

Light Treatment and Biological Rhythms

Bulletin of the Society for Light Treatment and Biological Rhythms



Volume 4, Number 3

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ANNUAL MEETING SCHEDULE

The SLTBR Program Committee has set the schedule for the Society's Fourth Annual Meeting to be held at Lister Hill Auditorium on the campus of the National Institutes of Health. The two-day meeting, which convenes at 8:30 a.m. on 30 April 1992, features oral research presentations, poster presentation sessions and corporate exhibits. In addition, an open forum on 1 May will provide the opportunity for participants to discuss current issues in diagnostic criteria for DSM-IV, light apparatus manufacturing standards and FDA regulations. A tutorial session, also on 1 May, will focus on current developments in the field and provide the opportunity for discussion of practical diagnostic and treatment strategies.

Late registration is available until 17 April with payment of a \$10.00 late fee. Meeting registrants who have not reserved banquet seating may do so prior to 17 April with payment of \$35.00. Please use the registration form and banquet reservation card mailed to each member in January 1992 and return completed information with appropriate payment to the SLTBR Executive Office, P.O. Box 478, Wilsonville, OR 97070. You may, instead, call/fax your request (VISA/Mastercard payment only) to the SLTBR office: 503-694-2404. On site registration will include a \$15.00 late fee.

ANNUAL MEETING SCHEDULE

Thursday, 30 April 1992

8:00 - 8:30	Registration, exhibits, refreshments
8:30 - 12:00	Oral Scientific Presentations I (break included)
10:10 - 11:00	Break: Posters, exhibits refreshments
12:00 - 13:30	Lunch
13:30 - 14:50	Oral Scientific Presentations II
14:50 - 15:00	Break
15:00 - 16:00	Business Meeting
16:00 - 17:30	Reception: Posters, exhibits
19:00 -	Banquet

Friday, 1 May 1992

8:00 - 8:30	Exhibits, refreshments
8:30 - 11:50	Oral Scientific Presentations III (break included)
9:30 - 10:30	Break: Posters, exhibits, refreshments
11:50 - 13:20	Lunch
13:20 - 15:20	Open Forum
15:20 - 15:30	Break
15:30 - 17:30	Tutorial <i>Light Therapy and Circadian Rhythms</i> <i>Circa 1992</i>

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



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Unsolicited manuscripts, letters to the editor, and Bulletin Board announcements should be submitted to Dr. Anna Wirz-Justice, Editor, Psychiatric University Clinic, Wilhelm-Klein-Strasse 27, CH-4025 Basel, Switzerland. Please submit one double-spaced hard copy and a diskette file (Macintosh: Ms-Word, MacWrite; IBM: WordPerfect as Textfile); BITNET: WIRZ@URZ.UNIBAS.CH. Manuscripts and diskettes will not be returned. We reserve the right to edit and condense letters to the editor.

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ORAL SCIENTIFIC PRESENTATIONS I

Seasonality

N. Rosenthal, Chair

Carney et al.: Climate, seasonality and psychiatric illness in a west of Ireland adolescent population.

Eberhardt et al.: Seasonality of deaths in infanticide and sudden infant death syndrome (SIDS).

Schlager et al.: Winter depression and disability in 685 primary care patients at 41° N latitude.

Kasper et al.: Evidence for a seasonal type of recurrent brief depression (RBD-seasonal).

Mixed Physiology

Lovell et al.: The effect of bright light on agitation: Case reports.

Sack et al.: The alerting effects of nocturnal bright light exposure in humans are reversed by oral melatonin.

Barker et al.: Age-related changes in human lenticular transmission.

ORAL SCIENTIFIC PRESENTATIONS II

Seasonal Affective Disorder

R. Sack, Chair

Byrne et al.: Can hypnotic suggestion mimic the effect of bright light on melatonin production?

Danilenko et al.: Daytime melatonin and serotonin in seasonal affective disorder (SAD).

Norden et al.: A controlled study of dawn simulation treatment of subsyndromal seasonal affective disorder.

Glod et al.: Circadian rest-activity disturbances in seasonal affective disorder.

ORAL SCIENTIFIC PRESENTATIONS III

Seasons and Physiology

D. Kripke, Chair

Carskadon et al.: Parental reports of seasonal mood changes in children.

Wehr et al.: Daily patterns of human hormones, temperature and sleep respond to changes in photoperiod.

Ancoli-Israel et al.: Light exposure in nursing home patients.

Light Treatment

Terman et al.: Light-refractory vs. light-responsive SAD patients: Depression scale predictors.

Avery et al.: Dawn simulation treatment of winter depression: A second controlled study.

