

Light Treatment and Biological Rhythms

Bulletin of the Society for Light Treatment and Biological Rhythms



Volume 2, Number 5

August 1990

SLTBR ORGANIZATIONAL CHANGES

In mid June, the Executive Office moved from New York to Oregon (P.O. Box 478, Wilsonville, OR, 97070. Tel/fax 503-694-2404), under the stewardship of our newly-appointed Executive Secretary, Ms. Marty McCullough, who now also serves as Managing Editor of *LTBR*. McCullough has extensive experience in the coordination of professional organizations, including their membership, publication and public liaison activities. We give her our warmest welcome.

Concurrently, Michael Terman, Ph.D., has resigned as Secretary of SLTBR, but continues as Editor of *LTBR* and member of the Board of Directors. The newly combined post of Secretary-Treasurer has been accepted by Robert L. Sack, M.D. (Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97207. Tel 503-494-8430; fax 503-494-5738).

We wish to offer thanks and appreciation to the part-time administrative staff members who helped to manage SLTBR through its formative years: In New York, Ms. Martha Link, who is starting medical school at SUNY-Downstate, and Ms. Deborah Guest, who continues on the research staff at New York State Psychiatric Institute; and in Oregon, Ms. Carol Simonton, who ably coordinated the membership rolls and the books, far beyond the call of duty.

ANNUAL MEETING 1990: REPRISE

The meeting at Columbia's Health Sciences campus drew more than 150 attendees. The breakdown is of great interest in that it reflects SLTBR's continuing dynamic growth: the ratio of presenting to non-presenting members to non-members (who automatically received membership with meeting

registration) was 1:1:2. Six commercial firms helped to sponsor the meetings and presented exhibits of their latest lighting and light-monitoring apparatus.

A tutorial symposium, offering continuing education credit to psychologists and psychiatrists, introduced new members to basic concepts and clinical techniques. Sixteen research papers were presented orally and 24 were given as posters (*abstracts are reprinted in the Complete Works; see publications order form, attached*). A consensus-building symposium focused on the controversial issues of Experimental Design and Placebos, and Efficacy and

In This Issue

<i>James Gaddy</i> on non-SAD applications of light therapy . . .	2
<i>Michael Young</i> on the recent NIMH light visor study	3
<i>Norman Rosenthal, Douglas Moul</i> Response to Young	3
<i>Mark Bauer</i> on <i>The Infinite Voyage</i>	4
Light therapy and ocular health	6
<i>Scott Campbell et al.</i> on Czeisler et al.'s recent shift work study . . .	9
<i>Charles Czeisler et al.</i> Response to Campbell et al.	10
Bulletin Board	13

also enclosed:

public information brochure
membership application
publications list/order form

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

**Editor**

Michael Terman, Ph.D.

Managing Editor

Marty McCullough

Editorial Board

Charmane I. Eastman, Ph.D.

Alfred J. Lewy, M.D., Ph.D.

Norman E. Rosenthal, M.D.

Anna Wirz-Justice, Ph.D.

Unsolicited manuscripts, letters to the editor, and Bulletin Board announcements should be submitted to Dr. Michael Terman, Editor, 722 West 168th Street, Box 50, New York NY 10032. Please submit one double-spaced hard copy and a diskette file (DOS: text or WordPerfect; Macintosh: text, Word, MacWrite or WordPerfect; MCI Mail: 308-7099; BITNET: MTERMAN AT MCIMAIL.COM). Manuscripts and diskettes will not be returned. We reserve the right to edit and condense letters to the editor.

This publication is provided to SLTBR members as an entitlement for part of their dues. Annual subscription rate for non-members is \$15.00. Single copies are available at \$2.50 for members; \$3.50 for non-members.

Copyright © 1990, Society for Light Treatment and Biological Rhythms, Inc., P.O. Box 478, Wilsonville, OR 97070. All rights reserved.

Treatment Time of Day, the proceedings of which are in press in *Psychopharmacology Bulletin*.

Three work groups debated issues of Efficacy of Light Therapy for SAD and S-SAD, Efficacy of Light Therapy for Non-SAD Conditions (including PMS, jet lag, shift work, sleep phase disorders and non-seasonal depression), and Safety of Light Therapy Devices. Those debates continue, with the goal of generating consensus statements that will serve as a basis for formulating SLTBR's official positions vis-à-vis clinical recommendations and standards and external regulatory agencies. The Work Group reports will be published in *LTBR*, with opportunity for non-attendees to offer input before the SLTBR policy statement is formalized.

ANNUAL MEETING REVIEW

Scientific and Clinical Advisory Work Group on Efficacy of Light Therapy for Non-SAD Conditions

This panel — which met in New York on 14 May 1990 (Daniel F. Kripke, Chair) — was asked to

consider the efficacy of light therapy for several non-seasonal conditions that have been the focus of recent research: (a) major depression, (b) late-luteal phase disorder (PMS), and (c) circadian rhythm disorders. Deliberations were to consider parameters of effective treatment, contraindications to light treatment, and known side-effects. The final committee report, still in preparation, will be submitted to the Board of Directors for integration into an official SLTBR position statement on these and related issues [*Ed's note: upcoming issues of LTBR will summarize work group deliberations on light therapy for SAD and its subsyndromal variant, and safety factors involved in use of light treatment.*]

Depressive Disorder. There is evidence that light therapy may be effective either by itself or as an adjuvant to pharmacotherapies. The data are thus far insufficient to make recommendations for general practice or to describe side effects. Light treatment may be contraindicated for Bipolar I patients who are not adequately maintained on lithium.

Premenstrual Syndrome. Light therapy appears to be effective against late-luteal phase dysphoria. Evening light exposure seems to be preferred, but there are insufficient data to make recommendations for general practice or to specify side effects or contraindications.

