleep propensity rhythm free runs in parallel with the melatonin rhythm (Adapted from Nakagawa [39]). The upper panel shows the melatonin profile (double plotted) in a totally blind individual with the filled circles indicating the timing of the melatonin onset (MO). In the lower four panels, the MOs are represented by black circles only. Sleep propensity rhythm was measured for a 24-h period on 4 consecutive weeks using the ultra-short sleep–wake protocol developed by Lavie *et al.* Each column represents the total sleep time for a 7-min nap opportunity which was provided every 20 min (there were 72 nap opportunities each test day). The data are double plotted. This experiment illustrates how sleep propensity free runs with the same circadian period as the melatonin rhythm, presumably generated by the same circadian pacemaker.

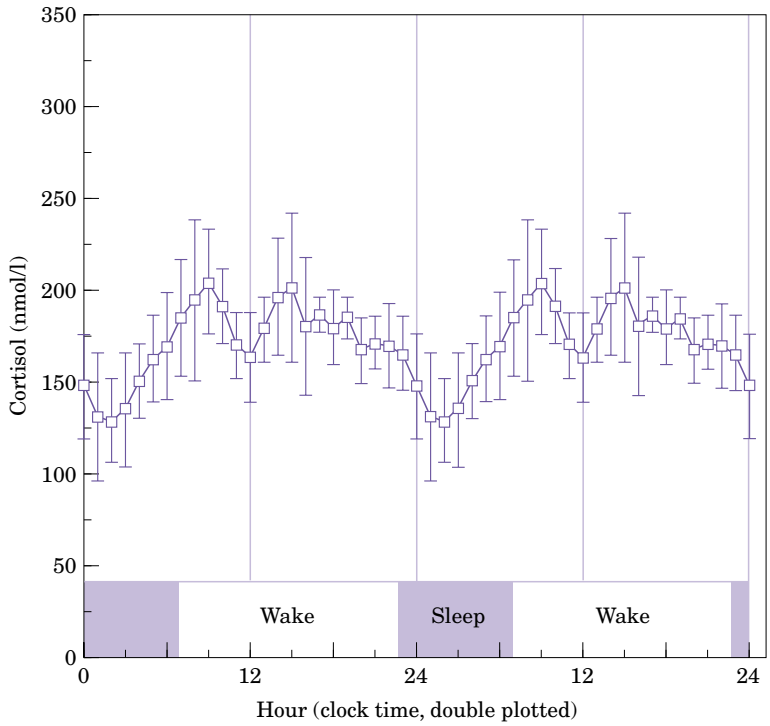

Figure 6a Cortisol rhythm plotted on "clock time" (Reprinted with permission [17]). Cortisol data from four free-running blind people was averaged and double plotted on a 24-h time scale. The data were obtained from four subjects who had a total of 33 24-h profiles. A weighted average was used so that each subject and each circadian phase of melatonin production was represented about equally. Variability due to pulsatile secretion is averaged out. Three-point smoothing was used to construct the final graph. A diurnal variation in cortisol concentration is apparent. The nadir is at the typical sleep time and may reflect masking. The highest values are during the active portion of the day.

contributions within subjects, and provide insights into individual differences.

TREATMENT AND MANAGEMENT ISSUES

Recognition and education

As in most kinds of clinical care, accurate diagnosis of sleep complaints is the place to start. As mentioned above, there are many causes of sleep disturbances in the blind (as in sighted people), so that circadian rhythm disturbances cannot be assumed to be the primary problem. In blind people with some light perception, the risk is probably no higher than for the general population. In totally blind people, the risk is probably about 70% (higher if both eyes are removed). At the present time, it is not easy to confirm a diagnosis with laboratory testing, but as melatonin assays become more accessible (for example, salivary assays), it should become practical.

The next step is education of the patient and family. The concept of a "free-running" rhythm going "in and out of phase" with the 24-h circadian cycle is not an easy one to grasp, and it may take some repeated explanations. Most patients are quite relieved to know that their sleep problems have an understandable physiological basis. One can advise families to encourage naps and flexible bedtimes. Most adult BFRs are able to conform to the 24-h day, but for young BFRs there may be no alternative to allowing the child to remain awake in a safe environment at night and sleep during the day when they are out of phase. Some parents go on "shifts" to supervise their children with irregular sleep times. It is unfortunate if parents view their children's sleep problems as manifestations of oppositional behavior, and take an excessively rigid approach to scheduling.