Teicher et al.: The phototherapy light visor: There is more to it than meets the eye.

Rothenberg et al.: A comparison of the efficacy of various spectral distributions and intensities of fluorescent light in the treatment of seasonal affective disorder.

POSTER PRESENTATIONS

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

Arbisi et al.: Taste discrimination and recognition in SAD.

Cole et al.: Seasonal variation in environmental light exposure in humans: Preliminary report.

Hagfors et al.: Seasonal affective disorder (SAD) in Finland: An epidemiological study.

Hellekson et al.: Does weight gain in SAD predispose to sleep apnea syndrome?

Ito et al.: Effect of phototherapy on left-right asymmetries in the quantitative EEG of SAD patients.

Levine et al.: Melatonin and cortisol secretion in the Arctic: Effects of photoperiod on circadian rhythms and mood.

Meesters et al.: Early light treatment and the prevention of winter depression.

Parry et al.: Phototherapy in premenstrual depression.

Putilov et al.: Seasonality correlates of sleep-wake pattern.

Rice et al.: Physics of phototherapy.

Wacker et al.: Seasonality is correlated with affective and not with anxiety disorders.

Wirz-Justice et al.: Seasonality in Switzerland: An epidemiological survey.

OPEN FORUM

A panel discussion of important unresolved questions in the field, including optimum diagnostic criteria, light apparatus manufacturing standards and FDA regulations. Questions and comments will be invited from all meeting participants. Panel members include:

Frederick K. Goodwin, M.D.

Director, National Institute of Mental Health

Lillian Gill

Deputy Director, FDA Office of Science & Technology
Center for Devices and Radiologic Health

Norman E. Rosenthal, M.D.

National Institute of Mental Health
SLTBR President

Michael Terman, Ph.D.

New York State Psychiatric Institute
SLTBR President-elect

George Brainard, Ph.D.

Jefferson Medical College
Chair, SLTBR Federal/Industrial Relations Committee

Light apparatus industry representatives

TUTORIAL

Light Therapy and Circadian Rhythms Circa 1992

Discussion of current developments in the field as well as practical diagnostic and treatment strategies.

Speakers:

Robert L. Sack, M.D.

Oregon Health Sciences University

Anna Wirz-Justice, Ph.D.

University of Basel, Switzerland

Norman E. Rosenthal, M.D.

National Institute of Mental Health

EXHIBITORS

Ambulatory Monitoring, Inc.

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Neal Owens, President
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PRESS INVITED TO ANNUAL MEETING

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

LIGHT THERAPY IN THE UNITED KINGDOM

Studies of light treatment in the United Kingdom began in 1984. They are concentrated now in Southampton, with additional work also occurring at the Maudsley Institute and in Aberdeen. Both the Southampton and the Maudsley groups have been interested in light sensitivity, phase-change, and melatonin in SAD.

In Southampton, we run a clinic dedicated to SAD where we offer screening of new referrals using DSM III-R criteria, the SPAQ and the SIGH-SAD version of the Hamilton Depression Scale. Those who are diagnosed may enter one of a number of ongoing studies, most of which are nearing completion at this time (February 1992), having been run over two winters of experimentation. These studies encompass both treatment and chronobiological protocols. Some are real endurance tests for the patients who always amaze us with their willingness to take part, but, nevertheless, it does make recruitment rather slow.

We have become interested in the benefits for SAD patients of the serotonin reuptake inhibitors of which four are now marketed in the UK. We are studying one of them in a double blind efficacy study in collaboration with the department of psychiatry in Aberdeen (Dr. Eagles), one of the most northerly cities in Scotland. We are wondering whether this would be eligible for an EEC grant for multinational cooperation if Scotland becomes independent after the next election! We are also continuing studies on the effectiveness of light therapy but have been more interested in exploring its mechanism of action than in banging our heads against the difficulty of designing a better protocol to minimize the placebo effect.

To this end, we have been following up our findings (Thompson et al., 1990) on the seasonal change in light

sensitivity found in SAD but not in normals. From this we have predicted that SAD subjects will show a greater change than normals in light sensitivity and phase position [using the dim light melatonin onset (DLMO) as a marker] after a week of light therapy. One of the first subjects tested in the study was a man who developed SAD at the same time as insulin dependent diabetes. In the winter he noticed a doubling of his insulin requirement. In addition to testing his chronobiological indices, we also carried out an insulin sensitivity test before and after one week of light therapy. We were astonished to find that, in parallel with a reduction in light sensitivity and 4 hour phase advance of DLMO, he also had an increase of insulin sensitivity using the "clamp test" and reported more subjective symptoms during hypoglycemia. Thus, it was not solely the almond jam fingers he binged on in the winter which increased his requirement for insulin. There are several interesting hypotheses of the mechanism of action of light therapy underlying this effect but it will be important to replicate it and see how far it might extend to non-seasonal diabetics. How many others have a seasonal element to their diabetes?