Circadian Disorders. There is ample evidence that light can advance, delay, and entrain human circadian rhythms. There is evidence, primarily from uncontrolled studies, that light can be used to synchronize or phase-shift circadian rhythms that have become in some way disordered. Currently, delayed sleep phase syndrome is being treated by 30 to 120 minutes exposure to 2500 lux light beginning when the patient spontaneously awakens. Advanced sleep phase syndrome is treated with 30 to 120 minutes of 2500 lux light in the evening with the session timed to finish at least one hour before bedtime. Although irritability or difficulty initiating sleep — given evening light exposure — have been described as side effects, there are insufficient data to specify contraindications. Methods of treatment of other circadian disorders, such as those arising from shift work or rapid time-zone change, have yet to be delineated.

James R. Gaddy, Ph.D., Recorder. Dept. of Psychiatry, Jefferson Medical College, 1015 Walnut Street, Philadelphia, PA 19107. Tel (215) 955-5045; fax (215) 955-5515.

TO THE EDITOR

Light Visor as Treatment for SAD

The report by Moul et al. [(1990) *Soc. Light Treatment Biol. Rhythms Abst.* 2:15] on the effectiveness of the light visor raises several questions regarding the interpretation of surprising results and to how they are applied. The study was designed to test the effectiveness of a bright light visor (7000 lux) compared to the placebo-control condition of a dim light visor (400 lux). When pooled over 26 patients who received 30 min. of morning light and 20 who received 60 min., the *dim light* yielded a significantly greater percentage of responders.

What can be concluded from this trial? Some possibilities: (1) The bright light visor is worse than placebo. This is not usually considered but is possible (i.e., the cure is worse than the disease). This would mean that good responses were due to placebo effects only. (2) The bright light visor is equal to the placebo control but due to the chance of type 1 error, or some unknown problem in the study, it came out worse. This is always possible in any research. Is it the case here? (3) The dim light "control" really is better than the bright light visor and is an active treatment itself. The authors prefer the latter interpretation.

Following their hypothesis, the dim light condition is redefined as the treatment being tested. This is acceptable, because we are free to test anything as a potential treatment. However, there is no basis for defining the bright light condition as only a placebo and thus an appropriate control condition against which a proposed treatment can be compared. The original design compared the effect of "placebo + dim" to that of "placebo + bright". By assuming "dim" = 0, the effect of "bright" could be estimated. The redefined design makes the same comparison. But having no way of specifying the magnitude or direction of "bright", the separate effect of "dim" cannot be estimated [Young, MA and Fogg, LF. (1990) *Statistics in Medicine* 9:253-261]. The argument that the response rate to "placebo = dim" is similar to that of active treatments in other studies is not a strong one, because the rate of placebo response is quite variable and very context-dependent [as noted by Charmane Eastman in her SLTBR presentation on placebo response (*Psychopharm. Bull.*, in press)].

Therefore, the appropriate conclusion is that the dim light visor appeared to be an effective treatment in an *uncontrolled* trial. A controlled study of the dim light visor has yet to be done. The latter will require a suitable placebo-control condition, defined a priori. Until then, claims should be appropriately cautious concerning clinical application of the light visor.

Michael A. Young, Ph.D., Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612. Tel 312-942-4585.

Response from the Investigators

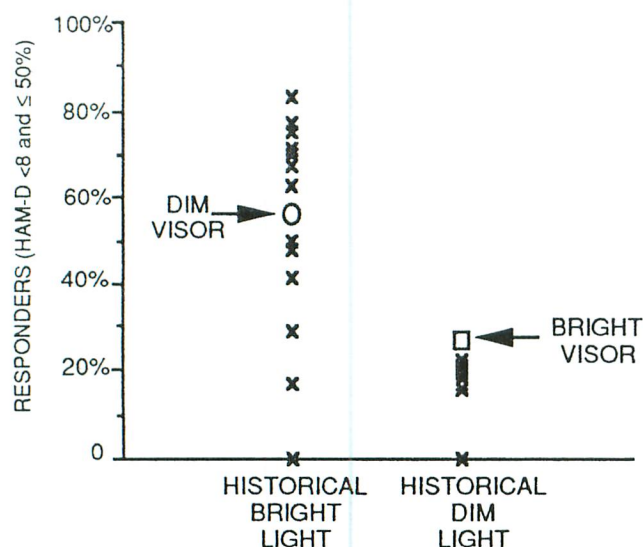
Dr. Young raises several interesting points about our light visor study. To start with areas of agreement, we do feel that claims based on the unexpected findings should be cautiously worded and that further studies are clearly warranted. However, we disagree with his statements that the study was in fact uncontrolled and that historical controls are of little value.

True, we were wrong in our prediction that the bright light visor would be superior to the dim. However, the whole point of using two-tailed statistics, even when one does have a prediction, is to take into account the possibility that one's findings may differ statistically in either of two directions. Thus, simply because the control differed from the active treatment in the direction opposite to that predicted does not invalidate the finding nor does it render the study uncontrolled. Interestingly, when the difference is found in the predicted direction, the researchers are then open to being criticized for inadvertently conveying their expectations to the subjects, as Charmane Eastman noted at the recent consensus-building forum at SLTBR's annual meeting [*Psychopharm. Bull.*, in press].

As to historical controls, we believe that we are on stronger ground in using the findings of previous phototherapy studies than investigators in other areas. Reasons for this include the clinical similarity of the populations studied, of the treatment modality — namely, light therapy — of the duration and season of treatment, and of the dependent measures used. For these reasons, perhaps, there is reasonable good consistency in response rates across studies of light therapy in SAD performed across different centers (see figure). The findings of the 400 lux light visor

are similar to those of previous bright light box treatments, whereas those of the 5000 lux visor are more comparable — though somewhat superior to — those of dim light box treatments.

