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Light on Sleep

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Exposure to environmental light, whether during waking or sleeping hours, can adversely affect sleep. There is an emergent consensus that light affects sleep primarily by inducing phase shifts of the circadian clock. Sleeping in an illuminated bedroom can cause insomnia, and in such cases – whether or not a circadian disturbance has been verified – clinicians advise switching off the lights before recourse to medication. On the other hand, light can ameliorate insomnia. A task force of the American Sleep Disorders Association and the Society for Light Treatment and Biological Rhythms has concluded that appropriately timed exposure to light holds the promise of effective treatment for circadian sleep disorders, but clinical applications are still at a nascent stage [1–7]. For healthy young subjects, the task force found that ‘light exposure schedules [which] do not curtail sleep but induce moderate shifts of the endogenous circadian pacemaker ... influence the timing of sleep and wakefulness without markedly affecting sleep structure’ [5]. Although there have been marked successes in clinical treatment of sleep phase disturbances by light [8], long-term follow-up and controlled studies are still largely lacking. Relapses are common, if only because of poor patient compliance.

The urbanized lifestyle fosters minimal exposure to bright outdoor light, often measured in minutes per day [9]. One might therefore conjecture that insufficient light exposure – or ‘daylight deprivation’ – contributes to sleep

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disturbances. Daylight deprivation, however, is an ambiguous construct. Without refinement, it cannot be tied to specific sleep disturbances and corrective treatments. True, current light therapy emphasizes the use of intense artificial illumination within the lower range of full daylight ($> 1,000$ lx), with total daily doses that greatly exceed normal outdoor exposure [10]. Yet we are beginning to appreciate the effects of ever-dimmer illumination, well below the daylight range.

From the therapeutic vantage point, the specific temporal pattern of exposure of light and dark is of primary importance; light intensity per se may prove to be more of a modulating factor. Current treatment emphasizes exposures at the edges of the subjective night, when the phase-response curve (PRC) to light predicts advances (in the early morning) and delays (in late evening). Nevertheless, there is a clinical impression that increased midday light exposure – which has been presumed to fall into the ‘dead zone’ of the human PRC – can also provide a benefit. First, it can serve an activating or alerting function [3] that relieves daytime fatigue and the pressure to nap, thus contributing to nighttime sleep quality. Second, recent data indicate that midday light can indeed elicit phase shifts in normals [11, 12] and patients with seasonal affective disorder [13, 14], with possible benefits for nighttime sleep efficiency.

Visual Deficit Adversely Affects Sleep

Although the timing, efficiency and subjective quality of sleep may depend on the pattern of environmental light exposure, there are additional, joint effects of light intensity and ocular status. In standard living and working environments, people with progressive visual loss appear more vulnerable to sleep disturbance than those with normal ocular transduction. Based on a survey of the literature, it has been estimated that about 70% of those classified as perceptually blind experience poor sleep, even though the classifications of blindness differ across investigations [C.E. Remé, pers. commun.]. Some perceptually blind people retain the capacity for melatonin suppression to light [15], presumably through a small number of residual retinal photoreceptors. In such cases, circadian entrainment is possible, and exposure to light might forestall sleep disturbance.

Given severe visual deficit, with or without the circadian free-runs often seen in the blind [16], there are, however, many cases without sleep complaints. Sack et al. [16] speculate that in some cases irregular sleep is so ingrained that the person does not perceive it as abnormal or something to complain about. They found only approximately one-third of free-runners to experience peri-

odic sleep disturbance when the objective and subjective nights are out of phase. Some noncomplaining free-runners may follow schedules that allow for compensatory napping and irregular bedtimes. For others, the timing of sleep may be determined primarily by the somnostat, while the circadian influence is weak (see section on sleep regulation, below). In those who do not free-run, sleep disturbance might arise from factors secondary to blindness, such as poor sleep hygiene, unemployment and unstructured daily schedules. An additional factor is sleep disturbance associated with mood disorders, which presents a conundrum: Does light deprivation – or do difficulties with social adjustment – trigger depressed mood, for which disturbed sleep is a symptom? Or does light deprivation foster circadian phase shifts that result in disturbed sleep, for which depression is a symptom?

Recent experiments have concentrated on three classes of visual deficit: *absolute*, in which residual transmission is absent, as with enucleation; *perceptual blindness*, in which case a subset of patients maintain circadian light sensitivity and melatonin suppression to light, and *partial blindness*, which is often progressive, as in glaucoma, diabetic retinopathy, and maculopathy. The absolute cases are simplest to interpret. Skene et al. [17] showed that 5/5 bilaterally enucleated subjects showed free-running melatonin rhythms accompanied by increased sleep disturbance and daytime napping. Such napping was closely tied to the drifting peak of melatonin secretion, at which time subjects also report nighttime sleep disturbance [16]. Skene et al. [17] found that subjects with normal melatonin rhythms, including some who were completely perceptually blind, reported significantly less sleep disturbance than those unable to maintain entrainment. However, just as for sighted insomniacs, some totally and partially blind people experience chronic sleep disturbance regardless of circadian phase, and there are indications that vulnerability increases with visual deficit.