We are also using our two-bed light-controlled clinical laboratory to examine the effects of one of the serotonin reuptake inhibiting classes of antidepressants on clinical state as well as various measures of melatonin secretion. Our strategy is now always to put matched normal volunteers through the same treatment interventions as the SAD subjects, to test the hypothesis of differential responses, not only on the clinical level, but also in the biological markers of circadian phase position and light sensitivity.

In addition to these treatment and biological studies, we have an interest in the seasonal epidemiology of affective disorders in the community and have some interesting data to suggest that the peak of onsets of major depressive disorders is in the winter months, regardless of the diagnosis of SAD. If this is the case, it bears on the DSM-IV debate because it suggests that lowering the threshold for diagnosis of SAD from three to two episodes would include a number of subjects without the seasonal diathesis but who, with no greater seasonality than the rest of the recurrent affective disorder population, just happened to have both onsets during the winter months. The data suggest that this would be more prejudicial to the diagnosis of winter depression than to that of summer depression, since summer is the nadir of the onset curve. SAD researchers will have to be more responsive to legitimate questions of epidemiologists if these difficult

issues of the relationship of SAD to other affective disorders are to be sorted out.

Stuart Checkley's group at the Maudsley Institute has also been working on light sensitivity and phase position in SAD patients. They have obtained findings contradictory to our own, with no excess in light sensitivity in any of a range of tests examining the whole visual system from retina to cortex and pineal. They also found no differences in circadian phase position or total melatonin secretion between SAD patients and normals. However, they did not retest subjects in the summer, nor did they use a dim light control night against which to estimate melatonin suppression, in contrast to our own protocols. So SAD research and controversy in the UK is alive and well.

Finally, we have noticed no abatement in the large number of referrals coming to our clinics, both self-referred and, increasingly, referred by general practitioners, who are recognizing more and more of their recurrent depressive patients as having SAD.

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HUMAN LIGHT STUDIES IN THE NETHERLANDS

The interest in the impact of light on the human circadian system, in the Netherlands, dates back to about 1980. At that time, collaborative research at the Institutes of Zoology and Biological Psychiatry in Groningen and the Institute of Pharmacology in Zürich, Switzerland resulted in the first drafts of a model of human sleep regulation. This model integrated two main influences on sleep timing into one regulatory scheme. The influences were a propensity for sleep determined by the central circadian pacemaker and a homeostatically controlled need for sleep in response to sustained wakefulness. The model is now known as the two process model of sleep regulation (Borbély, 1982; Daan and Beersma, 1984; Daan et al., 1984). The circadian aspect of the model was assumed to be similar to circadian regulation in animals. Therefore,

it was hypothesized that light would be the most important zeitgeber for the human circadian system, and it was assumed that light would directly influence the circadian pacemaker, unaffected by the alternation of sleep and wakefulness (Beersma et al., 1987). This latter hypothesis was tested in the so-called candle-light experiment by Dijk and coworkers. In this experiment a group of subjects was studied in two conditions. The conditions were identical with respect to the timing of sleep, but differed in the amount of light that the subjects received in the interval between 6 and 9 a.m. In one condition they were subjected to 2500 lux, in the other condition they were sitting at 1 meter distance from a candle, which means that they received 1 lux. Three days of each treatment resulted in differential effects on the course of body temperature and on melatonin secretion. Both curves showed an earlier rise in the 2500 lux condition. Also the spontaneous duration of sleep was shorter in the 2500 lux condition. However, the intensity of sleep as deduced from the spectral power density of the sleep EEG signal was the same for the two conditions (Dijk et al., 1987, 1989). This result confirmed that the circadian pacemaker could be phase shifted by light, and that this could occur without the involvement of changes in the activity-rest pattern.

In the meantime, there was an increasing interest in light from another point of view. For many years, the department of Biological Psychiatry in Groningen has been interested in the antidepressive effects of total sleep deprivation in patients suffering from Major Depressive Disorder. Studies have been performed to sort out the beneficial ingredients of this treatment, because it is obvious that total sleep deprivation consists of a series of interventions. Apart from the deprivation of sleep, patients are accompanied, taken care of, drink, eat, take a walk, are not lying awake in their beds, and are also exposed to light at a time where they normally would be in darkness. Van den Burg and coworkers (1990) combined total sleep deprivation either with low light intensity or with 2500 lux, in a cross over design, and noted no differences in therapeutic response. Apparently, light intensity is of little influence to the response to total sleep deprivation in severely depressed patients.