Light Therapy Response* in SAD Studies
using Light Box and Light Visor



*Results of light box data adapted from cross-center analysis by Terman M et al. (1989) *Neuropsychopharm.* 2:1-22.

There are many possible reasons why these paradoxical findings occurred, a full explication of which falls beyond the scope of this reply. Clearly, one possible reason is that there was some flaw in the study design, though we should point out that (a) the sample size was large in relation to those of previous light treatment studies, (b) there was good agreement between results in the two larger centers, Seattle and Bethesda considered separately, and (c) there was consistency in the results between the one-hour and 30-minute treatment arms of the study.

Nonetheless, we certainly agree that no one study is definitive, especially when the findings are unexpected. We await the results of further studies with eager anticipation.

Norman E. Rosenthal, M.D., and Douglas E. Moul, M.D. National Institute of Mental Health, Bldg. 10/4S-239, 9000 Rockville Pike, Bethesda, MD 20892. Tel 301-496-2141; fax 301-496-5439.

MEDIA REVIEW

The Living Clock

The Living Clock was aired nationwide on Public Broadcasting System television stations on April 11, and subsequently on several commercial stations. This layperson's introduction to biological rhythms and their applications was an episode in the WQED/National Academy of Sciences-produced series, *The Infinite Voyage*.

The content of a documentary may be judged on two major criteria. First, were the facts presented accurate? Second, and perhaps more important (since no one outside the field will remember specific facts, anyway) was the context in which the facts were imbedded misleading by emphasis or implication?

The program's major points were made accurately and well, and were presented in an easily understood manner. Viewers were informed that biological rhythms are endogenously generated by a neural substrate under genetic control, that they are synchronized to the environment by light; and that the quality of life for clinically ill, and perhaps normal, persons can be improved by attention to chronobiologic principles.

Three non-chronobiologic issues of great scientific and social significance were also raised implicitly during the program. First, the producers are to be commended for their inclusion of animal research and noting the critical role it has played in furthering our understanding of scientific principles that have already eased suffering for many. Second, the inclusion of several "real-world" patients and subjects underscored the collaborative effort between patient and clinical researcher that is necessary to advance biomedical research and its applications. Third, the choice of a young, strapping, Corvette-driving male as the SAD patient subtly delivered the message that major depressive disorder can happen to anyone. Yes, even cowboys get the blues.

However, there were several nagging factual inaccuracies and inconsistencies, probably not recognizable to the layperson, but irritating to those in the field. In the Moore-Ede segment, we are told that "brain activity slows down at night." Rather, brain electrical activity becomes more synchronized during

certain sleep phases, while in others it is indistinguishable from waking. To imply a torpor-like character to sleep perpetuates its misunderstanding in the lay mind. Also in this segment, it was odd to include a shift-work consultation in which the chronobiologic recommendations were rejected by the workers, followed by their singing the praises of a routine that was not optimal from a chronobiologic perspective. Further confusion came from alluding to the 12-hour shifts chosen as harmful "... because man was not made to work around the clock." Twelve hours does not a rotating shift — or sleep deprivation — make.

In the Czeisler segment, dawn light intensity is inaccurately noted as 5,000 to 10,000 lux, rather than about 1,000 lux. It also was unclear how five hours of light exposure at 0500 hrs — the putative phase-advance portion of the phase-response curve — would phase-delay an abnormally advanced sleep-wake rhythm and thereby relieve the patient's symptoms.

Finally, Hrushesky describes the prototypical hospital physician prescribing medications in these terms: "... he writes a dose, he doesn't write a time, and he walks away. Time is left to chance." This overstatement obscures a more important point that health care institutions — and the industrial and pharmaceutical bases that support them — are not oriented towards elucidating and implementing chronobiologic principles in drug delivery. If they were, we would see many more ultra-short-acting drugs targeted to specific phases of the diurnal cycle, and more outpatient facilities, treating cancer and other illnesses, open evenings and nights.

There is a temptation for the reviewer to make comparisons to a model program he or she would have designed, "if only they had asked me." While more or less successfully resisting this temptation, I do feel bound to point out two exclusions among the featured researchers. First, it is hard to discuss mammalian — and particularly human — circadian rhythms, or to summarize the history of chronobiology, without mentioning Jürgen Aschoff. Somehow the writers managed this feat. Second, I was surprised that Martin Ralph was not mentioned in connection with the mutant hamster work. Though initially a graduate student in Menaker's laboratory when the tau mutant was found, Ralph has had a major hand in developing this line of investigation,

and has been first author on the most notable publications on the topic.

Balancing these deficiencies are several particularly nice presentations that could easily have gone awry. The gentle introduction to actograms in the Young segment, elaborated in the Menaker segment, was quite effective. To see the actograms unfold across a computer screen greatly aided comprehension. Moore-Ede's even-handed view of the chronobiologic contribution to the terrible industrial accidents of this age (Three Mile Island, Bhopal, Chernobyl, and the Exxon Valdez) appropriately raised the issue without proselytizing. Finally, although ambivalent about the almighty "sound bite" — abhorring its frequent misuse but, admiring its power — I compliment the writers on their encapsulation, within a single phrase in the Menaker segment, of the issue on which so many of us have focused our careers: "how living things translate light into time."

As for contextual accuracy, what message did *The Living Clock* leave with the lay public? This issue is of particular importance, given the broad scope of content — e.g., circadian technology, light therapy for mood and sleep disorders, and timed infusion schedules for medications. At several points in the program, unfortunately, the context overwhelmed the facts. The viewers are repeatedly reminded that light runs their lives. Though this general point deserves emphasis, the program neglected to mention social cues, which may also be very important. The pioneering work of Aschoff and Wever in this regard — although it focused the field away from light effects on human circadian rhythms until Lewy demonstrated light-induced suppression of melatonin in humans — still stands as an important contribution. The recent Kupfer-Ehlers-Monk elaboration of this model under the rubric of "social zeitgeber theory" may leave us with a more complex, but also more accurate, picture of why we do what we do when we do it.

