# Light Treatment and Biological Rhythms

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

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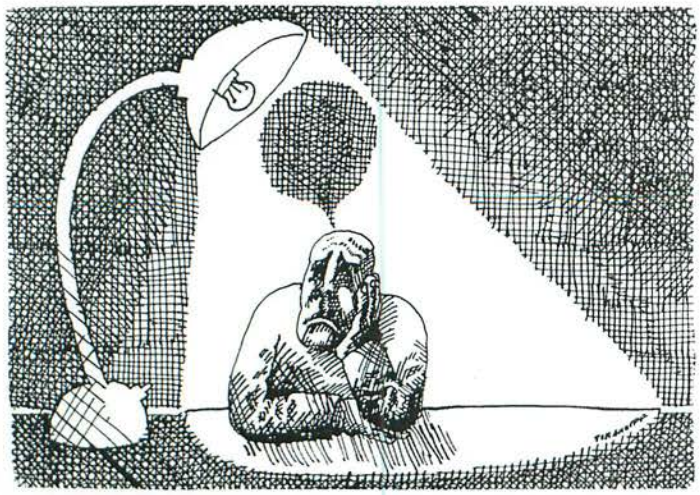
## EDITORIAL

It is indeed a challenge to take over as Editor of *LTBR* after Michael Terman's remarkable efforts. He has been scientifically rigorous, open to discussion, fair in judgment. I hope to maintain his exacting standards and neutrality.

The shift of editorship across the Atlantic brings with it a shift in focus. Although most light therapists are to be found in the USA, there are a growing number of research groups in other climates and continents. Since one goal of this Bulletin is to provide a forum for rapid exchange of information, I am implementing a series of informal updates from different countries. In the last issue of *LTBR* the Novosibirsk group reviewed its varied, intensive and original research on SAD. In this issue Raymond Lam, M.D., summarizes the growing body of work at another northern latitude. In one of the Canadian studies, he shows that the positive effect in SAD patients of light therapy that included the UV-spectrum was no longer significant when the sample size rose from 11 to 33. His conclusion, in these as yet unpublished studies, that *"the UV-spectrum does not significantly add to the antidepressant effect and therefore should be filtered out in clinical light therapy"*, is one that needs to be known now. Here, too, is an important additional message: it is no longer acceptable to draw major conclusions from significant findings in a small group of patients. The growing trend toward larger, focused studies over at least two winters is of much greater value.



*Artist: Tomaschoff, private collection of the Ed.*

## In This Issue

**Light Treatment and Biological Rhythms**

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

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In this remarkable year of political change, I would particularly like to open discussion and direct exchange of information with Eastern Europe. By mapping who is doing what, and where, researchers can establish direct contact with those carrying out similar projects. Those who have requests and questions are invited to publish them. Those who have methods that have proved useful are encouraged to share them. For example, we have completed an epidemiology study in Switzerland using an extended version of the *Seasonal Pattern Assessment Questionnaire* (SPAQ) with questions on light exposure. This has yielded the unexpected finding that SAD-like symptoms are not related to the amount of available sunshine in a given region, but to the individual's behavior (time spent outdoors). The questionnaire is freely available [*see Bulletin Board, this issue*].

Light therapy is viewed with a certain scepticism in Europe, often being considered a fashionable "alternative" therapy which fits the anti-drug zeitgeist. Yet a number of recent international meetings have held special symposia on light and biological rhythms. The diffusion of these discussions may aid us in developing more cogent arguments for an international consensus. For this reason, and since in these financially stringent days fewer can travel, another important focus in *LTBR* will be reviews of such conferences.

A significant proportion of the general population in temperate latitudes has troubles with mood and energy symptoms in the winter months. I find the application of circadian concepts to our built environment, for example, a new field with great promise. Architects and lighting engineers are responsible for the quality of our daily environment, and few design strategies have focused on any but technical solutions. The model presented by Douglas Cawthorne in this issue may stimulate such "cross-cultural" interactions.

The autumn equinox is past and the SAD season is upon us. May your efforts of this coming winter add more to our deepening knowledge of the importance of light for well-being. Please suggest themes for further Bulletins and keep us informed of upcoming meetings sufficiently ahead of time, for posting in the Bulletin Board (next deadline, 5 January 1992). — *A. W.-J.*

# DSM-IV UPDATE

The Work Group for Mood Disorders for DSM-IV, chaired by A. John Rush, M.D., has reviewed the current criteria for Seasonal Pattern (SP) in view of the existing literature and available unpublished data. As for all diagnoses in DSM-III-R, several options are being considered for DSM-IV. The options for SP have been delineated in view of the review carried out by David L. Dunner, M.D. and myself, for which Dunner solicited information from SLTBR members on several occasions over the past two years.

The process for designating criteria for SP includes opportunity for feedback from workers in the field. The American Psychiatric Press, Inc. (APPI) has allowed *LTBR* to reproduce the options for SP (below). Comments on the options can be forwarded to Allen Frances, M.D. or Wendy Davis, M.Ed., at the Office of Research, American Psychiatric Association, at the address below. In addition, options for criteria for all diagnoses considered for DSM-IV can be found in the *Options Book*, available for the nominal charge of $10.00 plus $5.00 handling from APPI at 1400 K Street, N.W., Washington, D.C., 20005 (1-800-368-5777). Those interested in receiving the ongoing

newsletter, *DSM-IV Update* can contact Ms. Cindy Jones at the APA Office of Research, American Psychiatric Association, at the above address.

*Mark S. Bauer, M.D., Department of Veterans Affairs Medical Center; Department of Psychiatry and Human Behavior, Brown University, Providence, RI 02908-4799. Tel 401-457-3083; fax 401-457-3370.*

The following is reprinted with permission from the *DSM-IV Options Book: Work in Progress*, 1 September 1991.  Please note that, in Option #2, suggested new wording is underlined and possible deletions are crossed out.

## Mood Disorders

**With Seasonal Pattern** (could be applied to Bipolar Disorder, Bipolar II Disorder, and Major Depressive Disorder, Recurrent)

*DSM-III-R introduced a seasonal specifier for mood disorder. This was done mostly because of treatment studies suggesting that individuals with winter depression may be responsive to the use of bright light therapy. The major problem is that there are very few studies on the psychometric properties of the various possible definitions for seasonal mood disorder. It is also not clear the degree to which the light treatment response is unique or specific to seasonal mood disorder because there are few data on the drug responsivity of such individuals or the efficacy of light therapy in those with nonseasonal depression. Moreover, researchers in the field have generally not adopted the DSM-III-R criteria. Two options to change this subtype have been proposed because of concern that the DSM-III-R definition is too narrow. The first more conservative option proposes to keep the criteria set for this disorder unchanged but to add a statement in the text intended to encourage clinical judgment by noting that some researchers use a more broad definition. The second option proposes to modify the criteria set in order to broaden the definition and allow more clinical judgment. This option deletes the narrowly defined 60-day window that in DSM-II-R specified the temporal relationship between episodes of mood disorder, and replaces it with the phrase "a particular time." It has also been suggested that the number of episodes that are required to fit the temporal pattern be reduced from three to two. Finally, criterion D, which is intended to clarify the relationship between seasonal and nonseasonal episodes, may be modified to reduce pseudoprecision and allow for clinical judgment.*

**Option #1:**

*No change in criteria. Add to text:* "Some researchers of seasonal depression apply a less stringent requirement (e.g., 90 days instead of 60 days) for the temporal relationship between the onset and offset of the mood episodes than the requirement noted above. Furthermore some investigators in the field make a diagnosis of seasonal pattern during the second episode."

