

Light Treatment and Biological Rhythms

Bulletin of the Society for Light Treatment and Biological Rhythms



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MUD IN YOUR EYE

I am sitting here at my kitchen table on the Monday morning following "Woodstock '94". The photos and verbal accounts spread across the pages of the New York Times over the past days make it clear that mud was perhaps the only common denominator linking this event with it's '60's predecessor. And apparently, there is even some question as to whether the mud fights were authentic: some reports indicate that they were staged by the sponsors of the event.

By most accounts that I have here in front of me, "Woodstock '94" just didn't measure up to the original event. But then, how could it? I mean, Crosby, Stills and Nash was born at Woodstock! America discovered Joe Cocker at Woodstock! Richie Havens entered the mainstream at Woodstock! Sex and drugs and rock-and-roll met one another at Woodstock — and hit it off famously!

In many ways, then, Woodstock was the defining event of an entire generation of North Americans and probably more than a few Europeans. It was a hard act to follow, and an impossible one to clone. On this Monday morning, I'm feeling a little like I think the organizers of Woodstock '94 must have felt when they began planning their sequel: "Wow man . . . like . . . how're we ever gonna match *that*?" In taking over the editorship of *LTBR* from Anna Wirz-Justice, I find myself asking the same question.

Under Anna's editorship, *LTBR* took on a distinctly international flavor; it became a handy reference piece for monitoring the state-of-the-art of light treatment research and practice, worldwide. Anna seemed to have her editorial finger on the pulse of the membership. Moreover, and perhaps more to the point, as many of us can testify, the woman was virtually impossible to say "no" to. This combination of charm and persistence is a rare and precious gift for an editor — or a mob boss — to possess. With this deft union of pulse-taking and

arm-twisting, Anna set a standard that will be difficult to equal and impossible to duplicate.

The challenge to uphold this high standard is unsettling indeed, as I sit here at my kitchen table, on this Monday evening following Woodstock '94. Fortunately, I will not face the blame . . . er, the task, alone. I am lucky to have experienced and enthusiastic collaborators, in the persons of Marty McCullough, Managing Editor since the Bulletin's inception, and David Schlager, the new Associate Editor.

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the Top Ten List. But first, let me take this opportunity to thank you in advance for your help. We will not be able to do it without you. And, on behalf of all of us, I take this opportunity to give Anna a huge "thanks" for her editorial efforts over the past three years.

To Anna! Here's mud in your eye!

S.S.C.

SLTBR MEETING A SUCCESS

The Society's annual meeting at Lister Hill Auditorium on the campus of the National Institutes of Health featured a varied program of oral presentations and education topics (see David Schlager's review, page 3). Lively poster discussions, corporate exhibits and an Italian banquet rounded out the two-day session in Bethesda, MD.

The business meeting of the Society was held on 23 June, and Regular members voted by proxy or in person. As described in the June *LTBR* (p.67), the Board of Directors has developed a staggered election process, increased its size to nine, but shortened each individual's term of appointment.

Elected were: J. Christian Gillin, M.D. (president-elect), Sonia Ancoli-Israel, Ph.D. (treasurer) and Scott Campbell, Ph.D. (*LTBR* editor). The Board appointed Raymond Lam, M.D., to serve the remaining one year of Dr. Wehr's unexpired Board term. Alfred Lewy, M.D., Ph.D., remains on the Board as secretary, and Norman Rosenthal, M.D., and Charmane Eastman, Ph.D., remain on the Board as "at large" members a further two years. Michael Terman, Ph.D., will serve on the Board this year as past-president before his current term expires. The Board also appointed David Schlager, M.D., as associated editor for clinical issues in *LTBR*. Committee chairs include George Brainard, Ph.D. (membership) and David Avery, M.D. (Federal/Industrial relations).

Robert Sack, M.D. (secretary-treasurer) and Thomas Wehr, M.D. (vice president, program chair) retired from the Board. We thank them for their collaborative efforts in these first fledgling years of SLTBR.

Marty McCullough, executive director, reported membership figures virtually unchanged from a year ago. Of the 400 current members, approximately 25% are Regular

And, of course, we have you. You, my fellow members, constitute the critical ingredient here. The organizers can put on the production, but it is the active, interactive, participation of the audience that will determine this sequel's success. So I take this opportunity to solicit your help. (Remember the chant?: "NO RAIN! NO RAIN! NO RAIN! . . ."). When I call you, please say "yes". But, better yet, pre-empt my call. Send me stuff! Mini-reviews, essays, letters to the editor, items for the Flash(light) Poll (see p. 19 and insert), meeting summaries, opinionated reviews of critical papers . . . there is room for it all. The stage is open, the mike is yours.

As I sit here at my kitchen table, late at night on this Monday following Woodstock '94, I realize that I have missed Letterman's opening monologue. I've got to hear

members. Associate members comprise about 65% of the total, and Student and Corporate members making up the remaining 10%. The Society's financial condition is stable, with reserves at approximately 45% of annual expenditures. Members who wish to receive a copy of the 1993 financial report may send a self-addressed envelope to the office at P.O. Box 478, Wilsonville, OR 97070 USA.

The lively and growing use of light- and melatonin-based therapeutic approaches to a number of clinical disorders dictates the need for more active recruitment of new members to participate in establishing standards for diagnosis and treatment. Given the discussion around the use patents granted to light and melatonin, we need active members to participate in consensus making.

Please, as a member of SLTBR, take a moment to think about the following and even do something about it!

HELP US AUGMENT ACTIVE MEMBERSHIP!

- Are those of your clinical colleagues who use light therapy members of SLTBR? Even though we have not yet developed accreditation programs, it would appear that up-to-date knowledge of the field, as provided by *LTBR*, annual meeting discussions, and consensus statements should be a professional minimum. Invite them, insistently, to join!
- Whenever you give a lecture this autumn and winter, inform the audience of the existence of SLTBR, and *never, ever*, travel without extra copies of *LTBR*, membership application forms, and the publications list and order form (the latter are enclosed for you to copy).
- When you are interviewed (star of stage, screen and radio), or write an article for a popular magazine or newspaper, *again, do not forget to mention SLTBR* and give the address for further information. This publicity helps to focus on our Society as an active, communicative professional body aimed to coordinate research-based information, manufacturers' efforts to develop innovative technology, and clinical knowledge.

SHOW THEM THE LIGHT!

Thank you in advance for your efforts to expand the Society's membership base.

Anna Wirz-Justice, Ph.D.

President

ANNUAL MEETING REVIEW

Society for Light Treatment and Biological Rhythms

The sixth annual meeting of SLTBR was held on June 23 and 24 at the National Institutes of Health in Bethesda, cosponsored by the National Institute of Mental Health and a designated satellite meeting of the Collegium Internationale de Neuro-Psychopharmacologicum. During two somewhat seasonally phase-advanced sweltering June days, and in competition for space with visiting throngs of World Cup Soccer fans, the gathering exchanged research findings, strategies, good cheer, and anticipation of next year's first European meeting site — Frankfurt. The proceedings reflected a maturation in the life history of the young organization, in the accomplishments of its members, in the breadth and complexity of the questions they address.

Leading off the meeting was Raymond Lam who, after noting the heightened pleasure of meeting participation derived from putting one's presentation behind one early on, proceeded to present important and long sought controlled-study evidence for the efficacy of a conventional antidepressant medication, in this case fluoxetine, for winter depression. In this multicenter Canadian trial, fluoxetine produced greater overall clinical response rates than placebo, with those patients having the highest baseline severity benefiting most from active treatment. He also noted that both placebo response rates (approximately 30%) and therapeutic effect-sizes were comparable to those reported in prior antidepressant trials among non-seasonal depressives.