On the one hand, there may be a global light-deprivation factor, such that reduced transduction accounts for disturbances regardless of the specifics of ocular pathology. On the other hand, examination of specific ocular diseases, in which retinal receptor systems, optic nerve, etc., are differentially affected, may reveal functionally distinct subgroups whose sleep disturbance differs. For example, rod-specific deficits peripheral to the macular region might show lower association with sleep disturbance than macular deficits. If so, the cone system might be identified as the principal light transducer relevant to sleep, just as the recent animal literature suggests that cones selectively input the circadian system even in rod-dominant species [18, 19]. Indeed, a small number of cones in the peripheral retina, whose presence and distribution still await description, may subserve the first stage of photopic input to the retinohypothalamic tract, irrespective of macular cone density. In this context, one may well recollect the early findings of circadian entrainment in albino rats given

2-hour red light pulses below 1 lx [20], and residual cones in rat retina after massive destruction of the rods by bright light [21].

Although perceptually blind subjects report more extreme sleep disturbance than subjects with partial visual loss, the latter group shows more disturbance than those with normal vision. In a recent survey of young to middle-aged patients with maculopathy, diabetic retinopathy and other retinopathies, subjects rated subjective quality and continuity of nighttime sleep, feeling rested upon awakening, and propensity to nap [M. Müntener, S. Anderegg, C. Fasser, C.E. Remé: Sleep disturbances in patients with reduced vision and blindness; in preparation]. Those with binocular visual acuity loss > 90% showed greatest sleep disturbance relative to normal controls. Successively less disturbance was reported by those with 40–90% binocular acuity loss, and 50–90% monocular loss. The bilateral groups reported approximately 5 times as much sleep disturbance as controls. Another survey of elderly glaucoma patients showed significantly more atypical depressive symptomatology – which prominently includes daytime fatigue and difficulty awakening – than in age-matched controls, whereas the frequency of classical depressive symptomatology (dysphoric mood, anxiety, etc.) did not differ [22]. In a planned experiment, Charlotte E. Remé, Virginia F. Lubkin and I seek to determine the severity of sleep disturbance in cataract patients without retinal pathology, and potential correlations of such sleep with melatonin secretion patterns and electroretinographic response. Progressive visual loss resulting from cataract growth might be analogous to placement of light filters of increasing density in front of the eyes. If sleep disturbances were similar in cataract patients and the retinally partially blind, a simple light-input factor – rather than retinal pathology – would be indicated.

Graded visual loss, of course, is age-related for the population as a whole. Increased cloudiness of the lens and ocular media, and reduced receptor viability are part of the normal aging process, although there is great interindividual variability. A priority is to investigate the potential relationship of such visual loss with age-related sleep disturbance. Such loss is likely to be one of several interactive factors including propensity toward advanced circadian phase, and reduced melatonin secretion and slow-wave sleep.

A more subtle class of visual deficit may contribute to the winter depression and altered sleep of seasonal affective disorder: threshold elevations within the normal range. Given the therapeutic antidepressant response to light therapy, along with benefits for sleep, there was an early hypothesis that winter depressives would show reduced retinal light transduction. One positive indication was the significant but marginal reduction in the Arden ratio of the electrooculogram relative to normal controls [23]. However, comprehensive tests of ophthalmic function – which included electroretinogram, dark adapta-

tion, visual-evoked cortical potentials, etc. – found no significant differences [24]. A study of photopic and scotopic dark adaptation in patients and controls revealed wintertime threshold elevations in both groups [see 60]. It remains to be established whether the subset of subjects with the highest dark-adapted thresholds are most prone to increased sleep length or delayed sleep phase in winter, irrespective of depressed mood.

Deficits in light input – whether they result from ocular pathology or threshold elevations within the normal range – should not be taken to imply that the therapeutic solution is necessarily intense stimulation with light. We cannot dismiss the potential efficacy of dim illumination in maintaining entrainment, eliciting circadian phase shifts and melatonin suppression, and positively influencing sleep timing and quality. Consider, for example, that the effect of a light stimulus needs to be gauged against the pattern and level of background illumination [25]. Thus the functional specification of the stimulus is relative, not absolute. Even small daily phase shifts to dim light are probably sufficient to maintain entrainment, given free-running periods in the range of 24.3 h [for discussion, see 26].

Most prior research on light's effects on circadian rhythms and sleep, and the derived therapeutic methods, have relied on stimuli that are presented at constant intensity as rectangular 'pulses' (which may, however extend for many hours). The sections below begin to describe how the effects of low-level illumination might be potentiated by manipulating the time-rate-of-change of light intensity in artificial mimics of dawn and dusk.

The Dawn Signal Has Potent Alerting Effects

A Gradual Dawn Signal Enhances Zeitgeber Action by Comparison with Sudden Dark-to-Light Transitions

'Photoperiod' is usually defined as the interval between sunrise and sunset. There is also, however, plentiful light availability at the transitional edges of the 'scotoperiod'. Depending on season and latitude, twilights can last for several hours, covering the period of the PRC's maximum sensitivity. Animal experiments over the last three decades suggest that gradual dawn and dusk signals do affect entrainment phase and stability. For example, under a short photoperiod the onset of nocturnal activity in hamsters occurs hours earlier given twilights than given rectangular light-dark (LD) transitions [27]. Following entrainment to photoperiods of varying length, the lake chub shows a clear aftereffect in free-running period only when the preceding LD cycle is bracketed with twilights [28]. The rat, when allowed to self-select a darkened chamber ('burrow') or an 'outdoor' chamber with twilights, emerges selectively

during dusk and dawn for a precise balance of phase-delaying and advancing exposures that maintains 24-hour entrainment [29]. Given gradual dawn signals, the rat's morning peak of rod outer segment disk shedding – a circadian variable in the retina under control of a local oscillator independent of the suprachiasmatic nucleus [30] – occurs significantly earlier than under rectangular LD cycles [31]. Given twilights at both edges of the night, hamsters uniformly track an expanding LD cycle up to 26 h, but show free-runs under rectangular LD cycles [32]. Do such experiments presage development of novel light exposure regimens for humans?