**Option #2:**

A. There has been a regular temporal relationship between the onset of an episode of Bipolar I or Bipolar II Disorder ~~(including Bipolar Disorder NOS)~~ or Major Depressive Disorder, Recurrent, ~~(including Depressive Disorder NOS)~~ and a particular time ~~60 day period~~ of the year (e.g., regular appearance of depression in the fall or winter). ~~between the beginning of October and the end of November.~~

B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic ~~within a particular 60 day~~ time of the year (e.g., depression disappears in the spring). ~~from mid February to mid April)~~

C. There have been at least ?two or three? episodes of mood disturbance in ?two or three? consecutive years that demonstrate the temporal seasonal relationship defined in A and B.
~~There have been at least three episodes of mood disturbance in three separate years that demonstrated the temporal seasonal relationship defined in A and B; at least two of the years were consecutive~~

D. Seasonal episodes of mood disturbance, as described above, substantially outnumber any nonseasonal episodes of such disturbance that may have occurred. ~~by more than three to one~~

# SAD AND LIGHT THERAPY RESEARCH IN CANADA

Seasonal affective disorder (SAD) is of great interest in Canada because of our northern exposure; this brief report summarizes recent research conducted in our country. Several centers in Canada have been investigating SAD and light therapy for a number of years. In Vancouver, we have had a clinical research program in SAD at the University Hospital since 1988. Our neurobiologic studies

have focused on retinal electrophysiologic tests as measures of retinal sensitivity to light. We found that electrooculographic ratios (EOG or Arden ratios), a measure of retinal response to light adaptation, are decreased in SAD compared to controls (Lam et al., 1991a). In preliminary studies with electroretinography (ERG), which assesses photoreceptor response to standardized flashes of light, we also found that b-wave amplitudes are significantly reduced in female SAD patients (Lam et al., unpublished manuscript). These results suggest reduced retinal sensitivity to light, possibly mediated by retinal or central hypodopaminergic function. We are now conducting ERG studies to specifically assess rod and cone photoreceptor response.

SAD patients assessed in our clinic have similar clinical features to previously described clinic samples, although we found that most SAD patients (88%) have unipolar depressions according to DSM-III-R criteria (Lam et al., 1989). We have compared clinical features in SAD to nonseasonal mood disorders (N-SAD), matched for age, sex, and unipolar/bipolar diagnoses. The atypical symptoms of depression are more common in SAD, even when matched for polarity (Allen et al., 1991). In addition, we assessed family psychiatric history using the more rigorous Family History Method, in which detailed pedigrees are charted by a trained genetics associate, other informants are interviewed, and all available medical records obtained for affected family members. We found that SAD and N-SAD did not differ in family histories of mood disorder, but that the SAD patients had significantly more alcoholism in their families than N-SAD patients. These results support SAD as a distinct clinical subtype of mood disorders.

Our clinical trials have examined the role of ultraviolet (UV) wavelengths in light therapy. The initial study (involving 11 patients in a complicated 3-condition crossover design) showed some superiority of light therapy using full-spectrum fluorescent lights that included the UV-spectrum (Lam et al., 1991b). However, our followup study (33 patients in a randomized, parallel design with two weeks of morning light) found no differences in response to light therapy with or without UV-A wavelengths (Lam et al., unpublished manuscript). We conclude that the UV-spectrum does not significantly add to the antidepressant effect and therefore should be filtered out in clinical light therapy (as per SLTBR recommendations: cf. *LTBR* 1991 *3*: 48-50).

This winter we are starting a multicenter study of fluoxetine versus placebo in SAD (Principal Investigator: Raymond Lam, M.D.), with the participation of clinics in Calgary, Toronto, Hamilton, and Halifax. We are also studying the issue of seasonality in bulimia. We have identified significant seasonal mood patterns, with winter worsening, in patients with bulimia (Lam et al., in press). Preliminary results with light therapy suggest that it is effective in reducing both mood and bulimic symptoms (Lam, 1989), and we have an ongoing controlled study of light therapy for seasonal bulimia. Similar investigations on seasonality in bulimia are currently being conducted by Dr. Robert Levitan and colleagues at Toronto General Hospital (Levitan et al., 1991) and by Dr. Arthur Blouin and associates at the Ottawa Civic Hospital.

Anthony Levitt, M.D., and Russell Joffe, M.D., are conducting a number of studies on SAD as part of their Mood Disorders Program at the Clarke Institute in Toronto. They coordinated the multicenter light visor study reported at the SLTBR meeting in Toronto (Levitt et al., 1991). Their group has looked at a variety of personality measures and found significant differences in the profiles of depressed SAD and N-SAD patients, despite a similar severity of depression between the two groups (Schuller et al., unpublished manuscript). This again supports SAD as a clinically distinct subtype of depression. Joffe (1991) reported that SAD patients following light therapy do not show reductions in thyroid function as found with antidepressant treatment of N-SAD patients. They recently published an open study of bright light augmentation in N-SAD patients who had not responded to an adequate trial of antidepressants (Levitt et al., 1991). After exposure to 1 hour of 5000 lux morning light therapy for two weeks, 7 of 10 patients showed substantial improvement. This is an important and promising finding for the use of light in nonseasonal depression.

Dr. Meir Steiner's group at McMaster University in Hamilton is doing interesting work on retinal sensitivity to light in nonseasonal depression. They published a recent study showing no differences in EOG ratios between N-SAD patients and controls (Seggie et al., 1991). Their recent studies of ERG support retinal supersensitivity to light in N-SAD (Seggie and Steiner 1990, Steiner et al., 1991), and provide an interesting contrast to our findings in SAD.

Other centers in Canada are also conducting research into SAD and light therapy. Dr. Max Michelon in Halifax is investigating cognitive dysfunction in SAD before and after light therapy. Chris Gorman, M.D., in Calgary has been using a light visor for the past two winters (Demjen et al., 1991). He has an interesting SAD case load that is

entirely physician-referred, in contrast to most other clinics where patients are recruited, in part, through advertisement or the media. Dr. Carl Blashko in Edmonton has also used the Calgary light visor to treat SAD patients (Blashko et al., 1991).

As noted by others in the field, the SAD research community seems particularly marked by active cooperation, collaboration and sharing of ideas. This has certainly been my experience in Canada where research into SAD continues to thrive.

*Raymond W. Lam, M.D., F.R.C.P.(C), Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, Canada V6T 2A1. Tel 604-822-7325; fax 604-822-7756.*

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# 5th WORLD CONGRESS OF BIOLOGICAL PSYCHIATRY

### *Florence, Italy, 9-14 June 1991*

In the first symposium, "Rhythm Disorders and Their Novel Treatment" chaired by T. Wehr and K. Takahashi, Wehr presented his novel work on the response of human sleep and circadian rhythms to changes in artificial photoperiods. Normal male volunteers, after having their melatonin circadian profile and sleep measured under a "summer" photoperiod (LD 16:8), were exposed to a "winter" photoperiod (LD 10:14, complete darkness from 6 pm - 8 am) for one month, after which melatonin circadian profiles and sleep were again measured. The subjects' duration of sleep and of melatonin secretion expanded under the winter photoperiod. The important implications of this study are that humans, like certain seasonally breeding species, are capable of responding to changes in the photoperiod by altering the duration of their sleep and melatonin secretion. In animals, duration of melatonin secretion has been implicated as a critical factor mediating the photoperiodic induction of seasonal changes in reproduction, weight, metabolism and thermoregulation. The capacity for such physiological and behavioral changes in response to photoperiodic changes in humans is usually masked by artificial lighting conditions in the environment that prevent exposure to a true winter photoperiod. Wehr's paper on this study is in press in the *Journal of Clinical Endocrinology and Metabolism* (December 1991).