Michael and Juan Terman, presenting interim data from their study-in-progress, reported that either morning or evening light, in treatment-naïve subjects, was superior to a control treatment of low-density negative ion exposure. They also presented new evidence to support their group's prior observation that a sequence effect in light cross-over studies — specifically evening light's diminished effect when preceded by morning light — may underlie morning light's previously noted superiority. Their findings add to

a growing preponderance of evidence for morning-evening equivalence in light's efficacy. Also of interest were preliminary findings that melatonin phase-shifts were correlated with clinical improvement and that high density negative ion exposure was associated with moderate improvement. Other suggestive evidence for Alfred Lewy's phase-shift hypothesis was provided by Anna Wirz-Justice, who presented preliminary analyses of her group's impressive collection of constant-routine data in female SAD patients and controls before and after midday light (10:00-14:00). They found rhythms of core body temperature but not salivary melatonin to be phase-delayed in SAD subjects compared to normals.

Al Lewy presented further evidence of a human phase response curve to exogenous oral melatonin (0.5 mg), noting no differences between younger adults and elderly subjects in phase-shift inflection points but a greater amplitude of melatonin-induced phase-shifts among the elderly. George Brainard presented evidence that continuous light exposure produced greater melatonin suppression than 10 minute on-off pulses over a similar 90 minute duration, thus providing some physiologic basis for the conventional recommendation of uninterrupted exposure during daily treatment sessions. Paul Arbisi presented basal prolactin data in male SAD subjects and controls which were especially notable for their consistency with prior evidence — from studies of electroretinography and L-dopa administration — that men and women differ in neurobiologic correlates of SAD.

Other reports reflected a broad spectrum of active research centers and topics, including vitamin B12-enhancement of phase-shift and melatonin suppressive effects of bright light (Honma et al.), further indications of seasonality in some substance abuse patients (Anderson et al.), melatonin changes in premenstrual dysphoric disorder (Parry et al.), actigraphic evidence of decreased sleep in light-treated SAD patients (Teicher et al.), and direct-interview evidence of comparable rates of major depression among relatives of seasonal and non-seasonal depressives (Schlager et al.).

This year's continuing education course was an inspired and well-attended event, owing much to the exuberance and good humor of its organizer Dan Oren. Talks included an elegant and definitive review on the psychophysics of ocular illumination by George Brainard, practically oriented talks on choosing and getting reimbursed for therapeutic lighting devices by David Avery and David Schlager, respectively, a strategic tutorial

on applying for current NIH grant-funding by Mary Blehar, and a very nice review and new findings on the increased rates of winter depression among adolescents compared to children by Susan Swedo.

A highlight of the course was Dan Oren's own presentation on "The top ten papers published in the field of Light Therapy and Biological Rhythms: A critique". (On top of the top, of course, was Lewy's 1980 paper on human melatonin suppression by bright light). Oren's format, in my opinion, supplied just enough dramatic tension to serve a useful and entertaining purpose in reviewing the major findings of the field. It provided due recognition of the difficult task of producing a piece of work which is both original and correct. And it evoked a decade or so of activity which, at least for those involved, seemed dizzy with discovery. It was also an apt finale for Dan Oren himself, who begins his new work with the FDA. We thank him for his contributions and wish him the best.

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MEETING REVIEW

Society for Research on Biological Rhythms

This was my first visit to Amelia Island, and I found it to be an idyllic location. Luxurious accommodation, sun, sand and sea. . . Although this was an excellent, well organized meeting, my major disappointment was the number of parallel sessions. Surely it would be better to stage the conference over an extra day, rather than having to choose between three or four parallel sessions. This became even more frustrating when the chairperson rearranged the order of speakers. My review focuses on basic rhythm research results; the human studies were summarized in the June *LTBR* by Marie Dumont (Vol. 6, p. 62).

There was a lively symposium on non-photic entrainment. Non-photic entrainment is clearly gaining interest as an exciting area of research, with the main questions being addressed focusing on the likely afferent pathways to the SCN, and the neurotransmitters involved in mediating these effects. Larry Morin revealed that the dorsal raphe projects to the intergeniculate leaflet (IGL) and not the

SCN, whereas the medial raphe projects to the SCN and not the IGL. Nicholas Mrosovsky showed how central injection of anti-NPY could block novelty-induced wheel running, suggesting NPY (neuropeptide Y) is involved in mediating the effects of non-photic stimuli on the circadian clock in hamsters. A second focus was the role of monoamines, in particular serotonin, in non-photic entrainment. Fred Turek showed how depletion of CNS monoamines with reserpine blocked phase shifts to activity-induced stimuli in the hamster. By depleting serotonin, using the selective neurotoxin p-chloroamphetamine, the phase shift to triazolam was blocked, suggesting serotonin is involved in the mechanism by which activity-induced stimuli influence the phase of the circadian system. Dale Edgar reported how 5,7DHT injections, another serotonin neurotoxin, into the area around the SCN, blocked activity-dependent entrainment in the mouse. Aging was also covered in this symposium, as well as in a workshop. Clearly this is an area which is generating much clinical interest. Mrosovsky claimed there was a deficit on the input side to the clock in old animals, since by increasing the stimulus (an oestrous female rather than a novel wheel) the old animals increased running and phase shifted; hence, "motivate the aged"! Turek suggested the difference between old and young animals was related to a depletion in the level of the monoamines in the CNS.

A second symposium considered ultradian, circadian and seasonal rhythms. Antonio Nunez looked at the photoperiodic control of prolactin, in particular changes in dopamine. An elegant (and heroic!) study by Suzanne Moenter looked at the control of LH secretion by GnRH during the preovulatory period. By measuring GnRH-immunoreactivity in portal blood at 30-60s intervals in ovariectomised plus or minus oestrogen implanted ewes, she showed that the negative feedback effects of oestrogen are at the level of GnRH secretion (although probably not on GnRH neurones) and the pituitary. Using an antisense mRNA probe to VIP, applied to the region of the SCN, Phyllis Wise showed the circadian rhythm in corticosteroid secretion could be disrupted. In an elegant presentation by Franziska Wollnik and colleagues the ability of light to induce phase delays in the activity rhythm in rats was blocked by prior administration of antisense probes to c-fos and jun-B. Antisense is clearly a valuable tool for investigating the role of various peptides and/or immediate early genes, especially where no antagonist exists. In a workshop on the wonderful world of SCN glia (are they necessary and/or sufficient for clock function?), Jacques Servier showed there to be a circadian variation in glial fibrillary acidic protein-immunoreactivity (GFAP-ir) in the

hamster, as did Vincent Cassone in the avian SCN; although Antonio Nunez, albeit using rats and different times, did not see an effect of time of day on glial retraction. David Glass considered whether glia may have a role in regulating glutaminergic activity in the SCN. However, the precise role for glia within the SCN has yet to be identified.

There was much interest in nitric oxide (NO) as a second messenger within the SCN. Martha Gillette and colleagues, using the in vitro slice preparation, demonstrated how a PRC to glutamate is identical to the light PRC. These phase shifts to glutamate (advances and delays) could be mimicked by NO donors or attenuated by inhibitors of extracellular NO, such as haemoglobin. Similar studies in vivo demonstrated that central administration of a NO-synthetase inhibitor attenuated phase delays and advances in the activity rhythm of free-running hamsters, without influencing light-induced c-fos expression.

