

Light Treatment and Biological Rhythms

Bulletin of the Society for Light Treatment and Biological Rhythms



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ANNUAL MEETING SCHEDULE

The SLTBR Program Committee has finalized the schedule for the Sixth Annual Meeting on Light Treatment and Biological Rhythms cosponsored by the Society and the National Institute of Mental Health. The two-day meeting, designated a Satellite Symposium of the CINP which will hold its XIX Congress the following week, will convene at 8:30 a.m. on 23 June 1994 in Lister Hill Auditorium at the National Library of Medicine. The schedule features oral research presentations, poster presentation sessions and corporate exhibits, as well as the annual membership meeting and a discussion on patent issues. The afternoon education program on 24 June will feature presentations on a variety of topics related to light treatment and related research. Social events include a reception in the poster/exhibit area of the meeting site and the annual banquet at Positano, a Bethesda restaurant.

Individuals who have not yet registered for the meeting may do so on site with payment of a \$15.00 late fee. Current members may register for the meeting with payment of \$105.00 (includes late fee); non-members \$145.00 (includes associate membership).

The National Institutes of Health is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The National Institutes of Health designates this continuing medical education activity for 11 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

ANNUAL MEETING SCHEDULE

Thursday, 23 June 1994

8:00 - 8:30 Registration, exhibits, refreshments
8:30 - 12:00 Oral Scientific Presentations I
(break included)
10:20 - 11:00 Break: Posters, exhibits, refreshments
12:00 - 13:20 Lunch

13:20 - 14:20 Oral Scientific Presentations II
15:20 - 14:40 Break
14:40 - 15:40 SLTBR Business Meeting
15:45 - 16:45 Patents Discussion
16:45 - 18:00 Reception: Posters, Exhibits
18:30 - Banquet

Friday, 24 June 1994

8:20 - 12:00 Oral Scientific Presentations III
(break included)
10:00 - 10:40 Break: Posters, exhibits, refreshments
12:00 - 13:20 Lunch
13:20 - 17:05 Education course

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Light Treatment and Biological Rhythms*Bulletin of the Society for Light Treatment and Biological Rhythms***Editor**

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Opinions expressed in this news bulletin are those of the author and do not necessarily represent the views of the Society or its Board of Directors.

Unsolicited manuscripts, letters to the editor, and Bulletin Board announcements should be submitted to Dr. Scott S. Campbell, Laboratory of Human Chronobiology, Cornell University Medical Center, 21 Bloomingdale Rd., White Plains, NY 10605, USA. Please submit one double-spaced hard copy and a diskette file (Macintosh: MS-Word, MacWrite; IBM: WordPerfect as Textfile; e-mail: sscampb@med.cornell.edu.) Manuscripts and Diskettes will not be returned. We reserve the right to edit and condense letters to the editor.

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ORAL SCIENTIFIC PRESENTATIONS I**SAD: Treatment and Biological Correlates****N. Rosenthal, Chair**

Lam et al.: A multicentre, placebo-controlled study of fluoxetine in seasonal affective disorder.

Terman et al.: A controlled trial of light therapy and negative ions.

Meesters et al.: Preventing SAD by using light visors?

Oren et al.: A controlled trial of cyanocobalamin (vitamin B₁₂) in the treatment of winter seasonal affective disorder.

Levitt et al.: A double blind placebo controlled trial of light box versus head-mounted unit.

Arbisi et al.: Basal prolactin concentration in male SAD.

Garcia-Borreguero et al.: Behavioral effects of the serotonergic 5-HT-1A receptor agonist ipsapirone in patients with seasonal affective disorders and controls.

Wirz-Justice et al.: Circadian rhythms of core body temperature and salivary melatonin in winter SAD before and after midday light.

ORAL SCIENTIFIC PRESENTATIONS II**Mechanics of Light Administration****S. Campbell, Chair**

Ando et al.: Light attenuation by the human eyelid.

Brainard et al.: Constant versus intermittent ocular exposure during light treatment: Is there temporal summation of photic stimuli?

Byrne et al.: Are melatonin responses to bright light a placebo-resistant biological marker for light therapy studies?

ORAL SCIENTIFIC PRESENTATIONS III**Circadian Rhythms; Clinical Aspects of SAD****D. Kripke, Chair**

Honma et al.: Vitamin B₁₂ enhances the phase-response of circadian melatonin rhythm to a single bright light exposure.

Lewy et al.: A phase response curve for melatonin in young and elderly subjects.

Parry et al.: Plasma melatonin circadian rhythms during the menstrual cycle and after light therapy in premenstrual dysphoric disorder and normal control subjects.

Okawa et al.: The relationship between sleep-wake rhythm and body temperature rhythm in delayed sleep phase syndrome (DSPS) and non-24-hour sleep-wake rhythm.

Teicher et al.: Effect of light therapy on actigraph-assessed sleep.

Avery et al.: Difficulty awakening as a symptom of winter depression.

Eastwood et al.: Seasonal affective disorder in the UK: Results of SAD Association survey 1993-94.

A. Magnusson: Validity of the seasonal pattern assessment questionnaire (SPAQ).

Schlager et al.: Psychopathology in relatives of seasonal winter depressives.

POSTER PRESENTATIONS

All posters will be mounted for viewing and discussion during both days of the meeting. Presenters will be available for discussion at their posters during morning breaks and the Thursday afternoon reception.

Anderson et al.: SPAQ-reported seasonality among patients in treatment for alcohol and drug dependence.

B. Barton and D. Kripke: Illumination exposure among medical students.

Danilenko et al.: Phase and period of menstrual cycle determine response to light.

Geerts et al.: Does non-verbal communication predict the response to treatment in seasonal affective disorder?

Glod et al.: Circadian rest-activity disturbances in children with SAD.

Hébert et al.: Evaluation of retinal sensitivity with ERG in normal subjects.

H. Kern: The correlation of solar irradiance with prevalence of seasonal affective disorder, multiple sclerosis, breast cancer and colorectal cancer.

Kohsaka et al.: Does bright light change sleep structures in seasonal affective disorder?

Kräuchi et al.: Depressed SAD patients exhibit impaired insulin-glucose homeostasis and altered palatability of sucrose in winter.

R. Loving and D. Kripke: A search for circadian markers in the human pupil and eyelid.

Myers et al.: A comparative study of childhood abuse in two patient groups with mood disorders and normal volunteers.

J. Rice and R. Bielski: White light composed of complementary pairs of narrow spectrum light: A placebo control for light therapy?

EDUCATION COURSE

An overview of light treatment parameters and applications as well as presentations on related issues — research, grant funding and reimbursement. Format consists of 35 minute presentations and discussion.

Dan A. Oren, M.D.

Food and Drug Administration, Bethesda, MD

The top 10 papers published in the field of light treatment and biological rhythms: A critique.

Mary Blehar, Ph.D.

Anxiety and Personality Disorders Branch, NIMH, Bethesda, MD

Applying for NIH Grants in an age of scarce resources.

George C. Brainard, Ph.D.

Jefferson Medical College, Philadelphia, PA

What does the clinician and researcher need to know about the properties of lamps and lights?