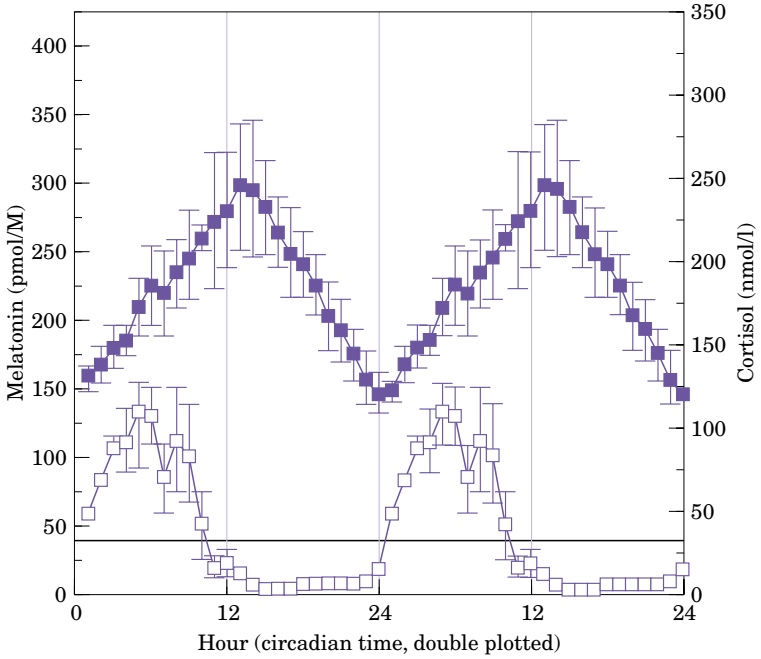

Figure 6b Cortisol rhythm plotted on "circadian time" (Reprinted with permission [17]). The cortisol data presented in Figure 5a are re-plotted so that the data are normalised to circadian time; that is, each cortisol profile begins at the time of the melatonin onset. A circadian day is defined as the time between two melatonin "onsets". A circadian hour is defined as a circadian day divided by 24. The fraction of samples drawn during sleep and wake is about the same for each circadian time point; thus the masking effects of sleep and activity are averaged out (variability due to pulsatile secretion is also averaged out). Three-point smoothing was used to construct the final graph. The cortisol begins to rise at the time of the melatonin onset and begins to fall at the time of the melatonin "offset". There is a remarkably linear rise and fall in average cortisol concentrations.

Entraining the clock with non-photic time cues

Is it possible to entrain the circadian pacemaker with non-photic cues? Experiments with animals such as rodents and hamsters indicate that exercise, activity, and social interaction may sometimes be able to entrain the circadian system [42] but these results have to be applied with caution to humans. As discussed earlier, initial temporal isolation experiments suggested that humans were especially sensitive to social and informational time cues; however, sleep may have gated exposure to light. In our previously described sample [17], eight of the eleven subjects with free-running melatonin rhythms had regular employment that required a regimented lifestyle; evidently, regular sleep and wake times were insufficient to maintain entrainment.

If the intrinsic rhythm is close to 24 h so that a small corrective phase shift would be sufficient, non-photic time cues may enable some totally blind individuals to maintain entrainment. For example, Okawa *et al.* used forced awakenings with blind retarded children and was able to regularise sleep in two out of four; however, it was unclear if rhythms other than sleep were entrained by this procedure [16].

As discussed above, Klerman *et al.* were able to entrain a BFR with an intrinsic period of 24.1 h to a 23.8 h sleep–wake schedule imposed in a time-isolated environment [18]. However, a second subject with a 24.1 circadian period failed to entrain to an imposed 24.8-h sleep–wake schedule. The sleep–wake schedule would seem to be the most likely non-photic time cue.

Pharmacological entrainment

It is clear that maintenance of a 24-h sleep–wake schedule is insufficient to entrain most totally blind people; there is therefore a pressing need for a pharmacological tool. Melatonin administration appears to be the most promising approach. In 1983,

