Light Treatment and Biological Rhythms

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President's letter

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Part One: DSM-IV

During the last three years — DSM-IV's gestation period — the Mood Disorders Committee of the American Psychiatric Association received multiple inputs from SLTBR members, with data relevant to honing the seasonal pattern specifier, and critiques and recommendations for the 1994 revision [see, e.g., *LTBR* (1991) *4*: 3, (1992) *4*: 21, (1993) *5*: 49, (1993) *6*: 18], but there was little response from the committee, and no meaningful interaction. The final revision, now typeset in galleys for imminent publication (American Psychiatric Association, 1994), follows:

Criteria for Seasonal Pattern Specifier

Specify if:

With Seasonal Pattern (can be applied to the pattern of Major Depressive Episodes in Bipolar I Disorder, Bipolar II Disorder, or Major Depressive Disorder, Recurrent)

A. There has been a regular temporal relationship between the onset of Major Depressive Episodes in Bipolar I or Bipolar II Disorder or Major Depressive Disorder, Recurrent, and a particular time of year (e.g., regular appearance of the Major Depressive Episode in the fall or winter).

Note: Do not include cases in which there is an obvious effect of seasonal-related psychosocial stressors (e.g., regularly being unemployed every winter).

B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring).

C. In the last 2 years, two Major Depressive Episodes have occurred that demonstrate the temporal seasonal relationships defined in A and B, and no nonseasonal Major Depressive Episodes have occurred during that same period.

D. Seasonal Major Depressive Episodes (as described above) substantially outnumber the nonseasonal Major Depressive Episodes that may have occurred over the individual's lifetime.

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Surely these criteria will enable clinicians to identify patients with SAD, and there is increased flexibility — i.e., room for discretion — in identifying the onset and end of the depressive episodes without the restrictive 60-day windows, and 1:3 limit of nonseasonal-to-seasonal episodes, of DSM-III-R. However, it is disappointing that three main recommendations from SAD researchers were by-passed: (1) Although DSM-III-R accommodated two "Not Otherwise Specified" categories, Bipolar Disorder NOS (reincarnated as Bipolar II Disorder in DSM-IV) and Depressive Disorder NOS (i.e., the prevalent milder Minor Depressive Disorder), the latter can no longer be specified with seasonal pattern, which serves to prevent an appropriate, official diagnosis for patients with sub-syndromal SAD. There were no data to justify such an exclusion; on the contrary, several groups have published convincing, positive reports of light therapy for sub-syndromal patients. (2) The identification of "obvious" psychosocial stressors most often cannot be conclusive, and this clause should have been dropped. In most cases one cannot say whether such a stressor is the cause or the result of a depressive episode. (3) If a patient with SAD has skipped a winter episode in the last two years — whether the result of successful medication, travel south, or chance — the diagnosis may not be given even if prior history is unambiguously seasonal. As a result, light therapy (or reimbursement for lighting apparatus) may be inappropriately denied.

My suggestion to researchers is to report the frequency of DSM-IV seasonal pattern in publications, but for subject inclusion to rely on the longstanding NIMH formula (Rosenthal et al., 1984): at least two consecutive years (exclusive of the present episode) in which the depression developed in the fall or winter and remitted by the following spring or summer. As for practitioners who recommend light therapy, clinical discretion should now be the name-of-the-game, without strict adherence to DSM-IV.

Part Two: Light Patents

Potential constraints on independent research using light treatment and clinical applications of light for circadian rhythm phase disturbances — based on a series of patents recently awarded to Brigham and Women's Hospital — was the focus of a *News and Comment* article written by Rachel Nowak in the 4 March 1994 issue of *Science Magazine*. She reported on two incidents in which basic researchers without commercial involvement were requested or required to sign licensing agreements, and widespread consternation in the field. The SLTBR Board of Directors has been studying this matter, and, as Nowak reported, came to the following consensus:

> Many scientists in several countries have reported on research carried out over the last 20 years concerning the use of light as a circadian rhythm phase-shifting tool and therapeutic agent in humans. In our view, this broad knowledge base is in the public domain. That which is in the public domain cannot be protected by patent claims.

This issue of *LTBR* furthers the discussion with Scott Campbell's editorial. We include two individually-written draft reports — on the history of research in this area (by Campbell), and on experiments that have elucidated the mechanisms of action of light (by Derk-Jan Dijk) — which have been submitted to the American Sleep Disorders Association/SLTBR Joint Task Force on Light Treatment for Sleep Disorders. Also included is a commentary on Campbell's section, by Serge Daan.

Colleagues who want to read the patents described by Nowak — which are listed by number in Daan's references below — may order copies at $3.00 each from the U.S. Patent and Trademark Office, Washington, DC 20231.

Discussion will continue at two upcoming meetings. A legal and scientific debate is scheduled for the annual meeting of the Society for Research on Biological Rhythms, 4-8 May 1994 at Amelia Island Plantation in Florida; for meeting information, you may fax 412-648-8376. For information about SLTBR's annual meeting, 23-24 June 1994 at the National Institutes of Health, see the registration materials enclosed.

Michael Terman

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Editorial

DEAR JOHN . . .

Flaubert once wrote to a close friend: "I am not writing to you on my ordinary writing paper — that is edged with black, and I want nothing sad to pass from you to me."

The author of the letter that I received toward the end of December of 1993 apparently did not share the same sentiment as Flaubert in this regard. Although the paper was not edged in black, it might as well have been. For the content saddened me as much as any Dear John letter ever written. I should say that sadness was my lasting impression, after the shock and anger — and a certain sense of the absurd — wore off.

Sent from a well-known northeastern medical center, the letter introduced me to a document concerning the licensing of certain technology found in patents owned by the prestigious institution. I was delighted to learn that it was the institution's "philosophy to encourage academic research", and that I was, therefore, in the fortunate position of being extended a "no charge license" to use this very important technology in my academic pursuits. Curiously, the nature of the proffered technology was described neither in the introductory letter, nor in the licensing document itself. However, the word "light" (ominously spelled in several places with an upper case L) was sprinkled liberally throughout both documents. I, therefore, assumed that the "Agreement", as it was cozily referred to, dealt with the licensing of certain technology that may be employed in some aspect of research on the biological effects of light exposure that I was currently investigating. Or perhaps it referred to a new and innovative procedure for reducing the fat in our subjects' meals.

In any event, I was intrigued and read on.

I quickly learned that although there was to be no money exchanged between myself and the granting party, I should not take this to mean that there was not a price to pay for the privilege of holding the presumably valuable license. And the price was substantial indeed. It was spelled out in excruciating detail in the aforementioned document . . . a seven-page maze of "Whereas's", "entered into's" and "heretofore's". A "Witnesseth" was even thrown in on page one.