David Schlager, M.D.

State University of New York, Stony Brook, NY

The current status of obtaining reimbursement for light therapy.

Susan Swedo, M.D.

Child Psychology Branch, NIMH, Bethesda, MD

The diagnosis and treatment of SAD in children.

David Avery, M.D.

University of Washington, Seattle, WA

Light boxes, light visors, dawn simulators and SSRIs: Which is the best approach to treat winter SAD?

EXHIBITORS

Ambulatory Monitoring, Inc.

William Gruen, President
Ardsley, NY

Apollo Light Systems

Henry Savage, Jr., President
Orem, UT

Bio-Brite, Inc.

Gordon Wallace, President
Bethesda, MD

Daylight Technologies, Inc.

Michael Speraw, President
Toronto, Ontario, Canada

Enviro-Med

Sherrie Baxter, President
Vancouver, WA

Northern Light Technologies

Steven Nador, President
Montreal, Quebec, Canada

The Sun Box Company, Inc.

Neal Owens, President
Gaithersburg, MD

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recommend any particular lighting product for clinical, research or general purpose use. Furthermore, SLTBR maintains no responsibility for implicit or explicit claims for efficacy, or instructions for use, that may be contained in literature written and distributed by its Corporate Members.

PRESS INVITED TO ANNUAL MEETING

Members of the press are cordially invited to attend SLTBR oral presentations, poster presentations, exhibits and the education course at no charge. Please request a press badge in advance by writing on letterhead to Marty McCullough, Executive Director, SLTBR, P.O. Box 478, Wilsonville, OR 97070.

A FAREWELL TO EDITING

Written during a hibernation in Cambridge, England

"... I sit over the gas in my sordid room. Why can't I write except in sordid rooms?... I have banged my door on parties, dug myself into a dank, dismal burrow, where I do nothing but read and write. This is my hibernating season." (Virginia Woolf, 5 February 1927).

It may be April, but I, too, have dug myself into that dank, dismal, Anglo Saxon room of one's own, wrapped in three sweaters, multitudinous socks and scarves, huddled over the heater, provisioned by cups of mint tea and Indian takeaways. The icy wind is roaring through the boarded-up ancient fireplace and rattling the single-glass sash windows, the rain and hail blur the green sward and the towers of the great Chapel. The groves of academe (archaic relicts in this brave new managerial world) are perfect for such relicts as I, who require a seasonal retreat from zeitgebers, adrift into a comfortably late circadian phase, with the freedom to do nothing but read and write.

So as the gates close at midnight, I consider how our field differs from that of three years ago. In April 1991, the thought of editing the *LTBR* was both terrifying (being quite naive) and exciting (being nevertheless somewhat brazen). I remember thinking how important it would be to keep the balance between the continents, open up a European viewpoint, develop a global network.

The *LTBR* reviews of light studies from 15 different countries — much of which has neither been published nor

is easily accessible — has achieved this aim. It is gratifying to see what a broad international consensus has emerged within the field, in spite of great diversity of approaches. This is the second point. Three years ago we were still a cozy little group, now, with SLTBR membership approaching 450, light therapy has come of age. Norman Rosenthal's seminal 1984 paper on SAD was recently recognized as a Citation Classic. It has led to studies of light as a treatment modality in a wide range of disorders. In particular, the pending ASDA/SLTBR Task Force Report on Light Therapy for Sleep Disorders may result in official guidelines for application in circadian-related sleep disturbances. Dedicated manufacturers have strived to develop new light devices that incorporate improvements arising out of research protocols (e.g., cutting out UV light, delivering higher intensity, configurations with greater portability).

An important, though controversial development has been the granting of US patents for the use of light. This is indeed the clearest indication that light therapy has come of age, when commercial as well as clinical applications are considered of sufficient importance to be legally protected. The European legal system with respect to patent law, however, is rather different from that in the US, and patent applications may meet a different fate (see report, p. 63).

I thank all contributors who have forborne my persistent, harrying deadline demands, and then had to suffer ruthless editing. Most of all, I thank Michael Terman, SLTBR President, and Marty McCullough, Executive Director, for the daily e-mail discussions that have forged a well-functioning team. E-mail addiction has not yet entered DSM-IV as a special category, but I predict advanced symptoms will soon emerge in epidemic proportions. To expedite this mutual enjoyment, I propose that we create an e-mail Bulletin Board for SLTBR as suggested by Raymond Lam in a recent editorial. It will broaden the basis for establishing consent, and vocalizing dissent, among SLTBR members, as well as providing more rapid dissemination of information than more conventional publications, as this.

A journalist once told me that he felt his work was like writing into a black hole. Nothing ever came back except criticism. So in bidding farewell to editing, I wish my successor, Scott Campbell, a greater success in activating dialogue and input!

AWJ

ASCHOFF, PITTENDRIGH RECEIVE MENDEL MEDAL

The Mendel Medal was established by the Czechoslovak Academy of Sciences in 1965 to honor outstanding contributions in the basic fields of biological sciences. Since 1993, this medal has been awarded by the Academy of Sciences of the Czech Republic.

In 1994, six Gold Medals were awarded, namely to F.J. Ayala (US), D.M.J. Lilley (UK), M. Braend (Norway), S. Riva (Italy), J. Aschoff (Germany) and C.S. Pittendrigh (US). In awarding the medals to the two last-named biologists, the Academy has recognized deep merits of Professor C.S. Pittendrigh and of Professor J. Aschoff in

the field of biological rhythms: both scientists belong to the handful of biologists who have laid conceptual foundations of circadian rhythmicity. Professor Jürgen Aschoff came personally to Prague to receive the medal from the President of the Academy of Sciences of the Czech Republic, Professor Rudolf Zahradník. Unfortunately, Professor Colin S. Pittendrigh could not come to Prague because of illness, and he will receive the gold G.J. Mendel Medal from the vice president of the Academy, Helena Illnerová, in Andechs, Germany.

Helena Illnerová, Ph.D., Institute of Physiology, Academy of Sciences, Vídeňská 1083, 14220 Prague 4, Czech Republic. Tel (42)-2-24 24 05 27; fax (42)-2-24 22 09 44.



Professors Pittendrigh (left) and Aschoff (right with Bavarian cow bell) together with Helena Illnerová (second from left) during the "non-scientific" program at the 1980 Ringberg Symposium.
Photo by AW-J.

COMMENT ON THE TASK FORCE CHRONOLOGY MARCH 1994 DRAFT

The following is a revised version of a contribution by Dr. Serge Daan which appeared in the last issue (LTBR 6: 3). Due entirely to our error, the earlier version contained several erroneous citations and changes in wording that compromised the accuracy of the piece. We apologize to

Dr. Daan, and to our readers, for any inconvenience this may have caused.

Scott Campbell

Marty McCullough

Recent literature (Czeisler et al., 1983, 1986, 1990) 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., 1992a, 1992b, 1993)

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 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 light-dark cycles alone had been revealed in other studies.

1) 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.

