

Light Treatment and Biological Rhythms

Bulletin of the Society for Light Treatment and Biological Rhythms



Volume 7, Number 4

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ANNUAL MEETING PROGRAM

The program for SLTBR's Seventh Annual Meeting June 9-11 in Frankfurt, Germany, has been finalized. The three-day meeting, the first to be held outside the United States, will feature overview lectures, oral research presentations, poster presentations and a special forum on patent law. The Sunday afternoon education course, to be presented concurrently in English and German, features presentations on "SAD and Light Therapy" ("Praxis der Lichttherapie"). Social events include a gala banquet evening featuring an after-dinner speech by Jürgen Aschoff.

Individuals who have not yet registered for the meeting may do so on site with payment of a \$15.00 late fee. Members may register with a payment of \$115.00 (includes late fee); non-members, \$165.00 (includes associate membership).

PROGRAM SUMMARY

Friday, 9 June

- | | |
|-------------|---|
| 10:00-13:00 | Registration, refreshments, exhibits |
| 13:30-13:20 | Welcome by Burkhard Pflug, Wilfried Köhler, Anna Wirz-Justice |
| 13:20-14:20 | Brief overview lectures by Frankfurt specialists: <ul style="list-style-type: none">• Light as Zeitgeber—A Phylogenetic Approach—G. Fleissner• Neuroanatomy and Cell Biology of the Mammalian Circadian System—H.W. Korf• Molecular Biology of the Mammalian Circadian System—J. Stehle |
| 14:20-16:30 | Main Poster Session |
| 16:30-17:30 | Round table poster discussions—N. Rosenthal, Chair. Focus: The Future of Light Therapy |

Saturday, 10 June

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| 09:00-10:30 | Oral Presentations I—Symptom and Biological Correlates for SAD |
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| 10:30-11:00 | Break, exhibits, refreshments |
| 11:00-12:30 | Oral Presentations II—Seasonality and Effects of Light Treatment |
| 12:30-14:00 | Lunch |
| 14:00-16:00 | Oral Presentations III—Circadian and Sleep Effects of Light and Melatonin |
| 16:00-16:30 | Break, exhibits, refreshments, posters |
| 16:30-17:30 | SLTBR Business Meeting |
| 17:30-18:15 | Forum: Can the Use of Light and Melatonin be Patented? |
| 20:00- | Gala banquet evening—Lichtof (light hall) of the Senckenberg Museum.
Jürgen Aschoff will present an after-dinner speech |

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Light Treatment and Biological Rhythms
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PROGRAM DETAILS

Friday, 9 June

Poster Session—14:20-16:30

Schlager and Schwartz: Seasonal Variation in Human Neo-Natal Mortality.

Anderson et al.: SPAQ and Seasonality: The Women are SAD and the Men are Subsyndromal—Is it a Problem?

Hagfors et al.: Seasonality in Finland and Sweden, an Epidemiologic Study, Preliminary Results.

Danilenko and Putilov: Factors Affecting the Typical Clinical Picture of SAD.

Krauchi et al.: Carbohydrate Eating in SAD is "Emotional".

Ozaki et al.: A Search for Serotonin-Related Candidate Genes in Patients with Seasonal Affective Disorder (SAD).

Ruhrmann et al.: Preliminary rCBF Findings with a Cognitive Stimulation Paradigm in Seasonal Affective Disorder.

Sachs et al.: Changes in rCBF After Light Therapy for SAD: Responders vs. Non-Responders.

Neumeister et al.: Serotonin Function and Mechanism of Action in Light Therapy.

Habrat and Swiecicki: Differences in Personality Dimensions Between SAD and Non-SAD Patients.

Putilov et al.: The Multiple Sleep Latency Test in Seasonal Affective Disorder: No Evidence for Increased Sleep Propensity.

Rieder et al.: Suicidality and SAD: A Case Report.

Magnússon A: Light Therapy in College Students with Symptoms of Winter Depression.

Partonen and Lonngvist: Prevention of Winter Seasonal Affective Disorder By Bright Light.

Meesters et al.: Preventing SAD by Using Light Visors: Bright White or Infrared Light?

Kurz et al.: Early Morning Exercises (Aerobic) Reduce Depression Scores in Winter Depressed Women (SAD/S-SAD).

Balzar and Hardeland: Light Effects and Melatonin, Ancient Principles Present in a Unicell, Gonyaulax Polyedra.

Murck et al.: Vasoactive Intestinal Peptide Decelerates non REM-REM Cycles and Modulates Hormone Secretion During Sleep in Men.

Zimmermann et al.: Does "Between-Subject LH-Pulse Coincidence" Reveal an External Zeitgeber for Circoral Rhythms?

Schmidt et al.: Assessing the Effect of Physical Activity on Core Temperature: A Method to Demask the Temperature Rhythm Under Field Conditions.

Ancoli-Israel et al.: Circadian Rhythms, Sleep, Light Exposure and Dementia.

Gordijn et al.: Manipulations of the Circadian System in Non-Seasonal Depressives.

Moog R: Circadian Phase Adjustment in Blind Persons.

Fey et al.: Monitoring of Daily Fluctuations of Depressive Mood by the Bright-Dark-Scale—A New Tool for the Assessment of Daily Mood Patterns.

Volk et al.: Polygraphically Defined Structure of Wakefulness as a Tool for Studying Sleep Deprivation Response in

Sunday, 11 June

- 09:00-12:00 • Education Course, SAD and Light Therapy (English)
 • Education Course—Praxis der Lichttherapie (German)
- 13:00-15:00 Open Workshop—Chaired by J. Arendt, C. Eastman, W. Köhler, C. Hagfors, A. Wirz-Justice
 Themes: Light and Architecture, Weather and Well Being, Methods for Phase-Shifting, and stimulating input from all participants (who are requested to bring slides or overheads of data related to the themes and any others they consider important).

Depressive Patients.

Yaron and Hila: Characteristics of Sleep-Wake Schedule Disorder (SWSD) Patients.

Gerbaldo H and Cassady: A Questionnaire for Light Intensity Preference and Related Behaviors: Detection of Photophobia and Photophilia in Schizophrenia and Depression.

Illnerová et al.: The Rat Suprachiasmatic Nucleus is a Clock for All Seasons—Possible Implications for Humans.

Daurat et al.: 36-Hour Moderate Bright Light Exposure: Influence on Alertness, Performance and Sleep.

Präeko et al.: Light Therapy in Patients with Nonseasonal Major Depressive Disorder.

Emser et al.: Effect of Bright Light on EEG, Actigraphy and 6-Sulphatoxymelatonin Excretion in Night Shift Workers.

Deacon and Arendt: Dose-Dependent Effects of Melatonin on Core Body Temperature, Endogenous Melatonin, Subjective Alertness and Sleep.

Saturday, 10 June**Oral Presentation I, Symptom and Biological Correlates for SAD—09:00-10:30**

Chair: Raymond Lam

Young et al.: SAD Symptom Onset as a Function of Calendar and Episode Time.

Oren et al.: Circadian Profiles of Cortisol, Prolactin, and Thyrotropin in Seasonal Affective Disorder.