The Dawn Signal, Presented to Sleeping Subjects, Is Antidepressant

People usually sleep in bedrooms that greatly attenuate or completely shield exposure to the outdoor dawn signal. The dusk signal – if it is experienced at all – occurs hours before bedtime, and typically is followed by late-evening exposure to artificial room light. Thus, the extent to which dawns and dusks affect sleep is not obvious. Patients with seasonal affective disorder (SAD) have responded therapeutically to artificial dawn signals presented in the darkened bedroom during the final hours of sleep on long winter nights [33, 34]. Although the simulated dawn is timed to mimic a springtime sunrise, its amplitude may be reduced to one-third that of the corresponding outdoor signal. Thus, patients might experience a maximum of 350 lx at the end of a simulated dawn, whereas the corresponding outdoor dawn would reach nearly 1,000 lx. Under these conditions, hypersomnic or phase-delayed patients can substantially advance their awakening. The typical awakening after adjustment to the dawn simulation regimen occurs near the end of the dawn, anticipating the moment of sunrise. Controlled studies have used nonnaturalistic light ramps (approximate log-linear increments) to simulate dawn, with clinical response gauged against placebo controls (far dimmer or briefer signals). Such 'faux dawns' also show distinct therapeutic benefits [35], with the rate and magnitude of clinical improvement similar to those of conventional postawakening bright light therapy. The amplitude of light stimulation required to achieve an antidepressant response is likely to depend on the 'shape' of the signal – its pattern of time-rate-of-change – in combination with the time of its presentation relative to the phase-response curve, the level of retinal dark or light adaptation, and sleep or wake state.

The Dawn Signal Elicits Circadian Phase Advances in Humans

After a week's presentation of a mid-spring dawn signal to sleeping patients with SAD, the melatonin cycle shows clear phase advances in onset, midpoint and offset [34]. In these clinical trials, patients were treated at home, but spent pre- and posttreatment nights in a sleep laboratory, when blood was sampled

under dim light conditions in the absence of the dawn signal. In another experiment, subjects received their first dawn presentation during melatonin sampling, and secretion was truncated starting at about the time of simulated sunrise. These data suggest that a single exposure to a dawn signal, rising gradually from near-darkness to a maximum of 250 lx, is sufficient to trigger complete melatonin suppression, and daily repetitions of the signal are sufficient to elicit phase advances in the hours range.

Konstantin Danilenko, Anna Wirz-Justice and I have begun systematic studies of the phase-shifting effects of the dawn signal, conducted under a modified constant routine. Healthy young males, without depression, were admitted to the laboratory for 2–4 days during which a constant routine was maintained during afternoon and evening, sleep was permitted at night, dawn simulation was presented in bed after awakening (i.e., to open eyes), and sedentary activities under dim light exposure were permitted in the morning and early afternoon. Rectal temperature was continuously monitored and blood samples taken for melatonin analysis during bedrest and sleep.

An initial case study provided within-subject controls (fig. 1). On one occasion the subject received a summer solstice dawn set for 50° N latitude. While the subject was asleep, light exposure began at 03:30 h at 0.001 lx (in the low range of astronomical twilight), using a halogen lamp diffuser. He was awakened between 06:00 and 07:30 h for observation of the dawn transition between 0.1 and 1,000 lx (upper nautical and civil twilight ranges), after which the daytime schedule commenced. In contrast to an uninterrupted baseline night with maintained darkness, the temperature rhythm showed a phase advance of 1.53 h. On a second occasion, the subject received a partial dawn exposure from 0.0001 to 0.1 lx followed by a 1.5-hour rectangular light pulse of 150 lx (equated for total illuminance, in lx·min, with the full dawn signal), which yielded a phase advance of 0.43 h. On a third occasion, he received a pulse of 1 lx, which yielded a phase delay of 0.27 h, which is typical of the human free-run under similar conditions: Boivin et al. [26] found a net delay of 1.05 ± 0.38 h over 3 days. The results suggest that the dawn signal has a phase-advancing effect larger than that of a matched rectangular pulse. Indeed, the magnitude of the advance is similar to that seen under bright light pulses of far longer duration.