One of the highlights was the special symposium dedicated to "A Biennium of Progress". Jim Krueger looked at the interaction between sleep and immune function, suggesting there is a link, and Rémy DeFrance discussed the development of chronobiotics. Joe Takahashi concentrated on the molecular approaches in studying clock function. In his 'decade of the mouse' talk, he described the genetic mapping of a "clock" (circadian locomotor output cycle kaput!) gene showing the mutation to be on the midportion of chromosome 5. Gene Block reviewed studies involved in understanding the cellular basis of the circadian pacemaker in *Bufo gouldiana*. In an excellent talk Steve Reppert revealed how the melatonin receptor was cloned. Several groups have been pursuing this goal, however it appears the source of tissue used ultimately proved to be very important. The receptor is G-coupled, with little homology with other known G-protein coupled receptors. There is a 61% homology between the receptor isolated from *Xenopus* and sheep, with a 75% homology across the transmembrane region. Both the pharmacological characteristics and distribution (so far) of the melatonin receptor using ISH to fragments of the receptor are identical to those reported in the literature. Clearly research into both seasonal and circadian rhythms will benefit greatly from these recent advances.

Despite the parallel sessions this was an excellent meeting, for which the organizers should be thanked. With the new technologies and approaches available for studying the clock this is an exciting and rapidly expanding area of research; I look forward to the next meeting!

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MEETING REVIEW

Melatonin: Mechanisms and Actions

In mid-April about 30 'melatonin people' gathered at the Banbury Center, Cold Spring Harbor Laboratory on Long Island just outside New York City, for a three day conference on the mechanisms and action of melatonin. The big news came from Steve Reppert who opened the proceedings with an account of how he and his co-workers have cloned the melatonin receptor. This is a major advance for the whole area and opens up many research and commercial possibilities.

Margarita Dubocovich presented more of her findings on melatonin analogues and antagonists which support the idea of melatonin receptor sub-types. Undoubtedly, the search for these receptor sub-types will keep the molecular people busy for the next few years, at least.

Bruce Goldman and Milton Stetson then took us back to the melatonin and seasonal reproduction story and the issue: is it phase or duration? They have decided to carry out the definitive experiment, together, and promise us that this will decide the question one way or another.

A series of papers then addressed the circadian effects of melatonin in both birds (Vinnie Cassone) and rodents (Jenny Redman and Larry Morin). Again we were reminded of the marked species differences in response to both pinealectomy and to exogenous melatonin administration. The message may be the same in all species — high levels of melatonin at night and low levels during the day — but the way in which this message is interpreted varies considerably. Of particular interest were data from both the Dubocovich and Redman groups showing that melatonin induced phase-delay in mice. Alfred Lewy has reported consistent melatonin-induced phase delays in humans, but delays in rodents have been more difficult to demonstrate.

The first day of the conference ended with Martha Gillette describing a series of studies concerning the action of melatonin on the SCN and some very elegant findings on intracellular mechanisms.

Next morning we turned our collective minds to the intricacies of Type-O and Type-1 phase resetting in humans, courtesy of Richard Kronauer and Domien Beersma. I think I understood the arguments, but somehow the discussion became diverted by more mundane issues like patents. Ken-ichi Honma and David Minors brought us up to date on the light PRC in humans, while Scott Campbell, Charmane Eastman, Michael Terman and Helena Illnerova reminded us that this work has important applications both clinically and in the workplace.

We then addressed the applied aspects of melatonin's circadian effects, with our conference organizer, Alfred Lewy, Robert Sack and Jo Arendt describing how melatonin may be used to phase-shift rhythms in humans, specifically in blind people, shift workers, intercontinental travelers and those with disorders of the sleep-wake cycle. Bruno Claustrat introduced us to alternative methods of drug delivery with his studies of melatonin being administered by infusion or by transdermal patch to migraine sufferers. Such patients have a disturbed melatonin rhythm and melatonin, given at night, advances the rhythm and improves the symptoms.

On the final day, another of those yet to be clarified issues was explored; namely, does melatonin induce sleep, or just increase our propensity to sleep, and what dose levels are necessary to do this? I can report that the issue is still unresolved. Orna Tzischinsky and Irina Zhdanova found time-of-day dependent soporific effects of exogenous melatonin administration. Replacing depleted melatonin levels in healthy elderly subjects did not restore youthful sleep patterns. But, as Cliff Singer pointed out, this may be due to a ceiling effect and melatonin may still have a therapeutic role in improving the disrupted sleep patterns of elderly Alzheimer patients.

Next, the relationship between melatonin, sleep and body temperature was addressed by Drew Dawson and Bryan Myers using both pharmacological and sleep manipulations. Thomas Wehr then described a study in which humans were held for long periods in a short photoperiod. Sleep duration and structure were altered, as in other animals. It came as no surprise when he concluded that, living the life we do, we are all chronically sleep-deprived.

As we have come to expect from the Reiter lab, Russ, together with David Blask, concluded the meeting with something completely different. In addition to its reproductive, circadian and sleep-related activities, melatonin

has further intracellular actions which may, in part, explain its anti-aging effects. David Blask has extended his findings concerning melatonin and cancer, an area yet to be seriously addressed by the pharmaceutical companies — yes, we did discuss melatonin patents as well as light patents! Finally, we were left to ponder on the possible effects of having our melatonin levels chronically reduced by environmental factors like electromagnetic fields.

Yes, we did eat and drink very well, thanks to Katya Davey. The setting at Cold Spring Harbour was wonderful, despite the rain. As one of those who came from afar, and, incidently, was living proof of the jet-lag-alleviating effects of the substance under discussion, I can only say thank-you to Alfred Lewy, Michael Terman and Martha Gillette for the invitation.

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LIGHT TREATMENT FOR SLEEP PHASE AND DURATION DISTURBANCES

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

Several sleep phase and duration disorders are responsive to daily administration of artificial light of appropriate intensity, duration and time of presentation. Sleep phase disorders include delayed sleep phase syndrome (DSPS; ICSD 780.5-50; American Sleep Disorders Association, 1990), sleep onset insomnia with normal awakening, advanced sleep phase syndrome (ASPS; 780.55-0), early-morning awakening with normal sleep onset, and non-24-h sleep-wake syndrome (780.55.2). Duration disorders include the hypersomnia that can accompany seasonal affective disorder (SAD) in fall and winter (DSM-IV 296.3, 296.4-296.7 or 296.89; American Psychiatric Association, 1994). Increased sleep length is usually specified as a change for a given individual ("relative" hypersomnia), and may fall within the normal range. Such sleep patterns may bear similarity to idiopathic hypersomnia (ICSD 780.54-7) and long sleeper disorder (ICSD 307.49-2), but the diagnostic matches are inexact.

A second light-responsive duration disorder is hyposomnia, usually accompanied by advanced sleep phase, which has been studied mainly in the elderly and is the focus of a separate section of this task force report (Campbell, 1993a).

DELAYED AND ADVANCED SLEEP PHASE SYNDROMES

Description of the syndromes and circadian rhythm correlates

ASPS is characterized by early sleep onset and early morning awakening. Patients experience difficulty staying awake in the evening, and maintaining sleep past a pre-dawn hour (e.g., 0300 h). DSPS is characterized by difficulty in initiating sleep before 0100-0300 h, sometimes later. Once sleep is initiated, patients have no difficulty maintaining it for a normal duration. Patients with DSPS often evolve work and social schedules with late morning starts and intense nighttime activity. Strictly speaking, the sleep phase disorders are present only when voluntary efforts to normalize sleep phase fail; many adolescents, for example, adopt abnormally late sleep schedules but can readjust at will. Whether or not the sleep pattern is subject to self-control, however, appropriate lighting interventions can serve to guide such sleep into a normal phase. Although DSPS predominates at younger age and ASPS at older age [see related task force section (Campbell, 1993a)], the syndromes may be chronic and can present difficulty throughout one's life, including occupational and marital risks.