2) 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 hours. 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 stably locked to the onset of darkness. No transients are visible in the records published. This demonstrates that the sleep-wake cycle was masked, 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 freerunning 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 25.0h). 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 hours 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 waveform as a criterion for entrainment. Furthermore, throughout the LD treatment, there was a clear temperature rise during sleep, and hence no "square wave", with the exception of Day 87/88 — after 14 days of LD. This was the day of the transition to freerun. Therefore, on the basis of the evidence presented, the conclusion that entrainment occurred was justified in neither subject.

3) Entrainment of both the temperature rhythm and the sleep-wake rhythm by a light-dark cycle, with additional gong signals, had been established in 6 subjects (Aschoff et al., 1969). Entrainment of the temperature rhythm alone (with the sleep-wake rhythm freerunning) by LD without additional signals, had been demonstrated in 3 subjects (Wever, 1979, 1981). In both of these studies, additional reading lights were available, which prevented the LD cycle imposing a sleep-wake cycle, but reduced the strength of the LD zeitgeber. The first demonstration of entrainment of the human circadian temperature rhythm by light cycles without any additional reading lights or social signals is due to Wever (1989).

Serge Daan, Zoological Laboratory, Groningen University, P.O. Box 14, 9750AA Haren, The Netherlands. Tel (31)-50-632046; fax (31)-50-635205; e-mail: DaanS@biol.rug.nl

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LIGHT TREATMENT FOR CIRCADIAN AND SLEEP DISTURBANCES OF SHIFT WORK

Draft report to the ASDA/SLTBR Task Force on Light Treatment for Sleep Disorders

Introduction

About 20% of the workers in industrialized nations are shift workers. The most common complaint of shift workers who work night, rotating, or early morning shifts is of sleep disruption. Other problems include fatigue, gastrointestinal disturbances, impaired performance, and diminished job and public safety (Johnson et al., 1981; Minors and Waterhouse, 1981; Folkard and Monk, 1985; U.S. Congress, Office of Technology Assessment, 1991).

The most serious problems are associated with the night shift, because the circadian rhythms of these workers do not usually phase shift to adjust to the night work and day sleep schedule (see discussion below). Therefore, workers are required to work during the "wrong" phase of their

circadian rhythms, when they are the most sleepy, inefficient, and prone to accidents (Åkerstedt, 1988; Mitler et al., 1988; Dijk et al., 1992; Johnson et al., 1992). Then they try to sleep during the day, again during the "wrong" phase of their circadian rhythms, which results in disrupted and shortened sleep (Czeisler et al., 1980; Åkerstedt and Gillberg, 1981, 1982; Zulley et al., 1981; Tilley et al., 1982; Kogi, 1985). Daytime noises (traffic, children), may compound the problem. Since circadian rhythms do not adjust, many researchers advocate rapidly rotating shift systems which are *not* intended to shift circadian rhythms (Knauth, 1993). However, circadian adaptation to the night shift would be preferable, especially in situations in which safety is a concern, e.g., intensive care units in hospitals, nuclear power plant control rooms. Although the greatest decrements are associated with the night shift, the morning shift can also produce sleep deprivation and its related negative consequences if it starts too early (Folkard and Barton, 1993).

Pre-bright-light studies

Studies of circadian rhythms may be hampered by masking effects. Therefore, we have only included studies here if we judged that their main conclusions were not invalidated by masking effects. Most studies show that the circadian rhythms of night shift workers usually do not phase shift, but instead maintain a phase relationship similar to that of their day-shift co-workers or to their own rhythms on the day shift or on days off (van Loon, 1963; Colquhoun et al., 1969; Åkerstedt et al., 1977; Knauth et al., 1981; Weitzman and Kripke, 1981; Folkard, 1989; Åkerstedt, 1990; Minors and Waterhouse, 1993; Roden et al., 1993). However, there have been a few studies, performed before the era of bright light experimentation, that showed complete or nearly complete phase shifting of circadian rhythms (Sharp, 1961; Knauth et al., 1978; Lynch et al., 1978; Moog, 1987). The discrepancies among studies were historically attributed to differences in "social synchronizers" (e.g., Rutenfranz et al., 1981), because "social cues" were thought to be the main zeitgebers for humans. Now that research has shown the importance of bright or natural light as a zeitgeber for man, these studies can be re-evaluated with regard to the sunlight exposure of the subjects.

Let us examine the studies in which there were large phase shifts of circadian rhythms. The study by Sharp (1961) was conducted during the constant light of the Arctic summer. Subjects wore blindfolds during sleep. The sleep schedule was shifted 12 h. Although temperature was only measured during waking, the waveform appeared

to return to normal after 3-4 days. In the studies by Knauth et al. (1978) and Lynch et al. (1978) [and see Fig. 15 in Aschoff (1981)] the subjects were confined to the laboratory and were probably not exposed to sunlight. The sleep schedule was shifted by 11-12 h and the circadian rhythms shifted gradually and became aligned with the new sleep schedule in about a week. These three studies suggest that complete physiological circadian adaptation is possible if subjects are isolated from the natural LD cycle or if natural light exposure is congruent with their new work and sleep routines. The latter situation occurs after transmeridian jet travel, and of course, the circadian rhythms of jet travelers eventually adjust to the new schedule.

In one study of permanent night shift workers (Blood et al., 1990; Sack et al., 1992) the circadian rhythm of melatonin was advanced by an average of 7.2 h (or delayed by 16.8 h) compared to day workers, to assume an abnormal phase relationship to daytime sleep. The fact that the circadian rhythms of these workers were shifted so much is unusual. It might be attributed to the fact that the studies were conducted during the winter in Portland, Oregon, when natural light exposure may be drastically reduced, especially for night shift workers. This type of explanation is supported by the study of Koller et al. (1989) in which the circadian rhythms of permanent night workers and their light exposure were measured. The two workers with the least light exposure over 1500 lux showed the most adjustment of their circadian rhythms.

Moog et al. (1987) studied the circadian rhythms of students working simulated night shifts at their university and sleeping at home. The circadian rhythms of evening types gradually shifted by about 1 h/day, but the circadian rhythms of morning types did not shift. "Evening types" are people who go to sleep and wake up later, and whose circadian rhythms are phase delayed compared to the norm. Thus, the circadian rhythms of evening types phase shifted despite their presumed exposure to the natural LD cycle.

Information or data relating to natural light exposure were not presented in the Moog study or most other studies of shift work. However, exposure to natural light may be one of the most important factors determining whether circadian adaptation can occur. Future studies should employ photosensors (e.g., Koller et al., 1993) or at least have subjects complete logs of when they go outside and are exposed to natural light (e.g., Eastman, 1990b). Other factors that affect circadian adaptation are individual

differences in circadian type, such as eveningness-morningness, as illustrated by the study of Moog (1987), and perhaps the strength or rigidity of the underlying oscillators. Another factor is the number of consecutive night shifts. Since night shift workers typically revert to sleeping at night on their days off (Lee, 1992; Sack et al., 1992), and may be exposed to natural light during the day, any partial adaptation of their circadian rhythms may be reversed.