In a further experiment, 8 subjects underwent a 3-day dawn exposure protocol similar to that performed with rectangular pulses by Boivin et al. [26]. The signal was scheduled initially to terminate at each subject's habitual wake-up time, at 2,000 lx (the level found outdoors 9 min after sunrise). It was presented 30 min earlier on each of the 2 subsequent days. The advancing light schedule and increased final intensity were designed to augment phase advances in body temperature and melatonin secretion. Although 5 of the

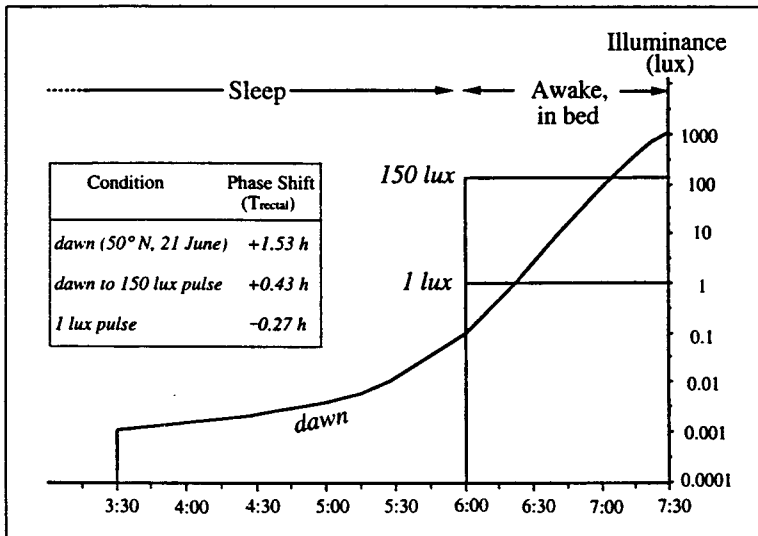


Fig. 1. Procedural diagram of trials of dawn simulation and rectangular pulses at 1 and 150 lx. On separate occasions separated by at least 1 week, the subject underwent two successive 'mini-constant routine' protocols from 15:00 to 23:00 h, followed by nocturnal sleep and awakening at 06:00 h for observation of the dawn signal above 0.1 lx and the rectangular pulses. The phase shift was quantified in terms of the midpoint between maximum and minimum rectal temperatures, excluding a 2-hour adaptation period at the start of session.

subjects did show varying degrees of phase advance in body temperature, the average final phase for the entire group of 8 did not differ significantly from that at baseline – an apparent negative result. However, this experiment lacked a rectangular dim light control, for which circadian phase would be expected to drift later across days as was found in the case study (above) at 1 lx, and by Boivin et al. [26] for 5-hour pulses at 0.03 lx. If we assume a daily delay drift of 0.3 h under such a dim light control, the final phase after 3 days of dawn treatment would be 0.96 h earlier than that under the control, representing a cumulative phase advance – i.e., maintained entrainment. Thus, the dawn signal was apparently active, although insufficient to push the phase of the temperature rhythm earlier than that at baseline.

Results for salivary melatonin contrast with those for body temperature. Using a highly specific direct double-antibody radioimmunoassay, a statistically significant – but small – phase advance (+0.36 h) could be detected on the evening following the first dawn presentation, with a larger cumulative advance (+0.60 h) after the third presentation. Such advances could well

subserve entrainment to the 24-hour day, and – given repetitions of the dawn signal – re-entrainment to novel phase positions. This positive result suggests that the salivary melatonin assay is more sensitive than the temperature measure, and thus able to resolve smaller phase shifts; a possible alternative is that melatonin provides a more reactive circadian endpoint marker.

The 'Work' of REM Sleep May Be, in Part, to Detect the Dawn Signal

Consider that the dawn signal serves as zeitgeber during the final hours of sleep, with up to several hours of gradually incrementing illumination preceding sunrise and awakening. The ultradian sequence of REM episodes, whose nocturnal phase is controlled by the circadian clock, might thus adjust relative to dawn. When one awakens spontaneously at the end of the night's final REM episode, there is greater alertness and sense of refreshment than awakening to an alarm that intrudes on REM. It might follow, then, that the final REM episode phase-locks to a specific point within the dawn transition, and the preceding episodes fall into place according to their ultradian pattern. Whether the timing of REM is tied to a specific illumination level during dawn, or by a mechanism that detects a specific momentary rate-of-change of the incrementing signal, is testable.

A decade ago, Livermore and Stevens [36] performed a series of experiments with rats, in which they severed the extraocular muscles, preventing the behavioral expression of REM sleep. While sham operated controls maintained entrainment to LD cycles, with appropriate adjustments to phase advances and delays of the cycle, the animals without rapid eye movements free-ran. Going somewhat beyond the data, they proposed that 'REM exposes the periphery of the retina to ambient light (or darkness) through the sclera and the red filter of the closed lids', and thus facilitates early detection of the zeitgeber. In this respect, if we extrapolate to humans, we would not conclude that 'subjects remain... essentially blind' during sleep [see Schwartz, this volume]... at least during REM sleep. During NREM periods, the eyes normally turn upward toward the orbital roof – Bell's phenomenon – which would indeed reduce light transmission. It is unknown whether the 10% of people who do not show Bell's phenomenon are more vulnerable to light at night.

The 'Dosing' of Dawn Simulation Involves Multiple Parameters

The strategy for optimum dosing of artificial dawns remains a challenge, because so many parameters are available for manipulation. The curve has a complex sigmoid shape dependent on variation of the earth's tilt, atmospheric refraction, etc. Maximum acceleration of light intensity occurs within the relatively brief civil twilight period preceding sunrise. The pattern of time-

rate-of-change, however, differs across latitudes and seasons. Clinically, some winter depressives have shown greater response to slow (2–3 h) dawns, typical of northerly latitudes and the solstices, than to the faster transitions (at fastest extreme, the equatorial signal spans only approximately 45 min). Using commercial apparatus that delivers ‘faux dawns’ with a log-linear transition, the rate of change of astronomical and nautical twilight (approximately 10^{-3} – 10^0 lx) is artificially accelerated, and premature awakening is a common side effect.