It has been commonly assumed that sleep duration and architecture are normal in the sleep phase syndromes, and that the sleep episode retains a normal phase angle with respect to the delayed or advanced internal clock phase. Early studies of DSPS (Czeisler et al., 1981; Weitzman et al., 1981) found no consistent abnormalities in the polysomnogram (PSG) except for delayed sleep onset. Similarly, Alvarez et al. (1992) and Okawa et al. (1993) found normal sleep architecture. Data concerning circadian phase vary. In a case report of ASPS (Singer et al., 1989), nocturnal melatonin secretion phase was found to be within the normal range; however, a group of early morning insomniacs showed phase advances in the core body temperature minimum (mean $T_{\min}$ at 0231 h) measured under a constant routine (Lack and Wright, 1993). Major delays in $T_{\min}$ have been found in DSPS (e.g., 0830-1230 h; Okawa et al., 1993), and a group of sleep onset insomniacs were delayed relative to controls (0718 h vs. 0315 h; Morris et al., 1990). Although sleep duration in DSPS has appeared normal according to clinical observation by many groups (e.g., Shirakawa et

al., 1993), a comparison with controls revealed an average hypersomnic pattern (approximately +1 h); specifically, the interval between $T_{\min}$ and the time of awakening was lengthened (Okawa et al., 1994).

To judge by available data, it appears that the initial or terminal insomnia seen in the sleep phase disorders is often associated with altered circadian timing (ASPS and early morning awakening showing advances, and DSPS and sleep onset insomnia showing delays). Considering that the phase angle of entrainment is known to depend on the intrinsic circadian period (cf., Pittendrigh and Daan, 1976), one might predict abnormally long periods for DSPS patients tested under free-running conditions, and short periods for ASPS patients. Although free-running data are lacking, such an explanation of displaced sleep phase under entrainment is plausible based on temporal isolation studies of elderly subjects, an age group vulnerable to ASPS, who showed short free-running periods (Weitzman et al., 1981; Czeisler et al., 1986). An alternate circadian explanation for DSPS — yet to be tested — is a reduced capacity for circadian phase advances, as would result from a diminished phase-advance portion of the phase response curve (PRC) (Czeisler et al., 1981; Weitzman et al., 1981). Even with a normal PRC, however, DSPS patients might miss the opportunity for a corrective phase advance due to extended sleep after $T_{\min}$ (Okawa et al., 1994).

In addition to the factor of delayed or advanced phase relative to external clock time, the sleep phase disorders are often characterized by variations in the internal phase angle between the circadian pacemaker and the sleep episode. Lewy (1990a) has posited three distinct classes of phase-angle relationship: (a) normal (e.g., with 10 h separation between the DLMO and final awakening), (b) sleep delayed relative to the internal clock (e.g., 13 h separation), and (c) sleep advanced relative to the internal clock (e.g., 7 h separation). An example of the third type is seen in the comparison of sleep onset insomniacs and normal controls by Morris et al. (1990): insomniacs slept more than two hours earlier relative to $T_{\min}$, even though $T_{\min}$ fell 4 h later than normal in external clock time. In an analysis of such internal phase relationships, Strogatz et al. (1987) identified regions of the temperature cycle during which spontaneous sleep onset rarely occurred during free-runs in temporal isolation. Thus, under 24-h day night cycles, if sleep is attempted during the evening wake-maintenance zone, sleep onset insomnia would result.

The loose association between sleep timing and circadian

phase implies the contribution of non-circadian factors to the abnormal patterns. Sleep onset and awakening are themselves to some extent under volitional control (e.g., guided by schedule commitments) and can deviate from times predicted by circadian sleep-wake thresholds (Daan et al., 1984). DSPS patients also frequently show psychosocial adjustment problems or personality disorders, which might interact with the choice of sleep timing. Another vulnerable group is shift workers, who may develop DSPS following shift rotations (Guilleminault et al., 1982).

Therapeutic interventions with light

An historical antecedent to light treatment for DSPS was chronotherapy, in which the timing of sleep was gradually shifted later in 3-h daily steps for about 1 wk, until the desired target phase was reached (Czeisler et al., 1981). The shift procedure was based on the observation of free-running periods > 24 h in temporal isolation studies (e.g., Aschoff, 1965; see also, related task force section, Dijk, 1994). The objective was to reset the phase of the circadian pacemaker, which would then regulate the timing of sleep at an earlier hour. Following chronotherapy, it has sometimes been possible to maintain the target phase for weeks or months. In a case report, ASPS was similarly treated by successive phase advances of sleep (Moldofsky et al., 1986). Although the method does not explicitly manipulate light exposure, by shifting the sleep schedule patients might be exposed to light at times of day (morning for DSPS, evening for ASPS) that would maintain entrainment at the normalized phase position. The chronotherapy procedure is arduous and requires reserving about a week's time for sleeping during daylight hours as the progression moves around the clock. Although it may succeed in resetting both circadian and sleep phases, maintenance of the effect has been difficult (cf., Ohta et al., 1992). Further, there is a risk of relapse if the target sleep schedule is not strictly maintained. Explicit light treatment presents an alternate strategy.

The development of bright light treatment for sleep phase disorders was prompted by the finding that such light is more effective than low intensity indoor light for suppressing nocturnal melatonin production (Lewy et al., 1980). It was demonstrated that the range of entrainment of the temperature and activity-rest rhythms was greater using a bright light/dark cycle than ordinary room light (Wever et al., 1983). In a more analytical approach based on the assumed characteristics of the human phase response curve (PRC) to light, exposure was confined to the morning or to the evening in order to advance or delay circadian

rhythms, respectively. Lewy et al. (1987) demonstrated selective phase-shifting effects of morning and evening bright light on the dim light melatonin onset (DLMO) while sleep-wake cycles were held constant. Similarly, Czeisler et al. (1986) demonstrated that evening light produced a large phase delay of $T_{\min}$, as assessed under constant routines, in a subject who showed an intrinsic period of 23.7 h under forced desynchrony. (See also, related task force section, Dijk, 1994).

Lewy et al. (1985) proposed that appropriately timed bright light exposure can alleviate DSPS and ASPS. They described a patient with DSPS for whom daily advances of light exposure at about 2500 lux for 1 h upon awakening served to normalize sleep phase in 3-4 days. Two case studies by Czeisler et al. (1988) demonstrated that 3 days of light exposure of 4-5 h at about 10,000 lux resulted in a phase advance of $T_{\min}$ of 3 h in a patient with DSPS (exposure upon awakening), and a phase delay of 2 h in a patient with ASPS (exposure before sleep). Both patients showed appropriate adjustments in their sleep-wake pattern. Similarly, maintenance treatment with evening light (2 h at 2500 lux) in an ASPS patient resulted in a phase-delay of the DLMO as well as the sleep-wake pattern (Singer et al., 1989). Relatively few studies of ASPS have been performed [cf., related task force section, Campbell (1993a)], although by now many DSPS patients have been treated (e.g., Rosenthal et al., 1990; Terman, 1993a). By exposing DSPS patients to light of 2500 lux for 2 h between 0600-0900 h, $T_{\min}$ was advanced by > 1 h relative to a 300 lux control (Rosenthal et al., 1990). Although they did not measure the accompanying advance of sleep onset and offset, patients reported improved sleep, and multiple sleep latency tests showed increased latency early in the day. Lack and Wright (1993) reported a delaying effect of evening light in a group of patients with early morning awakening but normal sleep onset. After two nights of 2500 lux light exposure at 2000-2400 h, $T_{\min}$ delayed from 0231 h to 0422 h, while the DLMO delayed from 2113 h to 2327 h. In addition, morning awakening was delayed by about 1 h, with a similar increase in sleep duration, and no change in sleep onset time.