From 1987 onward, a new dimension was added to the interest in light in the Netherlands, due to the initiation of experiments with seasonal affective disorder patients (Van Houwelingen and Van den Hoofdakker, 1987). A major concern at that time was the possible role of placebo effects as an explanation of the therapeutic results of light treatment. An unconventional idea of Van Houwelingen resulted in an experiment in which patients were either

subjected to 2500 lux between 9 and 12 a.m., or tried to imagine that they were subjected to very bright light, while actually sitting in the dark. This latter condition was considered an optimum placebo situation: in the 9 to 12 a.m. sessions, patients were assisted in their imagination by means of hypnotic techniques. After three days of treatment both groups showed a significant improvement of mood. However, this response rapidly faded away in the imaginary light condition, while the patients showed a continuation of the improvement in the real light condition (Jenner et al., 1990; Meesters et al., 1990; 1991b). Of course, a number of methodological problems are contained in this study. Placebo effects induced by imagination may be distinctly different from placebo effects induced by bright light, a notion which immediately hampers any placebo interpretation of the study.

In subsequent years the issue of optimization of light treatment has been studied in various ways. In two groups of patients the application of bright light in the morning (9-12 a.m.) was compared to bright light in the evening (6-9 p.m.). No significant differences were observed (Meesters et al., 1990, 1991b). Occasionally, patients have been encountered who not so much suffer from seasonal mood complaints, but from complaints about loss of energy. Light therapy can be very effective in these patients (Meesters and Lambers, 1990). Furthermore, we have attempted to see whether the application of light at a very early stage in the development of a winter depressive episode could prevent the full blown development of the depression. The study yielded the unexpected finding that none of the 10 early treated patients remitted to depression during the same winter season (Meesters et al., 1991a). In the mean time the group of patients has been approximately doubled, without any change in the conclusions.

As the literature well shows, there have been as many ideas concerning the mechanism of development of seasonal affective disorder and its response to light as there have been contradictory results. I have recently proposed that SAD perhaps could result from a supersensitivity to light at the level of the SCN and I have described how I thought that such supersensitivity could lead to depression. I also have speculated that the supersensitivity could already be present at the level of the retina (Beersma, 1990). So far, there is little support for a supersensitivity of the eye in SAD patients. However, a supersensitive central pacemaker cannot yet be excluded on the basis of the data.

The interest in light treatment of SAD patients is steadily increasing in the Netherlands. Four clinical centers apply

bright light as a treatment. The scientific research is still concentrated in Groningen, however, where we are continuing measurements of visual sensitivity. Investigations concerning the optimization of light treatment are concentrated on the influence of various clock times, as well as on the effects of short lasting high intensity treatments (10,000 lux for 30 minutes). Furthermore, an attempt has been made to prevent the occurrence of SAD during the entire winter season by the application of bright light during one week, 3 hours per day at the beginning of autumn. So far, such preventive treatment does not seem to work. Despite the application of light, a substantial fraction of the group appeared to develop a winter depression during the course of the season.

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CIRCADIAN RHYTHMS AND DEPRESSION: ANIMAL MODELS?

As readers of this bulletin are aware, alterations in circadian rhythmicity have been described in patients with affective disorders. However, because of the constraints on experimental manipulation that characterize clinical research, it has been difficult to establish cause-and-effect relationships. Thus, altered rhythmicity could be either a cause or an effect of altered affective state, or both could independently reflect the action of some other controlling variables. These same constraints make it difficult to identify the specific nature of the rhythm disturbances that occur in depressed patients. For example, much of the clinical data has focused on alterations in entrainment phase, even though phase angle could be influenced by the underlying period of the circadian pacemaker, the pacemaker's response to light, and pacemaker-independent phenomena such as "masking." These factors can be much more easily untangled in free-running conditions, but very few depressed patients have been studied under such conditions, for obvious reasons.

Since experimental animals are obviously more easily subjected to experimental manipulation and control, further insight into the nature of rhythm-depression interactions might be gained from analyses of circadian rhythms in animal models that purport to mimic various features of human depression. In this essay, I review the presently available data on circadian rhythms in several animal models of depression, as well as some related observations that have not been explicitly presented in the context of animal depression models. Although both depressed patients and experimental animals show alterations in the phase, period, amplitude, level, and coherence of their rhythms, this comment will mainly focus on free-running period and phase-control.