The time anchor for triggering or terminating the dawn transition is discretionary. The position of the signal relative to baseline sleep and the PRC needs exploration. Clinically, for oversleepers, we often anchor sunrise to the time of habitual awakening, and move it earlier as soon as the patient begins to awaken before the alarm clock sounds.

The amplitude of the entire transition curve is discretionary. One can choose to administer dawns that replicate open outdoor conditions under clear skies, cloudy skies, partial protective cover, and nearly darkened caves. One army veteran with delayed sleep phase syndrome reported sleeping the best in his life, with normal awakenings, under the thatched roof of barracks in Vietnam, with exposure to a thickly filtered dawn. In clinical practice, most oversleepers prefer somewhat brighter dawns similar to outdoor light under sparse vegetation, with the sunrise maximum around 350 lx. Others however, require very dim dawns to forestall premature awakening (see comments on blue eyes, below).

The factor of a lamp’s color temperature has been barely explored. My group’s earliest device, designed primarily for animal studies, maintained a constant broad spectrum by opening a set of rotating vanes placed beneath fluorescent lamps [37]. For convenience in bedroom applications, spectral constancy has been abandoned in favor of solid-state drivers and incandescent lamps, which fortuitously tend toward a red shift typical of twilight when dimmed, but fail systematically to replicate the complex red and blue shifts found outdoors. Recent animal research on photopic inputs to the suprachiasmatic nucleus may presage wavelength tuning of the twilight signal according to the spectral sensitivity of circadian photoreception (see comments on red and blue light reception, below).

The spatial distribution of twilight illumination is another critical dosing parameter, given the normal course of body movements during sleep, changing head position, and eye movements. Some apparatus uses highly directional illumination that can easily be escaped, while other apparatus mimics diffuse sky cover (fig. 2). Since exposure to such light is variable, it would seem reasonable for the retina or circadian system to incorporate a leaky integrator that factors out transient increases and decreases in received light

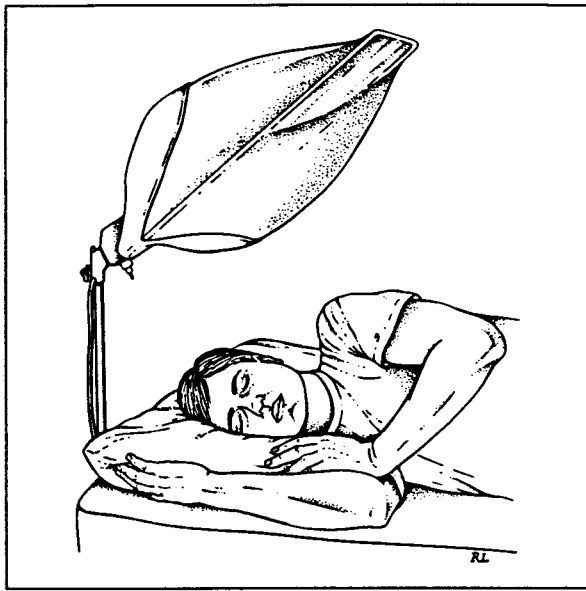


Fig. 2. Lighting apparatus for presentation of dawn and dusk signals in an otherwise darkened bedroom. A high-output halogen lamp is placed behind an opaque fabric base section. An internal reflector directs the light toward a translucent fabric enclosure that distributes diffuse illumination to the upper area of the bed and outward toward the walls and ceiling. [Reproduced with permission from *J Coll Physicians Surg Columbia Univ* 1996; 16:12–13.]

relative to the 'pure' dawn and dusk transitions, thus preserving the fundamental curve shape. It has long been known that stimulus variability in high-frequency range can serve to potentiate retinal responses [38]. Exposure to more gradual variations in light intensity during dawn stimulation may enhance the retinal effect by forestalling photoreceptor adaptation, as I have argued with respect to bright light therapy [39]. In one recent experiment, a series of 5-min bright-light pulses interspersed with darkness over 5 h – with total exposure duration only approximately one-fifth the interval – elicited circadian phase shifts approximately five-sixths that of continuous light [40]. For light presentation during sleep, enforced, continuous exposure can be assured by the use of a sleep mask [41] implanted with lamps or fiber optics interfaced to a dawn simulation driver. Such a configuration may be prerequisite for experiments that demand complete control over ocular illumination, with the ability to manipulate local variations in stimulus intensity.

Blue-Eyed Sleepers Show Supernormal Response to Dim Light

Blue-eyed people appear especially vulnerable to impinging bedroom light, and often take special measures – heavy curtains, sleep masks – to preserve the darkness. They have less pigmentation in the iris, and thus the protective filter is less efficient. They often complain of glare under bright artificial light and sunlight, and are more susceptible to maculopathy [42], which implicates a role for light in the etiology of the disease. Those who are light-skinned may also show heightened eyelid transmission [C.E. Remé, pers. commun.]. Such pigment loss in the iris and eyelid may lower the threshold for triggering the morning retinal cascade of scotopic and mesopic adaptation preparatory to daytime photopic vision. Possibly, this genetic variant incurs an advantage in northern Europe by facilitating circadian phase-advances in winter, and forestalling hypersomnia and depression. With migration southward, however, it presents a liability.

