Light Treatment for Sleep Disorders: Consensus Report.

I. Chronology of Seminal Studies in Humans

Scott S. Campbell,[1] Charmane I. Eastman,[2] Michael Terman,[3]
Alfred J. Lewy,[4] Ziad Boulos,[5] and Derk-Jan Dijk[6]

[1]*Laboratory of Human Chronobiology, New York Hospital, Cornell University Medical College, 21 Bloomingdale Road, White Plains, NY 10605;* [2]*Biological Rhythms Research Laboratory, Rush-Presbyterian-St. Luke's Medical Center, 1653 West Congress Parkway, Chicago, IL 60612;* [3]*Department of Psychiatry, Columbia University and New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032;* [4]*Department of Psychiatry, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201;* [5]*Institute for Circadian Physiology, 1 Alewife Center, Cambridge, MA 02140;* [6]*Institute of Pharmacology, University of Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland*

Abstract Examination of the influence of the light-dark cycle on circadian rhythmicity has been a fundamental aspect of chronobiology since its inception as a scientific discipline. Beginning with Bünning's hypothetical phase response curve in 1936, the impact of timed light exposure on circadian rhythms of literally hundreds of species has been described. The view that the light-dark cycle was an important zeitgeber for the human circadian system, as well, seemed to be supported by early studies of blind and sighted subjects. Yet, by the early 1970s, based primarily on a series of studies conducted at Erling-Andechs, Germany, the notion became widely accepted that the light-dark cycle had only a weak influence on the human circadian system and that social cues played a more important role in entrainment. In 1980, investigators at the National Institute of Mental Health reported that bright light could suppress melatonin production in humans, thereby demonstrating unequivocally the powerful effects of light on the human central nervous system. This finding led directly to the use of timed bright light exposure as a tool for the study and treatment of human circadian rhythms disorders.

Key words light, circadian rhythms, phase response curve, history of experiments

INTRODUCTION

The first hypothetical phase response curve (PRC) to light was offered by Bünning (1936), based on his, and others', pioneering studies of diurnal oscillations in various plant species. These studies showed that such oscillations were not passively driven by the daily light-dark cycle, but rather, were endogenously generated rhythms that were entrained by the daily alternation of light and darkness (Kleinhoonte, 1929;

AUTHORS' NOTE: All correspondence should be addressed to Michael Terman, task force chair, and to Scott S. Campbell, primary section author.

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Bünning and Stern, 1930). Based on a relaxation oscillator model of the circadian clock, with a tension phase and a relaxation phase, Bünning proposed that such entrainment was achieved via a phase-dependent responsiveness to light. He summarized the hypothesis in 1961:

> If light (as example, a light break in the dark phase) . . . is offered in the tension phase, this tension is made greater than it would otherwise have been. That is, the tension phase is extended by a given amount, for example, 1 to 2 hours. If the light treatment . . . is repeated for several days, the adjustment process is also repeated until the light no longer falls in the tension phase. Thus, the phases ultimately occur several hours later than they did before this treatment. If, on the other hand, light is given in the relaxation phase, . . . the relaxation process is brought to a halt 1 to 2 hours earlier than usual. The result is an advancing of the phase. (p 6)

As Pittendrigh (1961) has pointed out, such a hypothesis describing photic control of circadian rhythms was remarkable for the time, considering that the very existence of endogenous diurnal rhythmicity was still a matter of considerable debate. Subsequent research validated the phase-dependent nature of the endogenous clock's responsiveness to light, and the exact components of the phase response curve were shown to consist of a delay-sensitive phase in the early subjective night, an advance-sensitive phase in the late subjective night, and a nonresponsive phase corresponding to an organism's subjective day. Such research also clarified the mechanism of entrainment by light (see related task force section, Dijk et al., 1995 [this issue], for a more detailed explanation), and over the next 3 decades it was shown that the circadian systems of a wide variety of organisms responded in a similar manner to pulses of light (for reviews, see Gwinner, 1975; Daan and Pittendrigh, 1976; Pittendrigh, 1981; Aschoff et al., 1982).

This included human circadian rhythms, which were shown to persist in the absence of external time cues, but at a period different from 24 h (Aschoff and Wever, 1962), indicating that the human circadian clock apparently responded to an external signal, or signals, for synchronization. Although the rigorous study of the human circadian system was still in its infancy, the importance of the natural light-dark (LD) cycle as a synchronizer of human circadian rhythms was generally acknowledged (see, e.g., Lobban, 1958, 1961; Hellbrügge, 1961; Sharp, 1960).