For patients with DSPS, exposure to light is usually scheduled immediately upon awakening. At the start of treatment, DSPS patients often undergo a very unpleasant period of sleep deprivation. They continue to have difficulty falling asleep, while they are required to awaken for morning treatment. Although research studies have typically used a constant early-morning treatment time (e.g., 0600-0800 h), for practical clinical application it is

often wise to advance the treatment time in gradual steps (e.g., 10-30 min) toward the targeted hour. If sleep is truncated during this period of adjustment, the patient may require reassurance that a normal duration will be recaptured.

In a study of ASPS in elderly patients, Campbell et al. (1993) applied light of 4000 lux for 2 h between 2000 and 2300 h, which served to delay $T_{\min}$ by more than 3 h, and to increase sleep efficiency and Stage 2, REM and slow wave sleep. As a general clinical strategy in ASPS, sleep onset may be gradually delayed, with exposure to light 2-4 h before scheduled bedtime. Sometimes these patients complain of an energizing effect of light causing sleep onset insomnia, in which case light exposure is scheduled to end at least 1-2 h before scheduled bedtime. [See related task force section (Campbell, 1993b)].

Parameters of light exposure have varied widely, from 15 min to 4 h using illuminance levels from 2500 to 10,000 lux from fluorescent sources. Once the target phase has been achieved, some patients are able to reduce the duration of light exposures, or skip days occasionally, without slipping back toward their delayed sleep phase. For a given exposure duration, increased light intensity within the therapeutic range may result in increased phase shifts (cf., Lack and Wright, 1993). Exposure to sunlight also can be effective (Dagan et al., 1991), assuming that the time of awakening is after natural dawn. In addition, chronotherapy for DSPS has been reinforced with explicit morning bright light exposure at the target phase (Eastman et al., 1988; Terman, 1993a), including walks outdoors upon awakening.

Scheduling of light treatment for DSPS has usually been made without baseline assessments of circadian phase (as by core body temperature measurement or melatonin assay), but has been based on the sleep pattern itself. Given that sleep can occur out of phase with the circadian subjective night, there is a risk of obtaining exaggerated phase shifts, or even phase shifts opposite in direction to that predicted for light exposure at a specific time of day. In one such case, a patient scheduled for 30 min, 10,000 lux light exposure at 0715 h began awakening prematurely at about 0500 h (Terman, 1993a), but normalized with reduced exposure duration. In another case, a patient began treatment with 2500 lux, 2h exposures at 0600 h, rather than advancing gradually. Not only did the sleep interval fail to advance, but melatonin showed a phase delay which could have resulted from stimulation of the delay portion of the PRC if the delay-to-advance crossover

point were itself markedly delayed (A.J. Lewy and R.L. Sack, personal communication). Since circadian temperature and melatonin markers are not readily available in clinical practice, the clinician must closely monitor the progress of sleep phase adjustment for several weeks upon initiation of treatment in order to avoid undesired responses.

Although light treatment is simple in concept, in practice case management is often complicated [for a discussion of dosing and scheduling strategies, see Terman (1993a)]. Despite the formal diagnostic criteria for DSPS, it is rarely ascertained that patients lack the ability to shift their sleep phase without supplementary bright light treatment. Many of these individuals have adjusted to a history of delayed sleep phase and are reluctant to shift earlier. Despite high success rates for achieving the shift under acute treatment, a majority of patients subsequently fail to comply with the recommended light schedule and allow themselves to relapse. Some are able to maintain a normalized sleep phase without maintenance for periods of up to several months, while others drift back toward the delayed sleep phase within days. Some re-establish the advanced phase by periodic light treatment, in response to social or occupational demands.

Compliance with early morning light treatment, and success of the procedure, might be improved by automatic presentation of the lights in the bedroom toward the end of the scheduled sleep episode. Two such approaches hold promise. In a report by Jacobsen et al. (1990), oversleepers presented with 500 lux light — switched on automatically 10 min before their pre-selected wake-up time — showed earlier rising and decreased sleep duration. In an attempt to simulate spring and summer sunrises in the bedroom, Terman developed a device that presents a gradually increasing naturalistic dawn signal at the bedside, and patients with winter depression showed improved mood accompanied by earlier rising (Terman et al., 1989). Dawn simulation has the potential advantage of avoiding the shocking effect of sudden bright-light onset during sleep; however, even a dim dawn signal can result in premature awakening if the intensity ramp is too rapid or occurs too early (Avery et al., 1992, 1993). The efficacy of dawn simulation for treatment of DSPS remains to be tested.

NON-24-H SLEEP-WAKE SYNDROME

Yet another type of sleep-wake disorder results from progressive phase delays of sleep onset and awakening relative to the 24-h day, even when living in normal social

environments (Elliot et al., 1971; Miles et al., 1977). Kokkoris et al. (1978) coined the term "hypernycthemeral" to describe such patterns. In the case they described, the period of the rectal temperature rhythm was 24.8h, and there were variable daily delays of the sleep-wake cycle such that the two rhythms moved in and out of phase with one another. During periods when sleep and temperature were desynchronized, the patient reported insomnia, fatigue and impaired functioning. The authors hypothesized that hypernycthemeral cycles result either from a reduced capacity for entrainment or weakened response to social zeitgebers (as would be consistent with the patient's personality disorder). Noting that some DSPS patients occasionally break into a transient hypernycthemeral pattern, Weitzman et al. (1981) reasoned that non-24-h sleep-wake syndrome and DSPS are associated disorders of varying severity.

In a recent case report, the intrinsic circadian period of a patient with non-24-h sleep phase syndrome was evaluated under a constant routine before and after a forced desynchrony protocol in which sleep was scheduled every 28 h (Emens et al., 1994). Although the baseline sleep-wake period was 25.17 h — similar to that found in normal subjects under temporal isolation — the intrinsic period of the core body temperature rhythm was found to be only 24.5 h. It was suggested that the shifting sleep resulted from the patient's self-selected pattern of light-dark exposure, such that sleep extended through the phase-advance portion of the PRC, facilitating phase delays. This case suggests that non-24-h sleep-wake syndrome may result from inappropriate photic exposure, rather than from an abnormally long intrinsic circadian period or weakened entrainment mechanism. However, in earlier work under temporal isolation, in which two patients with non-24-h sleep-wake disorder showed free-running temperature rhythms with periods of 25.6 h and 25.9 h (toward the long end of the normal range), Honma et al. (1988) were unable to achieve phase advances or entrainment using 5000 lux illumination for 3 or 6 h, administered 1 h after awakening or on a 24-h schedule. They ascribed these failures to reduced light sensitivity of the circadian clock. Positive treatment results have been obtained in two case studies in which hypernycthemeral patterns were halted or greatly decelerated with bright light administered immediately upon awakening (Eastman et al., 1988; Hoban et al., 1989).

The covariation of sleep cycles with circadian rhythms in the blind provides an added perspective. Many blind subjects show free-running rhythms despite adherence to

24-h work and sleep-wake schedules (Lewy and Newsome 1983; Sack et al., 1992). Some, however, show periodic insomnia and daytime sleepiness when core body temperature and other rhythms drift away from the normal nocturnal phase (e.g., Klein et al., 1993). Indeed, sleep propensity — as measured by a multiple napping protocol (Lavie, 1986) — may free-run with other rhythms even though the patient is able to maintain a normal sleep-wake schedule (Nagakawa et al., 1992). However, non-24-h sleep-wake syndrome in the blind is apparently rare (but see Arendt et al., 1988). Okawa et al. (1987) identified 4 retarded blind children with hypernycthemeral patterns; a light treatment trial failed in a patient with 24.8-h periodicity, but electroretinogram response and visual evoked potentials were absent. The recent demonstrations of melatonin suppression (Martens et al., 1992) and pupillary contraction (Sack et al., 1992) to light in blind patients without conscious visual perception suggests that the residual retinal function may be sufficient for entrainment of circadian rhythms and treatment of sleep phase disorders with bright light.