In the controlled bedroom environment, blue-eyed people provide a lesson for the dosing of dawn simulation treatment, and insight about the mechanism of action of low-intensity light. A series of cases showed that when the signal was gradually increased to a maximum of 350 lx, awakening occurred up to 2 h earlier than is typical for those with normal pigmentation. Signal intensity at the time of premature awakening would fall into the nautical twilight range, with less than 1 lx at the level of the eyelids. In some cases, it was necessary to reduce the amplitude of the artificial dawn curve by 80% (with a resultant sunrise level of 70 lx or below) in order to eliminate the side effect of premature awakening.

Does Circadian Sensitivity to Dawns Involve Both Rods and Cones?

After stabilization under dawn simulation for several days, awakening usually occurs toward the end of the civil twilight segment (approximately 10^{-3} – 10^0 lx), near the time of sunrise, by which time rod saturation has occurred and photopic vision is fully active. That said, however, the photopic threshold is quite low, falling within the range of moonlight and nautical twilight (approximately 10^{-2} – 10^0 lx), at which time rods and cones show joint, mesopic activity [43]. Whether awakening under the dawn signal and/or elicitation of circadian phase advances utilizes mesopic light transduction, or is purely photopic, has yet to be sorted out. Indeed, while active in the scotopic and mesopic ranges, rods suppress cone activity [44], a local retinal interaction that ceases with rod saturation during civil twilight. Anatomical complexities further suggest that during the major portion of twilight, photic input to the circadian system reflects the joint action of rods and cones:

There is a secondary pathway from rods to ganglion cells. Due to gap junctions between rods and cones, rod signals can be found in cones, in horizontal cells that have anatomical

input entirely from cones, and in cone bipolar cells... How much of the rod signal found in ganglion cells in the mesopic state come through the rod bipolar-rod amacrine pathway, and how much comes through the rod-cone gap junction pathway has not yet been determined [45 for review and references].

Thus, recent indications of specific cone-mediated neural input to the suprachiasmatic nucleus [18, 19] do not exclude a circadian function for rod activity. Indeed, the gradual course of light adaptation in the rods, leading to saturation, may open a retinal gate for zeitgeber action by enabling cone detection of the dawn signal [43; T.P. Williams, personal commun.].

Eyelid transmission favors long (red) wavelengths [46, 47]. Natural twilights are enhanced in red and blue/blue-green relative to daylight [48], with reduced energy in the yellow and orange ranges. While the red shift might serve to heighten cone activity and promote detection of the zeitgeber, the blue/blue-green shift closely matches the peak in human rhodopsin sensitivity, and thus might serve to heighten rod activity. Until proved otherwise, one may doubt that these hue shifts materially affect the circadian response to twilights, especially since there is substantial daily variation with meteorological changes [48]. Furthermore, control over circadian phase has been clearly demonstrated both in animals [29, 30, 32] and humans [33, 34], using simulated twilights with an unchanging spectrum. At higher intensity, with the rods mostly saturated, narrow-band red light successfully elicits phase advances in both core body temperature and melatonin rhythms [49], undoubtedly implicating a photopic input mechanism.

The Dusk Signal May Be Directly Hypnotic

We do not normally fall asleep during dusk. In the typical urban routine, sleep onset occurs hours after dusk, at a consistent clock time throughout the year, e.g., 23:00 h. In winter, the dusk-to-sleep interval can substantially exceed that of summer, depending on latitude. The dusk-to-sleep interval is filled with artificial room light, permitting evening activities and exerting a phase-delaying effect on the circadian clock. Many elderly people habitually turn down room light in the late evening, which may contribute to their advanced sleep phase; even modest increases in room light can help reverse this problem [50]. Explicit bright light treatment in the evening has a similar effect, although most subjects have not found the procedure to be user-friendly [51].

A spontaneous experiment occurs during community-wide electric power failures: many people report retiring shortly after sunset, hours earlier than usual. By contrast, although some patients with delayed sleep phase syndrome exacerbate their problem by maintaining room light into the night, others

routinely lie awake in a dark bedroom for several hours. A similar situation holds for milder forms of sleep onset insomnia, e.g., inability to sleep before 01:00 h when the desired onset is midnight. The question is whether the immediate response of normal sleepers to a power failure hints at a corrective measure for the insomniacs.