The view that the LD cycle was an important zeitgeber for the human circadian system seemed to be supported by studies of blind subjects. Most (see, e.g., Orth and Island, 1969; Hollwich and Dieckhues, 1971), but not all (Lund, 1974, 1976), of these studies indicated that free-running rhythms of various vegetative functions failed to be entrained by social cues, or established routines. Results of experiments in which normal subjects were exposed to forced living routines with periods ranging from 12 to 48 h also supported the view. In those studies, in addition to reported entrainment of certain rhythms to the new period (usually sleep-wake), other rhythms were reported to remain synchronized to a 24-h periodicity, strongly suggesting entrainment by environmental factors, the most obvious being light.

Further support for the synchronizing capacity of light on the human circadian system was provided by Sharp (1960), who reported a phase delay in the plasma levels of leukocytes, and in urine flow, in response to a 3-h extension of darkness following normal wake time. A similar finding was reported several years later by Orth and Island (1969), who demonstrated that adrenocortical activity could be entrained to LD cycles that were dissociated from the timing of the subjects' sleep-wake cycles. Subsequent studies of human circadian rhythms, under more highly controlled experimental conditions (specifically, the temporal isolation facility at Erling-Andechs, Germany), also seemed to confirm the role of the LD cycle as an effective synchronizer in humans. Artificial LD cycles were reported to effectively entrain subjects to non 24-h periods (Aschoff, 1969), and rapid re-entrainment of sleep-wake and temperature rhythms was accomplished by a single 6-h shift of the LD cycle (Aschoff, 1967).

In these early studies, the LD cycle was temporally linked with periodic auditory tones, which signaled subjects to carry out various experimental procedures (e.g., urine collection, performance test). On one occasion, however, shortly after the start of the study, the auditory signaling system failed. Despite the persisting LD cycle, subjects exhibited free-running rhythms (see Wever, 1979, pp 150-151, for complete description). Subjects later confirmed that they perceived the auditory signals, but not the LD cycle, as a form of "social contact" with the experimenters. Additional experiments designed to examine this chance finding more carefully (see, e.g., Wever, 1970; Aschoff et al., 1971; Aschoff et al., 1975; Wever, 1979; Aschoff, 1981) led the investigators to question the strength (but not the existence) of the LD cycle as a synchronizer of human rhythms, relative to that of social cues. In one

influential study (Aschoff et al., 1971), the authors concluded that an LD cycle was not necessary to entrain human circadian rhythms, "at least for [the] 4 days" of the study.

Based on all subjects studied ($N = 24$), it was determined that the range of entrainment for a "pure light-dark zeitgeber" was smaller than ± 1.0 h, whereas the range of entrainment for the same light-dark cycle "enriched" by social cues was about ± 2.0 h. The investigators concluded "that the zeitgeber effectiveness of light-dark cycles is small in comparison to that of social contacts" (Wever, 1979, p 191).

These results appeared to make humans the sole exception to a phylogenetic rule concerning the role of light as the principal synchronizer of circadian rhythms. There were two important limitations, however, in the studies that led to this conclusion. First, technical considerations limited illumination in the isolation apartments to a maximum of about 1000 lux. Thus the effects of higher intensity light could not be investigated. Second, the LD cycles imposed in the human studies were fundamentally different from those used in animal work, in that the dark phase of the LD cycles was not absolute. That is, in many experiments, subjects were permitted to use table and bedside lamps following onset of the "dark" phase of each cycle.

The investigators were aware of the importance of this latter aspect of the experimental design and conducted further studies to address the question. Using an "absolute" LD cycle in which auxiliary lighting was not permitted, in contrast to the "relative" LD cycle of the previous studies, they concluded that the range of entrainment for the activity rhythm, but not for the rectal temperature rhythm, was "much larger than with the weaker zeitgeber." With regard to its effect on free-running rhythms, the authors noted that "light exerts a clear and statistically highly significant effect. When the intensity of illumination does not stay constant during sleep and wakefulness, but the subjects switch the light on upon awakening and off when going to bed, the rhythm is decelerated" (Wever, 1973, p. 133; translated from German).

A paper by Czeisler and colleagues (1981) challenged the view that the human circadian system might have a reduced sensitivity to light. In a reassessment of the effects of LD cycles on human circadian rhythms, the authors presented rest-activity data obtained from two subjects (as well as temperature data from one of the subjects) to support their claim that both rhythms could be entrained to a 24-h LD cycle if absolute darkness was imposed during the "dark" phase of the cycle. However, as in the earlier protocols conducted in Germany, this study did not eliminate entirely the influence of social interactions, which were allowed throughout the study and which were "linked to chosen wake times." Thus, while these investigators controlled for the influence of self-selected LD cycles, strict control of social cues was not achieved.