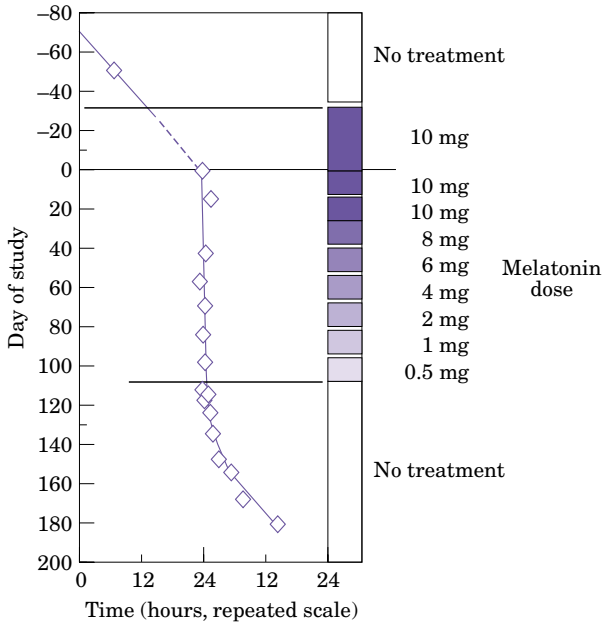

Figure 7 A clinical trial of melatonin entrains the free-running rhythm of a totally blind subject (Adapted from Sack *et al.* [51]). Plasma melatonin onsets are plotted for a subject who was treated with melatonin using a "step-down" dosing protocol. Melatonin (10 mg) was given nightly beginning 33 days before the first post-treatment assessment of plasma melatonin onset (day 0). Starting with day 28, the dose of melatonin was reduced every 2 weeks using the schedule shown. Plasma melatonin onsets during treatment remained consistently at about 2400 for 120 days, indicating entrainment, even with a dose as low as 0.5 mg. After treatment was discontinued, it took about a month for the circadian period to return to baseline, suggesting a persisting alteration of the circadian period (an "after effect" [52]).

studies by Redman *et al.* showed that daily injections of melatonin could entrain free-running rats (maintained in constant darkness) if the injections were given just before the onset of the animal's subjective night [43]. Based on this finding, we conducted a small clinical trial showing that oral melatonin (5 mg) given to melatonin at bedtime could modify endogenous free-running rhythms, producing cumulative phase advances of up to 16 h after 3 weeks of treatment [44]. However, we did not produce entrainment in any of the five subjects treated. In the same publication, we reported a case involving self-administration of melatonin for several years, which apparently resulted in normal entrainment [44]. There are other published reports of successful melatonin treatment of circadian sleep–wake disorders in blind people [15, 45–49].

Clock-resetting from melatonin administration probably involves melatonin receptors in the SCN (Fig. 1). In sighted people, we have shown that melatonin administration can cause both advances and delays in the endogenous circadian system depending on the timing of administration [50]; this could result in relative entrainment for blind subjects even if melatonin were unable to maintain a strict 24-h rhythm.

Recently, we renewed our efforts to entrain BFRs with melatonin administration [51]. Seven totally blind subjects who had free-running circadian rhythms were given 10 mg melatonin or placebo an hour before bedtime, for 3–9 weeks. The study was a cross-over trial, balanced for order of treatment. The timing of endogenous melatonin production was measured as a marker for their circadian phase and sleep was monitored by polysomnography. The circadian period of 24.05 ± 0.12 h during melatonin administration was significantly different ($P<0.001$) from the average circadian period during placebo administration of 24.43 ± 0.20 h, but was not significantly different from 24.00 h ($P=0.12$). One subject failed to entrain; it is noteworthy that he had the longest baseline circadian period (24.9 h). Following entrainment, when the subjects were sleeping at a more normal circadian phase, wake after sleep onset was lower ($P=0.02$) and sleep efficiency was greater ($P=0.06$).

Three subjects were entrained a second time with 10 mg melatonin, and the dose was then gradually reduced to 0.5 mg (an example is shown in Fig. 7). These subjects maintained entrainment for a 3-month interval, suggesting that long-term benefit with continuing treatment is likely. The lowest dose tested in this "step-down" protocol (0.5 mg) generates plasma melatonin concentrations that are close to the physiological range and are therefore presumed to be very safe. Based on these preliminary results, it would appear that high-dose (10 mg) melatonin treatment could be used to capture a free-running rhythm, but that a lower dose (0.5 mg) appears to be sufficient for maintenance. After treatment was discontinued in one of the subjects, the circadian period gradually returned from a 24-h cycle to the pre-treatment free-running period, suggesting that entrainment had produced persistent effects on the pacemaker ("after effects" [52]).

Lockley *et al.* have also successfully entrained

free-running rhythms in at least three (possibly four) of seven blind subjects treated with a 5 mg dose given nightly at 21:00 [53]. In their three subjects who continued to free-run, treatment was initiated during the phase-delay portion of the melatonin phase–response curve (PRC). They concluded that the phase at which treatment is begun may be a critical factor in response. If this conclusion is supported in a larger number of subjects, practitioners would need to accurately measure a patient's circadian period and phase so they could initiate treatment on the appropriate day(s) of the free-running cycle.