N. Rosenthal presented data supporting the use of light therapy for delayed sleep phase syndrome. Twenty patients were treated for 14 days in each condition in a crossover design utilizing 2500 lux for 2 hours in the morning with light restriction in the afternoon and evening vs. the control condition of dim (300 lux) light in the morning without light restriction. The patients reported improvement with the active treatment which was

associated with advances of the core temperature profiles and lengthening of sleep latency measures during the morning hours [*Sleep* (1990) *13*:354-361].

T. Ohta and M. Okawa discussed the use of vitamin $B_{12}$ treatment in patients with delayed sleep phase syndrome and other sleep-wake rhythm disorders. Although the preliminary findings are impressive, larger scale placebo controlled trials are needed to substantiate these results.

J. Arendt discussed the use of melatonin (5 mg) to hasten resynchronization of circadian rhythms in jet lag. Other potential uses of melatonin, with some initial experimental data, include rotating shift workers, blind subjects with free-running or delayed circadian rhythms and delayed sleep phase syndrome.

In another symposium on "Circadian Rhythms in Affective Disorders: New Concepts and Novel Therapies", F. Turek pointed out that phase shifts to dark pulses may actually be mediated by changes in dark-induced increases in the level of the animal's locomotor activity. J. Anderson reviewed the roll of energy and metabolism in depression and presented some preliminary data on temperature rhythms and energy expenditure in SAD patients under constant routine conditions. E. van Cauter discussed circadian time keeping in depression vs. aging as expressed in relation to neuroendocrine function: prolactin (phase shifts before vs. after sleep), cortisol (which in contrast to TSH has a dampened circadian profile under constant conditions), and the variability of amplitude in melatonin (which did not parallel that of cortisol). R. van den Hoofdakker discussed the importance of diurnal variations in mood, despite its wide variability, as a predictor for the antidepressant response to total sleep deprivation. A. Koukopoulos reviewed his own extensive, long-term data on seasonality of mood disorders and their modification by treatments. E. Holsboer-Trachsler presented differential effects of tricyclic (trimpramine) vs. tricyclic medication combined with second half of the night partial sleep deprivation (PSD) vs. tricyclic medication combined with light therapy in severe hospitalized depression. Although all groups showed improvement, patients with negative diurnality (morning type) tend to respond to tricyclic medication alone, whereas those with positive diurnality (evening type), to PSD augmentation of tricyclic medication. Light treatment was associated with arousal effects consisting of a decrease in slow wave sleep and an increase in number of awakenings and sleep onset latency.

The third major symposium was entitled " Clinical and Biological Issues of Therapeutic Sleep Deprivation", chaired by S. Kasper and H.J. Möller. Van den Hoofdakker, in his investigation on the mechanisms of action of therapeutic sleep deprivation, found that although urinary cortisol was increased by sleep deprivation, this increase was not related to the clinical effect. Body temperature was increased by total sleep deprivation: the higher the increase of the temperature minimum, the more there was an improvement of mood. Furthermore, the greater the decrease of the minimum during the subsequent night, the greater the clinical relapse. Responders to sleep deprivation appear to show activating effects consisting of both increases in cortisol and body temperature. M. Berger discussed the depressogenic effects of naps, illustrating in his data that afternoon naps were better tolerated than morning naps and that the occurrence of REM sleep in a nap did not turn out to be significant for subsequent relapses into depression. In his talk on "Sleep as heat: Investigation of a thermoregulatory mechanism for the antidepressant effect of sleep deprivation", T. Wehr showed that effects of sleep (associated with increased sweating, increased prolactin and growth hormone secretion, slow wave EEG, decreased TSH and motor activity) resembles the effects of heat. He tested the effects of total sleep deprivation (TSD) in warm (33°C) and cool (18°C) environments. The warm environment reduced the capacity of TSD to improve depression, to increase plasma thyrotropin and tri-iodothyronine levels and to decrease prolactin levels. Both antidepressant drugs and light therapy cause a sustained lowering of body temperature. Holsboer-Trachsler showed improved cognitive and psychomotor performance after sleep deprivation and light therapy as adjuvant therapy compared with antidepressant drug alone. Depressed patients who were treated with trimipramine (T) plus light therapy or T plus PSD (second half of the night) did better on all cognitive psychomotor tests than did patients treated with T alone, an effect observed within a week. S. Kasper discussed the capacity of serotonergic antidepressant medications to prevent relapses occurring after the recovery night of sleep deprivation.

In the oral communications, in a session on biological markers, van Reeth et al. showed that although dark pulses and short acting benzodiazapines such as triazolam appear to phase shift the circadian clock by inducing acute changes in locomotor activity in young hamsters, the circadian system of old animals becomes selectively unresponsive to synchronizing signals mediated by the activity-rest cycle. The data suggest that age-related changes in circadian rhythmicity may reflect a weakened coupling between the activity-rest cycle and the circadian clock. Klompenhouwer et al. presented data suggesting a

significant seasonal variation in the number of serotonergic binding sites ($B_{max}$), with men having significantly lower values than women. Lacoste et al. discussed melatonin, mood and sleep in the course of a year in morning, intermediate and evening type individuals. Müller et al. reported that a seasonality syndrome in the SPAQ did not necessarily implicate a diagnosis of SAD.

In the poster sessions, Lepp at al. found morning light an effective treatment of SAD, but there was no correlation between clinical effect and changes in urinary melatonin. Meesters et al. suggested from their use of bright light in winter depressives that early treatment could be of considerable preventive importance. Van der Velde et al. compared light and citalopram in a woman with winter depression. The efficacy of both treatments suggest the involvement of serotonergic mechanisms. Graw et al. demonstrated the wonders of a one week morning walk outdoors ("natural light") in SAD. Clinical features of SAD in Japan (Hanada et al.) include equal female/male ratios with increases in appetite and carbohydrate craving more common in females while hypersomnia was common in both males and females. Kräuchi et al. showed that in an epidemiologic survey in Switzerland, individuals with seasonal problems showed a selective higher carbohydrate intake in autumn/winter compared with non-seasonal individuals.

Gordijn et al. reported that although morning (06-09 hr) vs. evening (18-21hr) light advanced waking time in non-seasonal depressed patients with diurnal mood variations compared with controls, little therapeutic benefit could be observed. Parry et al. found melatonin to have an earlier offset, a shorter duration and a decreased area under the curve in patients with premenstrual depression compared with controls. In response to light treatment, the cortisol acrophase was phased-advanced in patients vs. controls under the dim red evening light condition. Mizuno et al. reported that mean levels of plasma free 3-methoxy-4-hydroxyphenylglycol were lower, amplitudes of plasma cortisol higher, and acrophases of cortisol earlier in bipolar patients compared with controls.