Stress-induced depression models

Stress-induced behavioral change is considered to provide one of the most valid animal models of depression (Willner, 1984), despite continuing controversy concerning the role of stress in the etiology of human depression. Stress-induced behavioral "pathology" extends to alterations in activity level, motivation, and learning, and these behavioral signs are reversible by antidepressant drugs with reasonable selectivity. Unfortunately, the available data on circadian rhythms in animals exposed to stress are fairly limited, especially with respect to free-running rhythms.

An early study demonstrated that some monkeys exposed to uncontrollable stress showed either 48-hour sleep-wake cycles or failure to entrain in the presence of a light-dark cycle (Stroebel, 1969), both reminiscent of circadian disturbances reported in bipolar affective patients. More recent studies showed that some rats exposed to several sessions of inescapable footshock exhibit clear lengthening of free-running period following stress exposure (Stewart et al., 1990a; 1990b). Assessment of escape performance ("learned helplessness") in these animals revealed that period-lengthening was associated with intact performance, or, in other words, with resistance to helplessness. On the other hand, period-lengthening was also associated with persistent long-term reductions in activity level, another behavioral response to stress that has been suggested to provide an animal model of depression (Desan et al., 1988).

Behaviorally-characterized strains as models

Certain behaviorally well-characterized inbred strains have been suggested to provide useful animal models of affective disorders. Such models may be particularly useful for understanding the role of genetic predispositions in the etiology of these disorders. For example, many studies have compared the behavioral profiles of spontaneously hypertensive rats (SHR) and the normotensive Wistar-Kyoto (WKY) "parent" strain. One problem in evaluating this literature is that SHRs and WKYs have only rarely been compared to other laboratory strains, and differences between the two strains are generally interpreted as reflecting an abnormality in the SHRs. However, recent studies comparing SHRs and WKYs to several other strains in a battery of behavioral tests generally thought to model human depression showed that WKYs, and not SHRs, deviate from more standard strains, and that the WKY strain may be a useful model for genetic susceptibility to stress-induced depression (Pare, 1989). In our studies, WKY rats showed significantly longer

free-running periods than SHR rats under moderate to high constant light intensities, but periods did not differ under constant darkness or very dim light (Rosenwasser, 1990c; Rosenwasser and Plante, unpublished manuscript). These results suggest that the two strains differ in their responsiveness to the period-altering effects of light.

The Flinders sensitive line (FSL) of rat was originally bred for sensitivity to pharmacological inhibition of cholinesterase. These rats show supersensitivity to cholinergic agonists, as well as to several other neuroactive agents, when compared with the Flinders resistant (FRL) line. Behaviorally, FSL rats show reduced activity, increased irritability, as well as a number of other signs that may model aspects of human depression (Overstreet, 1986). In recent studies, FSL rats were found to display both advanced entrainment phase and shortened free-running periods (Shiromani et al., 1991; 1992).

Free-running activity rhythms have also been compared in strains of mice selected for either high or low aggressiveness, and the aggressive mice showed longer free-running periods and reduced sensitivity to the phase-shifting effects of light (Benus et al., 1988). Although the authors did not explicitly relate their results to depression, these results do provide further evidence that circadian rhythms are altered in strains selected for specific behavioral or neurochemical properties.

It is possible that additional insight into the relationship between affective state and circadian rhythmicity might be gained by comparison of circadian and affective-behavioral characteristics in a large sampling of existing, standard inbred mouse strains. Indeed, a number of differences in circadian rhythmicity have been described among inbred mice (Possidente and Stephan, 1988; Rosenwasser, 1990b; Schwartz and Zimmerman, 1990.) However, this is likely to be a rather difficult enterprise, since mouse strains characterized by vulnerability to one stress-induced behavioral deficit are not necessarily vulnerable to other, apparently similar, deficits (Shanks and Anisman, 1988).

Ablation-based models

Behavioral and neurochemical studies of the olfactory bulbectomized rat suggest that such animals may provide a model for agitated, anxious depression. Such animals exhibit hyperactivity, irritability, aggressiveness, and performance deficits, and these behavioral signs are reversed by chronic antidepressant treatment with reasonable selectivity (Leonard et al., 1989). Olfactory bulbectomized rats, mice, and hamsters show alterations in

circadian rhythmicity that include delayed entrainment phase and lengthening of free-running period, and preliminary evidence suggests that these changes may also be reversible by antidepressant treatment (Lumia et al., 1987; Pieper and Lobocki, 1991; Possidente et al., 1990).