Currently melatonin is available in US health food stores under many different brand names. No therapeutic claims are allowed since melatonin has not been licensed as a drug, but the labeling typically implies that it benefits sleep or prevents aging. The usual unit dose is 3 mg, and formulations typically include vitamins and other added ingredients. Ingestion of 1 mg of oral melatonin will produce peak blood levels that are 10–50 times the concentration produced from pineal secretion; therefore, these preparations should not be considered physiological. However, up to 240 mg of melatonin have been ingested without significant acute toxicity [54], so melatonin can be considered remarkably nontoxic, at least in the short term. Recently, drug companies have begun testing compounds that are melatonin analogs or interact with the melatonin receptor.

Disconnecting the clock

The opponent process of sleep regulation proposed by Edgar *et al.* proposes that the circadian system exerts an alerting effect during the daytime (in diurnal species) that counteracts the accumulation of sleep drive [55]. We and others have drawn on this model to hypothesise that melatonin may promote sleep by dampening the circadian alerting effect [56]. This might explain why melatonin could improve night-time sleep in blind people when their rhythms are out of phase, even if it fails to entrain. Therefore, it is quite possible that melatonin administration at bedtime may benefit blind people with circadian rhythm sleep disorder by two mechanisms: (1) by resetting the body clock and promoting synchrony between internal rhythms and preferred sleep times; and (2) by directly promoting sleep and counteracting the alerting effect of the clock.

Other drugs may yield benefits via a direct sedative or stimulating effect. Research with shift workers may be relevant in this context because they have an analogous problem of sleeping and working out of tune with their endogenous rhythms. For example, short-term use of sedative hypnotics has been found to improve daytime sleep in night workers; however, benefits on wake-time alertness are not robust even if total sleep time is prolonged [57]. The risks of sedative use are minimal in the short term, but longer-term use is more controversial. However, since the insomnia associated with free-running rhythms is periodic and self-limited, a trial with sedatives may be indicated. Caffeine is a common-sense and easily available intervention for daytime sleepiness, and its alerting effects have been documented in studies with night-shift workers [57]. In summary, a combination of a short-acting sedative at night (for example, temazepam or zolpidem), and an extra amount of caffeine (250–400 mg) during the day may permit better functioning when symptoms are at their peak.

Whether to enucleate?

For some blind people, the eyes may become a burden. Pain, unpleasant phantom visual sensations (phosphenes) or cosmetic considerations may lead to the decision to enucleate. Should the possible circadian function of the eyes be considered in this decision? As mentioned above, some totally blind people have normal light-induced suppression of melatonin secretion (indicating functional neurosensory input to the hypothalamus), and therefore the eyes may be serving a role for circadian entrainment, even though an imaging function has been lost [30]. Enucleation for such patients might result in an iatrogenic circadian sleep disorder. Therefore, the decision to enucleate should involve weighing the benefits and risks, including loss of circadian entrainment. In difficult cases, a light-suppression test could be used to determine whether RHT function is intact.

SUMMARY

Totally blind people are prone to bouts of sleeplessness lasting for several days or weeks alternating with periods of normal sleep and alertness. The

severity of symptoms varies considerably among individuals and the periodic nature of the sleep symptoms may be overlooked. The underlying cause is circadian rhythm desynchronisation caused by the absence of photic input to the circadian pacemaker, resulting in free-running (non-24-h) circadian rhythms which go in and out of phase with 24-h sleep rhythms. It is important for the sleep specialist to recognise this problem and to educate blind people, their families and employers about its physiological basis. Melatonin administration is a promising non-photic method for entraining the circadian system. Sedative hypnotic agents can be used intermittently to promote sleep when the circadian system is out of phase with desired sleep times.

The occurrence of free-running rhythms in totally blind people has implications for a general understanding of the human circadian system. Most importantly, it underscores the fundamental importance of the light–dark cycle as a time cue for normal human entrainment. Studies in blind subjects can provide insights into the fundamental properties of the circadian system relevant to sighted people as well as the blind.

Practice Points

Free-running rhythms in a blind person are very likely if:

1. The person is totally blind.
2. There is a pattern of recurrent insomnia and daytime napping.

Recurrent insomnia and daytime sleepiness in blind patients with free-running rhythms can be alleviated with:

1. Avoiding an overly-rigid sleep schedule ("sleep when you can") and encouraging naps.
2. Short-term use of sedative-hypnotic agents.
3. Entrainment to a 24-h day using a daily dose of melatonin.

Research Agenda

1. Can totally blind people be entrained by non-photic environmental time cues? If so, which time cues are the most important?
2. Can extraocular light exposure shift circadian rhythms in blind people?
3. Why do some totally blind people entrain at an abnormal phase?
4. Are there individual differences in the strength of circadian versus homeostatic factors in the regulation of sleep?
5. What is the lowest effective dose of melatonin that can be used to entrain blind people with free-running rhythms?

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