By signing the document, I would lose all rights to "discoveries, inventions, innovations", not to mention "suggestions, know-how, ideas and reports" that I might make or develop as a result of my use of the graciously offered technology. And I would not lose these things for the duration of the three-year license agreement. No. I would lose claim also to anything I might make, think, suggest or develop related to the technology, for the rest of time . . . "in perpetuity" is how the lawyers put it.

And, perhaps just to add insult to injury, at the whim of the prestigious institution, I would be expected to provide a written report (within 10 days of the request) describing in detail "all research and testing performed" in my laboratory that related to the technology.

In short, it appeared that I would be expected not only to sell my scientific soul to gain access to this incredible technology, but also to write home about it.

I became less intrigued — and more saddened.

I considered more carefully the meaning and purpose behind the legalese. The cynic in me assumed that money was at the bottom of it. After all, patents are generally registered in anticipation of future profits that may derive from this invention or that process. But then, why would the prestigious institution solicit a licensing agreement with a pure researcher like myself? Why would they go out of their way to extend such valuable technology at "no charge" for my academic pursuits?

Several possibilities came to mind:

1) The prestigious institution was engaging in altruistic behavior, doing what it could to foster research for the good of humankind.

2) The prestigious institution was engaging in out-and-out harassment to keep me from conducting research in an area that it viewed as its own private domain.

3) The prestigious institution was not only hedging its bets against my turning as capitalistic as it apparently was, but also against my possible future arrival at some innovative solution or development that may challenge the commercial value of the institution's patented technology.

4) The prestigious institution was seeking to limit, or control, the extent to which basic scientific principles and concepts on which its technology was based could be replicated and reported in the public domain. Perhaps it was concerned that further study might bring to light errors or shortcomings in the patented technology.

5) The prestigious institution was seeking my explicit acknowledgment of its right to license my, and by default others', research activities. In so doing, of course, it was also seeking my implicit acknowledgment of its version of history as applied to the developments in our field that laid the groundwork for the patented technology.

Let us assume, for the sake of argument, that the technology in question was indeed associated with procedures involved in the assessment of certain characteristics of the human circadian clock and/or approaches to manipulating the clock with timed exposure to bright light. How would these possibilities shake out?

The first two, I frankly dismissed to my naiveté and my paranoia, respectively. I reasoned that the prestigious institution was probably neither *that* good, nor *that* bad. I liked the sound of the third possibility because, in a perverse way, it could be viewed as a backhanded compliment. The prestigious institution thought that perhaps I may actually do something important. On reflection, however, I concluded that even if those in charge believed that, they were unlikely to actually acknowledge it. That left me with Possibilities #4 and #5.

It was these remaining possibilities that rang most true. They also caused me the greatest distress. I was troubled by the thought of the replicability issue, since it struck at the very cornerstone of scientific knowledge. Would a prestigious institution with the "philosophy to encourage academic research" actually collude to obstruct academic freedom? It sure appeared that way. Even if such obstruction was an unintentional, unavoidable by-product of exclusivity and profit, the outcome would be the same: scientific knowledge would be sacrificed for selfishness and greed.

As contemptible as this possibility seemed, my repugnance was magnified by the realization that it must, necessarily, be associated with Possibility #5. This latter possibility reminded me of a favorite quote — "What is history, but a fable agreed upon?" (Napoleon). It seemed that in this context, my signature on the "Agreement" represented nothing short of conspiracy to bend history to suit a very selfish need. And, of course, it was that acquiescence to the distortion of history that would legitimize the very foundation on which the entire scheme was based.

It was around about here that sadness became the predominant emotion. How could this ugliness have crept so silently into our young field? How could our bright light be obscured by such an ominous shadow? It couldn't, could it? It simply could not! I called friends and consulted colleagues. I faxed my brother the lawyer. My friends consoled and my colleagues counseled. My brother faxed back additional "whenceforth's" and "whereas's" — about twenty pages worth. I sat dejectedly at my computer. I contemplated the use of morning bright light.

And that is when I saw the hint of a break in this horribly dark cloud. Perhaps I was mistaken in my initial premise! Maybe this despicable document had nothing whatsoever to do with the use of bright light to reset the human circadian clock after all! Could it be that our well-known northeastern medical center was not really interested in my research on bright light at all? That it was not bent on stifling scientific freedom? That it was, in fact, devoted to the removal of fat from my subjects' diets? Lab Chow

Light, as it were? It *was* another possibility, wasn't it? It was a ray of hope.

The thought was soothing enough to help me get to sleep that night. But the next morning, my sadness remained, along with some uncertainty. I concluded that regardless of the technology offered, it would be very difficult for me to sign such an appalling "agreement". I *agreed* with nothing in it. At the same time, I hoped that I was not missing out on something. I mean, they made it sound so important!

In closing, I would like to ask: Would you sign if you found yourself in my fortuitous position? For many of you, this is almost certainly not a rhetorical question.

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A BRIEF CHRONOLOGY OF LIGHT STUDIES IN HUMANS

Based on a draft report to the ASDA/SLTBR Task Force on Light Treatment for Sleep Disorders

To the extent that a record of past events forms the basis for replication and validation, the accurate history of a field is an important component of its future. The following is an effort to provide an objective chronology of events which led to the clinical use of bright light in humans. In generating this chronology, I have attempted to report milestones in terms of the findings and interpretations offered by the authors themselves, without the advantage (and bias) of 20/20 hindsight.

The task force welcomes comments or suggestions that may help us in finalizing our report in the coming months.

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; 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 1960:

> 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, one to two 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 one to two hours earlier than usual. The result is an advancing of the phase. (Bünning, 1960, p. 6).

As Pittendrigh (1960) 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, although 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 non-responsive phase corresponding to an organism's subjective day. Such research also clarified the mechanism of entrainment by light (see next section for a more detailed explanation), and over the next three 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 twenty-four hours (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 (e.g., Lobban, 1958; Hellbrügge, 1960; Lobban, 1960; 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 (e.g., Orth and Island, 1969; Hollwich and Dieckhues, 1971) , but not all (Lund, 1974; Lund,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 hours 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 twenty-four hour 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 hr 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 which were dissociated from the timing of the subjects' sleep-wake cycles. Subsequent studies of human circadian rhythms, under more highly controlled experimental conditions (i.e., 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-hour periods (Aschoff, 1969), and rapid re-entrainment of sleep-wake and temperature rhythms was accomplished by a single 6-hour 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 (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. Based on all subjects studied (n = 24), it was determined that the range of entrainment for a "pure light-dark zeitgeber" was smaller than $\pm$ 1.0 hr, whereas the range of entrainment for the same light-dark cycle "enriched" by social cues was about $\pm$ 2.0 hrs. 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 employed 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 light-dark cycle" in which auxiliary lighting was not permitted, in contrast to the "relative light-dark cycle" used in 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; translated from German).