Rosenthal et al.: Evidence for Hypothalamic Disturbance in Seasonal Affective Disorder.

Volf et al.: Winter Depression and Bright Light Effects on Hemispheric Functions.

Wehr et al.: Summer-Winter Differences in Duration of Nocturnal Melatonin Secretion in SAD Patients and Healthy Controls.

Oral Presentations II, Seasonality and Effects of Light Treatment—11:00-12:30

Chair: Michael Terman

Lam et al.: The Genetic Epidemiology of Seasonality.

Avery et al.: Dawn Simulation Treatment of Abstinent Alcoholics with Winter Depression: A Controlled Study.

Kripke et al.: Critical Interval for Light Treatment of Depression?

van Someren et al.: Indirect Bright Light Affects Circadian Rest-Activity Rhythm Disturbances of Demented Patients.

Oral Presentations III, Circadian and Sleep Effects of Light and Melatonin—14:00-16:00

Chair: Charmane Eastman

Endo et al.: Morning Bright Light Lowered Temperature and Increased REM Sleep During Initial Part of Sleep.

Terman and Terman: Phase Shifts in Melatonin and Sleep Under Light Therapy for Winter Depression.

Stewart et al.: Light Treatment Shifts Salivary Melatonin Rhythms in NASA Shiftworkers.

Campbell SS: Bright Light Exposure Does Not Facilitate Shift Work Adaptation in Middle-Aged Subjects.

Wirz-Justice et al.: The Phase Advance Induced by Evening Melatonin Administration is Mediated by Rapid Modulation of Thermoregulatory Mechanisms.

Cajochen et al.: Melatonin Increases Sleepiness and Theta Activity in the Wake EEG, But Does not Affect the Sleep EEG Except to Lengthen the First REN Sleep Episode.

Sunday, 11 June**Education Course—09:00-12:00**

(There will be a \$50.00 fee for the three-hour CME course.)

Praxis der Lichttherapie (German)

Chair: Burkhard Pflug/Wilfried Köhler

Presenters:

Björn Lemmer: Chronopharmakologie—Bedeutung der biologischen Zeitstruktur für die Medizin.

Hans-Joachim Haug: Diagnose und Epidemiologie von SAD.

Anna Wirz-Justice: Neurobiologie von SAD.

Wilfried Köhler: Von der Lichtquelle zur Uhr im Hypothalamus: Was der Anwender von Lampen und Leuchten wissen muß.

Alexander Neumeister: Möglichkeiten der medikamentösen Behandlung Saisonal Abhängiger Depressionen.

Jürgen Zulley: Licht bei Schlafstörungen, Schichtarbeit und Jet-Lag Syndrome.

SAD and Light Therapy (English)

Chair: Raymond Lam

Presenters:

Andrés Magnússon: Seasonal Affective Disorder—The clinical presentation, differential diagnosis and epidemiology of SAD.

Charmane Eastman: Placebo Effects—What is and isn't placebo, placebo effects in drug studies, placebo effects in light studies.

Raymond Lam: Clinical Use of Light Therapy in SAD—How to incorporate light therapy into your clinical practice; tips on using light (± drugs).

Dan Oren: Psychobiology of SAD—The latest theories about the etiology of SAD and the mechanisms of light therapy.

Editorial— THE FINE ART OF OVERSTATEMENT

Press Releases and Science

Most everyone has experienced it: You open the paper to the weekly Science Section of your local newspaper and see a story with familiar words in the headline, addressing a topic relevant to your specific field of study. You quickly skim the text for quotes from friends and colleagues—and yourself, of course—and then settle down for a closer read:

The Aspirin of the 21st Century?

Peoria—More effective than aspirin and just as effective as any current non-aspirin substitute. That's what researchers are calling melatonin, the wonder drug of the 90's, which is now believed to work better at reducing fever than any OTC medication currently available for that use. Melatonin is a hormone produced naturally by the brain, has no dangerous side effects, and has been approved for clinical testing in the United States. Scientists at the Institute for the Study of Hot and Cold simply refer to their melatonin capsules as "the magic bullet". This, based on the remarkable finding that the hormone inhibits the production of substances called prostoglandins, which are believed to cause fever. The researchers also reported, for the first time, that melatonin packs a double-whammie. A spokesperson for the Institute explained, "If you're feeling under the weather with flu-like symptoms, even as melatonin is reducing your fever, it promotes rest through its well-proven sleep-enhancing properties." The spokesperson went on to say that testing is now underway to develop a "magic bullet" that administers itself! Too sick to raise a finger? Not to worry.

"This is unbelievable!" you blurt out to your breakfast companion. "These knuckleheads are claiming to be the first people in the world to demonstrate the remarkable fever-reducing properties of melatonin!"

"Well, speaking as a layperson, dear, this 'magic bullet' does sound like quite a breakthrough in fever-relief." Your companion smiles across the table.

"Breakthrough, my rectal probe!" you counter. "Wouldn't you agree that 'Aspirin of the Next Century' is quite a claim? And besides, we've known about hypothermic effects of melatonin for almost 30 years! Moreover, rumors about its sedative effects have been around for at least as long. There's nothing new here! These guys are trying to pull a fast one!"

"Calm down dear, you'll disturb the neighbors."

"Okay, okay," you relent. "You're right, I'm probably over-

reacting. I'll reserve judgement on the extent and perniciousness of my colleagues' hyperbole until I read the actual article in *Acta Minutia*."

And, indeed, what is reported in the scientific article (see page 56, this issue) bears only marginal resemblance to the press report in your newspaper. That is to say, yes, melatonin reduced body temperature in most subjects, some of the time; but no, it did not appear to be the Antipyretic of the Next Millennium, at least not yet. In fact, in the scientific journal the authors interpret their results with a level of caution befitting a diplomat. What's going on here? Why the profound difference in the manner in which the findings are presented for their respective audiences?

What's going on here is what Lawrence Altman, M.D. referred to in a recent *New York Times* article as "the wave of enthusiasm of over-promise." Simply, press releases and press reports have become an effective, and frequently employed, means of making mountains out of scientific mole hills; a way of making the gradualness of science into a current event.

I say press releases have 'become . . . a means . . .' as if this is a recent development. But, in fact, science writing for public consumption has a long history, dating back to the turn of the century. And, almost from the start, it has been characterized by exaggeration. This was primarily the result of journalists needing their readers to sit up and take note of what might otherwise be perceived as mundane and mechanical. A lesson was learned in the early 1890's when readers expressed disappointment with press reports describing the latest observations of Mars, made possible by new developments in telescope technology. They had expected something greater from the astronomers. They had expected to see Martians.

Since that time, the public has become increasingly more jaded with respect to scientific discovery. In turn, science writers have been more than willing to provide readers with even more sensational 'news'. Each small step in the search for the cause of Alzheimer's Disease, or for an effective agent in the battle against AIDS, is hailed as a test tube triumph, a medical milestone—at least until the next issue of *Nature* appears. As a result, a vicious cycle has been set into motion, with increasingly sensational sound bites being met by an ever more difficult-to-impress public.