Pangerl et al. presented data showing that light exposure at night prevents the nocturnal reduction of $\beta_1$ adrenoceptor sites in Syrian hamster pineal glands. Azuma et al. presented data to suggest that exposure of high intensity illumination in the light period affects the diurnal variation of pineal indoles of NZB mice, an effect they suggested may be related to the therapeutic effects of light therapy in SAD.

*Barbara L. Parry, M.D., University of California, San Diego (0804), La Jolla, CA 92093. Tel 619-543-5592; fax 619-294-4106.*

# CONCEPTS AND MODELS OF SLEEP REGULATION

***An International Workshop held on 19 & 20 September 1991 at the University of Zürich***

The interest in mathematical models of the regulating processes underlying sleep and circadian rhythms has continuously increased over the past decade. One of the first symposia on this topic was held in conjunction with the APSS Congress in Hyannis in 1981. The proceedings of the symposium (Moore-Ede and Czeisler, 1984) provided an excellent overview of the major contributions to the field. In the meantime there have been important new developments, and the interest in the modeling approach has increased in the sleep and rhythm research community. This is reflected by recent symposia at international congresses (e.g., European Congress of Sleep Research, Strasbourg, 1990; Society for Research on Biological Rhythms, Amelia Island, 1990). In view of the recent advances, it appears timely to assess the present state of art and to discuss promising future avenues.

Eighteen invited participants gathered for a two-day meeting to present new data as well as novel concepts and models of sleep regulation. Since the abstracts had been distributed beforehand, no formal presentations were needed. Brief statements on specific topics were followed by lively discussions which were moderated by Alexander Borbély, the organizer of the workshop. A limited number of students and invited guests attended the discussions as auditors and presented their own data as posters.

Slow wave sleep (SWS) and slow-wave activity (SWA), indicators of sleep homeostasis and formalized in the two-process model as Process S, was the topic of the first session. D.-J. Dijk and P. Achermann (Zürich) summarized their data and simulations on extended sleep episodes that occurred at different circadian phases. They concluded that the occasional late recurrence of SWS and SWA can be simulated by a homeostatic process that is only dependent on the prior history of sleep and wakefulness. Yet it is still unclear which aspect of wakefulness favors the buildup of Process S. J. Horne

(Loughborough) reviewed the SWS promoting action of a heat load or an "information load" prior to sleep, and commented critically on theories postulating a thermoregulatory role of sleep. T. Wehr (Bethesda) drew attention to the similarities of the physiological responses to sleep deprivation and cold exposure, and made a case for REM sleep as a regulated thermogenic process. T. Åkerstedt (Stockholm) reported that a selective SWS suppression during sleep failed to significantly increase daytime sleepiness and reduce performance. I. Tobler (Zürich) reviewed sleep homeostasis in various mammalian species and presented data indicating that SWA is a general sleep intensity parameter. S. Daan (Haren) summarized intriguing recent observations in two hibernating species. The animals show periodic arousals and spend a large part of these euthermic periods in sleep. Moreover, SWA declines in the course of these episodes, and the initial level is a function of the duration of the hypothermic period.

The second session was devoted to circadian aspects of sleep regulation and their interactions with SWA. Dijk and C. Czeisler (Boston) presented first results obtained in a forced desynchrony protocol in which subjects lived on a 28-hour schedule. The spectral analysis of the sleep EEG demonstrated that SWA exhibited a declining trend in all sleep episodes occurring at various circadian phases. A strong circadian influence on SWA did not seem to be present. Czeisler and Dijk also addressed the question whether multiple circadian oscillators need to be postulated. They concluded that all rhythms are driven by a common circadian pacemaker, although the rest-activity cycle may become desynchronized from the output of the pacemaker. Daan and D. Beersma (Groningen) argued that a single circadian pacemaker is sufficient to account for different rates of reentrainment. They showed that waveform distortions and masking may account for the phenomena observed during fractional desynchronization.

The polyphasic sleep/wake pattern was a major topic of the discussions. R. Broughton (Ottawa) summarized the evidence in favor of an endogenous circasemidian sleep-wake rhythm in humans. He cited the occurrence of increased sleepiness in the afternoon which may result in napping, and which is particularly prominent early and late in life. P. Lavie (Haifa) advocated the notion of sleep gates and "forbidden zones" which were apparent in the 7/13 sleep-wake paradigm. However, three participants (Czeisler, Wehr, Wirz-Justice) concurred that an increased sleep tendency in the afternoon is not evident during a constant routine protocol. There is therefore no compelling evidence for the endogenous origin of the biphasic sleepiness rhythm. J. Zulley (Munich) limited sleep duration to 4 hours in subjects living in temporal isolation and observed a second sleep episode after a relatively short duration of waking. The first sleep episode occurred near the temperature minimum and had to be actively interrupted, whereas in the second sleep episode the subjects tended to awaken spontaneously. R. Kronauer (Cambridge) discussed two remarkable free-run studies of habitual nappers which showed spontaneous internal desynchrony patterns. Each sleep episode may be controlled by an individual oscillator, with the interpretation of the episode as a nap or a nighttime sleep being dictated by an underlying "x rhythm". The patterns are analogous to those seen in rodents during splitting. T. Wehr reported spectacular results on the effect of a 4-week shortening of the photoperiod to 10 hours. In addition to alterations of the secretion pattern of various hormones, sleep separated into two 4.5 h components with an intervening waking episode. Kronauer pointed out that a similar biphasic pattern is not uncommon in older subjects.

The regulation of the nonREM-REM sleep cycle and the underlying physiological mechanisms were reviewed by R. McCarley and S. Massaquoi (Brockton). Recent studies point to the importance of cholinergic activity in suppressing the EEG synchronization which corresponds on the neuronal level to the membrane hyperpolarization of thalamic relay cells. Spindles and delta waves may arise from the reduction or absence of cholinergic activity.

Finally, advances in the modeling of sleep regulation were reported in several presentations. Two groups attempted to integrate different models. Massaquoi and McCarley expanded their Limit Cycle Reciprocal Interaction Model by incorporating the exogenous excitatory input "E". Strong E-pulses may cause various types of phase resetting of the REM sleep cycle, whereas weak pulses ("E-noise") representing random background arousal activity during sleep, may affect the cycle length. Interactions with SWA and Process S were incorporated in accordance with the model of Achermann and co-workers. Achermann and Borbély reported first results on the combination of various "modules" into a "grand model" of sleep regulation. This integrated model is composed of the most recent version of the two-process model accounting for the changes in SWA, of the REM sleep oscillating process according to McCarley and Massaquoi, of a circadian process according to the "deep circadian oscillator" of Kronauer, and the 3-process model of Åkerstedt and Folkard for simulating daytime sleepiness. Achermann summarized also his recent work on the parameter estimation and quantitative simulation of human SWA patterns obtained for different

experimental protocols. A stochastic model of the generation of the nonREM-REM sleep cycle was presented by A. Belyavin (Farnborough). Furthermore, a data base was used to analyze the changes of SWA and REM sleep entry. D. Beersma and Daan proposed a multiplicative interaction of two circadian oscillators to account for the rest-activity pattern of *Tupaia*. Kronauer presented an analysis of the changes of sleep latency during 24-h baseline conditions and in the course of recovery from prolonged sleep deprivation.