A paper by Czeisler and colleagues (1981) was the first to challenge the view that the human circadian system might have a reduced sensitivity to light. In a re-assessment 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 subject) 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.

Moreover, 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. 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 (see Derk-Jan Dijk's contribution in this issue), and there is growing evidence that light may affect human physiology and behavior through non-circadian mechanisms, as well [see Campbell, *LTBR* (1993) *6*: 19]. 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.

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Comment on the Task Force Chronology, March 1994 Draft

Recent literature repeatedly attributes the demonstration of entrainment of the human circadian system by light to a publication by Czeisler et al. (1981). For instance, three recent U.S. patent descriptions (Czeisler et al., 1993, 1992a, 1992b) contain the identical text: "Subsequent studies under more rigorous control have revealed that a light-dark cycle alone is capable of entraining the human circadian timing system to a twenty-four hour day" (see Czeisler et al., 1981). This citation is incorrect for three reasons: 1) the light-dark (LD) cycle was not alone in the study; 2) no evidence of entrainment was presented in the publication; 3) entrainment by LD cycles alone had been revealed in early studies by other authors.

Light-dark cycle

Referring to the publication quoted (Czeisler et.al., 1981), Campbell mentions that ". . . this study did not eliminate entirely the influence of social interactions." The original text states: "Subjects were not isolated from social contact with other people. Members of the staff would frequently enter the apartment . . ." (p. 241), and, "Specifically, the subjects were never disturbed during the bedrest episode, . . ." (p. 242). Thus if an LD cycle induced the subjects to be in bed during darkness, they additionally were exposed to a cycle of social interaction. The effect of these social cues on the circadian system cannot be separated from that of the LD cycle itself.

Circadian entrainment

There were two subjects in the study. For one of these (DB), the sleep-wake rhythm alone was used as evidence for circadian entrainment by the LD cycle (Czeisler et al., 1981, fig. 2, p. 243), and for the other subject (CA), both the sleep-wake cycle and the core body temperature rhythm were used (*ibid*, fig. 3, p. 244). In subject DB, presentation of an LD cycle after a prolonged freerun caused an immediate shift of sleep onset of about 6 h. After termination of the LD cycle sleep onset immediately shifted back by approximately 6 hours. In the intervening 19 days of exposure to LD, plus social zeitgeber, sleep onset remained locked to the onset of darkness. No transients are visible in the records published. This demonstrates that the sleep-wake cycle was masked, and not entrained by the light-dark cycle. Whether or not the underlying circadian system was entrained cannot be determined in the absence of data (i.e., body core temperature) addressing the issue. However, in view of the phase jump observed afterwards, it seems unlikely that the system was entrained. Connecting the free running wake and sleep onsets before and after the 19-day LD cycle, would yield a tau of approximately 25.2 h, which is consistent with the freerun before (tau = approx 25.0 h). However, this can neither be construed as evidence of continued freerun, nor of entrainment during the LD treatment.

In subject CA, the sleep-wake cycle showed similar phase jumps of approximately 6 h at the beginning and at the end of the LD cycle exposure. As in the case of DB, there

were no transients. In contrast, such a phase jump is not seen in this subject at the initial release, on Day 4, from real entrainment. The authors, nevertheless, argued for entrainment in this case, because in the temperature cycle ". . . following several transient cycles, the original 'square wave' shape characteristic of entrainment reappears (3d)". There is no precedence in the circadian literature for the use of a particular wave form as a criterion for entrainment. Furthermore, throughout the LD treatment, (with the exception of Day 87/88 — after 14 days of LD), there was a clear temperature rise during sleep, and hence no "square wave". This was the day of the transition to free-run. In summary, on the basis of the evidence presented, the conclusion that entrainment occurred is justified in neither subject.

Earlier demonstration of entrainment

Entrainment of both the temperature rhythm and the sleep-wake rhythm by a light-dark cycle, with additional gong signals, had been established previously in 6 subjects (Aschoff et al., 1969), and entrainment of the temperature rhythm alone (with the sleep-wake rhythm freerunning) by LD without additional signals, had been demonstrated in 3 subjects (Wever, 1981, 1989). In both of these studies, additional reading lights were available, which reduced the strength of the LD zeitgeber, and which prevented the imposition of an SW rhythm. However, the first demonstration of entrainment of the human circadian temperature rhythm by light cycles, without any additional reading lights or social signals, was reported by Wever (1989).

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EFFECTS OF LIGHT ON CIRCADIAN RHYTHMS AND SLEEP: BASIC PROCESSES

Based on a draft report to the ASDA/SLTBR Task Force on Light Treatment for Sleep Disorders

The rationale for the treatment of sleep disorders by scheduled exposure to bright light in seasonal affective disorders, jet lag, shift work, delayed sleep phase syndrome and the elderly is, in part, based on a conceptual framework developed by non-clinical circadian rhythm researchers working with humans and other species. The following is a brief review of some of the behavioral and physiological data that contributed to these concepts and points out some pitfalls related to their application to bright light studies in humans.

The light-dark cycle is a major synchronizer for endogenous circadian rhythms in mammals, including humans

It has long been recognized that in mammals, as in the alga Gonyaulax (Hastings and Sweeney, 1958) and the fruit fly Drosophila melanogaster (Pittendrigh and Bruce, 1957), light is an important synchronizer for endogenous circadian rhythms. As early as 1960, Patricia DeCoursey, working with flying squirrels (Glaucomys volans), demonstrated that a then-unidentified endogenous circadian pacemaker exhibited phase shifts in response to light pulses and, more importantly, that the effects of these light pulses were dependent on the phase in the circadian cycle at which they were applied (DeCoursey, 1960). The latter finding is a prerequisite for period and phase control, or entrainment, of circadian oscillators whose free running periods deviate from 24 hours (Pittendrigh, 1965). According to oscillator theory, which has been successfully applied to biological rhythms research, the phase angle between a 24-h synchronizer (or zeitgeber) and the endogenous oscillator depends on the endogenous period of the oscillator, the shape and amplitude of the phase response curve and the strength of the zeitgeber (cf Pittendrigh, 1965). More recent research on laboratory animals has shown that non-photic stimuli can also be zeitgebers.