Another possible ablation-based depression model is the thyroidectomized rat. Richter (1965) showed many years ago that thyroidectomy leads to the emergence of unusual long-term cycles in activity level, and proposed that this preparation could serve as a model for manic-depressive illness. This suggestion is consistent with the high incidence of thyroid abnormalities in affective disorders, and with the tendency toward hypothyroidism in rapid cycling bipolar patients. More recently, thyroidectomized (and thyro-parathyroidectomized) rats have been reported to display shortening of free-running period (Schull et al., 1988; 1989). In contrast, anti-thyroid drug treatments have been reported to lengthen free-running period in hamsters, but evidence suggests that these effects are not directly related to thyroid status (Morin, 1988).

Pharmacological models

Dysregulation of monoaminergic and cholinergic neurotransmitter systems has been implicated in human depression and in the various stress-induced, genetic, and ablation-based animal models described above. Pharmacological perturbation of these same neurotransmitter systems can alter circadian rhythms in animals. Cholinergic and noradrenergic agents have been reported to induce circadian phase-dependent phase-shifts (Cahill and Ehret, 1982; Meijer et al., 1988; Vogt and Rosenwasser, 1992; Wee and Turek, 1989; Zatz and Herkenham, 1981). The phase-shifting effects of the cholinergic agonist carbachol and the alpha-noradrenergic autoreceptor agonist clonidine seem to generally resemble the phase-shifting effects of light pulses, and cholinergic antagonists have been reported to block the phase-shifting effects of light (Keefe et al., 1987). In addition, free-running period is shortened during chronic administration of either carbachol or clonidine (Furukawa et al., 1987; Rosenwasser, 1989; 1990a). Manipulation of the serotonergic system also can induce phase-shifts, and may modify the phase-shifting effects of light (Cassone and Menaker, 1985; Prosser et al., 1990; Smaile et al., 1990). In contrast to carbachol and clonidine, the phase-shifting effects of serotonergic agonists are dissimilar to those seen with light pulses, and instead appear to resemble the phase-shifting effects of "dark pulses", induced activity (see below), and benzodiazepines. In addition, individual differences in free-running period

In addition, individual differences in free-running period are correlated with serotonin levels within the suprachiasmatic nucleus (SCN), site of the mammalian circadian pacemaker (Shioiri et al., 1991).

Antidepressants including clorgyline, imipramine, and lithium, have been reported to lengthen free-running period or phase-delay light-entrained behavioral and neurochemical rhythms (Duncan et al., 1988; Kripke et al., 1987; Tamarkin et al., 1983; Wirz-Justice and Campbell, 1982; Wirz-Justice et al., 1982). Although the period-lengthening effects of imipramine are small and variable (Aschoff, 1989; Wirz-Justice and Campbell, 1982, this agent has been reported to induce substantial phase-delays (Tamarkin et al., 1983). In addition to its effects on period, clorgyline also produces complex alterations in the phase-shifting effects of light pulses (Duncan et al., 1988). Delayed entrainment phase and lengthening of free-running period are also seen in wheel-housed rats during chronic treatment with methamphetamine, another agent producing a broad spectrum of monoaminergic agonist effects (Honma et al., 1991). However, period-lengthening does not appear to be a property of all antidepressants, since a recent study showed that chronic administration of desipramine or moclobemide could shorten free-running period, while other antidepressants were without effect on activity rhythms (F. Wollnik, personal communication).

In addition to these effects on period and phase, several monoaminergic agents have also been shown to induce complex dissociations or splitting of free-running rhythms (Honma et al., 1986; Rosenwasser and Plante, unpublished manuscript; Wirz-Justice et al., 1982). Such dissociations are thought to reflect the weakening of coupling relationships within a network of multiple coupled circadian oscillators (Rosenwasser and Adler, 1986).

Behavioral "feedback" effects

Until recently, it was thought that human circadian rhythms were primarily influenced by social and cognitive factors, rather than by environmental lighting, and that the opposite was true of animals. However, it is now clear that photic stimuli do independently contribute to circadian entrainment in humans, and that behaviorally-derived stimuli are of considerable importance in the control of rhythmicity in animals.

For example, social stimulation, cage-cleaning, and novelty-induced voluntary activity have all been shown capable of phase-shifting free-running activity rhythms in hamsters (Mrosovsky, 1989), and increased spontaneous

running wheel activity is associated with shortening of free-running period in mice and rats (Edgar et al., 1991; Shioiri et al., 1991). The phase-shifting effect of induced activity appears similar to that of dark pulses, benzodiazepines, and serotonergic agonists. Indeed, the phase-shifting effects of both dark pulses and benzodiazepines in hamsters may be largely mediated by the bursts of activity induced by these treatments (Van Reeth and Turek, 1989). The generality of such observations remains to be determined, but one recent report indicates that the effects of chronic methamphetamine administration on rhythmicity differ between wheel-housed and non-wheel-housed rats (Honma et al., 1991).