In summary, the presentations and discussions at the workshop showed that modeling has become one of the most dynamic areas of sleep research. It is planned to publish the proceedings of the meeting in 1992 in the *Journal of Sleep Research*.

*Alexander Borbély, Institute of Pharmacology, University of Zürich, Gloriastrasse 32, 8006 Zürich, Switzerland. Tel (41) 1-257-2676; fax (41) 1-261-5684.*

# THE CONSTANT ROUTINE

### *Highlights of a workshop at the Conference of the World Federation of Sleep Societies, September 1991, Cannes, France*

In the early 1970's John Mills, James Waterhouse and I, working at the University of Manchester, were studying the re-entrainment of the human circadian timing system following simulated time zone transitions. We were worried by the observation that when several rhythmic variables were measured in the same individual, re-entrainment of the different rhythms proceeded at different rates. Such an observation might have several explanations, but one possibility was that the different variables were masked to different extents by the phase shift of the subjects' habits (sleep-, meal-, etc. times). Thus, those variables which appeared to adjust to the time zone shift within a day or two might be markedly masked. To test this hypothesis further, we required a technique that would remove these masking effects. As a result, we developed the Constant Routine (CR). The basic Routine involved keeping a subject awake, in the same posture and in a room maintained at constant humidity and illumination. Results from such CRs were first published in my Ph.D. thesis and in the Journal of Physiology in the mid-1970's. Subsequently, several variants of the CR have been developed. Most of these, like the original CR, have eliminated sleep and concentrated upon the use of the body temperature rhythms as a phase marker, but have varied in their duration. In addition, however, some have permitted sleep and are not in the original sense a CR.

At the recent Conference of the World Federation of Sleep Societies (Cannes, France — September 1991) A. Wirz-Justice organized a workshop to discuss several of the variants and some of the problems associated with interpretation of results from — and performance of — the CR. In the workshop, which was attended by about 170 participants, five invited speakers were asked to present brief overviews of their use of the CR and to address a number of questions, some of which are considered below.

#### Does the prior history/amount of activity affect phase estimates during a CR?

O. Benoit presented results from two 24-hour CRs starting either at 09.00 or at 21.00. In the first CR, subjects remained sedentary throughout and took hourly meals. In the second CR, subjects were allowed to get up occasionally and were fed at 3 hour intervals. There was no difference in the subjects' body temperature during the nocturnal hours (01-09 hr) but daytime temperature was higher in the second CR when more activity was allowed, thus modifying apparent amplitude. These results indicated that the phase of the circadian pacemaker, if assessed by the time of temperature minimum, is unaffected whether the nighttime readings are preceded by normal activity or by several hours of a sedentary CR.

#### How accurate is the phase estimate during the CR?

C. Czeisler addressed this question by showing how he had validated results from his modification of the CR. Using very long CRs (60 hours), he showed how sequential estimates of circadian phase, assessed from the time of body temperature minimum derived from a dual harmonic least-squares fit, yielded a very high correlation. More importantly, in his view, he showed how, in experiments in which subjects underwent forced internal desynchronization (with the body temperature and sleep/wake rhythms adopting different periods), estimates of phase during CRs at the beginning and end of such experiments closely predicted the phases derived from the free running period of the temperature rhythm.

#### Can the CR be used to describe an endogenous rhythm in sleep propensity?

This question was addressed by L. Lack and J. Zulley. Zulley showed how, using a 32-hour routine in which subjects remained supine and were allowed *ad libitum*

sleep, a clear time-of-day effect on sleep efficiency could be described with a minimum sleep propensity around 20 h. Lack then presented results from experiments in which he compared a 26-hour CR, during which subjects were supine and awake, with an ultradian sleep/wake routine consisting of 20 min wakefulness and 10 min sleep. Circadian phase markers (the time of body temperature minimum and the times of melatonin onset and maximum) from the two routines were compared for their capacity to predict sleep propensity and sleep/wake behavior. The highest correlations were found between sleep propensity and the time of temperature minimum determined from the ultradian sleep/wake routine.

### Can endogenous phase be estimated by means other than the CR?

Waterhouse, in his presentation, reminded the audience that there are several circumstances in which the CR becomes impractical; in addition, the CR might affect the rhythm under investigation (e.g., the effect of the prolonged wakefulness required in the CR upon mental performance). Thus, he presented an alternative method to the CR for estimating endogenous phase-shifts which can be used in subjects living a normal nychthemeral existence. It is based upon the purification method of Wever and has been used in studying nurses during nightwork. By splitting a nychthemeral rhythm into endogenous and masking components, it was possible to "purify" raw body temperature data from a knowledge of an individual's hourly activity logs. This method enabled an estimate to be made of phase shifts of the endogenous component of the body temperature rhythm and showed that conventional estimates of adjustment to nightwork (e.g., by cosinor analysis) overestimated those obtained by "purification" of the data.

Following these presentations, two major questions arose during discussion from the floor. First, E. van Cauter questioned whether or not it is necessary to keep subjects in temporal isolation during CRs. Most of the speakers felt that this is a necessity, particularly in cases where volition (with the expectation of the end of a CR) might affect the rhythm being investigated.

The second question considered the need for external influences to be kept constant during a CR; in particular, whether or not regular, frequent, isocaloric snacks should be taken. T. Wehr pointed out that subjects tolerated such meals poorly and that even if tolerated, circadian variations in gastrointestinal function make it unlikely that there is constant absorption. Van Cauter indicated that she thought she had overcome this problem by performing CRs in which subjects were given constant intravenous glucose infusions. However, this does not result in constant plasma glucose levels because of circadian variations in metabolism/liver enzymes, etc. In my view, the major point is that it may not be necessary to attempt to remove a given exogenous influence if this factor is unlikely to affect the rhythm chosen as a phase marker. Indeed, one must be careful not to *induce* some circadian variation, that is, introduce a new masking influence. As a further example, one might ask about those cases where the CR is particularly long and more social input by the experimenter is required at some times to keep the subject awake. Might this act as a masking influence? And what about the increase in fatigue?

Wirz-Justice had opened the workshop by asking a number of important questions about the assumptions underlying the CR. As indicated above, some were addressed by the invited speakers. However, as is often the case with debate and discussion, nearly as many questions were raised. It is hoped that this brief report will encourage the debate to continue.

*David S. Minors, Ph.D., Department of Physiological Sciences, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK. Tel (44) 61-275-5370; fax (44)-61-275-5600.*

## PASSIVE LIGHT THERAPY BY IMPROVED BUILDING DESIGN?

Most people spend between 75-95% of their time in buildings. The primary function of any building is to modify the ambient external climate in order to allow people to carry out tasks that would be arduous or impossible otherwise. As well as modifying heat transfer, humidity, sound levels and all the other environmental parameters, buildings play a crucial role in modifying ambient light conditions.