In humans the role of light as a zeitgeber has been controversial and social cues have been postulated to be potent synchronizers, as well (Aschoff, 1971). Czeisler and co-workers (Czeisler et al., 1981) reinvestigated the role of the light-dark cycle and presented evidence that a 24 h ~150 lux light-dark cycle was sufficient to entrain human circadian rhythms although the authors carefully discussed the possibility that in their experiment the 24-hour sleep-wake cycle rather than the LD cycle was the effective zeitgeber. Subsequently they and others (Czeisler et al., 1986, 1989; Lewy et al., 1985, 1987; Dijk et al., 1987, 1989; Wever, 1983; Eastman, 1987; Drennan et al., 1989; Rosenthal et al., 1990; Campbell and Dawson, 1992; Eastman et al., 1992) demonstrated that human circadian rhythms can be phase shifted by scheduled exposure to bright light and that this effect of light is not mediated by the sleep-wake cycle, as was originally postulated (Kronauer et al., 1982). In many blind subjects free-running rhythms in various variables including plasma melatonin and sleep propensity have been observed even though these blind subjects were living in a 24-h social environment and tried to adhere to a 24-h sleep-wake cycle (Miles, 1977; Lewy and Newsome, 1983; Sack et al., 1992; Nakagawa, 1992; Kleinet et al., 1993). The entrainment of some blind subjects may be mediated by residual light input to the SCN, which can be inferred from the observed suppression of plasma melatonin after exposure to bright light (Martens et al., 1992). Alternatively, some blind subjects may be entrained by an as yet unidentified "social zeitgeber". Unfortunately the term social zeitgeber is vague and it is unclear what constitutes a "social zeitgeber". Taken together, the data demonstrate that in humans, light is the major synchronizer of endogenous circadian rhythms, and no solid evidence for direct zeitgeber properties of social cues or non-photic stimuli has accumulated.

Human phase response curves for light

Quantifying the response of the human circadian pacemaker to scheduled exposure to bright light is a prerequisite for the rational application of bright light therapy to sleep disorders. In classical circadian rhythm research the response to light has been assessed primarily by applying single light pulses to animals which were free running in constant darkness. This approach has revealed that in both nocturnal and diurnal animals the phase advance portion of the PRC is located at the end of the subjective night/beginning of the subjective day, i.e., at that part of the circadian cycle which under entrained conditions in both nocturnal and diurnal species would coincide with dawn. Phase delays are induced when light pulses are given at the end of the subjective day/beginning of the subjective night, i.e., that part of the circadian cycle which under entrained conditions coincides with dusk.

Application of this protocol to humans is not without problems. In contrast to most small laboratory animals, humans exhibit a monophasic sleep-wake cycle. Applying light to certain phases of the circadian cycle therefore necessitates a displacement of sleep, which in itself does not appear to be capable of inducing phase shifts (Kronauer et al., 1993). Furthermore, it is difficult to maintain human subjects in constant darkness. Therefore, unlike PRCs in animals, the human PRC has to be generated against a background of low intensity light. Since subjects close their eyes during sleep, or turn off the light when they go to bed, the sleep-wake cycle generates a light-dark cycle which may affect the observed response (cf Beersma et al., 1987). In humans the sleep-wake cycle is only loosely coupled to the circadian pacemaker and the sleep-wake cycle is not a very accurate phase marker of the circadian pacemaker. This implies that phase shifts have to be quantified by other, and preferably, by a number of variables (Czeisler et al., 1990; Shanahan and Czeisler, 1991).

Despite these problems, PRCs to three consecutive light pulses (Czeisler et al., 1989) and to single light pulses

have been obtained (Minors et al., 1991). In the single pulse experiment, the duration of the 5000 lux light pulse was 3 hours whereas in the triple pulse experiment the duration of a pulse was 5 hours and light intensity was 10,000 lux. According to both PRCs light exposure at ~3-1 hours before the minimum of the endogenous component of temperature rhythm, which under entrained conditions in healthy young subjects is located at approximately 5-6 AM (Czeisler et al., 1992), induces phase delays. Phase advances are observed when light is applied 1-4 hours after the minimum of the core body temperature rhythm. In both PRCs, no phase shifts are observed when light is applied during the larger part of the subjective day. The results of the single and triple pulse PRCs differ for light pulses given close to the minimum of the temperature rhythm. In the single pulse PRC, no large phase shifts were observed at this circadian phase, whereas in the triple pulse PRC large phase shifts up to twelve hours were observed (see also Eastman et al., 1992). An important characteristic of both PRCs is that a large portion of that part of the PRC on which phase shifts can be induced coincides with the nocturnal sleep episode during entrainment. This may explain why in some protocols in which sleep was not displaced or subjects were not awakenend during light exposure, no phase delay shifts after light exposure were observed (Honma et al., 1987).

Kronauer (1990) developed a mathematical model to account for the three-pulse PRC data. According to this model a single light pulse centered around the minimum of the core body temperature rhythm, even though it does not affect the phase of the pacemaker, does change the amplitude of the oscillator. This reduction of the amplitude then renders the pacemaker more sensitive to subsequent light pulses, which then can induce large phase shifts and exhibits so-called type 0 resetting. The predicted reduction of the amplitude after one or two light pulses centered at the minimum of the core body temperature rhythm, was subsequently verified (Jewett et al., 1991) and also reported by Minors et al. (1991). An implication of these findings and this model is that, besides phase, amplitude is an important parameter of the circadian system. Further-more, the model allows the prediction of phase and amplitude even if the light-dark schedule to which subjects are exposed is complex. This latter aspect is important to the clinical application of bright light because in real life situations humans are exposed to complex light-dark cycles, not just single bright light pulses.

Recently, Beersma and Daan (1993) have argued that the observed changes in amplitude may not reflect pacemaker amplitude but rather changes in oscillatory processes downstream from the central pacemaker. Furthermore, they argued that type 0 resetting as observed by Czeisler et al. in their three pulse PRC could be produced by three type 1 resets. Kronauer et al. (1993) replied that some of the assumptions in the approach taken by Beersma and Daan are in themselves incompatible with a pacemaker which can only exhibit type 1 resetting (see also Strogatz, 1991). It has been pointed out by Laking-Thomas (1993) that a pacemaker which exhibits both changes in phase and amplitude and can therefore show type 0 resetting is probably the most parsimonious model for circadian pacemakers in many organisms. An important consideration in these discussions is that although the observed variable, e.g., temperature, may exhibit changes in amplitude and type 0 resetting this does not necessarily imply that the central nervous pacemaker itself is a complex oscillator with at least two state variables. However, as long as the central pacemaker cannot be accessed directly, these considerations remain speculative.