Given the competition for Page One space, such exaggeration by the news media might be considered justifiable. After all, science writers have to make a living, too. And even if

this form of popular hype is not entirely warranted, there is little that we, as investigators, can do about it. A journalist may check back with you concerning the accuracy of quotes, but the final product is typically out of your hands. Hyperbole is protected by the First Amendment.

But what about University Public Relations Departments? In recent years, these institutional press offices have become major players in the popularization-of-science game. And, inasmuch as press releases issued from institutions ultimately must compete for that same Science Section space, overstatement has too often become the currency of this medium, as well. Thus, a computer model of El Niño might be boldly promoted as a "critical new breakthrough in weather forecasting that will make drought-induced famine a thing of the past"; a press release describing protein-induced tumor reduction in a dozen common voles may carry the optimistic headline, "Cancer Cure In Sight!"

Is this kind of institutional hype justified? Probably not. Even in this age of cut-throat competition for funding dollars, and the general commercialization of university affairs, academic distortion still raises eyebrows, if not dander. So, whose responsibility is it to monitor this institutional tendency toward "over-promise"? Why, it is ours of course. We know better than anyone (well, other than our peer reviewers) what interpretations our results do and do not warrant; we know better than anyone (well, other than our statisticians) that a p of less than .05 seldom implies a biomedical revolution; we know better than anyone (well, other than our press officers, themselves) that this kind of hype should never see the light of day. As such, we know better than anyone that we have an obligation to stop it.

In Tom Stoppard's play, *Arcadia*, Hannah describes Barnard's headlong rush to publicize his tentative theory, as pure fact, as going "... from a glint in your eye to a sure thing, in a hop, skip, and a jump." She goes on to tell him that he is "like an exasperating child pedalling its tricycle towards the edge of a cliff..."

It is our responsibility as owners of the vehicle to insure that the child in the press office looks before he or she leaps.

S.S.C.

Note—I borrowed from three sources in the preparation of this editorial: The idea for the piece came from a *New York Times* article by Lawrence K. Altman, M.D. entitled, "Promises of Miracles: News Releases Go Where Journals Fear to Tread" (January 10, 1995). I thank Patricia Murphy for introducing me to John Burnham's book, *How Superstition*

Won and Science Lost (Rutgers University Press, New Brunswick, 1987), from which examples were drawn, and I thank Anna Wirz-Justice for making me aware of Tom Stoppard's play, *Arcadia* (Faber and Faber, Boston, 1993).

MELATONIN AND TEMPERATURE: HANDS OF THE SAME CLOCK

Since the pioneering work of Marburg (1930) and that of Demel (1927), there has been considerable speculation concerning the relationship between melatonin and temperature (reviewed in: Badia et al., 1992; Myers et al., 1992). Both measures exhibit prominent circadian rhythms which are negatively correlated under a variety of experimental conditions. Also, direct manipulation of one measure tends to affect the other and in the opposite direction. However, this relationship is not always obtained. The purpose of this paper is to briefly review both types of evidence (i.e., correlational and experimental) suggesting an inverse relationship and to provide a possible explanation for the data not supporting this observation. The potential mechanisms underlying the relationship between the two measures are also discussed.

HISTORICAL PERSPECTIVE

Evidence supporting the notion that melatonin and temperature are associated dates to at least the late 1920s. In 1930, Marburg reported a case study of a man with a pineal tumor whose temperatures were unusually elevated (clock times not specified). At about the same time, Demel (1927) noted that pinealectomized sheep exhibited higher temperatures in both the morning and evening relative to controls. [It is now known that pinealectomy dramatically reduces circulating melatonin levels (Neuwelt and Lewy, 1983; Reiter, 1982). However, extra-pineal contributions may be more significant than currently recognized (Huether, 1993).] Subsequent studies testing pinealectomized rabbits obtained similar results (Ito, 1939; Komura, 1943, 1944).

The discovery of melatonin by Lerner et al., (1958) allowed more direct tests of the pineal's involvement in thermoregulation. Arutyunyan et al., (1964) administered 50-100 mg/kg of melatonin (i.e., 50-100 mg of melatonin per 1 kg of body weight) to mice and observed an immediate (within 15-30 min) decrease (2-3 degrees C) in temperature (clock

times not specified). However, a similar study (Barchas et al., 1967) testing rabbits (using 25 mg/kg; clock times not specified) failed to demonstrate hypothermic effects of melatonin perhaps due to dose, timing, and/or species differences. Two early human studies also support melatonin's role in thermoregulation. Åkerstedt et al. (1979) noted the melatonin and temperature rhythms were negatively correlated during extended periods of sleep deprivation and Carman et al. (1976) noted decreases in temperature (measured at 0800 h) following the administration of 150-1600 mg of melatonin to patients with depression.

Taken together, these studies suggest that melatonin and temperature are inversely related. During the last five years, there has been a tremendous resurgence of the interest in this relationship. This renewed interest has produced conclusive evidence that the two measures are, in fact, inversely related. This more recent evidence is presented next.

CORRELATIONAL EVIDENCE

The results of several ex post facto studies suggest that melatonin and temperature are inversely related. These studies include those measuring circadian, circalunar, and circannual rhythms as well as those assessing abnormal populations and aging.

A. Rhythmicity

As noted, Åkerstedt et al. (1979) found a negative correlation between melatonin and temperature during sleep deprivation. Similar results were obtained by Shanahan and Czeisler (1991). Our laboratory has recently obtained similar data (Murphy et al., in press b; Myers et al., 1994; Myers et al., in press; Wright et al., in press). In these experiments, participants were studied during 48-hour constant routines with melatonin and temperature assessed approximately every hour. Significant correlations between melatonin and temperature of about $r = .75$ ($N = 20$) were obtained in individual subjects studied under constant dim light (< 100 lx).

In addition to the circadian rhythms in melatonin and temperature being negatively related during sleep deprivation, there is also the trend for melatonin levels to increase (Åkerstedt et al., 1979; Myers et al., 1994; Salin-Pascual et al., 1988) and for temperature levels to decrease (Åkerstedt et al., 1979; Horne and Pettitt, 1985; Murray et al., 1958). However, a well-controlled study indicated that melatonin levels do not increase with sleep deprivation (Armstrong et al., 1993). This finding and the fact that the light levels typically used in sleep-deprivation studies are sufficiently high

to suppress melatonin suggest that the combination of sleep deprivation and photic stimulation produces these effects (i.e., melatonin increases and temperature decreases; Myers et al., 1994).

Another finding concerning circadian rhythmicity that supports the relationship between the two measures is that the melatonin and temperature rhythms have nearly identical free-running periods (usually about 25 h) and that both rhythms respond similarly to non-24-h periods (Wever, 1989). For example, both rhythms can be entrained using a light-dark cycle (3,000-300 lx) to a period of about 29 h while remaining in synchrony (Wever, 1989). Other studies showed that the two rhythms also respond similarly when attempts were made to entrain the rhythms to periods of 22.8 (Waterhouse and Minors, 1994) and 28 h (Shanahan and Czeisler, 1991).