If it is conservatively assumed that 10% of the UK's population suffers to a greater or lesser degree from some form of seasonal mood disorder, then there is a strong case for examining the way that the design of buildings could modify these manifestations. The concept of mass preventative light therapy by building design is, as far as I am aware, a new one, and has a number of advantages over the present treatment paradigm:

1. The treatment would be passive, i.e., the mere act of living and/or working in buildings that were designed to optimize lighting regimens for the occupants. Time would not have to be spent staring at light boxes.
2. All the components for light therapy already exist in conventional building design since most buildings have windows and artificial lighting. It is just a question of arranging them in the optimum manner.
3. By maximizing the use of daylighting, reliance on artificial sources can be reduced with related decreases in operating costs. This has significant implications for the overall energy efficiency of the building.
4. In difficult situations where the available natural light is reduced, such as in cities, special features including light shelves, light pipes, atria and reflectors can be used to introduce more natural light into the interior.
5. When natural light is not available (e.g., during the hours of darkness), artificial illumination can be arranged so as to provide high illuminance areas where they are most likely to benefit the occupants. This may be in the form of localized high intensity task lighting or "light walls" or "pass through" zones in entrances or corridors.

Sick Building Syndrome (SBS) is a term usually used to describe a range of complaints made by occupants against the buildings in which they work. The most common complaints are of lethargy, headaches and upper respiratory problems attributed to deficiencies in the internal environment such as poor indoor air quality and background noise. Light has rarely been considered as a possible factor.

Given the desirability and feasibility of introducing adequate circadian phase resetting into building design, it has been recognized that research is required to examine the the relationship between the design of buildings and the light mediated aspects of the occupants' health and well-being.

A research program carried out at The Martin Centre for Architectural and Urban Studies at Cambridge University has established a significant correlation between the occurrence of Sick Building Syndrome, the indoor lighting environment and the physical design of the building. Surveys using specially developed "light dose-meters" have shown that there are characteristic differences between the lighting regimens experienced by occupants in different generic office building types and that these lighting characteristics can be correlated to the occupants' perception of whether or not the building is sick.

## Examples of Light Exposure in Office Buildings

Figure 1 shows a typical light exposure trace from an occupant working in an office building with a medium, average daylight factor of 100-200 lux. The graph is characterized by the majority of readings being between the 100-200 lux levels with periodic "spikes" of anything up to 50klux. These spikes are known to coincide with periods spent close to windows or outdoors.

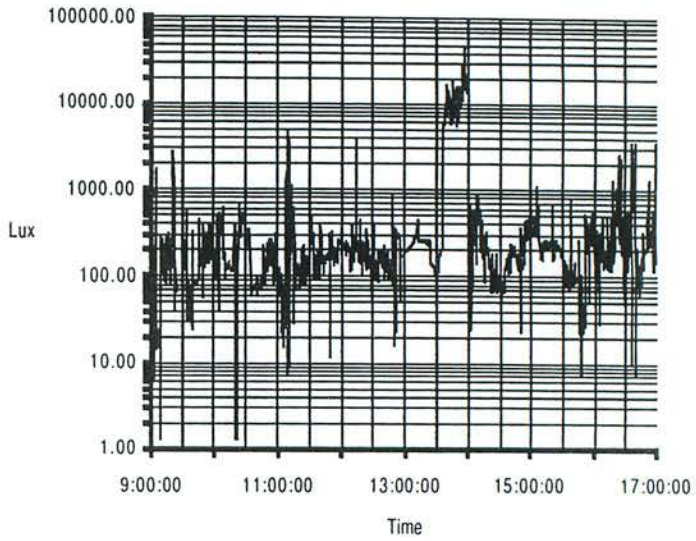


*Figure 1. A typical light exposure trace from an occupant in an office building with a medium average daylight factor.*

Figure 2 is a typical light exposure trace from an occupant working in a deep plan office building with a low average daylight factor. To compensate for this, a large proportion

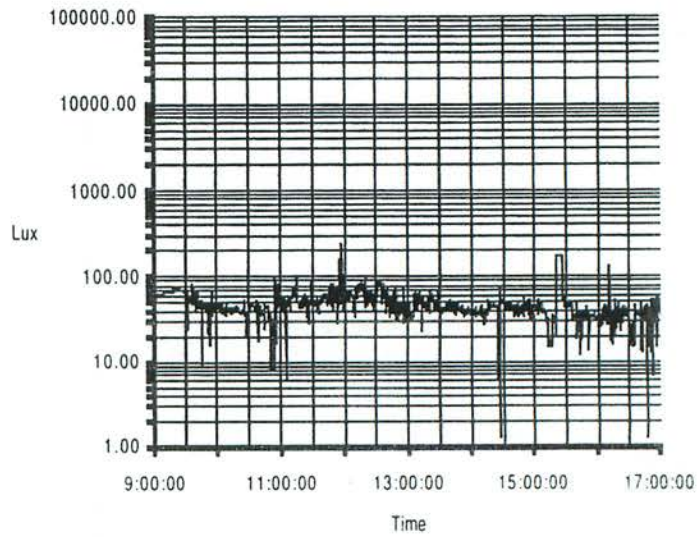


*Figure 2. A typical light exposure trace from an occupant in a deep plan office building with a low average daylight factor.*

of the illuminance in the building is provided by artificial sources. Despite this, the "background" level is still much lower than in the previous example and there is a notable absence of spikes. This could be described as an example of a relatively homogeneous, low-level lighting environment. A majority of the occupants in this building reported significant SBS symptoms.

A third example of a typical light exposure trace for an occupant working in an office with a high average daylight factor is shown in figure 3. The background level is much higher than for either of the previous examples and there are very frequent spikes. The high frequency can be attributed to large glazed areas which are more often within the occupant's field of view.

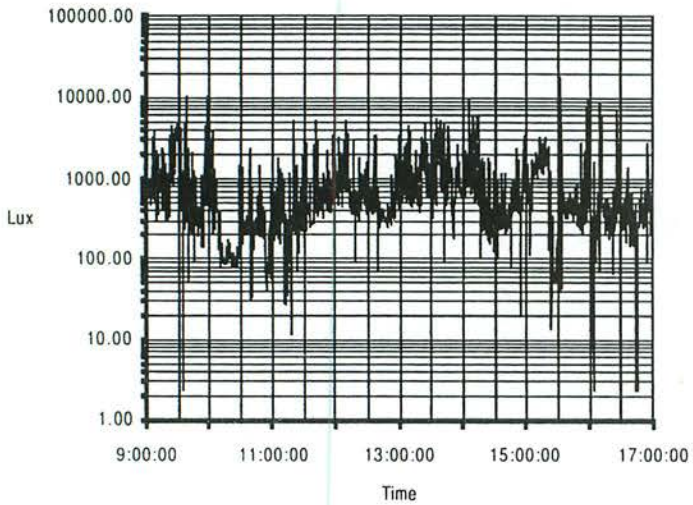


*Figure 3. A typical light exposure trace from an occupant in an office building with a high average daylight factor.*

The main influences on these characteristics in terms of the building designs seem to be the glazing/floor area ratio of the office buildings, the presence of external and internal obstructions and the occupants' spatial-behavior pattern.

While it is useful to link the characteristics of light exposure to anecdotal evidence of what the occupants feel about their offices, this is essentially a subjective method of assessment. Further research is needed to directly and quantitatively link daily exposure in different building types to stability and phase-position of circadian rhythms.

## Predicting Occupant Light Exposure & Phase Shifting in Buildings

In order to asses the possibilities of correcting the worst of these office building designs and to examine the light therapeutic potential of new designs while still on the architect's drawing board, a Macintosh based numerical daylighting model called G.O.L.D. (the Guide to Occupant Light Dose) has been developed. It has been integrated with a human circadian model to predict the effects on circadian phase of changes in the lighting within buildings caused by alterations in the building design. Both the daylighting model and the circadian model in G.O.L.D. are based on empirical data.

