Light Treatment and Biological Rhythms

Bulletin of the Society for Light Treatment and Biological Rhythms

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SLTBR ANNUAL MEETING JUNE 7-9 IN VANCOUVER

The 9th Annual Meeting of the Society for Light Treatment and Biological Rhythms (SLTBR) will be held June 7-9, 1997, at the Plaza 500 Hotel in Vancouver, Canada. The meeting will feature keynote speakers, new research posters and oral presentations, a Young Investigator award and presentation, a CME accredited clinical update course, and corporate exhibits. Topics range from basic circadian science, to research on seasonal affective disorder (SAD, or winter depression), to clinical applications using light therapy and applied chronobiology including the use of melatonin, serotonergic medications, and other treatments. David Schlager, M.D., SUNY at Stony Brook, Stony Brook, N.Y., is the chair of the Scientific Program Committee.

Preliminary Program

Saturday, June 7, 1997

1p.m . - 5 p.m. CME COURSE: An Update on SAD and Melatonin

- Light and Non-Pharmacologic Treatment of Winter Depression - Michael Young, Ph.D.
- Pharmacologic Treatment of Winter Depression - Adam Moscovitch, M.D.
- Clinical Use of Melatonin - Al Lewy, M.D., PH.D, and Colin M. Shapiro, Ph.D.

5 p.m. Welcome Reception

6:30 p.m. SLTBR Board of Directors Meeting

Sunday, June 8, 1997

8 a.m. - 9p.m. Registration, Posters, Exhibits, Coffee and Carbohydrates

9 a.m. - 11:30 a.m. Symposium

- Functional Neuroanatomy of the Circadian System - Larry Morin, Ph.D.
- Phylogeny of the Sense of Time: Melatonin Through the Dark Ages - Vincent Cassone, Ph.D.
- Biologic Night in the Human SCN - Tom Wehr, M.D.

11:30 a.m. - 12:45 p.m. Lunch (on your own)

12:45 p.m. - 2 p.m. Young Investigator Award Presentation and Poster Discussion - Norman Rosenthal, M.D.

2:15 p.m. - 4:15 p.m. Oral Paper Session I (6 Speakers)

4:30 p.m. - 5 p.m. SLTBR Business Meeting

6:30 p.m. - Banquet (at the UBC Anthropology Museum, transportation included)

Monday, June 9, 1997

8 a.m. - 10 a.m. Oral Paper Session II (6 Speakers)

10:30 a.m. - 12 noon Keynote Speakers

- Peaking at Dawn (and Dusk) - Michael Terman, Ph.D.
- Phase-shift Hypothesis of Winter Depression: an Update - Al Lewy, M.D., Ph.D.

12 noon - 1 p.m. Lunch (on your own)

1 p.m. - 2:30 p.m. Oral Paper Session III (4 Speakers)

2:30 p.m. - Closing

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LUX

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The Plaza 500 Hotel (Tel: 1-800-473-1811, 604-873-1811; Fax: 604-873-5103) is centrally located in Vancouver, only five minutes away from the downtown and other tourist sites including Granville Island Market, Science World, Stanley Park, Queen Elizabeth Park and Conservatory, and the beaches. The Plaza 500 Hotel has been recently renovated and will be an excellent venue for the meeting. It is located across from the art deco-ish Vancouver City Hall, and there are numerous restaurants and shops nearby. The Sunday evening banquet will be held at the UBC Anthropology Museum. Situated on a spectacular site overlooking the ocean at the University of B.C., the Anthropology Museum houses an outstanding collection of West Coast Native Indian artifacts.

Vancouver is a wonderful tourist destination with a unique blend of natural and metropolitan activities. The spectacular natural setting invites outdoor activities of all types — hiking, fishing, sailing, biking. The cosmopolitan city offers a particular focus on the Asian Pacific Rim. Whether your interests are in spending time in the nearby mountains, or exploring Native Indian culture, or dining in outstanding Chinese or Japanese restaurants, or shopping in the latest stores, you will be guaranteed to fall in love with Vancouver. In addition, the favorable exchange rates on the Canadian dollar makes Vancouver very affordable compared to other world-class cities.

Registration materials have been sent to SLTBR members. Non-members may contact the SLTBR office: Francine Butler, Ph.D., Executive Director, SLTBR email: sltbr@resourcenter.com; Tel: (303) 424-3697; Fax: (303) 422-8894; Web site: http://www.websciences.org/sltbr

SO YOU THINK YOU UNDERSTAND PLACEBO EFFECTS?