Thus it remained unclear from the results of this study whether the putative entrainment occurred in direct response to the LD cycle or whether it occurred because of the influence of absolute darkness on the subjects' behavior (i.e., enforced sleep-wake cycle). Using a mathematical model of the human circadian system that assumed the existence of two interacting oscillators, these investigators concluded subsequently that the oscillator governing sleep and wakefulness (the y oscillator) "is the direct recipient of environmental zeitgeber information" and that "any drive of z [zeitgeber] exerted directly on x [the oscillator controlling body core temperature] must at most be very small" (Kronauer et al., 1982). The investigators cited evidence to suggest that the suprachiasmatic nuclei (SCN) of the hypothalamus were the site of the y pacemaker.

That light exposure could have a significant, direct impact on human physiological brain function was demonstrated unequivocally for the first time in a paper published by Lewy and coworkers in 1980. These investigators showed that light of substantially higher intensity than that used in the Andechs studies (2500 lux) was effective in suppressing nighttime melatonin concentrations to daytime levels. Based on this finding, and on the intimate neuroanatomical links between the pineal gland and the endogenous circadian pacemaker located in the SCN, these investigators speculated that "humans may require brighter light for the entrainment of circadian rhythms" than do other species (Lewy et al., 1980).

This paper marked a turning point in the study of the effects of light on the human circadian system, and over the next decade numerous investigators helped to further clarify and extend our knowledge in this regard (see related task force sections in this issue: Boulos et al., 1995; Campbell et al., 1995; Dijk et al., 1995; Eastman et al., 1995; Terman et al., 1995). Fifty years after the publication of Bünning's hypothetical PRC for plants, PRCs for humans were established based on laboratory data (Honma and Honma, 1988; Czeisler et al., 1989; Wever, 1989; Minors et al., 1991).

Today, it is well accepted that bright light exposure can influence dramatically both the amplitude and phase of human circadian rhythms, and there is growing evidence that light may affect human physiology and behavior through noncircadian mechanisms as well. While a great deal more research is required, it is also quite clear that timed exposure to bright light may have an important place in the treatment of various disorders involving circadian rhythm disturbance. The following sections address these issues with specific reference to the use of light therapy in the treatment of sleep disorders.

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REFERENCES

Aschoff J (1967) Human circadian rhythms in activity, body temperature and other functions. In *Life Sciences and Space Research V*, pp 159-173, North Holland, Amsterdam.

Aschoff J (1969) Desynchronization and resynchronization of human circadian rhythms. Aerospace Med *40*:844-849.

Aschoff J, ed. (1981) *Biological Rhythms. Handbook of Behavioral Neurobiology*, Plenum Press, New York.

Aschoff J, Daan S, and Groos GA, eds. (1982) *Vertebrate Circadian Systems: Structure and Physiology*, Springer-Verlag, Berlin.

Aschoff J, Fatranska M, Giedke H, Doerr P, Stamm D, and Wisser H (1971) Human circadian rhythms in continuous darkness: Entrainment by social cues. Science *171*:213-215.

Aschoff J, Hoffmann K, Pohl H, and Wever R (1975) Reentrainment of circadian rhythms after phase-shifts of the zeitgeber. Nippon Seirigaku Zasshi *37*:4-6.

Aschoff J and Wever R (1962) Spontanperiodik des Menschen bei Ausschluss aller Zeitgeber. Naturwissenschaften *49*:337-342.

Boulos Z, Campbell SS, Lewy AJ, Terman M, Dijk D-J, and Eastman CI (1995) Light treatment for sleep disorders: Consensus report. VII. Jet lag. J Biol Rhythms *10*:167-176.

Bünning E (1936) Die endogene Tagesrhythmik als Grundlage der photoperiodischen Reaktion. Ber dtsch bot Ges *54*:590-607.

Bünning E (1961) Opening address: Biological clocks. Cold Spring Harb Symp Quant Biol *25*:1-9.

Bünning E and Stern K (1930) Über die tagesperiodischen Bewegungen der Primärblätter von *Phaseolus multiflorus*: II. Die Bewegungen bei Thermokonstanz. Ber dtsch bot Ges *48*:227-252.