The Czeisler segment concluded by stating that the clock "speeds up" as one ages, which is controversial, implying that many normal elderly people may be helped by light treatment. Supporting data are sparse, even in dramatically light-deficient environments such as nursing homes.

After a nice description of the phenomenology of SAD by Rosenthal, the program stated that seasonal

changes in behavior are a "problem for about one in four or one in five," and subsequently that "... the one in four or one in five who do say that winter changes are a problem will actually benefit [from light treatment] and they do not have to be suffering from the fully fledged SAD." The published data in support of this statement come from prevalence figures gleaned primarily from retrospective questionnaire studies in two eastern metropolitan areas, coupled with treatment data from a single sub-syndromal SAD study by the NIMH group. The contextual implication here is that 20 to 25% of Americans would benefit from light therapy. Although some may disagree, I do not consider such recommendations ready for prime time.

Similarly, the Hrushesky segment implied that chronopharmacologic principles have extended the life of a woman with metastatic kidney cancer by two years, and that scheduling mastectomy for a particular time in the menstrual cycle may increase "four- to five-fold your chance of dying." We are first told that "the findings are preliminary," but then that such research "heralds a new chapter in medicine."

Are we really ready to congratulate ourselves on writing a new chapter in the history of medicine? Or should we humbly turn off our TV sets and put our noses back to the grindstone? Probably a bit of each is in order. Aside from the collective gratification of having a prime-time documentary on subjects and colleagues close to our hearts, *The Living Clock* does our field a substantial service by increasing public awareness of research progress and promising new applications. Indirectly, this should help to motivate increased research funding, the interest of new investigators and research-subject recruitment.

[Transcripts of "The Living Clock" can be obtained for \$4.00 from: *The Infinite Voyage* #12, P.O. Box 701, Kent, OH 44240. For additional information, contact Ms. Kelley Murray, *The Infinite Voyage*, WQED, 4802 Fifth Avenue, Pittsburgh, PA 15213.]

Mark S. Bauer, M.D., Affective Disorders Program, University of Pennsylvania, 133 South 36th Street, 5th floor, Philadelphia, PA 19104. Tel 215-662-2803; fax 215-662-6911.

LIGHT THERAPY AND OCULAR HEALTH

The June issue of *Photochemistry and Photobiology* includes the first extensive review of ocular factors that may interact with bright-light treatment [Terman, M. et al. (1990) 51:781-792]. The authors conclude that standard light therapy regimens, providing 2500 or 10,000 lux from a diffuse light screen, are unlikely to cause problems in healthy eyes. Certain classes of pre-existing ocular pathology, however, would mandate periodic ophthalmological evaluations or would contraindicate light therapy. A complicating factor is the use of medications (including tricyclic antidepressants and lithium) that may photosensitize the retina.

An ad hoc committee of ophthalmologists — including SLTBR members Charlotte E. Remé, M.D. (University of Zürich), Pamela F. Gallin, M.D. (Columbia-Presbyterian Medical Center), and Ronald M. Burde, M.D. (Albert Einstein College of Medicine) — forged the outline of a minimal "core battery" of readily-available eye tests, which they recommend prospective light therapy patients receive in order to define any potential problems at the outset.

A derived structured eye-examination chart, which might be provided the optometrist or ophthalmologist, is presented on the following pages and may be photocopied for use in the field. Use of indirect ophthalmoscopy with mydriasis is left to the examiner's discretion; ordinarily direct examination of central retina will suffice.

At SLTBR's recent annual meeting, these and related issues were discussed by the Work Group on Safety of Light Therapy Devices. The next issue of *LTBR* will include a summary of their debate and any consensus reached. At present, SLTBR has not yet developed an official position on the advisability or necessity of ocular screening and follow-up of light-treated patients.

EYE CHECK-UP FOR USERS OF LIGHT TREATMENT

PATIENT	_____	EXAMINED BY	_____
ADDRESS	_____	ADDRESS	_____
	_____		_____
	_____		_____
PHONE	_____	PHONE	_____
REFERRED BY	_____	DATE OF EXAM	_____

CHECKLIST

RETINA			OTHER		
Detachment	+	-	Inflammatory diseases of anterior		
Diabetic retinopathy	+	-	segment/uveal tract	+	-
Retinal vasculitis/			Glaucoma	+	-
Chorioretinal inflammation	+	-	Cataracts	+	-
Vascular retinopathies	+	-	Optic nerve affections	+	-
Central serous retinopathy	+	-	Keratoconjunctivitis sicca	+	-
Degenerative disease of the macula	+	-	Hypothyroidism	+	-
Tapeto-retinal degenerations	+	-	hormone supplement	+	-
Solar/radiation retinopathy	+	-	stable	+	-
Drug-induced retinopathy	+	-			
Post-traumatic retinopathy	+	-	CURRENT MEDICATIONS		
			Antidepressants (tricyclic)	+	-
EYE COMPLAINTS			Neuroleptics (phenothiazine)	+	-
Photophobia	+	-	Lithium	+	-
Glare	+	-	Tryptophan	+	-
Dry eyes	+	-	Psoralens	+	-
Blurred vision	+	-	Antimalarial/antirheumatics	+	-
Metamorphopsia	+	-	Diuretics (hydrochlorothiazide)	+	-
Color vision	good	poor	Porphyria	+	-
Night vision	good	poor	Tetracycline	+	-
Other complaints:			Sulfonamides	+	-
			Other photosensitizers:		

EXAMINATION

Best corrected visual acuity

	R	L	
V _{SC}	_____	_____	
V _{CC}	_____	_____	W _____

Ocular motility (9 cardinal directions of gaze)

R		L
---	--	---

Stereopsis (Titmus, circle no.)