Bright light laboratory studies

The discovery of the importance of the intensity of light for human nocturnal melatonin suppression (Lewy et al., 1980) triggered studies of the phase shifting effects of artificial high intensity light. Several studies involved large phase shifts of the sleep-wake schedule, and are thus relevant to both shift work and jet travel. However most of them were performed in temporal isolation units or in laboratories in which subjects were confined to the lab. Therefore, these studies lack the conflicting (shift work) or congruent (jet travel) natural zeitgebers of the real life situation, such as the natural LD cycle. While these laboratory studies are invaluable for learning how the human circadian system responds to bright light combined with phase shifts of sleep, they cannot answer the question of how bright light protocols will work in the field. We know that complete circadian adaptation (complete phase shifting) can be produced in laboratory situations when subjects are isolated from the natural LD cycle, even without the use of bright light. However, it is much more difficult to shift circadian rhythms in the field, against the competing 24-h zeitgebers. Therefore, we will review the laboratory studies briefly, and then concentrate on the field studies.

A few laboratory studies compared higher intensity ("bright") light to lower intensity ("dim") light using large (6 h or more) abrupt phase-shifts of the sleep-wake schedule, either an advance (Moline et al., 1989; Honma et al., 1991), or a delay (Wever, 1985; Dawson and Campbell, 1991). Three of the four studies found greater phase shifts in the bright compared to the dim light conditions. The exception (Moline et al., 1989) could be due to inappropriate timing of the bright light given the direction that the sleep-wake schedule was shifted. Although it is difficult to compare the results of these studies which used different circadian rhythms for phase markers and different methods with precision, it appears that circadian rhythms shifted about 1 h/day in the dim light conditions, and as much as 2-3 h/day in the bright light conditions.

There were also two laboratory studies that compared different timings of bright light after large abrupt phase advances (Samel et al., 1992) or phase delays (Gander and Samel, 1991) of the sleep-wake schedule. The results of these studies are puzzling because circadian rhythms shifted about 2 h/day regardless of the timing of the bright light exposure. There was little difference between the conditions predicted to enhance phase shifting and the conditions predicted to inhibit the phase shift.

Wever (1983, 1985, 1989) compared the strengths of various zeitgebers in temporal isolation experiments in which the period of the zeitgeber was gradually increased or decreased (fractional desynchronization). A bright-light/dim-light zeitgeber (3000:300 lux) produced a range of entrainment of about ± 4 h. Since there were no acoustic signals (gongs) and no darkness to force the subjects to go to bed, entrainment cannot be attributed to social cues or to the imposition of a sleep-wake schedule. This was the first demonstration that bright light alone can be an effective zeitgeber for human circadian rhythms (cf., Daan, *LTBR*, this issue). An "information zeitgeber" (acoustic signals for bed and wake times) in otherwise constant dark or constant light produced a range of entrainment of about ± 2 h. This showed that a sleep-wake schedule alone could be an effective zeitgeber for humans. The largest range of entrainment (about ± 6 h) was obtained with bright-light/dark cycles (3000:0.1 lux) plus acoustic signals. Thus, the strengths of the bright light and sleep-wake schedule zeitgebers appeared to be additive. Alternatively, the bright-light/dark zeitgeber could have been stronger than the bright-light/dim-light zeitgeber.

Bright light field studies

Eastman designed bright light schedules intended for use in the field by real shift workers. One schedule (Eastman, 1987, Fig 2) was designed for a work schedule common in nursing, an alternation between day and night shifts every 2 weeks. The sleep-wake schedule gradually delayed by 1-3 h/day around the transitions between the day and night shifts. Another schedule (Eastman, 1990a, Fig 3) was designed for a weekly rotation from day to evening to night shifts. The sleep-wake schedule delayed by no more than 2 h/day during some parts of the schedule. In both schedules bright light was timed for the hours immediately before sleep (to coincide with the delay portion of the PRC) and bright light was to be avoided after sleep (in case subjects woke before the end of the advance portion of their PRC). Bright light exposure could be obtained by going outside during some parts of the schedules. These

However, in this study the circadian rhythms of a few subjects in the evening light condition did not phase shift, but remained entrained to the 24-h zeitgebers. Another bright light field study with gradually shifting sleep-wake schedules (Gallo and Eastman, 1993) showed that the circadian rhythms of many subjects could not be phase shifted with the technology employed. The failures might be attributed to many factors including insufficient artificial bright light exposure (e.g., portable light boxes that were too small and did not cover enough of the visual field, cf., Dawson and Campbell, 1990) or greater exposure or sensitivity to the 24-h zeitgebers in some individuals.

Other bright light field studies used a large, abrupt shift of the sleep schedule, which is what most shift workers experience when they change from the day or evening shift to the night shift. In one study (Zeisler et al., 1990), light exposure was delivered during four simulated night shifts in the lab (7000-12,000 lux from 00:15 to 07:45).

It was important to determine whether such light-sleep schedules could actually phase shift the circadian rhythms of subjects living at home, exposed to the competing 24-h zeitgebers. Therefore, the first field study of the phase shifting effect of artificial bright light combined with shifts in the sleep-wake schedule was conducted (Eastman, 1986; Eastman and Miescke, 1990). Subjects slept at home in bedrooms made dark by covering the windows with black material. They followed a 26-h sleep-wake schedule "around the clock," until they were once again sleeping at their usual time. They used portable light boxes at home either before bed or after waking (2 h of about 2000 or 4000 lux). They stayed indoors, or wore dark welder's goggles when outside in daylight, at other times. As predicted, the "evening light" condition (bright light before sleep and avoidance of bright light after waking), was the most likely to produce entrainment of the temperature rhythm to the 26-h schedule, i.e., about a 2 h/day phase delay shift of the temperature rhythm. Thus, this study showed that a schedule of bright light, dim light, dark and sleep could phase shift and entrain human circadian rhythms, despite the conflicting 24-h zeitgebers.

The sleep schedule was shifted by about 9 h, and subjects slept at home in specially darkened bedrooms. Circadian rhythms measured on the sixth night shift were completely shifted in all 5 subjects (an average of 9.6 h). In contrast, when the subjects were kept in dim light during the simulated night shifts, and were not required to sleep at a specified time or in the dark, the circadian rhythms did not phase shift (the average shift was 1.1 h). The phase shift of 9.6 h over 5 days in the bright light condition, is consistent with the 2 h/day phase shifts in the other bright light studies. After bright light the subjects were more alert and performed better on the sixth night shift compared to the first, whereas after dim light they showed no improvement in performance, although they did report feeling more alert. Self reported daytime sleep after bright light averaged 7.7 h out of the required 8 h of dark, in-bed time. In the dim light condition, when no specific sleep schedule was required, sleep averaged 5.7 h.

In another simulated night shift field study (Eastman, 1992), the sleep schedule was shifted 12 h. Many rotating shift workers experience a shift of about this magnitude in the change from day to night shifts. The bedrooms of the subjects were made very dark. Subjects wore dark welder's goggles (1% transmission) whenever they went outside during daylight. There was a 2-h "travel home window" between the end of the 8-h simulated night shifts and bed. Bright light exposure was produced by an array of light boxes surrounding the subject, positioned to produce about 5000 lux. Various patterns of bright light exposure were tested, but they all occurred around the trough of the temperature cycle, to hit the most sensitive portions of the phase response curve (PRC). There were moving ("nudge") and stationary ("squash") patterns composed of 6 h of bright light on the first 4 nights and 3 h/night thereafter.