Some neuroanatomical pathways mediating the effects of light on circadian rhythms have been elucidated

The evidence that in mammals the suprachiasmatic nuclei (SCN) of the hypothalamus are the loci of the endogenous circadian pacemaker is overwhelming (Meijer and Rietveld, 1989; Klein et al., 1991). Conclusive evidence was provided by the demonstration that a key parameter of the circadian system, its intrinsic period tau, can be transplanted by transplantation of fetal SCN tissue in a previously SCN lesioned host animal (Ralph et al., 1990). In humans the SCN has been described in detail (Mai et al., 1991) and changes in the SCN have been documented in relation to gender and aging (Swaab et al., 1988). A case study has been reported in which a lesion of the SCN resulted in severe disruption of the sleep-wake cycle (Cohen and Albers, 1991).

In the intact animal, light information reaches the SCN via the retino-hypothalamic tract (RHT), a monosynaptic pathway from retinal ganglion cells to the suprachiasmatic nuclei, which has also been demonstrated in humans (Sadun et al., 1984), and via a second pathway (the geniculate-hypothalamic tract, GHT) via the intergeniculate leaflet of the geniculate nucleus. Light pulses induce long-lasting increments or decrements in firing rates of specialized neurons in the SCN (Groos and Meijer, 1985). Furthermore, light pulses have been shown to increase the expression of the immediate early gene c-fos and other immediate early genes in a phase dependent way (Rusak et

al., 1990; Kornhauser et al., 1990; Sutin and Kilduff, 1992; see also Ginty et al., 1993). Surprisingly, no consensus has been reached over which neurotransmitter system is primarily involved in transducing light information to the SCN. Early findings indicated that acetylcholine (Earnest and Turek, 1985) and GABA (Ralph and Menaker, 1985, 1986) were key factors in transducing information via the RHT, and more recent evidence points to a critical role for excitatory amino acids (Meijer et al., 1988; Colwell et al., 1991; Abe et al., 1991; Vindlacheruvu et al., 1992) in conjunction with GABA (Moore and Speh, 1993). Neuropeptide Y is generally believed to be the neurotransmitter of the GHT (see Meijer and Rietveld, 1988 and Morin, 1994 for references).

Wave length and light intensity response curves have been generated for the phase shifting effects of light in rodents (Nelson and Takahashi, 1991). The wave length response curve suggests an involvement of rods whereas the involvement of cones is suggested by the intensity response curve since the threshold for inducing a phase shift is rather high (Takahashi et al., 1984). Some evidence for species differences has been obtained (Meijer et al., 1989) and it also has been suggested that the effects of light on the circadian pacemaker are mediated via an as yet unidentified photoreceptor (Foster et al., 1991) .

For humans, neither an intensity nor wavelength response curve for phase shifts of the circadian system is available.

The light-dark cycle has a direct "masking" effect on many variables, including sleep

Aschoff has distinguished between two different effects of zeitgebers on rhythmic processes: "it entrains the rhythm by controlling the phase of the pacemaker's oscillation, and it may influence the variable measured (the overt rhythm) in a more direct way, with or without a relationship to the process of entrainment" (Aschoff et al., 1982). The distinction is of special importance in the present context because many variables which are used as markers of the circadian pacemaker are also subject to masking by light. For instance, plasma melatonin, which can be considered to be a reliable marker of the circadian system, and for which the neuroanatomical pathway by which the pacemaker generates the overt rhythm is well documented (Moore and Klein 1974), can be suppressed by light exposure of sufficient intensity (Lewy et al., 1980; McIntyre et al., 1989). As a consequence, melatonin cannot be used as a phase marker when measured during a treatment with bright light. Similar arguments apply to core body temperature, which can be readily manipulated by exposure to bright light (Badia et al., 1990; Dijk et al., 1991; Cajochen et al., 1992; Bunnell et al., 1992), an effect which may be mediated by the light-induced suppression of melatonin (Strassman et al., 1991). Sleep itself is subject to masking effects by light. In the rat the amount of REM sleep is enhanced during schedules with continuous or intermittent light (Borbély, 1980). In the squirrel monkey masking effects of a light-dark cycle have been described for brain temperature and sleep propensity even in the SCN lesioned animal (Edgar, 1986). Although it is not known by which neuroanatomical pathways these effects of light are mediated, there is growing evidence that beside the SCN several hypothalamic areas are innervated by direct or indirect retinal projections which are not part of the primary visual system (Card and Moore, 1991). These findings point to the possible involvement of non-circadian mechanism in the effects of light treatments [see Campbell, *LTBR* (1993), *6*:19] and stress the importance of experimental designs which allow to distinguish between these two effects (see also Wirz-Justice et al., 1993).

Assessment of circadian phase, amplitude and wave form

To investigate whether a bright light therapy has affected circadian parameters, adequate assessment of these parameters is of critical importance. Sleep itself has marked effects on many physiological variables. Although in a strict sense this effect cannot be called masking, it poses similar problems. Thus, body temperature is affected by posture, sleep and maybe by sleep structure (Kleitman and Doktorsky, 1933; Barret et al., 1993). If a bright light treatment affects sleep it may thereby also affect the time course of core body temperature during sleep. The time course of core body temperature during sleep can therefore not be considered a reliable marker of the circadian system.

It has been proposed that the masking effects of sleep on body temperature can be removed mathematically (Folkard et al., 1991). This procedure may be of some help, especially when only average responses are studied and temperature data of several weeks, collected under steady-state conditions, are available. However some of the assumptions underlying the "demasking" procedure may not be valid. Thus the masking effect of sleep on temperature is not independent of circadian phase, and large inter-individual differences in the masking effects of sleep on temperature, which are not taken into account by these mathematical procedures, do exist (Wever, 1985). Alternatives are to use phase markers, such as plasma melatonin, which are thought not to be affected by sleep,

or to use the elaborate constant routine protocols as developed by Mills and colleagues (1978) and refined by Czeisler et al. (1985). The constant routine protocol distributes masking effects of posture, sleep, meals, etc. equally over the 24-h day and thereby allows for an accurate assessment of circadian phase, amplitude and wave form (Brown and Czeisler, 1992), also in sleep disorders (Morris et al., 1990). Some caution in the interpretation of the results is needed because the constant routine protocol usually needs to be longer than 24 hours, thereby introducing sleep deprivation as a new confounding variable.