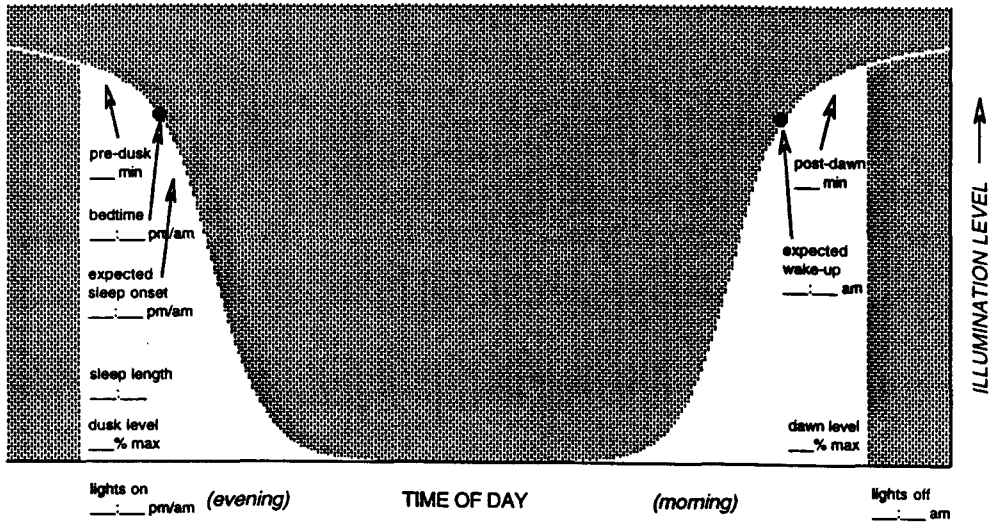
In several clinical case studies, patients with mild to moderate delayed sleep phase were given artificial dusks beginning shortly before desired bedtime. They promptly nodded off hours earlier than otherwise. This observation suggests that the dusk transition exerts a hypnotic effect, by comparison with the sudden switching off of lights. The amplitude of the dusk signal may be a relevant parameter. While for dawns one usually seeks a fairly bright signal at sunrise – e.g., 350 lx – dusks appear most comfortable and effective with intensity 50–70% lower, thus minimizing activating and phase-delaying effects at bedtime.

Optimum Control of Sleep Phase and Duration May Require Couching the Sleep Episode in Dusk and Dawn

There is an indication from patients with SAD, and others without depressive illness who experience bothersome night-to-night variation in sleep onset and awakening, that the sleep episode regularizes most efficiently when initiated under dusk illumination and terminated under dawn illumination. In one such case, the dawn signal alone served to normalize the time of awakening, but sleep onset remained variable [34]. The combination of dusk with dawn brought both ends of sleep into the normal range, along with complete remission of the depression. Such dual nightly exposure may act by balancing small phase delays and advances of the circadian clock, which are known in animals to stabilize entrainment in relation to the PRC [27].

In nature, dusk and dawn light transitions occur symmetrically with respect to midnight. Thus, an 8-hour night would begin with sunset at 20:00 h and sunrise at 04:00 h, which is an atypically advanced sleep interval for most people. For adjustment to the typical contemporary sleep schedule, one can artificially displace the scotoperiod in the bedroom. A 3-hour delay of the dusk-to-dawn schedule, for example, establishes a conventional interval for sleep, i.e., 23:00–07:00 h. Under such conditions, I have observed in field studies (using information from sleep log records and interviews) that sleep onset typically occurs about 20 min after simulated sunset, with light level at approximately 15 lx, and awakening occurs around the time of simulated sunrise. The light turns on at the selected sunset level (e.g., 150 lx) before the downward transition begins, so there is no abrupt light switching after entering

Dawn/Dusk Simulator Worksheet



STANDARD SETTINGS: sleep length, 8 h; sunrise, 7:00 am; pre-dusk, 90 min; post-dawn, 90 min; dusk level, 50%; dawn level, 100%
 STANDARD SEQUENCE: light on, 9:10 pm; bedtime, 10:40 pm; sleep onset, 11:00 pm; wake-up, 7:00 am; light off, 8:30 am

Fig. 3. Patient's and clinician's worksheet for specification of dusk and dawn parameters.

Over the course of treatment, parameters are adjusted to maintain the desired sleep phase and duration. Dots indicate the times of simulated sunset and sunrise. In one application, the desired sleep length is entered, and the logic controller finds a geographic latitude where sunset occurs 20 min before expected sleep onset and sunrise occurs at the expected time of awakening. The dusk and dawn segments can be presented at equal or different amplitudes (% max). Maximum output is determined by the choice of lamp and distance and angle of the diffusion box relative to the patient's head position in bed. In a typical application, illuminance rises from about 0.001 to 350 lx at sunrise (in comparison with about 780 lx global outdoor illuminance under clear-sky conditions), and the lamp saturates a few minutes later at 450 lx.

the bedroom. Similarly, the light remains on for an interval after sunrise in order to avoid – in the words of a patient – a 'dreadful plunge' into dim room light after early-morning exposure to higher illumination. Parameters are individually adjusted over the first weeks of treatment to maximize comfort and effect, as illustrated in a user's worksheet (fig. 3).

In the case of delayed sleep phase syndrome, the illumination interval is edged earlier over successive nights at a rate that the patient can feasibly track, while maintaining the asymmetrical balance of dim dusk and bright dawn. The opposite pattern – successive delays with bright dusk and dim dawn –

has been applied effectively for several patients with advanced sleep phase. Two potential applications, yet to be investigated, involve major displacement of the dusk-to-dawn schedule to serve shift workers with daytime sleep, and to prepare air travellers for time zone shifts or expedite post-flight adjustment. A basic question is whether this method can facilitate sleep outside the circadian subjective night through the hypnotic effect of dusk and alerting effect of dawn.