Other evidence that melatonin affects temperature relates to circalunar rhythmicity; that is, the human menstrual cycle. The nocturnal surge in melatonin was lower at the time of ovulation (Wetterberg et al., 1976) and temperature is higher whether the women were awake or asleep (Rogacz et al., 1988; Webley and Leidenberger, 1986).

Melatonin also exhibits circannual variation in birds (John et al., 1978; Binkley et al., 1971) and mammals (Beasley et al., 1986). The changes in melatonin levels across the year have direct consequences on the reproductivity of these species, but may relate to temperature as well. Temperature in these species is lower and melatonin levels higher during the winter months. This pattern reverses during the spring and early summer (i.e., mating season). There is a suggestion that such annual rhythms may be present in humans as well (Hofman and Swaab, 1993; Wehr et al., 1993); however, there are not yet sufficient data to support the claim that melatonin and temperature are inversely related on a yearly basis in humans.

B. Pathology and Aging

Results from studies measuring melatonin and/or temperature in humans with a variety of pathologies also support the relationship between melatonin and temperature. These pathologies include mood, eating, and psychotic disorders. Typically, these populations exhibit either high melatonin and low temperature levels (e.g., anorexia) or low melatonin and high temperature levels (e.g., depression). A review of these findings is published elsewhere (Badia et al., 1992).

Other correlational evidence relates to ontogenetic changes in melatonin and temperature (reviewed in: Myers and Badia,

in press). With normal aging, the period of melatonin across the night is shortened and the amount of nighttime melatonin released decreases as well (Van Coevorden et al., 1991). Older adults also exhibit elevated nighttime temperatures relative to younger controls whether the older adults are awake or asleep (Vitiello et al., 1986; Monk and Buysse, 1989).

EXPERIMENTAL EVIDENCE

There is also a considerable amount of experimental evidence indicating that melatonin and temperature are inversely related. This evidence includes that obtained from photic and pharmacological manipulation of melatonin and temperature. In addition, the effects of exogenous melatonin on temperature and other indices of thermoregulation support the inverse relationship between melatonin and temperature.

A. Photic and Pharmacological Manipulation

Other supporting evidence of melatonin's role in thermoregulation comes from studies recording melatonin and/or temperature as a function of exposure to bright light. It was known that light suppressed melatonin (Wurtman et al., 1963) and increased temperature (Sulzman et al., 1979) during the nighttime hours in nonhumans. However, initial reports suggested that light did not have similar effects in humans (Jimerson et al., 1977). Subsequent reports using a higher light intensity clearly showed suppression (Lewy et al., 1980) and that such suppression was dose dependent with brighter light associated with greater suppression (McIntyre et al., 1989). Light-induced melatonin suppression is apparent within 30 min of exposure and recovery of melatonin synthesis is apparent 30 min after exposure (Lewy et al., 1980).

Studies conducted in our laboratory have focussed on the immediate effects of bright light ($> 2,500$ lx) on melatonin and temperature (Badia et al., 1990; Badia et al., 1991; Murphy et al., 1991; Myers and Badia, 1993b; Myers et al., 1994; in press). These studies tested subjects during either 24 or 48 h of sleep deprivation and assessed the effects of exposure to bright ($> 2,500$ lx) or dim (< 100 lx) light. The findings suggest a close link between melatonin levels and nighttime temperatures in response to photic stimulation. Nighttime exposure to bright light suppressed melatonin and enhanced temperature (Badia et al., 1991; Myers and Badia, 1993b; Myers et al., 1994; Myers et al., in press). In contrast, there were no differences in temperature under bright light versus dim light during the daytime hours when melatonin levels are low (Badia et al., 1991; Murphy et al., 1991; Myers and Badia, 1993b). Similar results were obtained by French

et al. (1990) and by Dijk et al. (1991). The results of one nighttime study suggested that light-induced temperature increases were dose dependent with brighter light associated with greater temperature enhancement (Myers and Badia, 1993b). Also of interest, light-induced melatonin suppression and temperature enhancement were obtained for successive nights in humans (Myers et al., 1994; Myers et al., in press); a finding similar to that obtained in nonhumans (Phillips and Berger, 1992).

Additional convincing support for the close association between melatonin and temperature comes from studies that presented alternating bright light and dim light blocks (either of 90 or 180 min duration) to subjects during the nighttime hours (Badia et al., 1991; Myers et al., 1994). Within 30 min of exposure to bright light, melatonin decreased and temperature increased. In contrast, within 30 min of exposure to dim light, melatonin increased and temperature decreased. This alternating pattern was observed throughout the nighttime hours. Again, alternating exposure to bright or dim light did not induce temperature changes outside of the melatonin window period (i.e., exposure to bright light and dim light during the daylight hours did not affect temperature). This latter result is expected since very small amounts of melatonin are released by the pineal during the daytime hours.

There are limited data concerning the effects of pharmacological agents on melatonin and temperature. However, these data are also consistent with the inverse relationship between melatonin and temperature. For example, tricyclic antidepressants increase melatonin (Hariharasubramanian et al., 1986) and decrease temperature (Souetre et al., 1988) in patients with depression. We have recently shown that the administration of nonsteroidal anti-inflammatory drugs such as ibuprofen, aspirin, and acetaminophen during the nighttime hours suppresses melatonin and increases temperature (Murphy et al., in press a). Like light, these drugs do not have an effect during the daytime hours (Murphy et al., in press a) when melatonin levels are low. The opposite relationship was obtained with the administration of ethanol. Ethanol increased nighttime melatonin and tended to decrease nighttime temperature (Badia et al., 1994). Again, no effect was noted during the daytime (Badia et al., 1994).

B. Exogenous Melatonin

The effects of exogenous melatonin on body temperature are unequivocal, as they have been replicated many times; therefore, only a brief review of them is provided here. Following the study of Carman et al. (1976) and those of

Badia et al. (1990) and French et al. (1990) described above, Strassman et al. (1991) showed that infusion of exogenous melatonin (0.05-0.10 micrograms per min) reversed light-induced (2,500 lx) increases of nighttime temperature in males. Similar results were obtained by Cagnacci et al. (1993) with oral administration of melatonin (1.75 mg) and light (3,000 lx) in females and also by Sack et al. (1992) with oral administration (7 mg) and light (2,500 lx) (gender not specified). Cagnacci et al. (1992) also demonstrated that oral administration of melatonin (2.5 mg) decreased daytime temperature in females. Subsequently, similar results with doses of melatonin between 1 and 40 mg have been obtained by several groups (Dawson et al., 1992; Dawson et al., 1995; Deacon et al., 1994; Dollins et al., 1994; Hughes et al., 1994). Additionally, the studies of Dollins et al. (1994) and Hughes et al., suggest the hypothermic effects of melatonin are dose dependent with higher doses associated with greater temperature decreases.

In nonhumans, exogenous melatonin also affects other indices of thermoregulation. These indices include nonshivering thermogenesis, brown adipose tissue production, and changes in body weight, pelage, and behavioral thermoregulation (reviewed in: Badia et al., 1992). In addition, there are functional melatonin receptors in the circle of Willis of rats (Capsoni et al., 1994). (The circle of Willis is a network of arteries in the base of the brain and is considered an integral part of thermoregulatory processes; Hayward and Baker, 1969).