Although these phenomena are not explicitly related to human affective disorders, they do demonstrate that alterations in behavioral arousal state or activity level can lead to alterations in circadian period and phase. Such observations thus raise the possibility that the altered rhythmicity seen in affective disorders could largely be a consequence of, rather than a cause of, behavioral depression and mania.

Relationship to clinical observations

Although advanced entrainment phase is the most commonly described circadian rhythm disturbance in depressed patients (see Wehr et al., 1983), phase-delayed circadian rhythms have been documented in patients with Seasonal Affective Disorder (SAD) (Lewy et al., 1987) and in a population of geriatric depressed inpatients (Teicher et al., 1988). The existence of both phase-advanced and phase-delayed rhythms in different populations of patients should not be surprising in light of the heterogeneity of affective syndromes and symptoms. Similarly, both lengthening and shortening of free-running period have been observed in putative animal models of depression. The challenge now is to identify the critical variables that distinguish phase-advanced and phase-delayed patients, and to relate these variables to the distinguishing behavioral and neurochemical features of the different animal models.

One attractive hypothesis is that psychomotor disturbances (i.e., agitation vs. retardation), or perhaps the presence of associated anxiety, may distinguish affective subtypes with different circadian characteristics. Teicher and co-workers (1988; 1989) have suggested that phase-delayed rhythms may be associated with agitated, anxious, and generally unipolar depressions, while phase-advanced rhythms may be associated with the anergic depressions of bipolar patients. Comparison of the animal models provides some

support for this hypothesis. For example, olfactory bulbectomized and WKY rats have both been suggested as models of anxious depression, and both are characterized by long periods, while FSL rats test negative in a standard animal test of anxiety (Schiller et al., 1991) and are characterized by short periods.

On the other hand, alterations in free-running period and activity level do not consistently covary across the various models. For example, chronic clonidine-treated and stressed rats both show reduced activity levels but show opposite changes in free-running period. Similarly, thyroidectomized and olfactory bulbectomized rats both show increased activity but show opposite changes in period. While this suggestion is very tentative at present, it may be that the presence or absence of associated anxiety is a better predictor of circadian period than is locomotor activity level. Of course, the various behavioral characteristics of depression-model animals may not covary any more consistently than those of depressed patients.

Finally, what can be said about the nature of the causal mechanisms underlying these relationships? Certainly, rhythm disturbances could play a causal role in depression, as suggested by the now-classic "phase-advance hypothesis" (Wehr et al., 1979; 1983) and by several more recent (and more integrative) theories (Healy, 1987; Healy and Williams, 1988; Ehlers et al., 1988). Conversely, the alterations in arousal, activity, and affect that characterize depressive disorders may be the cause of the altered rhythmicity, as suggested by recent animal experiments; or alterations in both affective state and circadian rhythmicity may be caused in parallel by the same kinds of genetic predispositions, environmental stressors, and neurotransmitter dysregulations. Indeed, these hypotheses are clearly not mutually exclusive: most likely, various causal loops together comprise a complex causal network linking mood, behavior, and the biological clock.

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MEETING REVIEW

BIOLOGIC EFFECTS OF LIGHT SYMPOSIUM

On 13-15 October, 1991 over 120 scientists from 10 different countries attended **Biologic Effects of Light** in Atlanta, GA, a symposium aimed at presenting a comprehensive review of recent advances in the knowledge of the effects of solar irradiation and artificial light sources on humans.

The symposium opened with a general session entitled "The Biologic Effects of Light" followed by oral sessions on Photoimmunology, Circadian Rhythms, Effects on the Eye, Photomedicine, Ozone, UV and Skin. In addition to the oral sessions, 30 posters were presented. The abstracts have been published in *Photodermatology, Photoimmunology and Photomedicine* [(1991) 8: 21-50] and a book of manuscripts is currently in press under the title *Biologic Effects of Light* (Walter de Gruyter & Co., NY).

This symposium had an interesting balance of presentations that highlighted the beneficial ("biopositive") effects of light such as vitamin D synthesis, immune enhancement, phototherapy for tumors, light therapy for SAD and light treatment for sleep and shift work problems alongside presentations that detailed the hazards of light including immunosuppression, skin aging and damage, dermal cancer and ocular hazards.