Regardless of the pattern of artificial bright light exposure, the circadian rhythm of temperature phase shifted by about 2 h/day in 21 out of 24 subjects. The circadian rhythms of 3 subjects did not shift. The direction of phase shift (advance or delay) was determined by the timing of the 6 h exposures relative to the baseline phase of the temperature rhythm. When most of the light exposure occurred before the temperature minimum, the circadian rhythms usually delayed; when most of the light exposure occurred after the temperature minimum, the circadian rhythms usually advanced. Thus, this study showed that the crossover point for the light PRC is when the middle of the bright light exposure occurs at about the time of the temperature minimum, as shown by others.

The subjects reported increased fatigue during the first few night shifts, and reduced sleep (average of about an hour) during the first few day sleeps. These symptoms decreased as the circadian rhythm of temperature phase shifted to align with the daytime sleep period.

A subsequent study assessed the relative contributions of the bright light and dark goggles to the circadian temperature rhythm phase shifts (Eastman, 1993). There was a 2 x 2 design: light (bright, dim) and goggles (present, absent), with a total of 50 subjects. Many elements were the same as in the previous study (Eastman, 1992), a 12-h shift of the sleep-wake schedule, sleep at home in a very dark bedroom, a 2-h travel home window, etc. However, bright light exposure only occurred during the first 2 of the 8 simulated night shifts. The light was 6 h in duration, about 5000 lux, and occurred around the temperature minimum. The subjects in the goggles groups wore goggles with 0.35% transmission during the travel home window. The day sleep period ended after sunset, and thus subjects were not exposed to natural light at any time except during the travel home window.

The results were that both bright light and goggles were important for producing temperature rhythm phase shifts. The temperature rhythm of the subjects in the dim-light, no-goggles group did not shift, or shifted very little. A few subjects in the bright-light-only and goggles-only groups had substantial phase shifts. But, the combination of bright light and goggles was the most effective for circadian rhythm adaptation. Larger temperature rhythm phase shifts were associated with better subjective daytime sleep, less subjective fatigue, and better mood.

When the temperature rhythm phase shifted, the direction of shift depended on goggles. When subjects wore goggles, their circadian rhythms either advanced or delayed after the 12-h shift of the sleep schedule, as in the previous study (Eastman, 1992). However, when they did not have goggles, the circadian rhythms only advanced, they never delayed. Apparently sunlight during the travel home window was enough to keep the circadian rhythms from delaying. Light at this time is expected to coincide with the advance portion of the PRC. This study showed that goggles are important for producing circadian rhythm adaptation by phase delay.

Another field study (Eastman, 1994) compared bright light durations of 6, 3 or 0 h during the simulated night shifts, with a total of 46 subjects. The method was similar to the previous study (Eastman, 1993) except that dark goggles

were not used. To compensate, bright light was used during all 8 night shifts. As expected, the 0-h bright light condition (the dim light condition) produced little circadian phase shifting. In contrast, both the 3 and 6-h conditions were very effective in shifting the temperature rhythm to the daytime sleep schedule. There was no significant difference between the 3 and 6-h conditions. Thus, extremely long bright light durations may not be necessary to treat real shift workers, making the procedure more convenient and feasible.

Although these subjects did not have special dark goggles, in some cases the temperature rhythm phase delayed to align with daytime sleep. However, many more subjects phase advanced than phase delayed. Thus, repeated bright light exposures can produce phase delays despite daylight exposure during the travel home window. In the study by Czeisler et al. (1990) the subjects were not given dark goggles, and the circadian rhythms may have delayed with four nights of bright light. However, with constant routines applied 5 days apart, it is difficult to distinguish between a 9.6 h delay and a 14.4 h advance.

All the bright light field studies discussed so far employed volunteers, usually students, instead of shift workers working their regular jobs. NASA was one of the first to implement bright light for phase shifting the circadian rhythms of shift workers. The astronauts of the Space Shuttle mission STS-35 were exposed to bright light at night during the week-long pre-launch quarantine period to phase shift their circadian rhythms prior to night work while on orbit (Czeisler et al., 1991). The sleep schedule was abruptly delayed by about 9 h and the light exposures were about 9 h long, occurring at about the time of the previous sleep periods. The light intensity was about 10,000 lux for the first 4 nights, and 1500-3000 lux for the last 2 nights. The enthusiasm of these astronauts, as well as melatonin data that supported a phase shift in circadian rhythms, attested to the success of this procedure.

Bright light was then employed in 10 subsequent Space Shuttle missions (Stewart and Eastman, 1992; Stewart et al., 1992a). Protocols were designed to advance or delay circadian rhythms, depending on the sleep times required on orbit. Based on the field study by Eastman (1992), bright light was used primarily before the presumed temperature minimum to induce phase delays and primarily after the presumed temperature minimum to induce phase advances. Schedules were designed based on the assumption that circadian rhythms would shift about 2 h/day. Light exposures varied from 1 to 6 h depending on

the schedule, and the day of the schedule. Some schedules contained abrupt shifts of the sleep-wake schedules, whereas others had gradual shifts, based on the preferences of the astronaut crew and the constraints of their duties. In some cases the timing of the bright light exposure was gradually changed to keep up with the presumed phase shift of the circadian rhythm; in other cases light exposure was scheduled to occur at the same time each day. Astronauts were provided with the same dark goggles used in previous studies (Eastman, 1992, 1993) to wear if their duties forced them to be outside at times when bright sunlight exposure might interfere with the desired phase shift.

The bright light phase shifting procedure is so successful that it has become a permanent part of the Space Shuttle program. When new crew quarters were built, architectural lighting was included to provide high intensity light in many areas, including bathroom and the exercise room. The astronauts represent a special case of shift workers. They are highly motivated to perform optimally. Individual astronauts only have to phase shift their sleep schedules on rare occasions, because their missions may be months or years apart. Most importantly, they have optimal physical conditions for phase-shifting, special living quarters with convenient high intensity lights, away from their families and noises that might disturb daytime sleep.

It is even more of a challenge to phase shift the circadian rhythms of shift workers who must live at home. Two controlled studies were performed using members of the payload support crew who work in control rooms at NASA's Marshall Space Flight Center (Stewart et al., 1992b, 1993). These individuals work shifts during some of the space shuttle missions because they must coordinate operations on the shuttle. Subjects in the experimental groups received bright light exposure at home with portable light boxes placed in reflective work stations producing about 9000 - 10,000 lux. The same welder's goggles used in previous studies (Eastman, 1992, 1993) were provided for times at which bright light was to be avoided. Bedroom windows were covered with black plastic.