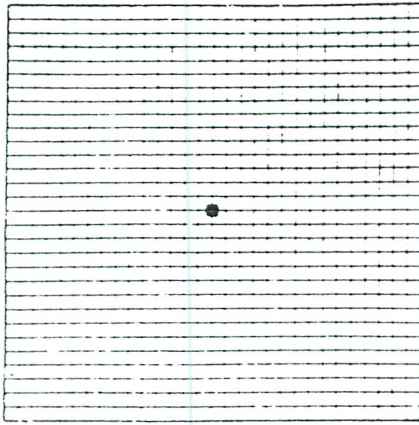
1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

Intraocular pressure (applanation), noting time of day: _____

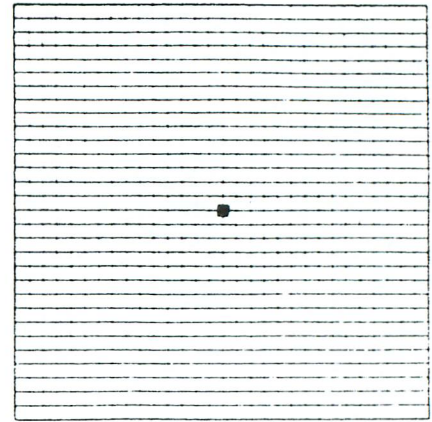
R _____	L _____
---------	---------

Note: Examining doctor should include a summary note indicating any problematic ocular conditions.

Reference: Terman, M., C.E. Remé, B. Rafferty, P.F. Gallin, & J.S. Terman (1990) In: Photochemistry and Photobiology 51: 781-791.

Amsler grid

R nl, abnl (specify)



L nl, abnl (specify)

Pupillary reactions

R

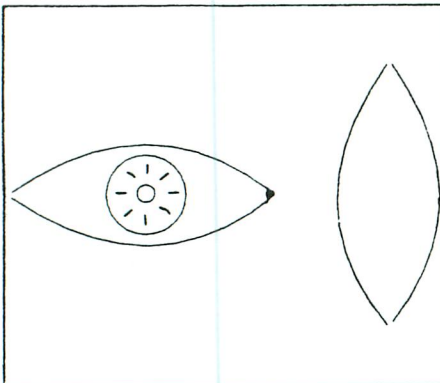
direct + -

indirect + -

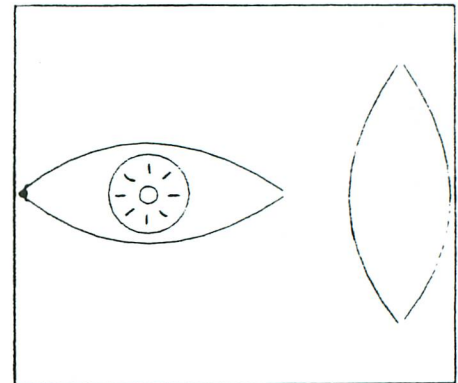
L

direct + -

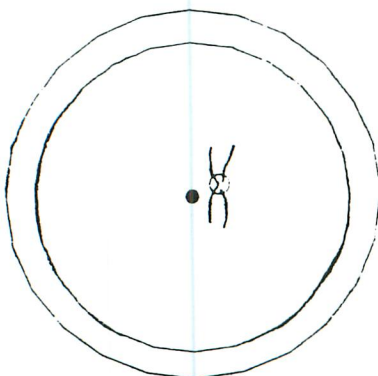
indirect + -

Slit lamp examination

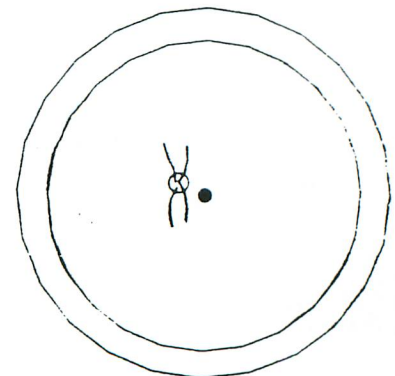
R



L

Ocular fundus (check which: direct / indirect / mydriasis)

R c/d = _____



L c/d = _____

TO THE EDITOR

Light Treatment for Shift Work

The article by Czeisler et al. [(1990) *New Eng. J. Med.* **322**: 1253-1259], addressing the effects of bright light exposure to treat maladaptation to night work, received considerable attention in the media and within the scientific community. Although the results of the study suggest that the phase resetting effects of bright light and darkness are beneficial in the shift work domain, we believe that the authors' conclusions are compromised by significant flaws in design, as well as the analysis and interpretation of their data.

The first critical issue concerns protocol differences between the treatment and control groups that confound the stated experimental manipulation. In addition to bright light exposure during the simulated work shift, the treatment condition included a fixed sleep-wake schedule in which subjects were instructed to remain in completely darkened rooms between 0900 and 1700 hrs. As such, they had no behavioral option other than to sleep. In contrast, the bedrooms of the control group were not intentionally darkened and subjects were permitted to sleep (or not) at "times of their own choosing". It is possible then, that the differences in the circadian phase, sleep duration, alertness and performance, which the authors attribute solely to differences in the light-dark schedule, were due, instead, to differences in the sleep-wake schedules, instructional sets and behavioral options between the groups. In this regard, it is important to note that the authors did not observe any physiologic adaptation to night shift in the control group. This is in contrast to other home sleep and continuous bedrest studies [Moog R. (1987) *Ergonomics* **30**:1249-1259; Moog R, Hildebrand G. (1989) *Chronobiol. Int.* **6**:65-75] that report some adaptation within 6 days of transition to night shift. Thus, the authors understate the degree of adaptation that can occur in untreated workers.