INCONSISTENT EVIDENCE

Despite the convincing evidence noted above indicating that melatonin and temperature are inversely related and that the two measures respond oppositely to experimental manipulations, inconsistencies remain. The most troublesome of these inconsistencies is the recent data presented by Wehr et al. (1993). In a series of experiments designed to assess the photoperiodic response of humans, Wehr et al., measured the melatonin and temperature rhythms during constant routines. Close examination of these data reveals that the temperature rhythm begins to decrease approximately 2 h prior to the increase in melatonin. There are several possible explanations for these data including that they result from (a) measurement error or accuracy limitations and/or (b) differential masking. Each of these explanations are considered in detail below.

It has been suggested that the measurement of melatonin and temperature in the periphery may not accurately reflect levels of the two measures in the brain. The data indicating

that melatonin in the pineal and in the circulation are highly correlated are convincing; however, the data indicating that temperature in the brain and in the periphery are highly correlated are less so. However, this notion is unlikely to explain the findings of Wehr et al. (1993) since the temperature precedes melatonin and, if anything, temperature should be lagged relative to melatonin given the close relationship between pineal and plasma melatonin levels (Wilkinson et al., 1977).

A more likely explanation relates to differential masking of the two rhythms. Factors affecting (or "masking") the "true" rhythm of melatonin and temperature have recently been summarized (Myers and Badia, 1993a; Reiter and Richardson, 1992); therefore, only a brief summary of these masking factors is provided here. Although both melatonin and temperature have been used extensively, melatonin is often considered the superior measure as it is supposedly unaffected by common masking effects such as physical activity and sleep-wakefulness (Lewy and Sack, 1989). However, several factors which affect the underlying melatonin rhythm have been reported. These masking agents include photic stimulation, sleep deprivation, exercise, electromagnetic radiation, food (or lack thereof), pathology, age, drugs, and naturally occurring substances. Many of these factors also affect temperature; however, not all factors affect both measures to the same extent. The primary difference between the two measures is that the agents which affect melatonin (e.g., psychiatric medications) are more easily controlled by rigorous screening whereas those which affect temperature (e.g., physical activity) require experimental control (i.e., a constant routine).

A study originally conducted by Minors et al. (1988) provides an excellent example of how differential masking can affect the relationship between melatonin and temperature. In this study, the researchers attempted to entrain the melatonin and temperature rhythms of humans to a period of 22.8 h. During this attempt, the acrophases of the melatonin and temperature rhythms appeared to respond differently to the manipulation. However, the data were not obtained during a constant routine; thus, while changes in activity and sleep probably had little effect on the melatonin rhythm, it probably had considerable effect on the temperature rhythm. In fact, when the data were reanalyzed using a "purification" technique to remove the masking effects, the two rhythms responded much more similarly to the manipulation (Waterhouse and Minors, 1994).

Data collected in our laboratory also show how the relationship between melatonin and temperature can be

weakened by the presence of masking agents. As noted, individual correlations between melatonin and temperature obtained during constant dim light (Myers et al., in press; Wright et al., in press) are about $r = .75$ ($N = 20$). However, similar correlations obtained during constant dim light and during the administration of caffeine (Wright et al., in press) are about $r = .65$ ($N = 9$).

Taken together, these data suggest that measurement error, accuracy limitations and/or differential masking may explain the data that are inconsistent with the inverse relationship between melatonin and temperature.

MECHANISMS

Several mechanisms have been proposed to explain the close relationship between melatonin and temperature. The most common explanation is that melatonin has a direct effect on temperature (Cagnacci et al., 1992). This effect could be mediated either directly by affecting the preoptic area (POA) of the hypothalamus (the primary site of thermoregulation in the mammalian brain; Saarela and Reiter, 1993) or indirectly by altering thermoregulatory processes in the periphery (e.g., via altering blood pressure, Badia et al., 1992) which may then provide feedback to the POA. While it is known that melatonin decreases blood pressure (Birau et al., 1981) and could thereby lower temperature, connections between melatonin and the POA are speculative (e.g., there are not a large quantity of melatonin receptors in the POA; Saarela and Reiter, 1993). However, Reiter et al. (1993) have recently shown that some actions of melatonin do not require a receptor as melatonin is so lipophilic that it can penetrate each cell in the body (Menendez-Pelaez et al., 1993); thus, melatonin could conceivably act directly on the POA.

Another explanation is that the relationship may be mediated by prostaglandins (immunomodulators involved in thermoregulation and sleep as well as in the synthesis of melatonin; Badia et al., 1992). While intriguing, there are not yet sufficient data to support this hypothesis.

A third explanation, described in detail here, proposes that the close relationship between the two measures results from both being accurate indicators of, and generated by, the suprachiasmatic nuclei (SCN) of the hypothalamus. Considerable evidence indicates that the SCN are the primary generator of mammalian circadian rhythms (Ralph et al., 1990). Among this evidence is the recent finding that complete lesions of the SCN abolish the temperature rhythm of hamsters (Refinetti et al., 1994). However, SCN transplants have not yet been shown to restore the

temperature rhythm. Also, it is known that melatonin can inhibit activity of cells in the SCN (Yu et al., 1993) and that there are melatonin receptors in the SCN (Reppert et al., 1988). Therefore, it is possible that exogenous melatonin could decrease temperature indirectly by acting upon its receptors to decrease cellular activity in the SCN and thereby decrease temperature since the signal to the preoptic area would presumably be attenuated. Another finding in support of this hypothesis is that the SCN are necessary for the mediation of other circadian effects of melatonin (e.g., seasonal changes in period, Bartness et al., 1991; e.g., entrainment, Cassone et al., 1986); therefore, it seems reasonable to speculate that the nuclei are necessary for the effects of exogenous melatonin on the circadian rhythm of temperature. This explanation seems most consistent with the current knowledge of the circadian system (i.e., an anatomical and chemical network including the retinas, the intergeniculate leaflets of the thalamus, the SCN, and the pineal gland) and it can explain a finding inconsistent with the relationship: the presence of a robust temperature rhythm in a subject without a detectable melatonin rhythm (Shanahan and Czeisler, 1991). That is, because the SCN and not melatonin are hypothesized to generate the temperature rhythm, it is possible to have a temperature rhythm in the absence of a melatonin rhythm. The explanation suggesting that melatonin has direct effects on temperature would not be able to adequately explain this finding. However, the critical experiment for the SCN explanation—determining if melatonin decreases temperature in the absence of the SCN—has yet to be done.

SUMMARY

In summary, melatonin and temperature are inversely related under a variety of experimental conditions. In addition, photic and pharmacologic manipulation tends to affect the two measures in the opposite direction. However, the strength of the relationship between melatonin and temperature appears to decrease under some circumstances. While this finding is likely the result of measurement error or accuracy limitations, it also may result from differential masking. That is, factors that affect one of the measures either do not affect the other or affect it to a different extent. Of the several potential mechanisms that may underlie the relationship, the notion that both measures reflect the rhythms in the SCN (i.e., are hands of the same clock) seems most consistent with the current literature; however, the experiment critical to this hypothesis has yet to be conducted.