The possibility that vitamin B₁₂ (methylcobalamin) can forestall non-24 hr sleep-wake cycling has recently received much attention, based on an early report by Kamgar-Parsi et al. (1983). Studies by Okawa and associates (e.g., Okawa et al., 1993) indicate that either the vitamin alone, or in combination with morning bright light exposure, can be used effectively to treat this syndrome as well as DSPS. However, in a multicenter study, the vitamin was not more effective than placebo (Takahashi et al., 1994). Honma et al. (1992) has proposed that vitamin B₁₂ serves to increase light sensitivity, based on their finding of increased melatonin suppression and enhanced phase advances of the melatonin rhythm in a group of healthy subjects. Additionally, a patient with non-24-h sleep-wake syndrome (period length, 25.9 h) showed distinct subsensitivity to light by similar measures.

EXOGENOUS MELATONIN ADMINISTRATION AND LIGHT

There have been several reports of the effectiveness of exogenous melatonin in alleviating sleep disturbances in blind patients. For example, in a case of non-24-h sleep-wake syndrome, 5 mg of oral melatonin at 1700 h succeeded in synchronizing the sleep-wake cycle to a nocturnal phase, with an apparent phase shift in endogenous melatonin production (Arendt et al., 1988). In a similar case, a nocturnal dose of 20 mg also served to regularize the sleep pattern, although endogenous melatonin and cortisol rhythms were unaffected (Folkard

et al., 1990). A clear case of re-entrainment associated with sleep improvement was reported in a retarded blind boy given 0.5 mg at 1800 h (Palm et al., 1991). Most such studies do not resolve whether the improvement in sleep timing is mediated by circadian or hypnotic actions of the drug. Indeed, sleep has been potentiated by exogenous melatonin administered at times of day that do not foster circadian phase shifts (Dawson et al., 1992).

Sack et al. (1991) were able to show that 5 mg melatonin given at bedtime induced phase advances in endogenous melatonin production in five free-running blind patients, three of whom also showed concurrent phase advances in the cortisol rhythm. A sixth patient showed apparent entrainment of the melatonin rhythm for about a year, using 7 mg doses at 2100 h. The analysis was strengthened by the derivation of a PRC for exogenous melatonin using a group of sighted subjects without sleep disturbance (Lewy et al., 1992). Doses of 0.5 mg in the afternoon or early evening advanced the onset of melatonin production, while morning doses delayed the rhythm. The melatonin PRC thus provides a potential guide for the timing of exogenous melatonin in the treatment circadian phase disorders, including the sleep phase syndromes. In the first such study, daily 5 mg doses at 2200 h succeeded in phase advancing the sleep episode in patients with DSPS (Dahlitz et al., 1991). This result was confirmed and extended in a similar study that used 5 mg doses at 1930 h (2 h before bedtime), with continued improvement at 6 mo follow-up (Tzischinsky et al., 1993).

Although oral melatonin has been used successfully as a hypnotic agent throughout a wide dosage range (Dollins et al., 1994), results across studies have been variable (for review, see Dawson and Encel, 1993). Delayed sleep phase may thus be responsive to combined circadian and hypnotic effects of the drug administered at or before bedtime, especially at relatively high, pharmacological doses (e.g., 5 mg). For treatment of ASPS with morning melatonin, however, low, physiological doses (e.g., 0.5 mg) may be preferable, given that they are sufficient to elicit phase shifts without hypnotic effect.

A potential interaction between light and melatonin administration seems likely given that the two PRCs bear an opposite phase relationship. Thus, morning light elicits phase advances while morning melatonin administration elicits phase delays. Indeed, the melatonin PRC shows formal similarity to the dark-pulse PRC of hamsters (Boulos and Rusak, 1982) and may reflect a similar mechanism of action. The ambient lighting environment

is a factor likely to modulate therapeutic response to exogenous melatonin administration, especially at the dawn and dusk transitions when both PRCs are active (Lewy et al., 1994). Thus, it may be important for patients to remain under minimal illumination after ingesting the drug at these hours, in order to avoid an opponent interaction. That said, however, a promising avenue for clinical research is the combined use of exogenous melatonin and bright light at antiphase (morning light/evening melatonin, and vice versa), which may serve to expedite and stabilize desired phase shifts of circadian rhythms and sleep.

HYPERSOMNIA OF SEASONAL AFFECTIVE DISORDER

Description of the syndrome

Beyond the cardinal characteristic of mood reactivity — i.e., the ability to respond temporarily to positive external events — hypersomnia is one of the defining symptoms of atypical depression (Liebowitz et al., 1984). By contrast, sleep onset insomnia and early morning awakening typify melancholic depression. Although hypersomnia can be observed clinically without seasonal pattern, it often appears specifically in fall and winter at northerly latitudes, in association with seasonal affective disorder (SAD) (Rosenthal et al., 1984). Indeed, more than 90% of patients with SAD fulfill DSM-IV criteria for depressive disorder with atypical features (Terman and Stewart, 1993). About 80% of winter depressives report increased sleep duration, though the symptom is not strongly correlated with other symptoms of SAD (such as carbohydrate craving). Indeed, reports of wintertime hypersomnia (sleep duration at least 1 h longer than in spring or summer) without accompanying depression are common in the general population (Terman, 1988; Anderson et al., 1994). Sleep log studies of SAD patients suggest that retrospective reports of winter hypersomnia are often exaggerated (Anderson et al., 1994). PSG studies have found only marginal increases in sleep duration in SAD patients relative to normal controls (Anderson et al., 1994) and either similar (Endo, 1993; Anderson et al., 1994) or shorter (Kohsaka et al., 1994) sleep durations following light treatment. There are many individual cases showing significant reductions under treatment (cf., Terman, 1993a). Seasonal sleep change is sometimes better described as reduced sleep duration during spring and summer — a symptom of hypomania — than hypersomnia during fall and winter. Some patients show extreme variation in both seasons, e.g., < 6 h sleep in summer and > 11 h in winter.

The most comprehensive studies of sleep architecture in

SAD have been performed over the past decade at the National Institute of Mental Health, and summarized by Anderson et al. (1994): "Nocturnal EEG recordings of depressed SAD patients in winter showed decreased sleep efficiency, decreased delta sleep percentage, and increased REM density (but normal REM latency) in comparison with recordings: (1) from themselves in summer; (2) from themselves after ≥ 9 days of light treatment; or (3) from age- and gender-matched healthy controls." By contrast, although Kohsaka et al. (1994) found improved sleep efficiency after light treatment, slow wave percentage did not change. In a comparison of depressed patients with and without seasonal variation, Thase (1989) found the seasonal group to show longer sleep latency and reduced sleep efficiency, but similar percentage of delta, REM density, minutes of REM and number of awakenings. Similar results were reported for SAD by Brunner et al. (1993b).

Whether or not a patient is objectively verified as hypersomnic, many report an increased sleep need, i.e., that they would sleep longer if their schedule permitted. Such self-imposed limitation on sleep duration — which is confirmed by significantly longer weekend sleep (Anderson et al., 1994) — may contribute to the nearly universal complaint of daytime fatigability. However, many SAD patients with long sleep durations still complain of fatigue. The common symptom of difficulty awakening — which could be associated with self-imposed sleep deprivation — is not correlated with complaints of hypersomnia, although it is correlated with severity of depression (Avery et al., 1994). Even so, several studies have found the symptom of hypersomnia to be a predictor of clinical response to light treatment (Avery et al., 1991; Lam et al., 1992; Oren et al., 1992; Terman, 1993b).