A number of SLTBR members contributed papers and posters at this meeting. George Brainard demonstrated that melatonin can be suppressed by very dim light if ocular conditions are optimized. He also discussed data which shows that acute bright light exposure can enhance

performance of night workers. Alfred Lewy showed his data on a phase-response curve to oral melatonin administration and compared this with the phase-response curve for light stimuli. Michael Terman reviewed the current state of SAD research and focused on different strategies of light therapy and implications for underlying mechanisms. Scott Campbell discussed the effects of bright light pulses on sleep quality and performance efficiency in people who have disrupted circadian rhythms. James Gaddy's results indicate that bright light stimuli produces a stronger suppression of melatonin with the whole retinal field exposed rather than with partial retinal exposure. Joan Roberts provided data on the increased lymphocyte proliferation responses in SAD patients treated with light. Theodore Williams described animal studies on retinal photostasis and related these results to potential mechanisms of light modification of circadian rhythms as well as light therapy. Morris Waxler reviewed the current status of light exposure safety standards and ocular hazards.

This symposium was organized by Michael F. Holick, M.D., Ph.D. and Albert M. Kligman, M.D., Ph.D. and was sponsored by the Light Symposium Foundation. This foundation was established to sponsor symposia and other educational programs for the purpose of furthering a better understanding of the beneficial and adverse effects of ultraviolet and visible radiation on human health and disease. A follow-up symposium will take place from 3-5 June 1993 in Basel, Switzerland. Details of next year's program will be announced in a future issue of *LTBR*.

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BULLETIN BOARD

WELCOME TO NEW MEMBERS

We welcome the following new members who have joined SLTBR since publication of the February 1992 issue:

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APPEAL ON BEHALF OF "SOVIET" NEUROSCIENTISTS

We reprint below, with permission, an article published in the March/April 1992 issue of *Neuroscience Newsletter*. Those wishing to contribute should send their checks to *Nancy Baeng, Society for Neuroscience, 11 Dupont Circle, N.W., Suite 500, Washington, DC 20036*.

Dr. David Ottoson, Secretary General of IBRO and a long-time friend of the Society for Neuroscience, has recently called our attention to the plight of neuroscientists in the former Soviet Union.

The unparalleled economic changes that have resulted from the break-up of the Soviet Union and the attempts of the individual states to establish new democratic forms of government and free market economies have devastated almost the entire academic and research enterprise of the various states. According to Dr. Ottoson, the salaries of professors of neuroscience currently amount to about \$10 per month. There are virtually no funds for equipment, supplies or technical personnel. The situation is so grave that without a substantial infusion of funds from outside, the entire structure of biological science in the newly-independent republics is likely to collapse.

While efforts are being made to solicit support from various funding agencies in Europe, Japan and the United States, we wish to appeal to individual members of the Society for Neuroscience. If each member were to pledge as little as \$10, we believe the Society could make a significant and timely contribution to the problem.

Nancy Baeng has arranged for the Society's headquarters to serve as a conduit for contributions. Checks should be made payable to: **Society for Neuroscience - "For 'Soviet' Neuroscientists."** Your contributions will be tax deductible. Whatever monies are raised will be distributed through IBRO in a manner yet to be determined, but undoubtedly under Dr. Ottoson's careful supervision.

We hope you will join us in contributing generously to this deserving cause.

Joseph T. Coyle
W. Maxwell Cowan

SUMMER COURSE IN BIOLOGICAL TIMING

The National Science Foundation is sponsoring a "Biological Rhythms Course" at its Center for Biological Timing on the University of Virginia campus. Each week of the course, which runs from 15 July through 14 August, is comprised of five morning lectures, afternoon laboratory and tutorial sessions, and four evening research lectures. Advanced workshops and technical tutorials are scheduled for Saturdays. Course applicants will be selected following a review of academic credentials and a statement of personal and professional reasons for wanting to attend the course. For more information contact the *Center for Biological Timing, Gilmer Hall, University of Virginia, Charlottesville, VA 22901; tel 804-982-5226*.

SIGH-SAD NOTES

Researchers and clinicians using the SIGH-SAD, SIGH-SAD-SR, and HIGH-SAD instruments are advised of editorial revisions that will be available by the time of the SLTBR annual meeting, and included in a new edition of the *SAD Assessment Tools Packet* available from the Executive Office at a postpaid cost of \$15.00 for members and \$19.00 for non-members (prepaid orders only, please). Colleagues who are translating these instruments into other languages should use these revised editions. While the domain of symptoms assessed remains the same, the questioning is now simplified, more specific, and more naturally conversational. Higher scoring accuracy and inter-observer reliability are the expected results. Beginning with the fall 1992 season, the new versions, all dated April 1992, should be substituted for those currently in use.



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