A second issue also involves the experimental design. Performance and alertness measures were reported for nights 1 and 6 during the "constant routine" procedures, rather than during the actual simulated work shifts. This raises two concerns. First, the literature indicates that the first and second shifts of night work produce maximum performance decrements [Åkerstedt T. (1988) *Sleep* **11**:17-34]. Thus performance measures for the intervening period,

while subjects were working, would have more relevance for deciding whether the treatment provides any "real" benefit or not. Second, in contrast to the authors' conclusions, there is no evidence presented to indicate that performance or alertness improved *on the night shift*. Rather, the authors simply show that bright light enhances adaptation to the "constant routine".

A third critical issue concerns the authors' failure to state unequivocally in the text the actual number of subjects studied. This obscures the tentative nature of the data. Although the authors suggest (*cf.* Figure 2) that 10 subjects were studied, closer inspection reveals that only eight data sets were employed in the statistical analysis ["in the case of two men (one control and one treatment subject) whose behavior during the study did not conform to the protocol, the results were excluded before the outcome of their experimental trials was determined" (Czeisler et al. *op.cit.* p. 1254)]. Moreover, the first two subjects studied were used in both the control and the treatment conditions. Thus, only 6 *individuals* were actually studied. In their discussion, the authors acknowledge the inappropriateness of including the same subjects in both treatment and control groups. The authors maintain that the results remain statistically significant when some of the offending data are removed. However, description of this post-hoc analysis is absent. Moreover, the validity of any parametric statistical test for independent groups (*t*-test) or non-parametric test for matched pairs (Wilcoxon) based on three subjects in each group must be questioned.

In conclusion, the trends identified in this study are consistent with previous results. Indeed, phase-shifting properties of appropriately timed exposure to bright light are well-established [Honma K et al. (1987) *Experientia* **43**:1205-1207; Lewy AJ et al. (1987) *Science* **235**:352-354; Czeisler CA et al. (1989) *Science* **244**:1328-1333]. There is also growing evidence that bright light treatment is effective in managing maladaptation to shift work [Eastman CI. (1990) *Perspectives in Biology and Medicine* (in press); Campbell SS, Dawson D. (1990) *Physiol. Behav.* **48**:25-29]. However, in our opinion, it is important to stress the degree to which the authors have drawn premature conclusions that may be misleading and are clearly not warranted on the basis of the evidence provided. Decisions regarding treatments for shift work maladaptation should be

made on the basis of studies that employ appropriate experimental designs and suitable cell sizes. The temptation to publicize a new treatment should not override the requirements of scientific validity.

Scott Campbell, Ph.D. and Drew Dawson, B.A., Institute for Circadian Physiology, 617 Beacon St., Boston MA 02115-3203. Tel 617-247-4900; fax 617-247-9047.

Charmane I. Eastman, Ph.D., Rush-Presbyterian-St. Lukes Medical Center, Chicago, IL.

Alfred J. Lewy, M.D., Ph.D., Oregon Health Sciences University, Portland, OR.

Response from the Investigators

We reject the assertion of Campbell et al. that we failed to state unequivocally the number of men who participated in our study [Czeisler CA et al. (1990) *New Eng. J. Med.* 322:1253-1259]. We did so on at least two occasions. Our methods section begins: "Ten two-week studies were carried out in eight healthy men . . ." The abstract states: "We assessed the functioning of the circadian pacemaker in five control and five treatment studies in order to assess the extent of adaptation in eight normal young men to a week of night work." Our description of the Overall Study Design begins: "Five control and five treatment studies were performed . . ." We can understand that our statement that two additional subjects did not complete the study successfully may have been initially misconstrued by the authors of the letter to mean that only six subjects were studied. However, one of us (C.A.C.) has explained the basis for this misunderstanding both publicly to Martin Moore-Ede, M.D., Ph.D., Director of the Institute for Circadian Physiology, at the June 1990 meeting of the Association of Professional Sleep Societies and, on another occasion, privately to Campbell after he had initially submitted the above letter to the *New England Journal of Medicine (NEJM)* and prior to his subsequent submission of it to *LTBR*.

Furthermore, we never indicated that studying a subject in both the control and treatment conditions would be inappropriate. In fact, it was our initial intention to study all subjects under both conditions separated by several weeks of reentrainment to a day-work schedule in order to reduce the effect of inter-subject variability, but this proved to be impractically long for most potential subjects. We find our use of

subjects in both the control and treatment condition to be no less appropriate than that of Lewy et al. in their seminal report that exposure to bright light suppressed melatonin secretion, based on a study of six subjects first studied in a control condition (nocturnal awakening in 10 - 20 lux of light) and then in a treatment condition (nocturnal awakening in 2500 lux of light), with two of the subjects also studied at an intermediate light intensity [Lewy AJ et al. (1980) *Science* 210:1267-1269].

Our clarification that 10 studies (five control and five treatment) were successfully completed in eight subjects (*after* accounting for the two drop-outs) renders moot the next two objections raised by the authors: the appropriateness of our cell size and the validity of our statistical analysis. Given the inter-individual variability in estimates of endogenous circadian phase from core temperature series, sample size calculations reveal that we had a 95% chance of detecting an average phase difference as small as 3 hours in the outcome of the control and treatment studies with cell sizes of five. Indeed, the average phase difference of 9.6 hours which we observed was three times as large as that which we had the power to detect. In fact, *NEJM's* statistical reviewer complimented the thoroughness of our statistical analysis.