By Charmane Eastman, PhD.

The following contains excerpts from a paper (Eastman, 1990) which was based on a presentation at the 1990 SLTBR Annual Meeting. Al Lewy asked me to talk about placebos. At first I protested and said something like "No, I can't. Why me? I'm no expert in this area." He insisted and said something like "You are doing research with a good placebo control. You're a logical choice." Soon I stopped arguing and agreed to give the talk. I immersed myself in the vast and fascinating body of scientific literature on placebos. I was surprised, even shocked, by much of it. I had actually thought that I knew what a placebo was, and what a placebo response was. But I really didn't, and I had no idea of how powerful placebos can be.

It's been 6 years since the papers from that symposium have been published, which included two other excellent papers about placebos and light therapy (Brown, 1990; Stewart,

1990). When I was asked to reprint my paper in this SLTBR newsletter I was very pleased. It turned out to be one of my favorite papers, and it's cited a lot. But sometimes when I read SAD light therapy papers I get the feeling that the authors haven't read any relevant placebo papers, or perhaps they just don't believe it. It's been said that the disdain for the placebo effect stems from fear that acknowledging the power of placebos will detract from the power, authority and expertise of the medical establishment, and be a source of embarrassment (Ross and Buckalew, 1985). I, myself, find the placebo issue a diversion from my main interest in circadian rhythms. So we have to force ourselves to think about placebo effects. The following is designed to make it easier. Let me also suggest an outstanding, very short review (Wall, 1992). Read that if you still think that there is *one* placebo response rate for SAD patients, or that a fixed fraction (one third) of the population responds to placebos. If you're willing to read a somewhat longer but also excellent review, I suggest Lundh (1987). Or write or e-mail me and I'll send you the long version of my paper.

For this reprinting of my paper, I thought about how I could get people to pay more attention to it this time. I decided to remove some sections in order to make it shorter, and to sprinkle it with quotes from others people's SAD light therapy papers that reveal some type of misconception about placebos. When inserted in the appropriate places I hope they will help illustrate the points I was trying to make. However, I don't want to single out or embarrass anyone, so I've altered the quotes in order to disguise them. Finally, let me say that I have a lot of respect for the researchers who wrote the papers I borrowed quotes from. Don't forget, I pulled these quotes out of context. Often the authors followed up with thoughtful, accurate statements about placebos in the same paper, or in subsequent papers. At least they were trying to address the placebo problem. This is much better than writing a whole paper about light therapy for SAD without even mentioning the word placebo.

EXCERPTS FROM:

What the Placebo Literature Can Tell Us About Light Therapy for SAD

A component of any successful treatment of any disorder can be attributed to a placebo effect (Grunbaum, 1986; Shapiro, 1971; Shapiro and Morris, 1978). In addition, spontaneous recoveries and remissions can occur in the course of any illness. This factor is difficult to separate from the placebo effect. When we are asked as scientists, whether bright light treatment works, we are really being asked two separate questions. One is whether the bright light treatment significantly reduces symptoms; the second is whether bright light treatment has any benefit beyond its placebo effect. These are known as baseline and incremental effectiveness, respectively (Critelli and Neumann, 1984). We can absolutely answer yes to the question of baseline effectiveness. Incremental effectiveness, however, is a more difficult and controversial issue.

Pharmacology of Placebos: Dose Response

What's Wrong with This Statement?—"Light therapy is not just a placebo because patients generally improve or relapse within two to four days and not immediately, as one might expect if a placebo effect were operating."

Drugs usually become more efficacious with multiple administration, presumably due to factors such as an increased concentration of the drug in the body. However, placebos show similar "pharmacological" effects. A good example is an experiment in which patients with tuberculosis were given a yellow tablet daily for seven days (Lasagna et al., 1958). They were told that the tablets would increase their appetite and improve their pep and energy. All the pills were placebos. This experiment was performed before our modern era of informed consent, and there was no comparison with an active drug. The ratings (Figure 1) showed a gradual build-up of pep and appetite over the week of placebo therapy, and a carryover effect when the pills were withdrawn.