Feedback on Pacemaker

Although it originally was thought that the endogenous circadian pacemaker was rather insensitive to stimuli other than external zeitgebers it has become apparent that outputs of the pacemaker can feedback onto the pacemaker and change overt rhythmicity. Wheel running activity and arousing stimuli have been shown to influence the phase and period of circadian rhythms in rodents (Mrosovsky and Salmon, 1987; Van Reeth and Turek, 1989; Edgar et al., 1991). At least some of these effects are mediated via the light-entrainable pacemaker, i.e., the SCN (Mead et al., 1992). For humans such a feedback of activity, arousal or the sleep-wake cycle (Kronauer et al., 1993) on the endogenous circadian pacemaker has not been demonstrated conclusively.

Animal studies (Cassone et al., 1986; Armstrong, 1989), as well as recent human studies (Lewy et al., 1993) have demonstrated that melatonin can induce phase shifts of overt rhythmicity. In humans evidence has been put forward to indicate that melatonin alleviates jet lag, stabilizes sleep onset, but not the rhythms of cortisol and core body temperature, and can induce phase shifts in the free-running rhythm of melatonin in blind subjects, and maybe entrainment (Arendt et al., 1986; Folkard et al., 1990; Sack et al., 1991). Melatonin receptors/binding sites have been identified in the rodent and human SCN (Vanecek, 1987; Reppert et al., 1988). In the rat, melatonin receptor density is affected by light conditions (Gauer et al., 1992). The circadian rhythm of discharge rate of the SCN can be reset by melatonin in vitro (McArthur et al., 1991) and melatonin induces expression of the immediate early gene c-fos (Kilduf et al., 1992). Since in mammals the rhythm of melatonin is driven by the SCN, it has been suggested that melatonin provides a feedback to the SCN, which conceivably could stabilize entrainment.

The monophasic sleep-wake cycle of humans and their practice of sleeping in a darkened room creates another feedback: the perceived light-dark cycle is influenced by these behavioral characteristics. This feedback may be responsible for a phenomenon called "phase trapping", i.e., a periodic modulation of the phase relation between the sleep-wake cycle and the core body temperature rhythm, which has been observed in free-running studies (Kronauer et al., 1982; Beersma et al., 1987). It may also be responsible for the classical observation that in humans who free-run while self-selecting their light dark-cycle, tau is close to 25 hours, whereas period assessed in protocols in which this influence is absent or controlled for, tau is much closer to 24 hours (Dawsonet al. 1991; Klerman et al., 1992, Sack et al., 1992; Campbell et al., 1993). This feedback (i.e., the light-dark cycle created by the sleep-wake cycle), may play a role, for instance, in delayed sleep phase syndrome, and it may affect the efficacy of bright light therapy. If the sleep episode is located late in the circadian cycle of light-sensitivity, sleep will prevent light from reaching the pacemaker. During light therapy sleep could be displaced and the circadian cycle of light sensitivity be advanced relative to clocktime, but upon termination of the light therapy, sleep may resume its normal phase relation with the circadian cycle of light sensitivity and environmental light may again not reach the pacemaker at its sensitive phase. This would result in a drift of the pacemaker to later hours.

Not only the rest-activity cycle but also the retina influences the light input reaching the pacemaker. It has been demonstrated for the rat and for humans that retinal sensitivity exhibits a circadian variation (Remé et al., 1991) There is growing evidence to suggest that in the rat a circadian rhythm of visual sensitivity persists after SCN lesions (Terman and Terman, 1985; Terman et al., 1993). This circadian variation, whether generated by as yet unspecified efferents from the SCN or generated by an oscillator distinct from the SCN, constitutes a mechanism which may contribute to variations in entrained phase.

Interaction between the circadian and homeostatic regulation of sleep: Some implications for the design and interpretation of bright light studies

The endogenous circadian pacemaker is a major determinant of sleep propensity, sleep timing, sleep structure and the consolidation of sleep and wakefulness. Adjustment of circadian phase or amplitude by bright light treatment can be expected to induce changes in these parameters. The circadian variation of sleep propensity exhibits a maximum at the trough of the circadian rhythm

of body temperature and sleep duration is longest when sleep episodes are initiated shortly after the maximum of core body temperature (Czeisler et al., 1980; Zulley et al., 1981). Sleep episodes initiated on the later part of the rising limb of the body temperature rhythm are disrupted and of short duration. REM sleep reaches its maximum shortly after the minimum of the body temperature rhythm. The deep stages of nonREM sleep, i.e., the stages 3-4 or slow wave sleep (SWS) appear to be little affected by the circadian pacemaker, at least during nocturnal sleep (Hume et al., 1977; Weitzman et al., 1980; Campbell and Zulley, 1989).

The prior history of sleep and wakefulness is another, equally important, determinant of sleep propensity and sleep structure (Webb and Agnew 1971; Borbély et al., 1981; Dijk and Czeisler, 1994). Thus SWS and computer-detected slow-wave activity (SWA) in the EEG, decrease in the course of sleep independent of circadian phase (Åkerstedt and Gillberg, 1981; Dijk et al., 1990a, b, 1991) and an extension of wakefulness results in an enhancement of SWS and SWA in subsequent sleep (Webb and Agnew 1971; Borbély et al., 1981). Even REM sleep, which is generally thought to be primarily under circadian control, is affected by the prior history of sleep and wakefulness. After total sleep deprivation a REM rebound has been observed in the second recovery night (Williams et al., 1964). Furthermore, the observed increase of REM sleep duration in the course of the nocturnal sleep episode is in part due to a sleep dependent disinhibition of REM sleep (Dijk and Czeisler, 1993). Likewise, the latency to REM sleep can be reduced by reducing the pressure for nonREM sleep (Campbell, 1987; Feinberg et al., 1992).

The process tracking the prior history of sleep and wakefulness is not located in the SCN, since sleep deprivation in SCN lesioned animals still results in compensatory responses (Tobler et al., 1983; Mistlberger et al., 1983; Trachsel et al., 1992). Observed sleep-wake patterns result from an interaction between the output of the endogenous circadian pacemaker and the regulatory processes subserving sleep homeostasis (Webb and Agnew 1971; Borbély, 1982; Daan et al., 1984; Beersma et al., 1987; Edgar et al., 1993). The neuroanatomical locus of and the neurophysiological processes involved in this interaction between the output of the pacemaker and sleep homeostasis are not known (Watts, 1991).