Bright light treatment for the night shift workers began several days before the first night shift, in order to pre-shift rhythms, and continued during the mission to maintain phase shifts. Light exposure was also used near the end of the mission, to phase shift the rhythms back to their normal phase. For most schedules, the sleep

schedule was gradually delayed before the night shifts, remained stable or was delayed slightly during the mission, and was delayed again after the mission, until the normal time for sleep was reached. Light exposure durations were as long as 5 h when phase shifts of circadian rhythms were desired, and were reduced to as little as 1 h for phase maintenance. The night shift control subjects did not receive any treatment, and were free to cope with shift work in their own way. Many took the precaution of making their bedrooms dark and delaying their sleep times a little before the mission. Questionnaires included daily sleep logs, daily symptom rating scales, twice daily Stanford Sleepiness Scales and a post mission questionnaire.

Night shift workers who received light treatment fared better than control subjects on virtually all measures, especially self-rated job performance, fatigue and sleep quality. Evening shift workers were also included in the first study. The required phase delay of sleep was only about 4-5 h, and the treatment protocols included much less bright light exposure. However, an important part of this protocol included bright light treatment after the mission, to phase advance the rhythms back to normal. Light treatment had beneficial effects on most symptoms. However, the most impressive effect of treatment was after the mission ended, when the treatment group recovered sooner and took fewer days off from work.

Conclusion

It is clear that bright light exposure can be used to help shift workers adapt to their unusual work and sleep routines. However, the desired results were not produced in all studies (Moline et al., 1989; Gallo and Eastman, 1993) and puzzling results were obtained in other studies (Cole and Kripke, 1991; Gander and Samel, 1991; Samel et al., 1992). Many basic research questions remain to be answered. For example: What are the optimal and minimal intensities and durations of light exposure necessary to produce a given phase shift? For each desired phase shift and bright light pattern, how important is the avoidance of bright light and the attenuation of sunlight exposure with dark goggles? The technology for producing high intensity light has grown in recent years, whereas the development of dark goggles has lagged behind. There is an urgent need for very dark goggles that fit snugly over eyeglasses, that quickly change transmittance with ambient light intensity, and that do not block the peripheral vision necessary for driving. Other research questions include: If light treatment is used to shift circadian rhythms for the night shift, then what type

of treatment is needed when workers have to change shifts, e.g., to the day shift, or on days off? Will the repeated phase shifting of circadian rhythms be a greater health hazard than repeatedly working and sleeping at the "wrong" circadian phase? Finally, most experiments have been performed on young adults. Studies on middle-aged and older subjects are necessary since their response to circadian rhythm phase shifts and to the phase shifting effects of bright light may change with age.

The author welcomes comments, corrections, and any new reprints from bright light shift-work studies.

Charmane I. Eastman, Ph.D., Biological Rhythms Laboratory, Rush-St. Luke's-Presbyterial Hospital, 1653 W. Congress Parkway, Chicago, IL 60612-3864. Tel 312-942-4472; fax 312-955-3958.

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MEETING REVIEW

Society for Research on Biological Rhythms

Every two years, SRBR meetings provide a multidisciplinary forum for all scientists interested in biological rhythms. The 1994 meeting at Amelia Island Plantation, Jacksonville, Florida (May 4-8) was, once again, a special opportunity to meet researchers working with humans, hamsters, mice, snails, genes, or just nice mathematical equations. . . . It was quite unfortunate that concurrent sessions posed a constraint since the 420 participants had to choose between sessions where they could hear about (or present) new material obtained in the past two years in their own field of interest, and sessions where they could learn a little about what is happening in others fields of biological rhythms research. Only two activities were scheduled for all participants and had a multidisciplinary flavor: the Presidential Address given by R.Y. Moore, and the Society Symposium devoted to breakthroughs over the past two years in some major fields of biological rhythms research. For the rest, simultaneous activities were the

rule: symposia were held three at a time, workshops went by packages of four, and participants had to make heart-breaking choices between 4 or 5 simultaneous slide presentations. More than 130 posters were also on display. And all this without speaking of the unfair competition from the sun and the beach of beautiful Amelia Island.

My own selection favored presentations related to light and melatonin, and to relationships between circadian rhythms, mood and sleepiness. Symposium 2, on circadian control of alertness and sleepiness, was mainly devoted to the question of distinguishing between homeostatic and circadian influences on sleepiness. This problem is complicated by the fact that these influences do not have a constant relationship. S. Folkard presented his 3-process model, an extension of Borbély's 2-process model for sleep regulation, and reminded us that the circadian variations in sleepiness increase with the duration of time awake. D. Dinges added that the relative contribution of the homeostatic and circadian components varies according to the tests used to measure sleepiness. As an example, he showed that reaction time tests revealed a smaller circadian component than analog vigilance scales. T. Monk and M. Carskadon emphasized that circadian influences on sleepiness and alertness vary greatly from infancy to old age. Finally, P. Lavie explored the relationship between melatonin and sleepiness, and developed the hypothesis that endogenous melatonin might have a role in opening the "sleep gate" in the circadian sleep propensity rhythm. Lavie also presented a very interesting case of a child with a pineal tumor and complete absence of melatonin secretion. This child suffered from very severe insomnia, which was successfully treated with daily administration of 3 mg of melatonin.

In Slide Session 3 on jet lag, shift work and their treatment, A. Samel presented a "natural approach" to help recovery from jet lag, which consists of specific scheduling of the sleep-wake cycle called "fractional desynchronization", and M. Moline explored the phase-shifting properties of caffeine and its potential use to treat the symptoms of jet lag. The preliminary results of her very systematic randomized double-blind study showed that a single daily dose of caffeine at breakfast may enhance the phase advance of the temperature rhythm following a 6-hour advance in the sleep schedule. The next three presentations were concerned with the use of bright light to help circadian adaptation to shift work, and focused on the applicability of this treatment in real world situations. K. Stewart reported the first successful bright

light treatment in real shift workers — ground support staff for Space Shuttle missions. S. Campbell studied the effects of bright light exposure during three nights of simulated shift work in middle-aged subjects, and found no improvement in alertness, performance or sleep quality compared with controls, in spite of a significant phase-delay in the temperature rhythm. These results raise the important question of the pertinence of results obtained in healthy young adults to the treatment of older populations of real shift workers. C. Eastman compared 6 hrs to 3 hrs of bright light exposure during simulated night shifts, and found that for most subjects, 3 hrs of bright light sufficed to produce circadian rhythm adaptation. Reducing the duration of bright light exposure may increase the feasibility of field applications of this treatment. Next, a presentation from our laboratory showed the effects of bright light exposure on sleep tendency throughout the following day, with the sleep schedule being held constant. Latencies on the Multiple Sleep Latency Test increased after morning bright light exposure, whereas they decreased after afternoon and evening exposures. Finally, A. Lewy showed that when the sleep-wake schedule is shifted in concordance with melatonin administration, the circadian phase-resetting is more robust than resetting obtained with melatonin alone. The combination of melatonin with darkness caused by closing the eyes during the sleep period makes melatonin administration as effective as bright light in producing phase shifts. As Dr. Lewy nicely put it: "Melatonin tells the clock that this darkness is the real darkness".