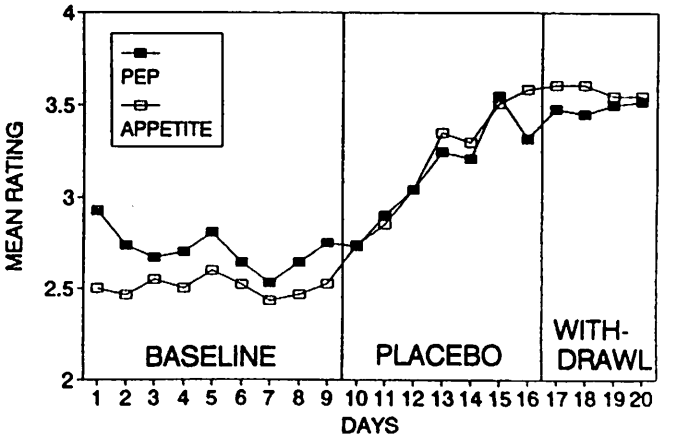

Figure 1. Daily pep and appetite ratings in 34 tuberculosis patients treated with placebo. Data taken from Lasagna et al., 1958.

The antidepressant effects of bright light for winter SAD show similar build-up and carryover effects, with gradual improvement over the first few days and carryover effects for days to weeks after the light are withdrawn (Rosenthal et al., 1984, 1985; Wirz-Justice et al., 1986). The mere existence of a characteristic time course of response to bright light treatment cannot be used as evidence that the bright lights produce an antidepressant effect beyond their placebo effect.

What's Wrong with This Statement?—"The existence of some specific therapeutic factor in light therapy is suggested by the existence of a dose-response curve for duration and intensity."

In another study which demonstrates the "pharmacological" properties of placebos, depressed or anxious outpatients were randomly assigned using double-blind procedures to one or four tablets per day of either drug or placebo (Rickels et al., 1970). The study was conducted on patients from two settings, a medical clinic and private psychiatric practices. We will only be concerned with the response of patients given the placebos. In the medical clinic, 50 percent of the patients improved with one placebo pill and 87 percent improved with four placebo pills. For the private psychiatric patients, 33 percent improved with one placebo pill and 50 percent improved with four placebo pills. Thus, in both settings four placebo pills worked better than one.

The important point for our purposes is that placebos, like "real" drugs, show dosage effects. In this example, higher "doses" of placebo produced greater effects. Other studies have demonstrated this principle, for example that two placebo pills work better than one, or that a larger placebo pill works better than a small one (Honigfeld, 1964a; Merin, 1973; Ross and Olson, 1981).

Applying these principles to phototherapy we would expect larger doses of light to work better than smaller doses, even if the antidepressant response were entirely due to a placebo effect. Longer durations of treatment should be more efficacious and more intense or brighter light should be more efficacious. The mere existence of dose response relationships (Wirz-Justice et al., 1987) or reciprocal intensity-duration relationships (Terman, 1988) cannot be used as evidence that the antidepressant effect of phototherapy is more than a placebo effect.

Situational, Physician, and Staff Factors: Expectations

The therapeutic situation, for example, the information given to the patients, the zeal of the doctor, etc., can influence the placebo response. One example is from the treatment of patients with bleeding ulcers (Volgyesi, 1954). There were two contrasting situations. In one, doctors injected the patients with the medication. In the other, nurses administered the injections and admitted to the patients that they were serving experimental purposes. In both cases only placebo was given. In the first group the result was excellent in 70 percent of the patients over a period of 1 year. Actual and complete cures were achieved as verified by gastroscopy and roentgenography. On the whole the results were better than after the approved ulcer cures of that time. In the second group only 25 percent had a favorable response.

What's Wrong with This Statement?—"Bright light is probably not a pure placebo for SAD because the effect has been independently replicated in many different research centers."

Other studies have shown that the efficacy of both placebo and active drug is increased when the physician has faith in the effectiveness of the drug he is administering (Berg, 1977; Feldman, 1956; Grunbaum, 1986; Honigfeld, 1964b; Shapiro, 1959, 1964). The prestige of the physician is an important factor and a common element in "bandwagon effects" in science and the success of quacks (Shapiro, 1971; Shapiro and Morris, 1978).

What's Wrong with These Statements?—
"The amount of placebo effect was presumably the same for both the bright morning light and the bright evening light because the exposure times were of equal duration."

"The differential clinical effect of morning and evening light in SAD supports the hypothesis that light therapy has more than a placebo effect."

Extrapolating these principles to bright light treatment, we might expect to see better responses when treatment is prescribed by an enthusiastic, prestigious doctor in a prestigious hospital, than when it is offered as part of an experimental research program with a more neutral attitude. Similarly, research centers in which the staff genuinely believe that light treatment can produce powerful effects might produce better results than research centers with a more pessimistic staff. Furthermore, researchers who believe morning light is more effective than evening light are more likely to produce data in that direction, just as researchers who believe bright light is equally effective regardless of the time of day are more likely to produce that result. Presumably, these biases will be passed on to the patients before or during the course of their therapy.