Campbell SS, Terman M, Lewy AJ, Dijk D-J, Eastman CI, and Boulos Z (1995) Light treatment for sleep disorders: Consensus report. V. Age-related disturbances. J Biol Rhythms *10*:151-154.

Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jewett ME, Brown EN, and Ronda JM (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science *244*:1328-1333.

Czeisler CA, Richardson GS, Zimmerman JC, Moore-Ede MC, and Weitzman ED (1981) Entrainment of human circadian rhythms by light-dark cycles: A reassessment. Photochem Photobiol *34*:239-247.

Daan S and CS Pittendrigh (1976) A functional analysis of circadian pacemakers in nocturnal rodents: II. The variability of phase response curves. J Comp Physiol *106*:253-266.

Dijk D-J, Boulos Z, Eastman CI, Lewy AJ, Campbell SS, and Terman M (1995) Light treatment for sleep disorders: Consensus report. II. Basic properties of circadian physiology and sleep regulation. J Biol Rhythms *10*:113-125.

Eastman CI, Boulos Z, Terman M, Campbell SS, Dijk D-J, and Lewy AJ (1995) Light treatment for sleep disorders: Consensus report. VI. Shift work. J Biol Rhythms *10*:157-164.

Gwinner E (1975) Circadian and circannual rhythms in birds. In *Avian Biology*, Vol. 5, D Farner and J King, eds, pp 221-285, Academic Press, New York.

Hellbrügge T (1961) The development of circadian rhythms in infants. Cold Spring Harb Symp Quant Biol *25*:311-323.

Hollwich F and Dieckhues B (1971) Circadian rhythms in the blind. J Interdiscipl Cycle Res *2*:291-302.

Honma K and Honma S (1988) A human phase response curve for bright light pulses. Jpn J Psychiatry Neurol *42*:167-168.

Kleinhoonte A (1929) Über die durch das Licht regulierten autonomen Bewegungen der Canavalia-Blätter. Arch néerl Sci ex et nat *5*:1-110.

Kronauer RE, Czeisler CA, Pilato SF, Moore EM, and Weitzman ED (1982) Mathematical model of the human circadian system with two interacting oscillators. Am J Physiol *242*:R3-R24.

Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, and Markey SP (1980) Light suppresses melatonin secretion in humans. Science *210*:1267-1269.

Lobban MC (1958) Excretory rhythms in indigenous arctic peoples. J Physiol (Lond) *143*:69P.

Lobban MC (1961) The entrainment of circadian rhythms in man. Cold Spring Harb Symp Quant Biol *25*:325-332.

Lund R (1974) *Circadiane Periodik physiologischer und psychologischer Variablen bei 7 blinden Versuchspersonen mit und ohne Zeitgeber*. Technical University of Munich.

Lund R (1976) Circadiane rhythmen bei blinden. Abst. 30th Kongress der Deutschen Gesellschaft für Psychologie, pp 391-392.

Minors DS, Waterhouse JM, and Wirz-Justice A (1991) A human phase-response curve to light. Neurosci Lett *133*:36-40.

Orth DN and Island DP (1969) Light synchronization of the circadian rhythm in plasma cortisol (17-OHCS) concentration in man. J Clin Endocrinol Metab *29*:479-486.

Pittendrigh CS (1961) Circadian rhythms and the circadian organization of living systems. Cold Spring Harb Symp Quant Biol *25*:159-184.

Pittendrigh CS (1981) Circadian systems: Entrainment. In *Handbook of Behavioral Neurobiology (Biological Rhythms)*, Vol. 4, J. Aschoff, ed, pp 95-124, Plenum Press, New York.

Sharp GWG (1960) The effect of light on diurnal leucocyte variations. J Endocrinol *21*:213-223.

Terman M, Lewy AJ, Dijk D-J, Boulos Z, Eastman CI, and Campbell SS (1995) Light treatment for sleep disorders: Consensus report. IV. Sleep phase and duration disturbances. J Biol Rhythms *10*:135-147.

Wever R (1970) Zur zeitgeber-strärke eines licht-dunkel-wechsels für die circadiane periodik des menschen. Pflugers Arch *321*:133-142.

Wever R (1973) Die Einfluss des Lichtes auf die circadiane Periodik des Menschen. I Teil: Einfluss auf die autonome Periodik. Z. physik Med *3*:121-134.

Wever R (1989) Light effects on human circadian rhythms: A review of recent Andechs experiments. J Biol Rhythms *4*:161-184.

Wever RA (1979) *The Circadian System of Man: Results of Experiments Under Temporal Isolation*, Springer-Verlag, New York.