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MELATONIN: POSSIBLE THERAPEUTIC USE AS AN ANTIPYRETIC

Some of the putative roles of endogenous melatonin in humans include immunomodulator (Maestroni et al., 1989), regulator of seasonal breeding, reproduction, or sexual maturation (e.g., Reiter, 1980; Waldhauser et al., 1985), circadian timing signal (e.g., Armstrong, 1989; Reiter, 1991), endogenous sleep substance (e.g., Dawson & Encel, 1993), anti-anxiolytic agent (Lissoni et al., 1986), free radical scavenger (Reiter et al., 1993), and temperature regulator (Badia et al., 1991; Cagnacci et al., 1992; Strassman et al., 1991). Some of the corresponding roles of exogenous melatonin that have thus been proposed and tested include aging retardant, oncostatic therapeutic, contraceptive, chronobiotic, and sedative. Based upon evidence for melatonin's involvement in thermoregulation, another therapeutic use of melatonin is proposed: antipyretic agent.

Abnormal elevation of body temperature due to an immune response is termed "fever." A simplistic description of the fever response is that there is an elevation of the thermoregulatory set point which is subsequently defended by intact homeostatic thermal control processes (as opposed to "hyperthermia" in which thermal control processes fail, and temperature is elevated beyond the set point) (Lipton, 1980). The main protagonist of the elevated set point in a fever is IL-1, a cytokine produced in mononuclear phagocytes that acts as an endogenous pyrogen (Dinarello et al., 1984). IL-1 is carried from the site of insult or inflammation, through the circulation to the brain, where it acts directly on the preoptic area of the hypothalamus (POA), the thermoregulatory control center. The main action at this level is to induce a cascade of phospholipase metabolism, and the proliferation of prostaglandins in the central nervous system (Bernheim, 1986). These prostaglandins then act to modify the firing rates of thermosensitive hypothalamic neurons, resulting in elevated thermoregulatory set point (Stitt, 1986).

The term "antipyretic" is applied to fever, and relates to "preparations that, without necessarily intervening causally in the pathological sequence of events, reduce body temperature in febrile conditions resulting from infectious or noninfectious processes." (Krupp & Ziel, p. 384). Traditional antipyretics such as aspirin, indomethacin, and acetaminophen are believed to exert their antipyretic effects via prostaglandin synthesis inhibition (Vane, 1971). (While

acetaminophen is an ineffective PG-synthesis inhibitor in the periphery, it suppresses PGs in the CNS with a potency similar to that of aspirin; Flower & Vane, 1973). Although there are data to suggest that prostaglandin inhibition is not the only mechanism of action for antipyresis (e.g., Abramson & Weissman, 1989), the body of evidence supporting prostaglandin-mediated regulation of fever is substantial. Prostaglandins of the E series directly induce a fever, as micro-injections of these substances into the POA result in a temperature increase without a subsequent homeostatic response (Milton & Wedlandt, 1970). PGs of the E series are found at elevated levels in the CSF of febrile animals of various species, and return to normal levels following antipyretic therapy (Feldberg & Gupta, 1973; Feldberg et al., 1974). Further, when PGEs are applied directly to the brain, subsequent antipyretic therapy does not reduce the fever (Milton & Wedlandt, 1970). Thus, inhibition of prostaglandin synthesis, especially of PGs of the E series, is responsible for antipyresis.

Regarding the role of melatonin in this picture, there are several disparate empirical findings, that when coherently synthesized (a feat not necessarily accomplished herein), imply that melatonin could indeed be used to "reduce body temperature in febrile conditions."

First, consider endogenous melatonin and its involvement in normal, afebrile thermoregulatory processes. Evidence for a melatonin/body temperature link is outlined in detail (see Myers, this issue). Basically, the well-recognized inverse relationship between melatonin and body temperature is examined, and studies in which manipulation of one of these rhythms resulted in a corresponding change in the other are described. The implication is that the relationship between melatonin and body temperature is more than temporal, and melatonin may be responsible for regulating the circadian decrease in body temperature.

Exogenous melatonin indisputably affects body temperature. From Barchas et al.'s (1967) report of hypothermia produced by melatonin in non-humans, to Carman's (1976) study documenting reduced temperature in humans following oral doses of melatonin, to the recent surge in studies assessing melatonin's acute effects on temperature, the results have been quite consistent. In doses as low as 1 mg (which still induce pharmacological levels), melatonin reduces temperature (Cagnacci et al., 1992; Dawson et al., 1993; French et al., 1993; Hughes et al., 1994). A temperature decrease occurs when exogenous melatonin is administered during the times of day that endogenous melatonin is synthesized only at very low levels (e.g., Cagnacci et al., 1992; Hughes et al.,

1994), or during the night when endogenous melatonin synthesis is suppressed by exposure to bright light (Strassman et al., 1991). This reduction in temperature may be dose-related (French et al., 1993; Hughes et al., 1994). Additional data directly relevant to the melatonin as an antipyretic hypothesis relates to melatonin's role in thermoregulatory control areas. Melatonin receptors have been located in the POA of the hypothalamus (Kennaway and Hugel, 1992), and microinjections of melatonin modify neuronal firing in this area (Demaine, 1983). Functional melatonin receptors have also been located in the vasculature of rat brain (Viswanathan et al., 1990). These authors proposed that melatonin altered the tone of these arteries to affect heat dissipation in the brain.

Another empirical finding, and the crux of the hypothesis proposed, is that melatonin suppresses prostaglandin synthesis. Originally, a striking similarity between the chemical structures of melatonin and the potent prostaglandin inhibitor and antipyretic drug indomethacin, led researchers to investigate whether melatonin altered neuroendocrine function via prostaglandin synthesis inhibition (Cardinali et al., 1980; Leach & Thornburn, 1980). In a related attempt to understand prostaglandin activity in the pineal gland, Cardinali and colleagues discovered that melatonin (or a melatonin metabolite) was indeed a potent inhibitor of prostaglandin synthesis (Cardinali et al., 1981). Subsequent studies determined that N-acetyl-5-methoxy-kynurenamine, a metabolite of melatonin, suppressed prostaglandins synthesis in the CNS even more potently than aspirin, and to a similar degree as indomethacin (Kelly, Amato, and Seamark, 1984). As these authors state, very few naturally-occurring inhibitors of PG cyclooxygenase had been reported, and none yet with action similar to that of nonsteroidal anti-inflammatory drugs. They go on to say that their findings suggest that this metabolite of melatonin may play a key role in modulating the effects of melatonin and raise the possibility that similar metabolites of 5-methoxytryptamine may also inhibit prostaglandin synthesis. Other researchers have confirmed the inhibitory effect of melatonin on CNS prostaglandin synthesis (Franchi et al., 1987; Leach et al., 1982; Martinuzzo et al., 1991; Pawlikowski et al., 1984). Several empirical findings have been attributed to melatonin inhibition of prostaglandin synthesis as well, including reduction in pituitary and adrenal weights in stressed rats (Richardson & Keeling, 1981), anti-cancer effects of indomethacin (Szkudlinski, 1992), and antigonadotrophic activity (e.g., Leach et al., 1992). Further, the failure of melatonin to suppress prostaglandins has been implicated in spontaneous abortions (Sandyk et al., 1992a) and postmenopausal osteoporosis (Sandyk et al., 1992b). To summarize, it is now clear that one of the roles of endogenous melatonin may be to alter the

metabolism of arachidonic acid and suppress prostaglandin synthesis in the CNS.