The interaction between circadian and homeostatic regulation of sleep complicates the interpretation of observed changes in sleep parameters during and after bright light treatment if during treatment sleep is displaced, or curtailed. Sleep displacement or curtailment may be necessary in order to be able to expose subjects to bright light at a circadian phase which normally is shielded from light input by sleep. Observed changes in sleep parameters such as SWS, sleep latency or subjective alertness, which are very sensitive to prior sleep loss (Carskadon and Dement, 1979; Borbély et al., 1989; Dijk et al., 1990; Brunner et al., 1990) may not be due to bright light induced changes in phase or amplitude of the circadian system, but rather may be related to sleep loss during the treatment. Conversely, inadequate EEG analysis may result in failure to detect treatment induced changes in the EEG. Adequate control procedures, polysomnographic recording of sleep during the treatment period, and quantitative EEG analysis (Borbély, 1990) may help avoid misinterpretation of the data.

Conclusion

Remarkable progress has been made in the understanding of the neuroanatomical structures and neurophysiological processes underlying circadian rhythmicity. The empirical findings and theoretical concepts are transparent and their application provide powerful tools in the study and treatment of circadian disorders. The rigorous application of these concepts to the study of sleep disorders related to circadian rhythm abnormalities has until now been limited. Strict experimental designs and quantitative models in which all of the processes involved in the timing of sleep are taken into account, will aid in the development of new — and understanding of existing — effective bright light therapies for sleep disorders related to the circadian system.

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BOOK REVIEW

How to Beat Jet Lag: A Practical Guide for Air Travelers

By D.A. Oren, W. Reich, N.E. Rosenthal, and T.A. Wehr (New York, NY: Henry Holt and Company, Inc., 1993, 137 pp., US$14.95).

How to Beat Jet Lag: A Practical Guide for Air Travelers provides the prospective transmeridian air traveler with a set of detailed instructions on how — and especially when — to seek exposure to light and darkness for accelerating the reentrainment of circadian rhythms to new time zones, thereby reducing the duration and severity of jet lag.

The book opens with a very readable overview of the circadian timing system and its entrainment to the day-night cycle, of the effects on sleep and alertness of abrupt shifts in external time cues consequent to transmeridian travel, and of the ensuing adjustment process. This is followed by a clear description of phase-dependent resetting of the human circadian clock by timed exposure to bright light, and an explanation of the guiding principles for the authors' recommendations, based on a flourishing literature documenting the efficacy of timed exposure to bright light for phase shifting human circadian rhythms. The authors are careful to point out (a sign of the times?) that the strategy they are recommending is one of gradual, cumulative, phase-shifting, 'fundamentally different' from the amplitude flattening strategy advocated by Czeisler and colleagues: in the words of Charmane Eastman, the 'nudge' rather than the 'squash' approach.

The literature on the use of bright light for resetting human rhythms, however, consists primarily of studies in controlled laboratory settings, using specific light exposure parameters. The application of these findings to a real jet lag situation therefore entails a number of simplifying assumptions. The first of these has to do with the transition point between phase delays and phase advances on the human PRC to light. There is general agreement that this occurs near the time of the nightly minimum of the circadian rhythm of body temperature, but that time can vary considerably from one individual to the next. In the book, the transition point is assumed to occur at 4:00 A.M. for individuals who usually go to sleep between 10:00 P.M. and 12:00 A.M., and who wake up between 6:00 A.M. and 8:00 A.M. Travelers with earlier or later sleep times are instructed to change the recommended light exposure times accordingly. Such a range in habitual sleep times may leave room for considerable interindividual variability in temperature minima and PRC transition times. An accurate estimate of the transition point is critical because maximum phase delays and phase advances are induced by light exposure just before and just after this point, respectively, and the authors in fact recommend that travelers be exposed to light (or darkness) for 3-h periods either ending or beginning at 4:00 A.M. (or the subjective equivalent).

The main portion of the book consists of step-by-step instructions for specific trips, depending on the direction of travel and on the number of time zones crossed (3-12 zones east and 3-13 zones west). Local time of day is generally given for the point of departure as well as for the destination. However, only Standard Times are specified and there is no mention of Daylight Saving Time. Not all countries adopt Daylight Saving Time (most countries near the equator remain on Standard Time year-round), and

those that do may switch at different times of the year (the U.S. switches on the first Sunday in April and the last Sunday in October, whereas much of Western Europe does so on the last Sunday in March and the last Sunday in September). These and other country-specific practices can therefore add to the uncertainty of the 4:00 A.M. estimate of the PRC transition point.

For flights across 5 or more time zones, the book recommends light exposure on 2 or more consecutive days. The strategy here is to track the gradually shifting circadian timing system such that the traveler is always exposed to light and darkness at the maximally sensitive phases. To do so, the authors assume that the circadian rhythms of travelers using the recommended procedures will shift at the rate of 2 h per day following both eastward and westward flights. In the absence of any special treatment, average reentrainment rates have been estimated at about 1 h/day and 1.5 h/day following eastward and westward flights, respectively (for a recent summary, see *LTBR*, 1993, 5: 51-57). To this must be added any additional phase shifts induced by timed exposure to light and darkness on the preceding day. Single 3-h light pulse PRC data show maximum phase shifts of $\pm$ 2 h, with phase advances being somewhat larger and/or more consistently obtained than phase delays. Thus, a daily shift of 2-3 h seems a reasonable, though still highly uncertain, estimate of the rate of adjustment to both eastward and westward trips in travelers following the recommended procedures.

Surprisingly, the procedures recommended in this book do not take into account the fact that following large phase advances of the day-night cycle, reentrainment may be faster by phase delay than by phase advance, an effect attributed to the tendency for the endogenous period of the human pacemaker to exceed 24 h. This phenomenon, known as antidromic reentrainment, has been observed both in laboratory studies after 6-h phase advances and in field studies after eastward flights across 8-9 time zones. Yet in the book, advance-inducing light exposure is recommended for all eastward flights, even flights across 12 time zones. On the other hand, delay-inducing light exposure is recommended for westward flights across 12 and 13 time zones, even though such flights are equivalent to eastward flights across 12 and 11 time zones, respectively.

The levels of light intensity required for achieving beneficial effects are not specified in any detail. Travelers are encouraged to seek exposure to natural sunlight whenever possible, and to brightly illuminated indoor areas at other times. Sources for purchasing light boxes and light visors are also provided. It may have been useful to list light intensity levels for natural daylight at a few standard times of the day and year (e.g., twilight, sunrise/sunset, noon in winter/summer with and without cloud cover) and for artificial light in typical indoor environments to provide the reader with a scale of reference, as most people are poor judges of absolute illumination level. The authors also encourage physical, or at least mental, activity during scheduled light exposure times, and rest or quiescence during scheduled darkness. The efficacy of these procedures is still uncertain, but they can certainly do no harm. Finally, the book includes a time zone map, a table of cities listing the number of time zones separating 60 common destinations around the globe, as well as a cloth eyemask and a pair of eyeshades to block or reduce light exposure at times when such exposure would be detrimental to the adjustment process.