Some SAD patients show DSPS specifically in the fall and winter (e.g., Endo, 1993), which is not necessarily accompanied by hypersomnia. Sleep specialists who encounter complaints of DSPS during these months are advised to screen for associated depressive and atypical neurovegetative symptoms, and not to treat the sleep disorder in isolation. Seasonal recurrence of DSPS may, however, occur without depression (Uruha et al., 1990).

Origins of hypersomnia in circadian and sleep processes

The origin of hypersomnia is not yet understood but may be related to circadian phase. An early study found relatively long sleep episodes to occur when sleep was initiated at a phase of high core body temperature, while

shorter episodes were found with sleep onsets near $T_{\min}$ (Czeisler et al., 1980). Cases of extreme circadian phase delay — with the onset of melatonin production after midnight — have been noted in winter depressives (e.g., Terman et al., 1988). If a patient maintains a normal bedtime, with sleep onset earlier relative to a delayed core body temperature rhythm, hypersomnia could result given the association of spontaneous awakening with the morning rise in temperature (Zulley et al., 1981).

An expanded, complementary account of hypersomnia derives from the two-process model of sleep regulation (Borbély, 1982; Daan et al., 1984), in which sleep timing and duration result from an interaction between distinct homeostatic (S) and circadian (C) processes. Process S reflects sleep debt and is indexed by slow wave (prominently, delta) EEG activity which predominates in the early hours of sleep, and decays across successive NREM-REM cycles. Sleep is initiated and terminated when Process S reaches an upper and lower threshold, respectively. Process C consists of a circadian variation in these thresholds, which is generated by a single pacemaker that also drives the rhythms of body temperature and melatonin production.

Theoretically, there is a variety of ways in which changes in Process S and C, or their interaction, could produce hypersomnia. An acceleration of Process S during waking hours would result in an elevated level at sleep onset; if the decay were unaltered during sleep, hypersomnia would result. An experiment performed on recovery sleep in SAD patients who had been sleep-deprived under a constant routine found no differences in EEG power density between winter and summer or before and after light treatment (Brunner et al., 1993a). However, it must be pointed out that these patients did not exhibit winter hypersomnia, and even during baseline sleep, EEG power density was similar across all conditions (Brunner et al., 1993b). Thus it remains possible that patients with hypersomnic baseline sleep would show a contrasting response to sleep deprivation.

In contrast to an acceleration of Process S during waking hours, hypersomnia could also result from a reduced decay rate of Process S during sleep, under which it would take longer to reach the wake-up threshold. By this account, EEG power density in the first part of the night would increase following light treatment. Such change could represent a direct influence of light on Process S, or reflect the compression of slow-wave sleep into a normalized sleep interval. Study of a small sample of SAD patients

did suggest an increase in the power density of delta activity (Mendelson et al., 1989), and a significant enhancement of EEG sleep stages 3 and 4 has been found in the first 3 h of sleep — following light treatment as well as in summer — without a change in REM activity (Endo, 1993). On the one hand, prolonged sleep duration might augment the depletion of Process S, accounting for reduced slow wave sleep while depressed. On the other hand, since delta activity normally reaches a lower plateau after 3-4 NREM-REM cycles, extending sleep might not result in further reductions. Rather, reduced slow wave sleep might result from the shorter waking period of hypersomnic patients, which would provide less time for Process S accumulation.

Even if Process S were undisturbed, there are three types of change in Process C that could lead to hypersomnia: phase delay (as discussed above), lowering of the mean level or amplitude, or altered wave form of the lower (wake-up) threshold. The amplitude hypothesis, originally proposed by Czeisler et al. (1987), has not been confirmed in constant-routine measurements of SAD patients (Wirz-Justice et al., 1994). The wave form hypothesis remains viable, given that morning and evening oscillatory components of the pacemaker can vary independently across the seasons (Pittendrigh and Daan, 1976; Illnerová et al., 1982). The distributions of sleep and melatonin production broaden significantly under artificially imposed long nights in normal subjects (Wehr, 1991), and it remains to be determined if such responses to night length are magnified in SAD.

Therapeutic interventions with light

As mentioned earlier, hypersomnia — with or without delayed sleep phase — is characteristic of some but not all patients with SAD and is also seen as a seasonal variation in sleep duration in the general population. Based on clinical interviews, sleep logs and actigraphy, patients who show an antidepressant response to light treatment often also show normalized sleep duration. In one study, light treatment served to advance the average time of awakening and to reduce total sleep duration under either morning or evening exposures of 10,000 lux in 30 min sessions (Terman, 1993a). However, when there was no antidepressant response, sleep duration failed to contract even though morning light succeeded in inducing phase advances of sleep and evening induced phase delays. An actigraph study also showed reduced sleep duration after 10,000 lux light treatment in 30-60 min morning sessions (Teicher et al., 1994), but no relationship to the magnitude of antidepressant response.

The relative contribution of specific effects of light and placebo effects to the global antidepressant response, or to contraction in sleep duration, remains unresolved. Two studies have found that the response to a placebo control — a deactivated negative ion generator — was similar to that for bright light (Eastman et al., 1992, 1993b), which suggests that contraction in sleep duration may accompany improved mood due to nonspecific factors. In another study, however, a similar placebo control — low-density negative ions — yielded clinical improvement in fewer than 20% of cases, which contrasts with about 60% after bright light treatment (Terman and Terman, 1994).

Exposure parameters for light treatment of winter depression have been similar to those used in the sleep phase disorders, ranging from 30 min to 4 h per day, at illuminance levels of 2500 to 10,000 lux. A tradeoff relation between duration and intensity is generally assumed, although this rests on the limited observations that remission rates are roughly equal for 2500 lux, 2 h exposures and 10,000 lux, 30 min exposures, and that 2500 lux, 30 min exposures are less effective (J.S. Terman et al., 1990). That said, however, the results of individual studies vary widely, and indeed there have been several studies which used 2500 lux, 2 h exposures and obtained minimal clinical response (for review, see Terman et al., 1989).

The hypothesis of a pathogenic circadian phase delay in SAD, leading to the prediction of superior response to morning over evening light exposure (Lewy et al., 1987; Sack et al., 1990), is only partially confirmed by clinical trials including hundreds of patients. Patients studied in parallel groups (e.g., Wirz-Justice et al., 1993) usually have not shown this time-of-day difference. In crossover studies, however, patients who receive a period of evening light following an initial period of morning light show reduced antidepressant response [for review, see Terman (1993)]. When evening light is given as first treatment, clinical response is superior. Phase delays of the DLMO to evening light are greatly magnified following phase advances to morning light, which may account for the differential evening-light deficit.

The importance of the phase angle difference between sleep and the circadian pacemaker is suggested by a pilot study that directly manipulated the timing of sleep rather than light exposure (Lewy, 1990b). Patients showed clinical improvement when instructed to go to sleep and arise later. It was surmised that the phase-angle difference between sleep and the (delayed) circadian pacemaker thus

contracted, as might also happen when morning light serves to advance the circadian rhythm relative to sleep. By this view, depressive symptoms and hypersomnia emerge when circadian rhythms drift later relative to sleep, in response to the delayed winter dawn signal (see also Illnerová et al., 1993). However, recent findings of similar circadian phase positions in winter depressives and normal controls (e.g., Eastman et al., 1993; Wirz-Justice et al., 1993) raise doubts about the importance of phase delays in predicting antidepressant to light. The phase-shift hypothesis may apply specifically to vulnerable hypersomnic patients (cf., Dahl et al., 1993). One study has shown a positive correlation between clinical improvement and the magnitude of phase advances of the DLMO to morning light, but no significant correlation with phase delays to evening light — even though light at either time of day yielded similar antidepressant response (Terman and Terman, 1994).