The media and popular press provide a wealth of optimistic information on phototherapy for SAD. Thus, most patients enter research protocols with preconceived notions about treatment efficacy. These notions may differ between countries or between cities. Presumably, the information patients receive when they enter a treatment protocol, given either intentionally or unintentionally, will further shape their expectations. Few studies attempt to assess these expectations, and the method sections of phototherapy reports rarely state the specific information and instructions given to research subjects.

Some miscellaneous and situational variables that may influence placebo response include the cost of treatment, reputation of the doctor, atmosphere of the office (informed or intimate, busy or unhurried, etc.) use of nurses or aids to administer treatments, contact with other patients in waiting rooms (untreated patients may be favorably influenced by treated patients), etc. (Shapiro, 1971; Shapiro and Morris, 1978). Differences in response rates to bright light treatment across research centers might depend more on factors like these rather than the parameters that are usually given the most attention, such as light intensity and duration.

Another example illustrates how the expectations of doctors influence the treatment response of patients. The placebo response rates of anxious psychiatric outpatients were evaluated in a series of studies (Lowinger and Dobie, 1969). In one study three different drugs (which we will designate as A, B, and C) and placebo were evaluated in a double-blind design. The response rates are shown in Figure 2, top. Since the response rates were so low, a replication study was later performed, but with doubled doses. This time the response rates were larger, as expected.

The important point to note for our purposes is that the placebo response rate more than doubled, from 35 percent to 76 percent, although an inert placebo was used in both cases. The author's interpretation was, in part, that the doctors were more enthusiastic and more alert to toxicity in the large dose study (even though they did not know whether any particular patient was given drug or placebo) and that these attitudes were somehow conveyed to the patients. The investigators also noted that because the setting in which a new drug is evaluated is of considerable importance, it may be misleading to compare drug evaluations from different clinical settings. We would add that it may also be misleading to compare placebo response rates from different research centers.

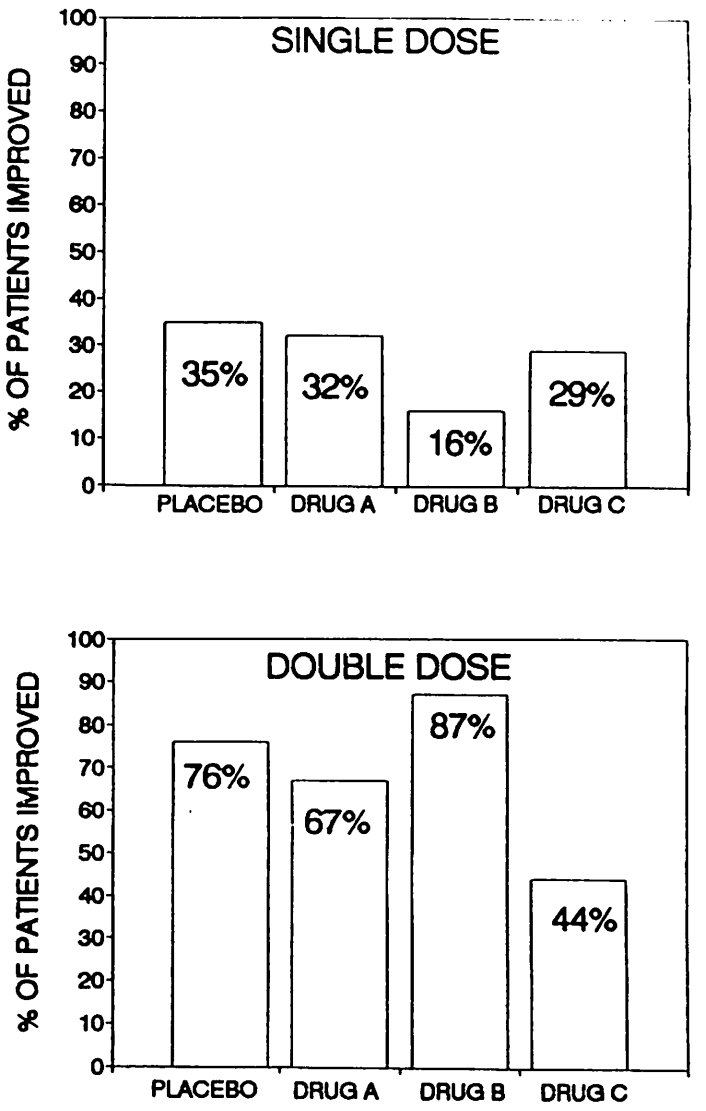

Figure 2. Response rates of psychiatric patients to drugs and placebos from a series of studies by Lowinger and Dobie, 1969. Top: Study performed in 1960 with an n of 94. Bottom: Study performed in 1962 with an n of 65, which was similar to the 1960 study, but with doubled doses of the medications. Note the increased placebo response rate in the second study.