There are definitely caveats and discrepancies with this developing hypothesis, especially when the biochemical actions of melatonin administered at different times of day, and the incredibly complex fever response, are considered. However, stripped down to the bare, simplistic, empirical findings, what we know is the following:

- 1) Antipyretics inhibit prostaglandin synthesis, and this is thought to be the mechanism of antipyretic action. Melatonin inhibits prostaglandin synthesis.
- 2) The chemical structure of melatonin is similar to that of the antipyretic drug indomethacin.
- 3) Antipyretic drugs modify neuronal activity in the POA. Melatonin receptors are located in the POA, and melatonin microinjections in this area modify neuronal activity here.
- 4) Antipyretic drugs decrease febrile body temperature, and may alter nonfebrile body temperature (during the diurnal hours). Exogenous melatonin decreases nonfebrile body temperature (during the diurnal hours).

What we do not know:

- 1) The mechanism by which exogenous melatonin reduces temperature.
- 2) Whether exogenous melatonin will reduce febrile temperature in humans.

Further investigations aimed at defining the parameters of the melatonin-prostaglandin relationship are justified. In this regard, we are in the process of assessing the physiological and behavioral effects of exogenous melatonin in febrile humans. With appropriate cautions in mind, given that we are proposing similar effects of endogenous and exogenous melatonin, it seems reasonable that exogenous melatonin may inhibit prostaglandin synthesis in febrile as well as afebrile situations, resulting in temperature changes. A desirable result would be that exogenous melatonin administered to febrile humans may yield a safe and tolerable antipyretic agent.

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DOCTOR, MY EYES

In the letter reprinted below (with permission from *Academic Medicine* 1995, 70(2):86) Mr. Barton's data demonstrate (as might be expected) that medical students in their clerkship years receive very little bright light, and that low light might be a factor in the depression often seen among medical students.

There may be some medical schools where it would be practical to set up a treatment trial for medical students by placing light boxes in their offices in clinical settings and randomizing. If we could prove that bright light helps medical students, and if this proof made it customary to provide light boxes to medical students, then future generations of doctors would be introduced to the value of bright light treatment.

We would be delighted if any colleagues are able to test bright light for medical students. Because of our setting, there is probably even more light starvation at other schools.

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Not Enough Light for Medical Students?

Several reports indicate that medical students' notoriously long hours, lack of time to deal with personal needs, and exposure to much death and suffering may make them susceptible to depression. However, data that relate both non-seasonal and seasonal depression to inadequate light exposures suggest the possibility that low illumination could also be a factor. We thought *Academic Medicine's* readers would be interested in what we learned when we recorded the illumination exposures of a group of medical students to determine whether they experienced less than average daily illumination.

Third- and fourth-year medical students at the University of California at San Diego who were assigned to clerkship rotations were recruited for illumination recordings. The ten volunteers were six third-year students and four fourth-year students assigned to various clinical settings. Some were in the intensive care unit at a busy Veterans Administration hospital, and others were on night call at a trauma center emergency department. Some volunteers did medicine clerkships and one was on an outpatient psychiatry rotation. For three days, the volunteers were asked to wear a photo-

metric monitor, a wrist-mounted device that records both illumination and wrist activity. Controls' data were taken from a large illumination survey of 208 San Diego adults who were randomly recruited.

The ten medical students ranged from 25 to 30 years of age. The controls ranged from 19 to 64 years of age. The average mean 24-hour illumination of the ten medical students was 200 ± 176 lux, which was much less than the mean illumination for the controls of $645 \pm 1,108$ lux. Since illumination exposure was not correlated with age or gender in the large control group, the comparison of students and community adults appeared valid. The San Diego medical clerks averaged only 25.8 minutes in illuminations greater than 1000 lux (daylight is almost always more than 1000 lux) compared to 50-90 minutes > 1000 lux for normal controls.

Recent studies investigating the effects of light on mood have found correlations between decreased light exposure and depression (Espiritu et al., 1994). The success of bright light as treatment for Seasonal Affective Disorder supports this idea (Wehr and Rosenthal, 1989). Increased light exposure apparently elevates a person's emotional well-being. Consequently, one might infer that medical students could increase their vitality while enduring their busy clinical rotations by spending more time in bright illumination.

Our study showed that the volunteer medical students received less than one-third the overall amount of light exposure experienced by average adults in the same community. Even in sunny San Diego, the students managed to spend less than a half hour a day outdoors in the daytime. If such light deprivation is widespread among medical students, further studies will need to be done to determine whether students actually feel better when receiving more bright light. If so, one way that might achieve more illumination would be to schedule a post-rounds morning walk as part of the daily routine. If time or weather constraints prohibit such walks, then perhaps bright light devices could be installed in hospital areas where students work so they could continue work while receiving proper light. We would be interested to hear of any other investigations into the possible relationship of low illumination and medical students' depression.

*Bradley P. Barton
Daniel F. Kripke, M.D.*

Mr. Barton is a medical student and Dr. Kripke is professor of psychiatry, both at the University of California, San Diego, School of Medicine.

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FLASH(LIGHT) POLL RESULTS

The Flash(light) Poll solicits opinion from the membership, primarily in the form of a yes/no response, concerning a current, hopefully provocative, issue. The feature was introduced in the October 1994 issue of *LTBR*. Here, the results of the latest poll are presented.

The issue for debate was: *"I believe that the therapeutic use of light and melatonin should be patentable."*

This issue of patents and patentability of the therapeutic uses of light and melatonin has been a topic of intense debate within our discipline for the past several years. At the most recent meeting of the Society for Research on Biological Rhythms (Amelia Island, Florida, May, 1994) a well-attended debate on "Patenting Specified Uses of Melatonin and Light: Facts and Evaluation" provided valuable and timely information on legal, ethical and scientific aspects of the question. These issues will be revisited this year, at our own annual meeting, with a forum on "Patent Law and Ethics for Scientists: Can the Use of Light and Melatonin be Patented?"

The simple answer to this nominal question clearly is "yes". Use patents have already been awarded for both bright light treatment and for exogenous melatonin administration. The issue for debate in the current poll was not whether such patents *can* be obtained, but whether they *should* be granted.

The usual, approximately 10% (N = 43) of our membership found the issue worthy of a response. Of the respondents, 15 were researchers, 8 were clinicians, and 13 identified themselves as both researcher and clinician; we heard from a student, a student/manufacturer/distributor, a researcher/clinician/manufacturer/distributor (when do these people sleep?), and 3 manufacturers/distributors. In addition, we heard from 1 journalist. Responses came from 14 states in the US, three Canadian Provinces, 8 European countries, Japan and Australia. Seven respondents used e-mail, 6

people faxed me, 28 of you used "snail mail", and two responded in person.