G.O.L.D. has a user-friendly interface, making analysis of building designs for their circadian phase shifting effects both rapid and easy to carry out (figure 4). This is essential if architects are to accept models like G.O.L.D. as practical design tools and lighting for occupant health as a valid design concern.

The daylighting model operates simultaneously upon a series of up to six user-defined rooms, each of which can have a number of user-defined windows and variable internal and external reflectances, window transmittances, external obstructions, etc. Each room is divided into one hundred equally spaced points and the mean cylindrical illuminance is calculated at each one. Internally and externally reflected components are included. G.O.L.D. can function solely as a daylight distribution model as well as a daylight exposure model.

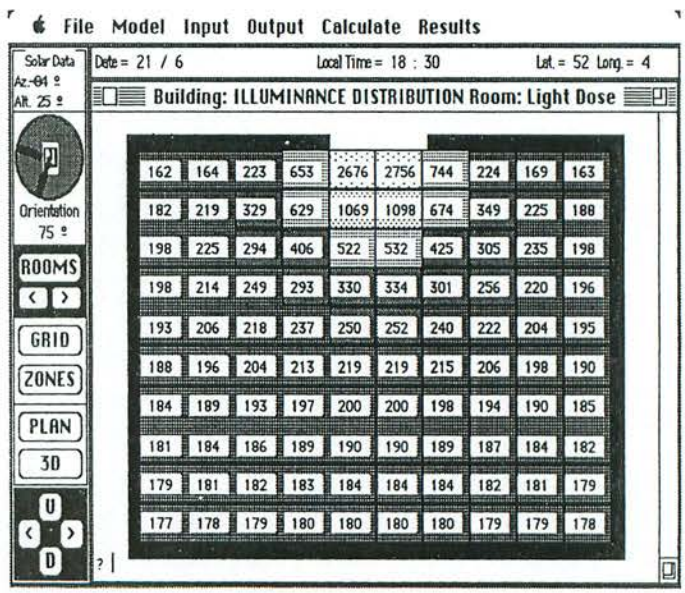


*Figure 4. The G.O.L.D. user interface. It has full 24-bit color, clic and drag data entry and Macintosh pull-down menus and dialogu boxes. It also has real-time data displays of temporal information suc as current sun altitude and azimuth.*

For the daylight exposure calculations each room can b divided into six types of zones of occupation, using a clicl

and drag user interface. Time allocations for the periods spent by an occupant in each zone type can then be made in a similar way using the occupant behavior pattern routine, which is again fully user interfaced. In this way a notional occupant can be located at different points within any of the rooms at different times of day. G.O.L.D. then integrates occupant movement with changes in mean cylindrical illuminance during the course of a working day (08-18 h) and writes the resulting record of light exposure to a file.

In order to assess the effect that the light exposure has upon the occupant's circadian system, the predicted light exposure is applied as the input to the circadian model which is based on the coupled van der Pol oscilla-tor model of Kronauer et al. (1982). It assumes a discrete and instantaneous phase shift response to light exposure over the course of the day and produces as its result a cumulative phase shift. The shift is then compared with an optimum, and performance percentage points are produced as an absolute measure of the difference between the optimum and the actual phase shift experienced by the occupant. In this way, particular designs can be assigned indices of their capacity to provide sufficient light for adequate entrainment as well as compared for their overall suitability. All output data can be exported to spreadsheet or statistical analysis packages accepting text, Lotus 123, Excel or ASCII file formats. Further details are presented in: D. Cawthorne, Buildings, Lighting and the Biological Clock, Building Technical File No. 32, January 1991, pp. 25-34 (ISSN 0264-6978), Building (Publishers) Limited, 1 Millharbour, London E14 9RA.

It is hoped that both G.O.L.D and the light-dose meters and survey technique can be improved as research refines our models of circadian rhythmicity and the effects of light. Further funding to enable this to happen and to develop more cross-disciplinary investigation between the bio-sciences and architecture is required. Inquiries are welcomed by the author.

*Douglas Cawthorne, B.Sc., B. Arch., The Martin Centre for Architectural & Urban Studies, Cambridge University, 6 Chaucer Road, Cambridge. England CB2 2EB. Fax (44)-223-332983.*

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# *TO THE EDITOR*

## Clinical Efficacy of the Light Visor

Reference is made to your editorial "Clinical Efficacy of the Light Visor and Its Broader Implications" (Terman, 1991). I found the editorial to be thoughtful and reasonable, except for the statement: "the overall 40% remission rate is so much lower than that found in the most successful light-box studies". You do not provide data, nor rationale for this conclusion. In fact, the data presented by Levitt et al. (1991) at the annual SLTBR meeting in Toronto, from which I assume the editorial conclusions were drawn, indicated that the responder rate for the light visor compared favorably with the light boxes — in the 50% range — as reported by you using very conservative criteria (Terman et al., 1989). Applying more liberal criteria, the response rate is in the 60% range. Unfortunately, there does not seem to be a consensus in the clinical community on standards for efficacy.

It seems unreasonable to me to prejudge the results of the trial; rather, it would be more appropriate to wait until all of the details of the study, the data and the authors' conclusions are published, so that all interested parties may draw their own conclusions. It is my understanding that a manuscript has been submitted for publication.

*Gordon D. Wallace. D.V.M., M.P.H., President and Scientific Director, Bio-Brite, Inc., 7315 Wisconsin Ave., Suite 900E, Bethesda, MD 20814-3202. Tel 301-961-8557; fax 301-907-8637.*

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## Response to Wallace

Data and rationale for the assertion that the remission rate obtained in the visor study is lower than that of the most successful light box studies are found in the review by Terman et al. (1989), which Wallace cites. The strict

remission criterion used in that cross-center analysis was pre- to posttreatment reduction in the Hamilton depression scale score $\geq 50\%$, accompanied by posttreatment score $\leq 7$. Seven studies showed a proportion of patients responding to 2500 lux morning light $\geq 0.70$, although the pooled proportion across studies was indeed much lower, i.e., 0.53.

In their presentation to SLTBR, Levitt et al. (1991) described a somewhat different remission measure: pre- to posttreatment score reduction $\geq 50\%$ on the expanded Hamilton depression scale (which includes both "typical" and "atypical" items), accompanied by posttreatment typical score $\leq 10$ and atypical score $\leq 4$. After two weeks of visor treatment the proportion of patients responding to each intensity was: 60 lux, 0.41; 600 lux, 0.46; and 3200 lux, 0.38. Although the precise correspondence of the two sets of remission criteria needs to be clarified, their underlying logic (and "strictness") is similar.

The two sets of studies differ greatly in duration of light exposure. The light box studies all used 2 h sessions, in contrast with 30 min in the visor study. The cross-center analysis considered 30 min exposures as "brief" controls that yielded an overall remission rate — 0.31 — far lower than that for 2 h sessions. Only by using 10,000 lux stimulation has a light box study shown high remission rate with 30 min exposures (0.92, cross-center criteria), far exceeding the response under the 3000 lux control condition (0.25) (J.S. Terman et al., 1990).