There are software and hardware systems that can implement the twilight signals for laboratory studies (MacLite™, with a Macintosh™-driven peripheral controller; SphereOne, Inc.) and home bedroom applications (a simplified Dawn/Dusk Simulator™; SphereOne, Inc.). In designing this apparatus, the goal was a flexible means for light presentation that is not theory-driven (e.g., with preselected parameters), to provide for a wide variety of experiments and clinical applications. Both versions of the system allow selection of any latitude at any day of year, the desired time of sunrise (natural for the location, or phase-displaced), and proportional attenuation of the output signal. They also include an algorithm that automatically selects an appropriate latitude based on specification of desired sleep length (e.g., for a longer night at the summer solstice, the program finds a location closer to the equator). The hardware bypasses endpoint trimming, which is conventional for dimming systems, thus allowing accurate presentation of very dim astronomical twilight signals (approximately 10^{-3} – 10^{-2} lx). The laboratory version allows scheduling of progressive phase shifts across days, continuous calendar progressions (daily or accelerated), expansion or contraction of the time base (for non-24 h days), upper and lower intensity cutoffs, optional moonlight cycles, and standard rectangular LD cycles including one- and two-pulse skeleton photoperiods matched for total illuminance with corresponding dawn/dusk signals.

Dawn-Dusk Simulation May Affect Both Sleep and Retinal Regulatory Processes

Following an abrupt artificial photoperiod reduction, Wehr [52] found that subjects confined to a darkened room for 14 h beginning at 18:00 h, without a dusk twilight, required about 1 week for stabilized adjustment with earlier sleep onsets and longer sleep durations. The changes in sleep – which included some transient awakenings in the middle of the night – were accompanied by a phase advance and expansion of the melatonin secretion interval. Such a result illustrates the dramatic response in humans to a shortened photoperiod, given confinement to complete darkness in the bedroom during the imposed long nights. Whether the addition of dusk and dawn signals at

the start and end of confinement to the bedroom would accelerate adjustment of the onset and duration of sleep, and affect the transient awakenings, awaits testing.

Beyond their potential role in facilitating circadian phase shifts, dusk and dawn signals have apparent direct hypnotic and alerting effects that can immediately influence sleep onset and awakening. These might be explained by shifts in the upper and lower 'C' thresholds of the Borbély-Daan model of sleep regulation [for review and comparison with other models, see 53]. Sleep onset occurs after accumulation of Process S of the somnostat during waking hours, to the point of intersection with the oscillating upper threshold of Process C, the circadian variable. The somnostat then reverses into a depletion phase during sleep, until the point of intersection with the lower C threshold, triggering awakening. The distance between the two C thresholds varies with a person's current level of arousal, and is thus responsive to environmental stimulation. If the lower threshold rose in response to dawn exposure, awakening would occur earlier than in darkness, even before the circadian phase advance to dawn is established. Likewise, if the upper threshold fell during dusk exposure, it would accelerate sleep onset.

Consider also the shape of the C oscillation, which for normal sleep is not modelled as a symmetric sinusoid. Rather, the duration above the midpoint of the oscillation covers less than half the day, thus accommodating a sleep length of approximately 8 h [for a graphic representation, see 53]. The results of photoperiod contraction observed by Wehr [52] may reflect an adjustment of the duration of C above its midpoint, as distinct from a threshold shift due to imposed darkness. Thus, long nights do not merely set the occasion for phase delays of the nocturnal melatonin secretory episode – tracking the delayed dawn of winter – but result in a longer secretory episode, an expansion of the subjective night. The effect can also be interpreted as the phase separation of evening and morning oscillators that are anchored to the edges of the scotoperiod. For sleep, the result is hypersomnia. A large proportion of the general population reports sleeping longer in midwinter, irrespective of mood swings [54]. Perhaps these people are relatively insensitive to evening dim room illumination, which in others maintains a summer-like contraction of the C oscillation above its midpoint.

Colleagues and I have postulated a deficiency in photostasis as predisposing people to winter depression [55]. This retinal mechanism responds to low-light conditions by increasing the availability of receptor pigments, thus maintaining a consistent daily photon catch [42, 56]. Retinal disk shedding maintains a cap on pigment availability, thus holding the photostatic growth process in check. The interaction of the photostat and the retinal clock may be analogous to that of the somnostat and Process C. Thus, a lowered retinal

C threshold could serve to magnify the receptor loss through disk shedding, limiting the ability of dim room light to maintain a summer-like sleep pattern.

Does the Link between Sleep and Light Exposure Exclude the Antidepressant Response?

In winter depression, sleep abnormalities are common but not ubiquitous. Patients variously report hypersomnia, fractionated sleep, difficulty awakening and delayed sleep phase, separately or in combination. Retrospective reports of hypersomnia are inconsistently verified by sleep logs, although there are certainly many documented cases (e.g., 11-hour sleep durations in winter with 6-hour durations in summer). Polysomnographic studies show only a marginal average increase in sleep duration in patients relative to controls [57], although a study in Siberia found marked increases [58]. Reports of hypersomnia may often reflect perceived sleep 'need' more than the behavior itself – as is universally corroborated in reports of daytime fatigue. Ratings of difficulty awakening are not statistically correlated with those of hypersomnia [59]. Although several studies show decreased sleep efficiency while depressed, only some indicate decreased slow-wave sleep, increased sleep latency or increased REM density [for review, see 7]. Despite the variable clinical and polysomnographic profile, some studies report reduction of behavioral symptoms and abnormalities in the electroencephalogram under bright light treatment. Dawn/dusk simulation studies are pending. Research is needed to determine whether, above-and-beyond the response of the circadian system, the benefits of light on sleep are mediated by the antidepressant response. I posit not, since similar sleep disturbances are experienced by people who are not depressed, and they, too, may be light-responsive.

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