Regarding the experimental protocol, the authors of the letter misapprehend the intentions of our experiment. The purpose of our study was not to determine whether light exposure could reset the circadian pacemaker independent of the timing of sleep. We have tested that question in laboratory studies under conditions of strictly controlled exposure to light, darkness and sleep, and have already reported the results [Czeisler CA et al. (1986) *Science* 233:667-671; Czeisler CA et al. (1989) *Science* 244:1328-1333]. The present study was instead designed to answer two questions: (a) To what extent does the circadian pacemaker adjust to a week of night work as it is currently practiced, with subjects living at home and commuting daily to and from work while exposed to outdoor light? and (b) Can physiologic adaptation to night work as it is currently practiced be improved by controlling subjects' exposure to light during their week of night work? Neither of these questions could have been answered if both groups were instructed to remain in the dark from 0900 to 1700 hrs each day, since both groups would then have received at least partial treatment.

Such a protocol would not have revealed the extent to which subjects adapt to a typical summertime week of night work as it is now practiced. Nor would the questions have been answered if we had only exposed subjects in the treatment studies to bright light during nighttime work and not controlled their exposure to outdoor light during the daytime, a common flaw in light therapy trials which has been criticized in the past by Lewy et al. [(1987) *Science* 235:352-354.]

We recognize that our study design did not enable us to determine the relative importance of scheduled exposure to bright light at night vs. darkness during day sleep in the induction of the observed differences between the control and treatment studies. This is stated explicitly in the Discussion, where we cautioned: "Although this study is a step toward the development of a practical treatment for maladaptation to nighttime work, a number of important questions remain to be answered. They include the relative importance of exposure to bright light during nighttime work as compared with darkness during daytime sleep . . ." In addition, we attempted to prevent this type of misinterpretation by even the most casual reader by including both bright light and darkness in the title of the article and by stating twice in the abstract (and elsewhere) that the treatment included exposure to *both* bright light during night work and darkness during the day.

Furthermore, we acknowledge that our study design could not answer the secondary question — first raised by Van Cauter and Turek in a *NEJM* editorial that accompanied our publication [Van Cauter E, Turek FW. (1990) *New Eng. J. Med.* 322:1306-1308] — as to whether the light-dark schedule to which we exposed our subjects had a direct physiologic effect on the circadian pacemaker or an indirect effect on the pacemaker via a behavioral mechanism. Although we feel that the weight of currently available evidence indicates that the former mechanism is most probably the dominant one, neither would detract from our primary finding that maladaptation of the human circadian system to night work can be treated effectively by scheduled exposure to bright light at night and darkness during the day, a conclusion shared by the authors of that editorial.

The final protocol issue raised by Campbell et al. concerns our use of the constant routine procedure. As we stated in the text, constant routines were carried out concurrent with the first and sixth nights

of work. During the night shift hours, subjects on the constant routine were sitting up in bed in a semi-recumbent posture, rather than sitting at a desk as they had during nights 2 through 5. In addition, they ate small snacks every hour rather than having dinner and a snack during that time. Their activities and social contacts were otherwise the same. That is why we stated, when reporting the data, that there were significantly higher levels of alertness and performance observed during the *hours of the night shift* on the final constant routine of the treatment vs. the control studies. In addition to misstating our claim, the writers of the letter have failed to grasp the purpose of our constant routine evaluation, which was to determine the extent of adaptation of endogenous circadian rhythms of both physiologic and behavioral variables in the control vs. treatment studies to a week of night work. Failure to use a credible procedure for unmasking endogenous circadian rhythmicity renders the findings of a number of other field and laboratory studies — such as Eastman's claim to have reduced circadian temperature amplitude to zero based on ambulatory home monitoring of temperature data of a single subject [Eastman CI. (1990) *Perspectives in Biology and Medicine* (in press)] — as essentially uninterpretable from a circadian point of view. In contrast, our use of the constant routine procedure allowed us to establish an unambiguous difference between the control and treatment studies in the extent of their endogenous circadian adaptation to their night work schedule.

We find Campbell et al.'s next argument regarding the timing of our evaluations to be rather curious. In Campbell and Dawson's article in press, on the enhancement of nighttime alertness and performance with bright ambient light [Campbell SS, Dawson D. (1990) *Physiol. Behav.* (in press)], they performed their evaluations on the first and second nights of work, as they argue we should have. However, in their discussion they explicitly state: "It is unlikely that the enhanced alertness and performance observed in the bright light group was due to a phase delay in circadian rhythms, since the effect was observed *immediately*, i.e., on the night of bright light presentation. Any improvement associated with phase shifts would likely not be observed until subsequent nights." They thus appear to have understood at that time the reason why it was necessary for us to carry out our circadian phase evaluations after the fourth night of treatment rather than the first, since our purpose was to determine whether an adaptive phase

shift of the circadian system had occurred in either the control or treatment studies. Furthermore, we wanted to eliminate any influence of what Lewy has called the direct energizing effect of the light itself on our measures of alertness and performance, and we thus evaluated subjects in both the control and treatment studies under identical lighting conditions of ~150 lux.

Regarding our results, the writers of the Letter have asserted that we understate the degree of adaptation than can occur in untreated workers. As far as our data are concerned, we can only report what we actually observed on the sixth night of work, not what *can* occur. Perhaps the Letter writers are instead referring to our introduction, in which we cite a number of articles and state that "complete physiologic adaptation of endogenous circadian rhythms to such inversion of the daily routine does not occur even after years of permanent night work." The review of the same literature by Eastman which was cited in their Letter came to the same conclusions. She states: "The internal circadian rhythms [of workers] rarely shift completely to match the work and sleep schedule of the night shift . . . One reason for the incomplete adaptation of circadian rhythms is that the sleep-wake (SW) schedule is not consistently maintained at the new phase . . . Another reason is that many of the zeitgebers or time-cues, such as the natural light-dark (LD) cycle and social cues, maintain their original phase position and may oppose the shifting of circadian rhythms. Thus, while jet-lag eventually abates, 'shift-lag' is a more or less permanent affliction" [Eastman CI. *op.cit.*].