The data do not rule out the possibility that response to evening light is primarily a placebo effect. By this interpretation, once a patient has experienced the specifically active effect of morning light, response to evening light is reduced (J.S. Terman et al., 1990). In clinical practice, most patients have been treated with morning light, but a trial of evening light is recommended if morning light fails (Rosenthal, 1993). Most patients given 30 min treatment sessions prefer morning to evening exposures even when evening light is equally effective, while those receiving 2 h sessions often find the evening hour more convenient because it conflicts less with the work day (M. Terman and J.S. Terman, personal communication).

In summary, hypersomnia in SAD can be effectively treated with bright light, especially in patients who report hypersomnia. However, the symptom need not be present for light to be beneficial. The efficacy of light treatment for non-seasonal hypersomnia, either as a primary sleep disorder or a symptom of atypical depression (cf., Stewart et al., 1990), remains in question.

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BOOK REVIEW

Bodyrhythms: Chronobiology and Performance

By Lynne Lamberg (New York, NY: William Morrow and Company, Inc., 1994, 256 pp., US\$25.00).

Lynne Lamberg, known for her previous well-received books on sleep and dreams, has written a comprehensive, credible book on biological rhythms for the lay person. The book is divided into four sections, including how

biological clocks work, how to fix "broken clocks," interfacing biological rhythms and modern life, and an appendix. The latter includes strategies for self-help in a variety of domains, with sample sleep-wake diaries, sleepiness/alertness charts and a glossary.

This book is a useful guide for the interested public and for people in a position to make or change policies that affect shift work and shift workers. It is clearly organized and easy to read.

Since the target audience for this book is the lay public, it is not surprising to find that statements are generally not attributed to an individual or research group. Nevertheless, it is especially important to convey to readers which information is currently generally accepted by the scientific community and that which is less well supported by basic or clinical data. Lamberg sometimes fails to do this. An example is her description of the view that manipulating the diet can alter one's mood or alertness directly, such as by consuming protein at breakfast to promote alertness or by eating carbohydrates, thereby increase brain serotonin and improving mood. Both of these points require additional research support. Similarly, in a section on treatments for jet lag, she could have pointed out that the majority of the currently available sedative/hypnotics have not been tested for this purpose.

It would also have been helpful to the reader if cause and effect relationships had been better defined. For example, Ms. Lamberg writes that disruptions or lack of social zeitgeber can cause depression and other health problems.

For our current level of knowledge on this topic, the statement is too strong. In a section on Premenstrual Syndrome (PMS), progesterone is described as disrupting sleep, leading to irritability, mood swings and depression. While progesterone is involved in the etiology of PMS, its effect on sleep and the role of sleep disruption *per se* are not clearly established. A final example involves the influence of temperature levels on daily rhythms such as alertness. More research is required before one can assert either that having a particular temperature value at a specific time of day matters or that altering temperature levels directly will have an impact on alertness levels.

Ms. Lamberg has provided the reader with several self-help sections. Much of what is recommended makes sense, but again it would have been desirable if the reader was informed as to what is supported by research and what has not been put to the test. The self-help section for PMS is too lengthy and seemingly out of place alongside the other sections that deal with shift-work, insomnia and other problems much more clearly associated with disturbances in biological rhythms.

Nevertheless, I found this book to be thorough and informative. The field of biological rhythms needs a book such as this as a lay resource.

Margaret L. Moline, Ph.D., Institute of Chronobiology, New York Hospital-Cornell Medical Center, 21 Bloomingdale Rd., White Plains, NY 10605. Tel 914-997-5863; fax 914-997-5958.

BULLETIN BOARD

WELCOME TO NEW MEMBERS

We welcome new members who have joined SLTBR since publication of the June 1994 issue:

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1995 SLTBR MEETING DATES SET

For the first time, the Society will hold its annual meeting in Europe. The 1995 meeting will be held in Frankfurt, Germany on June 9-11. Plan your European vacation now to coincide with these dates. With the help of Frankfurt host Wilfried Köhler, M.D., Ph.D., this promises to be an outstanding event, with an international flavor that can only accompany a European venue. For further information, please contact *Dr. Wilfried Köhler, Zentrum der Psychiatrie, Heinrich Hoffmann Strasse 10, D-60528 Frankfurt am Main, Germany; fax (49) 69-6301 5936.*



Looking forward to the 1995 meeting in Frankfurt, Germany are SLTBR President Anna Wirz-Justice, Ph.D., Frankfurt host Wilfried Köhler, M.D., Ph.D., and Juan Su Terman, Ph.D., of the New York State Psychiatric Institute.

THE SLTBR FLASH(LIGHT) POLL

With this issue we introduce a new feature to *LTBR*. In each issue we will solicit opinion from the membership, primarily in the form of a yes/no response, with the option of a brief comment, concerning a current, hopefully provocative, issue. Results of the poll will be published in the following Bulletin.

We hope that the **FLASH(LIGHT) POLL** will encourage participation in your Society's publication, while giving us all a general indication of the current thinking of our colleagues. Our first item for debate: *I believe the therapeutic effect of bright light therapy in SAD is primarily a placebo effect.* Please express your opinion on

the enclosed form and mail, fax or e-mail to Scott Campbell at the address indicated.

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE

This new quarterly, peer-reviewed journal, will make its debut in January 1995. Its formation follows upon the establishment of a new Office of Alternative Medicine at NIH, and the Rosenthal Center for Alternative/Complementary Medicine at Columbia University, which will offer medical school courses in this emerging specialty area. Publication criteria will be strict and scientific, and light therapy will be a focus, along with behavior therapy and topics outside the traditional mental-health armamentarium, such as nutritional, chiropractic, and vitamin therapies, and Chinese medicine. Marc S. Micozzi, M.D., Ph.D. (National Museum of Health and Medicine) is editor-in-chief; Fredi Kronenberg, Ph.D. (Columbia University) is senior editor; Kim Jobst, M.R.C.P. (University of Oxford) is European editor. The editorial board includes C. Everett Koop, M.D., Candace B. Pert, Ph.D., and our own Michael Terman, Ph.D. Reports of clinical studies and studies of the mechanism of action of light, as well as incisive case reports, are solicited. For the style guide, submission procedures, and preliminary announcement, contact *JACM, Mary Ann Liebert, Inc., Publishers, 1651 Third Avenue, New York, NY 10128; tel 212-289-2300, fax 212-289-4697.*

SCIENTIFIC OPPORTUNITIES IN SLEEP-RELATED RESEARCH: CALL FOR SUGGESTIONS

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

As part of its responsibilities, the Center was directed to advise the Director of the National Institutes of Health in the development of a comprehensive plan for the conduct

and support of sleep disorders research, to identify and periodically update research priorities, and to coordinate research supported by the National Institutes of Health.

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

Interested members of the public and scientific community are invited to submit written recommendations for future research directions in sleep and related fields. These suggestions should be forwarded by January 15, 1995 to J. Christian Gillin, Chairman of the Research Subcommittee of the Advisory Board to the NCSDR: *SLEEP RESEARCH OPPORTUNITIES*, J. Christian Gillin, M.D., Professor of Psychiatry, University of California, San Diego, San Diego Veterans Affairs Medical Center (116A), 3350 La Jolla Village Dr., La Jolla, CA 92161. All recommendations will be reviewed and summarized by the research subcommittee of the Advisory Board.