Of the 43 respondents, a full 93% believed that the therapeutic use of light and melatonin should NOT be patentable. Only four individuals believed the opposite. Interestingly, relatively few people accompanied their responses with comments.

Several comments accompanying the "NO" response addressed the general principle of "prior art":

"These therapies have developed from the work of many investigators, working over long periods of time. They belong in the public domain."

"The research base and clinical efficacy trials derive from a broad research community supported largely by public money . . . Patenting would inhibit rather than stimulate research and result in private profit rather than community benefit."

"It's beyond the limits of common sense to patent the use of naturally occurring phenomena. It's as crazy as patenting a low-fat diet, or sleep deprivation as an antidepressant."

Other "NO" responders expressed concern about the effects of such patents on patients and practitioners:

" . . . may hinder application of [effective] therapies . . . and may also hinder discontinuation of therapies when scientific studies suggest that they are ineffective."

" . . . there is no clinical or ethical justification."

"Such patents could restrict the availability of needed treatments, increase costs . . . and put earnest practitioners in the moral dilemma of choosing between violating the law or violating the treatment needs of their patients."

"YES" respondents cited patent law and investment advantages:

"As any other treatment that has been developed, it is the intellectual property of the patentee. . ."

"Without it, the industry will never attract the dollars needed to develop and market products. Marketing money is the biggest need."

In summary, the overwhelming opinion of our underwhelming sample is that patents on the therapeutic use of light and melatonin should not be granted. It is conceivable—no, likely—that the outcome of this poll will precipitate a barrage of returns to the US Patents Office of already-granted patents. In addition, these opinions will undoubtedly act as a strong deterrent to individuals considering future patent applications. In the event that we hear of specific occurrences in this regard, we will be sure to let you know.

BULLETIN BOARD

SLTBR 1995 Business Meeting

We would like to remind all current Regular Members of the Society that the upcoming business meeting will be held on Saturday, June 10 from 16:30-17:30 in the auditorium of the Department of Biology, Johann Wolfgang Goethe Universität, Frankfurt am Main.

The new policy of establishing staggered succession of Board membership means that terms expire for three current members of the Board of Directors. Two further changes are pre-programmed: the President-Elect, J. Christian Gillin, M.D., will move to President and the Vice-President, Raymond W. Lam, M.D., will move to President-Elect.

Regular members are encouraged to contact Francine Butler, Ph.D, Executive Director, or any officer of the Society by June 8 (fax only) with names of persons interested in serving on the Board in the future. Nominations will also be taken at the Business Meeting, in order to have a general discussion of this important issue. Then the Board will prepare a slate of names for election, which will take place by mail ballot immediately following the meeting. This will allow the new Board members of the Society to take office in June 1995.

Welcome New Members

SLTBR extends a warm welcome to our new associate and regular members! We appreciate the dedicated effort of the Resource Center for Associations in initiating the membership drive and specifically the assistance of the Membership Department in quickly processing the new applications

As an important reminder, please encourage prospective members to include their curriculum vitae and a copy of one or more relevant manuscripts along with their application and membership fee.

George C. Brainard, Ph.D.
Chairman, SLTBR Membership Committee

Regular Members

Bruce Diamond
Michael Smolensky

Associate Members

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Gabriel C. Ticho
 Marc Vatin
 Valerie A. White
 R. Jane Williams
 Gary K. Zammit

Mae Vaivods
 Alan M. Weinberg
 Mary C. Williams
 Antonio J. Wood

APSS ANNUAL MEETING

The APSS Annual Meeting will be held May 30-June 4, 1995 in Nashville, TN. The meeting will present many aspects of chronobiology and light in relation to sleep. Further information from APSS, 1610 14th St. N.W., Suite 300, Rochester, MN 55901, Fax 507-287-6008.

RHYTHMS, BEHAVIOUR, AND MOOD

A Symposium on Rhythms, Behavior, and Mood is being organized as a Festschrift for Professor Rudi van den Hoofdakker, June 7-8, 1995 in the Department of Biological Psychiatry, University of Groningen, The Netherlands, with international participation. Information can be obtained from the Secretariat, Biological Psychiatry, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands, Fax (31)-50-696 727.

UNDERSTANDING THE BIOLOGICAL CLOCK

The American Physiological Society will sponsor a consensus meeting this summer entitled "Understanding the Biological Clock—From Genetics to Physiology." It will take place at Dartmouth Medical School, Hanover, NH from July 8-12, 1995, and is organized by Jay C. Dunlap and Jennifer J. Loros. Information may be obtained from APS Membership Services, 9650 Rockville Pike, Bethesda, MD 20814-3991, Fax 301-571-8313.

NEW DIRECTIONS IN AFFECTIVE DISORDERS

The 2nd International Conference on New Directions in Affective Disorders, to be held in Jerusalem Sept. 3-8, 1995, will have two Symposia of particular relevance to SLTBR members: "Seasonal Affective Disorders" (organized by N. E. Rosenthal and A. Pande) and "Chronobiological Aspects of Affective Disorders" (organized by M. Berger and P. Lavie). Information can be obtained from The Secretariat: Peltours-Te'um, POB 18388, Jerusalem 91082, Israel, Fax (972)-2-637 572.

CHRONOBIOLOGY AND CHRONOTHERAPEUTICS

The World Conference on Chronobiology and Chronotherapeutics (under the patronage of a number of rhythm societies) will be held Sept. 6-10, 1995 in Ferrara, Italy. Further information can be obtained from Francesco Portaluppi, WCC c/o Institute of Internal Medicine, University of Ferrara, via Savonarola 9, I-44100 Ferrara, Italy, Fax (39)-532-295 816.

1995 BRITISH SLEEP SOCIETY CONFERENCE

The British Sleep Society will sponsor a two-day conference on "Sleep Disorders: Assessment and Treatment" September 7 and 8, 1995, at St. George's Hospital Medical School in London. Basic and clinical approaches will be covered. For further information contact Phillipa Weitz, The Conference Unit, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, Telephone 0181 725 5534.

FEDERATION OF SLEEP RESEARCH SOCIETIES

The Second Intentional Congress of the World Federation of Sleep Research Societies will be held in Nassau, the Bahamas, September 12-16, 1995. Entitled *The Mystery of Sleep*, this congress is designed to bring together sleep researchers, clinicians and technicians from throughout the world. For further information contact Global Events, Congress Secretariat, 710 N. Trenton Drive, Beverly Hills, CA 90210 USA. Tel 310-247-8004; fax 310-247-8457.

LIGHT SYMPOSIUM CONFERENCE

The Light Symposium Foundation has scheduled its 1995 International Conference for October 9-11, 1995, in Atlanta, Georgia. For more information contact Michael Holik, M.D., Ph.D., Boston University School of Medicine, 80 E. Concord Street, M-1013, Boston, MA 02118 USA. Tel 617-638-4545; fax 617-638-8882.

TO REACH SLTBR . . .

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