We found the concluding statement of the Letter to be without foundation. The writers state without citation that the "trends identified in this study are consistent with previous results," although our review of the literature has found no other demonstration of any procedure which can induce circadian adaptation to a week of nighttime work in persons who live at home and travel daily to work. Next, the writers state, "Indeed, phase-shifting properties of appropriately timed exposure to bright light are well-established." Why, then, do Campbell and Dawson state in the article cited that since their " . . . subjects were exposed to the bright ambient light throughout the work shift . . . As a result, no significant [phase] shift, in either direction, would be expected"? [Campbell SS, Dawson D. *op. cit.*]. As we demonstrated in our study, that prediction is

misleading. When subjects are repeatedly exposed to sufficiently bright light throughout the night shift and darkness during day sleep, large phase shifts can and do occur. This represents the distinction between Type 1 and Type 0 resetting [Strogatz SH. (1990) *J. Biol. Rhythms* 5:169-174], which they have failed to recognize.

Finally, we found their admonition that treatments for shiftwork maladaptation should be based on studies that employ appropriate experimental designs and suitable cell sizes to be particularly ironic in light of the studies they cite as "growing evidence that bright light treatment is effective in managing maladaptation to shift work." In the study of Campbell and Dawson, subjects working the simulated night shifts slept in "sound attenuated, air conditioned bedrooms completely isolated from the times of day," hardly a relevant proxy for the conflicting zeitgeber conditions to which the average shiftworker is exposed [Eastman CI. *op. cit.*]. Moreover, half of the subjects in their mixed control group worked in near-darkness (10 lux), experimental conditions which are certainly not comparable to the environmental conditions of ordinary shiftwork, and their data on performance enhancement was based on a cell size of four subjects in the bright light group. Furthermore, they made no attempt to evaluate the effect of their intervention on the circadian timing system. The second manuscript, by Eastman [*ibid.*], which the writers of the Letter cite as providing more solid evidence for the "trends" identified in our study, was based on an experimental study with a cell size of one subject in each of two different treatment "groups" with no control group at all.

Charles A. Czeisler, Ph.D., M.D., Harvard Medical School and Brigham and Women's Hospital, Boston, MA 02115. Tel 617-732-4011; fax 617-732-4015.

Jeanne F. Duffy, Brigham and Women's Hospital.

Richard E. Kronauer, Ph.D. Harvard University, Cambridge, MA.

Emery N. Brown, M.D., Ph.D., Harvard Medical School and the Massachusetts General Hospital, Boston, MA.

Michael P. Johnson, A.B., Cornell University Medical College, New York, NY.

Joseph M. Ronda, M.S., Harvard Medical School and Brigham and Women's Hospital.

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*.

Regular Members

Alan Buchanan
Steven Dilsaver
B. Kishore Gupta
Emilia Martignoni
Rutger van den Hoofdakker

Ileana Chirtoc
Marie Dumont
Arthur J. Kranz
Arthur Spielman

Associate Members

Mary Ackerley
Sanford Auerbach
Earnest W. Baker
Cynthia Desmond
M.C.M. Gordijn
Joseph Heaney
Marie-Louise T. Kagan
Pamela Madden
Benjamin H. Natlesen
Dermot O'Rourke
Sally Popper
Ruth Ragucci
Douglas L. Roberts
Roy Schultz-Ross
Francis J. Sousa
Duncan Worthington

Joseph R. Alexander
Karen Baker
Ronald M. Burde
Andrew Dollins
Steven Hansen
Edith Holsboer-Trachslor
Daniel N. Karpen
Douglas Moul
Mary Ann O'Connor
Ira Pollack
Yves Prigent
Morris Ritchi
Sandra Rothenberg
Paul Siegel
Walter N. Tapp
Taylan Hakan Yoney

Corresponding Member

Nikola Ilankovic

Student Members

William A. Dawson
Bryan Myers
Orna Tzischinsky

Mary Moffit
Jerome Petrie

PUBLICATION CHARGES BENEFIT MEMBERS

Please note that the new publications list and order form give SLTBR members the advantage of lower charges for purchasing the Society's publications.

INFORMATION BROCHURE PUBLISHED

After several rounds of draft revision, SLTBR has now published its public information brochure, *Questions and Answers about Light Therapy*, to be used in response to phone and mail inquiries received at the Executive Office. In addition, the brochure is available in both limited quantities and at bulk rates for distribution through doctors' offices, clinics, research centers, and apparatus suppliers (*see publications order form, attached*). With future revisions in mind, we would appreciate members' feedback on the content and scope of the brochure and its usefulness in the field. Please send comments to Ms. Marty McCullough, Executive Secretary, SLTBR, P.O. Box 478, Wilsonville, OR 97070.

1991 ANNUAL MEETING LOCATION

The 1991 annual meeting of the Society will be held in Toronto, Canada in conjunction with the Association of Professional Sleep Societies' annual meeting scheduled for 15 - 19 June in the same city. The exact dates of SLTBR's conference have not yet been scheduled, but they will fall immediately before or after the APSS meeting. Additional details will be forthcoming in the fall issue of *LTBR*.

STYLE NOTE:

LIGHT THERAPY VS. PHOTOTHERAPY

Writers of *LTBR* articles will note that we have substituted "light therapy" for "phototherapy" when editing their pieces. Two reasons: stylistic consistency and an attempt to reduce confusion with UV or intense-blue skin exposure procedures (as for treatment of hyperbilirubinemia, psoriasis, etc.). When listing key words for *Index Medicus*, however, we suggest that authors of light therapy papers do include "phototherapy", given lack of the alternative.