Symposium 8, entitled "Implications of circadian rhythm abnormalities in depression" regrouped four studies using very different approaches. E. Frank described her group's work on the hypothesis that the loss of social zeitgebers may have a major contribution to depression. She emphasized that disrupters of circadian rhythms, which she called zeitstörers, can be social in nature, and may initiate manic or depressive episodes in predisposed individuals. Their therapeutic approach included identification of the social disrupters in the patient's life and the implementation of controls over the social rhythms. E. Van Cauter reported the results of a meta-analysis of cortisol rhythms in depression which support the hypothesis of a circadian phase advance in depressive patients. However, she pointed out that this observation does not necessarily reflect a change in the circadian pacemaker itself. R. Dahl also studied cortisol rhythms, but in children and adolescents, and found that circadian dysregulation is infrequent before puberty. He suggested that some maturational factors might be involved in the interaction

between circadian rhythms and depression. Finally, A. Wirz-Justice gave us our first taste of the results of her 4-year study on circadian rhythms in SAD women. In this study, temperature and melatonin rhythms were evaluated with the constant routine protocol before and after bright light treatment, during the winter and during the summer, in 11 SAD patients and 8 matched controls (ouf!). The circadian amplitude of temperature and melatonin rhythms was not different between SAD patients and controls, and was not affected by the midday light treatment. Phase analysis showed that the two circadian markers did not necessarily give the same results: melatonin was not modified by light treatment, but some parameters of the temperature rhythm showed a phase advance in SAD patients after the light treatment. Some interesting effects of bright light exposure on performance and heart rate were also suggested, and we will certainly hear more about this at the upcoming SLTBR meeting.

A lively theoretically oriented workshop on Type 0/ Type 1 resetting by light topped off the paper sessions. Following very clear and didactic presentations of the mathematical models, the discussion suggested that humans are not so different from hamsters, after all. This made me regret having missed most of the animal presentations during this very exciting meeting.

Marie Dumont, Ph.D., Laboratoire de chronobiologie, Hôpital du Sacré-Coeur et Université de Montréal, 5400 boul. Gouin ouest, Montréal (Québec) Canada, H4J 1C5. Tel 514-338-2246; fax 514-338-2531.

SRBR PATENTS WORKSHOP

A debate on "Patenting Specified Uses of Melatonin and Light: Facts and Evaluation" took place at the Fourth Meeting of the Society for Research on Biological Rhythms in Amelia Island, moderated with justice by Eve Van Cauter and Nicholas Mrosovsky during a hot lunchtime break. In spite of the temptations of the beach, this session was well attended, and discussion was lively, curious and courteous.

David Parker, a scientist and patent attorney, summarized the US situation with respect to patent infringement exemptions for research. His paper (a whirlwind in 30 minutes of about 30 years of patent law) covered the following headings:

The United States Patent System

A. Statutory Classes of Invention

1. Machines, manufactures, compositions of matter, processes
2. New uses for old compositions or processes

B. The Patent Specification and Claims

1. Enablement
2. The patent claims define the subject matter of the invention

C. Patentable advances measured against the "prior art"

1. The Prior Art
2. Novelty and Non-obviousness
3. Practical Usefulness

Patent Infringement and the Research Exemption

A. The "FDA" Exception

B. The Common Law "Research Exemption"

1. Overview
2. Problem areas
 - a. Distinguishing "commercial" from "non-commercial" research
 - b. Inventions used principally or exclusively for research will never be infringed if "research" is not infringement
 - c. Distinguishing between "studying" how the invention works and "using" the patented invention
3. Possibility of an infringement suit against a researcher using a patented invention in his or her research
4. Statutory proposals

What does this all mean, for the innocent scientist? It was made clear that Alfred Lewy's patent for melatonin (U.S. #5,242,941) was a rather specific use patent "for less than 1 mg dose of melatonin to be applied more than 6 and less than 19 hours before the normal sleep phase", whereas the wording of the Harvard light patents (U.S. #5,163,426; #5,167,228; #5,176,133 and #5,146,927) were much more global, more difficult to judge, and impinged on what many scientists consider "prior art". Discussion focused on the duty of the applicant to disclose every bit of prior relevant information to the patent office, and doubts were raised that this had been correctly done. An invention must be new, and not be general knowledge, and must have the characteristic of "non-obviousness" for a specialist in the area. Many researchers argued that the concept of phase-response curves has been in the public domain since Pittendrigh's early work, and the human PRC is no exception — i.e., is obvious "to one skilled in the art".

The "research exemption" category means using light with no intent to profit (to sell, to use, or an experiment with commercial applications). It is clear that most clinical research, that **might** (hopefully will) lead to clinical use dances on a fine tightrope separating "pure" from "applied". Yet, if doing research, you don't need a license. Thus, the unfortunate letter to a researcher requesting licensing of this technology (see *LTBR* 6: 29-30), that he courageously did not sign, has been retracted, with a public apology, that it was a mistake.

Parker concluded saying that "just because someone has a patent, doesn't mean it's valid. The courts determine the validity of patents." Of course, the consequences of infringement in the US are daunting: he estimated that a budget of \$1.5 million for 1.5 years would suffice to contest the patents. There is also a possibility of requesting re-examination of the validity by the patent office, by identifying prior literature, and at far lower expense. It remains an important task to elucidate the "prior art" of circadian rhythm phase shifting and entrainment by light, and of melatonin suppression by light.

The linguistic facility and amazing flexibility required of a patent lawyer is illustrated by the following discussion. Worried clinicians who use light treatment routinely in their practice were met with rhetoric but no clear answer. A more specific question was eloquently posed: "If I, as a physician, establish the Curt Richter Memorial Sleep and Type O Clinic and Wellness Center and proceed to treat my patients with timed light therapy and/or low dose melatonin for various sleep disorders, SAD, jet lag, and life-style dysphoria, will my use of these treatments be affected by these patents? Would the patent-holder be within his rights to demand licensing fees and/or royalties?" Although the response lacked clarity, emphasized lack of knowledge or responsibility, and uncertainty, the gist was "Maybe" and I and the majority of the audience inferred "Yes" (but see letter from the Brigham, this issue).

It was emphasized that the patent is a **method** of modifying circadian amplitude and phase after defining steps by which it is initially estimated. This is crucial: "Do you arrive at circadian phase by specified means?" Indeed, it appeared that it was not the use of the constant routine per se that is patented, but that the method can be extended to so-called "normative data". This of course means that anyone using a light pulse at a certain time of day based on knowledge of PRCs is using patented

"normative data". Thus, to treat a sleep disorder with light, such as clinical applications in a sleep center, is an infringement. What is still not clear, even after the new assurances from the Brigham (see letter, this issue) is the right to technology that may develop (or has already been developed) from independent research, and enforcement that may apply to not-for-profit and for-profit groups of researchers, clinicians, consultants and companies.

I have been studying European patent law as a new hobby in my spare time. At the meeting, I briefly reviewed the differences from US patent law:

- **US:** Patents become public only after being granted and no possibility of recourse. Validity is tested in the courts.

Europe: Submitted patents are published 18 months after submission. Then recourse is possible at any time if one provides literature supporting the objection that "this invention is not patentable on the following grounds" The Patent Office must investigate the relevance of the documents submitted, and recourse is possible within 9 months once the patent has been granted.

- **US:** The university patents, not the professor.

Europe: The professor is free to patent, not the university.