In summary, if someone were to come up behind me on a moonless night, put a gun to my head, and demand a simple formula for light treatment of jet lag, my recommendations would, with a few exceptions, resemble those described in this book. A more accurate prescription would certainly be possible — desperate jet-lagged muggers notwithstanding — but would require the use of specialized software to generate an individualized PRC that would be referenced to a person's specific sleep times rather than to a fixed clock time, and that the user could modify as new, more detailed, information becomes available, as it undoubtedly will.

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BOOK REVIEW

"Light Therapy", chapter in Alternative Medicine: The Definitive Guide

Compiled by The Burton Goldberg Group (Puyallup, WA, Future Medicine Publishing, Inc., 1068 pp., US$59.85).

For more than 15 years, researchers from the fields of psychiatry, psychology, sleep and biological rhythms have been investigating the effects of bright light on a variety of

physiological and psychological parameters. However, there are other factions promoting the use of different types of light such as colored light and cold lasers that are perhaps less well known in the academic setting.

The chapter on light therapy in *Alternative Medicine* reviews the use of different types of light for treatment of a wide variety of ailments. Unfortunately, the chapter does not provide the reader with any critique of the techniques or with any suggestion that some of the methods are not considered mainstream by the medical community. For example, the author reports on a "discovery" by a photobiologist that the absorption of certain nutrients from the digestive tract depends on exposure to particular wavelengths of light. Another claim is made that light reaching the brain stem "helps to provide coordination and balance" (page 320). The use of colored light — allegedly to stimulate hormone production, produce analgesia, and cure mood disorders — is presented. None of these theories is generally accepted. Interspersed among these sections, though, are descriptions of more conventional uses of light therapy that do have solid research support such as light therapy for postnatal jaundice and for SAD.

Furthermore, the reader is left without the sense that much is still unknown about the mechanism of action of light. In a highlighted section, the authors discuss "whole-brain light therapy" that is based on an unspecified measure of "light-generated photocurrents traveling from the retina to the higher brain centers" (page 327). Decreases in photocurrent transmission can allegedly cause decreased brain functions in key areas of mood and memory, among others. This theory is open to debate. While it is true that the etiologies of some disorders — such as SAD and insomnia — currently being treated with light are also not yet established, there should have been some discussion about the current status of research.

Finally, many of the disorders — such as depression and endocrine problems that are listed as being amenable to light therapy of whatever type — can be quite serious. It would have been useful to the reader to point out that in cases of depression or other types of mental illness, a consultation from a mental health provider or other health professional should precede a do-it-yourself light program.

In summary, the authors have been thorough in reviewing various purported uses of light as a therapeutic agent. However, the inaccuracies in descriptions of physiology and the lack of comment regarding the speculative nature of some of the methods limit the usefulness of this book as a reference guide.

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BULLETIN BOARD

We welcome new members who have joined SLTBR since publication of the December 1993 issue:

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SLTBR SEEKS REIMBURSEMENT INFORMATION

The SLTBR Reimbursement Committee, chaired by David Schlager, M.D., is asking members to help compile information on insurance reimbursement for light treatment apparatus. The questionnaire enclosed with this issue of *LTBR* provides the basis for this effort. We ask your help

in gathering this data on a timely basis by completing the questionnaire and returning it to the SLTBR Executive Office by 20 April. Your effort in contacting past patients to obtain additional information will also be of value. A sample letter is included in the questionnaire to provide continuty in responses. Please indicate on the questionnaire your intent to undertake this additional task and return a summary of responses by 1 June. Interim results of this effort will be reported at the SLTBR annual meeting with follow-up published in a subsequent issue of *LTBR*.

NIH TO HOST 1994 ANNUAL MEETING AT LISTER HILL

Accompanying this issue of *LTBR* are registration materials and an abstract submission form for the 1994 SLTBR Annual Meeting, scheduled for 23-24 June at Lister Hill Auditorium on the campus of the National Institutes of Health. We look forward to returning to this excellent facility and collaborating again with the National Institute of Mental Health as meeting cosponsor. We are also pleased to announce that our meeting has been named an official satellite of the XIXth CINP Congress (see below).

The Program Committee is applying for AMA Category 1 CME certification for the educational segments of the meeting. In addition to abstract presentations, a formal review course and the SLTBR membership meeting, we have planned for a 23 June discussion session on patent issues. As in the past, SLTBR Corporate Members are invited to exhibit at the meeting.

SLTBR members active in research are encouraged to submit abstracts for consideration by the Program Committee. The abstract submission form together with the completed conflict of interest statement must accompany all abstracts. Deadline for return of these materials is **2 May 1994.**

Meeting packets with travel information, meeting schedule and other information will be mailed to registrants shortly following the 1 June general registration deadline.

Meeting participants who wish to make room reservations at our designated hotel, the Holiday Inn Bethesda, should do so before the 8 June reservation deadline. The hotel, within walking distance of Lister Hill, also provides complimentary shuttle service to and from the NIH campus.

We have made arrangements with Positano, an Italian restaurant in Bethesda, for our annual banquet which will be held the evening of 23 June. We invite meeting registrants to complete the banquet reservation card included in the meeting brochure, indicating their choice of main entrée.

We hope that you will invite your non-member colleagues to attend the meeting. You may duplicate the meeting registration form for their use or request additional brochures from the SLTBR office by faxing 503-694-2404. We have also included a membership application in this issue so that new members may provide more detailed membership directory information. Non-member registration includes dues for the remainder of the 1994 membership year. New members will also receive a copy of this *LTBR* issue.

CINP LISTS SLTBR ANNUAL MEETING AS SATELLITE

The XIXth CINP Congress will include the SLTBR 1994 Annual Meeting as an official satellite of its Decade of the Brain celebration scheduled for 27 June - 1 July in Washington, DC. The Congress, which follows the SLTBR meeting in Bethesda, will offer over 160 symposia and satellite sessions covering the most recent contributions to basic and clinical neuroscience. Clinicians and research scientists from over 45 countries are expected to participate in the proceedings.

SLTBR meeting registrants are encouraged toextend their stay in the Washington, DC area and attend all or a portion of the Congress. For more information, call or write *XIXth CINP Congress Secretariat, 2014 Broadway, Suite 320, Nashville, TN 37203. Tel 615-322-2075; fax 615-343-0662.*

Society for Light Treatment
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