Of course, a comprehensive analysis should compare both strict and liberal outcome measures (see M. Terman et al., 1990), as Levitt et al. (1991) nicely illustrated in their SLTBR presentation. Using the more liberal criterion of pre- to posttreatment score reduction $\geq 50\%$ on the expanded Hamilton scale, the proportion of patients showing improvement after two weeks of visor treatment was approximately 0.60. Using the original Hamilton scale, a similar overall level of improvement was found after 1-2 weeks of light box treatment, i.e., 0.66. A general point of the cross-center analysis is sustained: the more liberal the response criteria, the more difficult it becomes to differentiate treatments.

My comments in *LTBR* (M. Terman, 1991) were based on a discussion at the Toronto meeting invited by the investigators, and I hope that the manufacturer of the visor will appreciate my constructive intent. The crux of the issue is whether differential response is obtained under experimental and control procedures (e.g., bright vs. dim visor light). Especially when this is not so, use of strict remission criteria is a *sine qua non*: we want to know the probability of full clinical response, not partial improvement only.

*Michael Terman, Ph.D. New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032. Tel 212-960-5712; fax 212-960-2584.*

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## *JOURNAL ARTICLE REVIEW*

## THE TIMING OF ANTIDEPRESSANT TREATMENT

*Review of **Double-blind study of the chronopharmacotherapy of depression** by H. Nagayama, K. Nagano, A. Ikezaki and T.Tashiro (1991) Chronobiology International 8: 203-209.*

A major clinical concern of chronopharmacology is the appropriate timing for medication. Although time schedules for the application of a number of drugs (antihypertensives and antiarrhythmic agents, bronchodilators and cortisol) are already established, recommendations for the timing of pharmacological treatment in psychiatry are rare. This is surprising, since chronobiological models of affective disorders are the center of much discussion.

For this reason, I would like to summarize the first — as far as I am aware — double blind study of the timing of antidepressant treatment in depression. Three groups of 10 patients were treated for four weeks with clomipramine, a

widely used and well investigated serotonin reuptake inhibitor, given at 8:20h, 12:20h and 20:30h. The group receiving clomipramine at noon improved significantly more than the groups treated in the morning or evening (according to the Hamilton Depression Rating scale). Side effects, which often cause compliance problems during the pharmacotherapy of depression, also differed according to time of administration. These results can be considered within the context of animal studies showing clear circadian rhythms in CNS neurotransmitter function, as well as the phase-advance hypothesis of depression. It is important for *LTBR* readers to be aware of this pioneer study and to encourage psychiatrists to replicate these findings.

*Wilfried Koehler, M.D., Dr. phil. nat., Zentrum der Psychiatrie, Heinrich-Hoffmann-Str. 10, D-6000 Frankfurt am Main 71. Tel (49)-69-6301-5419; fax (49)-69-6301-5290.*

# BULLETIN BOARD

## WELCOME TO NEW MEMBERS

The Board of Directors welcomes the following new members who have joined SLTBR since publication of the last issue of *LTBR*.

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## MEMBERSHIP RENEWAL INFORMATION

This issue of *LTBR* includes an invitation to renew your SLTBR membership together with a renewal form which provides space for you to correct address, communication and practice interests data currently on file in our Executive Office. Please note the renewal deadline of 20 January 1992. Renewals received after 1 February 1992 will be assessed a $10.00 late penalty. Following this renewal period, clinical referral information and corporate membership listings will be revised to reflect current members. Please note that SLTBR does not endorse either clinical services or products provided or manufactured by its members.

## 1992 ANNUAL MEETING INFORMATION

Complete registration and abstract submission information for SLTBR's 1992 annual meeting will be mailed to members in December 1991. The meeting, scheduled for 30 April - 1 May 1992 on the National Institutes of Health campus in Bethesda, Maryland, will feature abstract presentations and the opportunity to meet with colleagues in the field. **Please watch for this meeting information and be prepared to submit abstract proposals prior to the 6 March 1992 deadline.**

## JOURNAL OF SLEEP RESEARCH

The editor of the *Journal of Sleep Research*, a new international journal sponsored by the European Sleep Research Society, has issued a call for papers. The quarterly's first issue will be published in March 1992. Submission information and style sheet may be obtained from the Editor, Professor James Horne, at the Department of Human Sciences, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK. Tel 44-509-223004; fax 44-509-610724.

Delegates registering for the 11th European Sleep Research Congress, 5-10 July 1992, Helsinki, will automatically

receive a subscription to the Journal as part of their registration fee. Subscription prices for Volume One are £45.00 for members of all National Sleep Research Societies (£25.00 for members of the European Sleep Research Society not attending the 1992 European Sleep Research Congress) and for others as follows: £75.00 (Europe), £80.00 (overseas) and US$140.00 (USA & Canada — Canadians add US$9.80 to cover GST). Subscription orders should be sent to Anna Rivers at Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL, UK (fax (44)-865-721205).

## REPORT EXAMINES SHIFT WORK

The Office of Technology Assessment (OTA), an analytical arm of the US Congress, has published a report, *Biological Rhythms: Implications for the Worker* (September 1991). This publication recognizes the disruption of circadian rhythms engendered by shift work, provides a critical review of the Federal Government's research activities in the area and suggests options for possible congressional action related to biological rhythms and shift work. Torbjörn Åkerstedt (Stockholm) will review this publication for the February issue of *LTBR*. In the meantime, copies of the report can be ordered at a cost of $11.00 from the U.S. Government Printing Office, Washington, DC 20402-9325 (tel 202-783-3238). Reference GPO stock number 052-003-01254-5.

## SPAQ MODIFIED

The *Seasonal Pattern Assessment Questionnaire* of Rosenthal has been modified with additional seasonal questions on light conditions indoors, time spent outdoors, sleep timing and naps, morning-evening type, and food choice. The *"SPAQ+ "* is available in German and English (translation: Stuart Armstrong, La Trobe University, Australia); a coded telephone questionnaire version exists in German, French and Italian. The *SPAQ+* is freely available for use (and improvement!) by interested researchers: Chronobiology Laboratory, Psychiatric University Clinic, Wilhelm-Klein Strasse 27, CH-4025 Basel, Switzerland.

## SIGH-SAD NOTES

Patients have noted a syntactical error in the phrasing of alternatives in the self-rating version of the SIGH-SAD (Williams et al., 1991), which has prompted an editorial revision of the last item (keypunch column 61):

0 - I have not been bothered by thoughts that run over and over in my mind but don't make any sense to me.
1 - I have been a little bothered by thoughts that keep running through my mind but don't make any sense to me.
2 - I have been very bothered by thoughts that keep running through my mind but don't make any sense to me.

Users of the SIGH-SAD-SR who have previously ordered copies from SLTBR (*SAD Assessment Tools Packet* and *Complete Works*) may write the Executive Office for a copy of the revised version (dated October 1991) at no charge.

REFERENCE

Williams, J.B.W., M.J. Link, and M. Terman (1991) Structured Interview Guide for the Hamilton Depression Rating Scale — Seasonal Affective Disorder Version (Self-Rating Version) (SIGH-SAD-SR). New York, New York State Psychiatric Institute.

## ENDNOTE: AMA on SAD

"SADS — Seasonal Affective Disorder Syndrome. SADS is an incompletely studied and proved phenomenon in which mood changes are alleged to occur with the seasons."

Clayman, C.B., Ed. (1989) *American Medical Association Encyclopedia of Medicine*, New York, Random House, P. 879.