- If the invention is made public, by a lecture or in print, it has two entirely different consequences:

US: Patent can be registered within a year of publication (i.e., "with due diligence").

Europe: This preliminary publication precludes patentability — requirements are for "absolute novelty".

- If a European invents before someone in the US, this is not relevant — for patenting in the US, only the US inventor counts. Therefore, a European inventor has to pass on his information to a US colleague who can then claim priority in the US.
- In the US, the criteria for patenting are "first to invent"; outside the US, "first to file".

These brief comparisons make it clear that each country has different strategies for protecting intellectual property. The Harvard applications to the European Patent Office have now received a first examination report (dated 23

December 1993 and 18 January 1994). The examiner has raised objections with regard to specific claims, under certain articles which are crucially different from US patent law, in particular Article 52 (4):

Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body shall not be regarded as inventions which are susceptible of industrial application. . .

The applicants now have time to file their observations with regard to the objections raised by the examiner. It appears that they will have to file a new set of claims which will then again be considered by the European Patent Office.

In summary, the fact that a debate took place was useful, because not many scientists are at home in legalese. It did not clearly resolve the uncertainty about the boundaries of the US patent, since this can only be tested with individual cases. In Europe, the patents have not yet been approved. Reminded of *The Hunting of the Snark (An Agony, in Eight Fits)*, I will just reiterate the last lines as a possible outcome of all this discussion: "He had softly and suddenly vanished away — For the Snark was a Boojum, you see."

Anna Wirz-Justice, Ph.D., Psychiatrische Universitätsklinik, Wilhelm Klein-Strasse 27, CH-4025 Basel, Switzerland. Tel (41)-61-325 5473; fax (41)-61-325 5258.

Letter to the Editor

RESPONSE TO THE FIELD FROM THE BRIGHAM

For the past five months, chronobiology researchers and sleep disorder therapists have registered concern about the possibility that the Brigham and Women's Hospital (BWH) would use its patent position with respect to modification of circadian cycles to interfere with academic research and/or patient treatment in these fields. This concern arose because an unsolicited and ill-considered document was sent by BWH to one investigator before the problem was recognized. I am writing you this letter to tell you unequivocally that the BWH has not and will not ever use patents to interfere with academic research or patient treatment.

The BWH, as is true for every other academic bio-medical research institution in the United States, has a policy of seeking patents to protect the intellectual property created by its faculty. In 1987, the Hospital applied for patents on work by Drs. Charles Czeisler, Richard Kronauer and James Allan. The first patent, entitled "Assessment and Modification of a Subject's Endogenous Circadian Cycle" was awarded in 1992. Extensive research on circadian cycles and related matters is currently carried out at many institutions, and this has raised the question of whether the patent would be used to impede this research. There is, however, a research exemption under patent law, and academic researchers are free of the patent restrictions that otherwise might apply to commercial organizations.

There is therefore absolutely no need for any academic researcher to obtain permission from, send information to or obtain a license from the Brigham and Women's Hospital or any of its licensees in order to carry out academic research on any aspects of chronobiology. BWH is a research hospital. We demand academic freedom for our investigators and expect the same academic freedom for colleagues at other institutions.

Questions have also arisen about whether therapists who prescribe light treatment of the type covered by the issued patent would be sued as patent infringers. The BWH has not in the past and has no future intent of interfering with a therapist's freedom to prescribe light treatment for

a patient. I want to reassure the treatment community on this point. Neither BWH nor any of its licensees will ever use this or any other patent to interfere with the treatment of a patient.

It appears that there has been some misunderstanding about the nature of patents. Patents are typically issued for particular breakthroughs which usually build on years of preceding research by many individuals. Patents have no academic implications and are primarily of importance to commercial entities. All patents issued by the U.S. Patent Office are presumed to be valid. Determining whether an issued patent is not valid or whether it is unenforceable moves into the arcane arena of patent law, and those companies with commercial interests and their patent attorneys (who always have vested interests) should resolve these issues.

In closing let me apologize again to Dr. Czeisler for putting him in an embarrassing position and to the affected research and treatment communities for creating confusion and anxiety. Let me also again state that the patents in question will not be used in any way to limit academic research or patient treatment.

William D. Terry, M.D. Senior Vice President, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Tel 617-732-5504; fax 617-278-6996; e-mail: wdt@bustoff.bwh.harvard.edu

BULLETIN BOARD

WELCOME TO NEW MEMBERS

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

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SLTBR BOARD RECONFIGURATION, ELECTIONS ANNOUNCED

All current Regular Members of the Society were notified in May of the upcoming membership business meeting to be held on Thursday, 23 June at Lister Hill Auditorium. The meeting announcement included an explanation of the Board of Directors' decision to reconfigure the Board and stagger the election process for directors in order to increase member participation and foster greater continuity in the succession of directors. Historically, Board members have been elected in a single block for a seven-year term. The Board has expanded its number of members from five to nine, has shortened the term for directors and has provided for a "staggered" succession of Board membership, with one-third of the directorships coming up for election each year.

In order to establish the staggered succession of Board membership, two current members have had their terms shortened to expire in June 1995 (Class III Board members). The Board intends to appoint Raymond W. Lam to fill the remaining one year of the third Class III member. The other three current members have been designated as those (Class II) whose terms expire in June 1996. The remaining class (Class I), with terms expiring in June 1997, are being presented to the Regular Members for election at the business meeting. The persons nominated for Class I are J. Christian Gillin, M.D., Sonia Ancoli-Israel, Ph.D., and Scott S. Campbell, Ph.D. In the event these individuals are elected as Directors, it is the intent of the Board of Directors to appoint Dr. Gillin as President-Elect and Dr. Ancoli-Israel as Treasurer. Dr. Campbell will serve as Editor of *LTBR*.

Regular Members who attend the business meeting may vote in person. Those whose proxies have been received prior to the meeting date will also have participated in the

elections process. Regular Members are encouraged to contact Marty McCullough, or any officer or director of the Society with names of persons who might be interested in serving on the Board in the future.

COMMERCIAL REFERENCES TO SLTBR/QUOTATION OF SLTBR PUBLICATIONS

The Society reminds all corporate interests that its policy with regard to use of SLTBR's name, as well as quotation of its publications or reference to its membership and activities, is to prohibit such use and/or reference. The purpose of this policy is to avoid the appearance of endorsement by SLTBR of products or services as well as to maintain distance from interests whose products, services and/or interpretation of research and/or clinical data and protocols we have not evaluated.

A recent combined mailing by Lighting Resources and Med Ed Publications (both of Columbus, OH) solicited information from recipients concerning their potential interest in receiving SLTBR membership and publications information. The Society did not authorize use of its name in this instance and has requested that the companies in question cease distribution of any materials which include mention of SLTBR or its activities, refrain from such reference in the future and refer interested responders directly to the Society.

Commercial concerns who wish to refer interested individuals to SLTBR for potential membership, purchase of publications or general information, may do so providing they have first received permission from the Society and have submitted a copy of the proposed publication containing a draft of the intended referral language.



Society for Light Treatment
and Biological Rhythms

P.O. Box 478
Wilsonville, OR 97070