Once again we can speculate on how this principle could be applied to bright light treatment studies of SAD. Imagine that one winter a group of researchers conducts a study of light therapy, but finds disappointingly low response rates compared to some published reports. For the next winter's study they decide to purchase the most powerful (most intense) light banks on the market. The staff would naturally be more enthusiastic, expecting to get greater antidepressant responses. Given the principle illustrated above, we would expect the data to demonstrate a greater response to

light treatment in the second study, even if the antidepressant response were entirely due to a placebo effect.

Placebo Controls Reduce Active Treatment Response

What's Wrong with This Statement from a Bright Light Study with No Control Treatment?—"This response rate to bright light is higher than virtually all other published reports and may be inflated."

A review of antidepressant drug studies shows how the design of the study influences treatment response (Wechsler et al., 1965). All the appropriate studies of hospitalized depressed patients published in the 5-year period between 1958 and 1963 were included. The studies were placed into three categories according to the type of design: (1) studies employing no control group (n = 30); (2) the traditional double-blind comparisons of one active medication and a placebo control group (n = 22); and (3) a more complicated design comparing at least two active medications and possibly employing a placebo (n = 27). Each antidepressant drug was classified as to whether or not it produced improvement in at least 65 percent of the patients.

The results are shown in Figure 3. When drugs were evaluated against only a placebo control (right bar), they were less likely to produce a good response.

The authors' interpretation was that the studies were not triple-blind; the staff making ratings of improvement were aware of the research design. In the case of a study comparing drug to placebo, the staff knows that half the patients are receiving placebo. This may influence them to rate improvement more conservatively than in a study in which they know that all or most treatments are active. We should add that the staff would expect more patients to improve when the design includes mostly active treatments than when half the patients are on placebo. These expectations could be somehow communicated to the patients producing differences in the patients' actual responses.

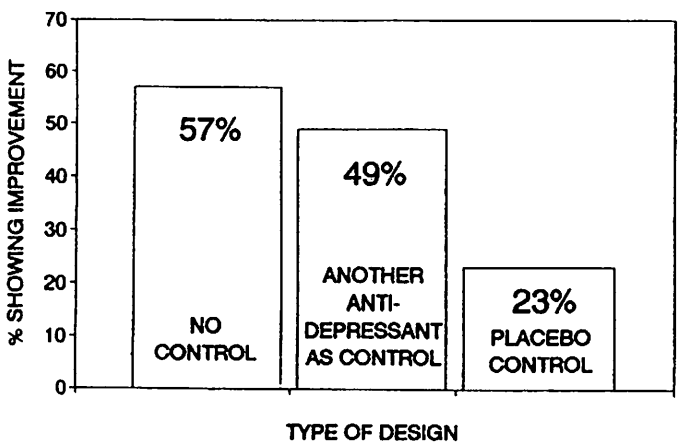

Figure 3. Percent of tests in which antidepressant drugs produced improvement in at least 65 percent of the patients classified according to design of study. There were 79 studies which included 107 tests of six different antidepressants. Data taken from Wechsler et al., 1965.

Once again we can speculate on how this principle could be applied to bright light treatment of SAD. Designs with no control treatment, or in which the control treatment is bright light at a different time of day are similar to those included in the two left bars of Figure 3. The staff and the patents know that in all cases the patients are receiving some type of bright light treatment. They are undoubtedly more enthusiastic about the chances for success in any individual patient than in the case of a placebo control, when half the patients are on a placebo. Thus, a placebo-controlled light study should produce the most modest response to bright light treatment.

Placebo Responses Are Underrated

What's Wrong with These Statements?—
"Light therapy for SAD is probably not just a placebo because the response rate for improvement is unusually high."

"A method for distinguishing between placebo and real responses is to use the criteria of Terman et al. The latter responses should bring the Hamilton Rating score to less than 8 points and to less than 50% of the baseline rating."

To summarize thus far, faith, enthusiasm, positive expectations, a prestigious investigator or physician, and bias for a particular treatment can increase the effectiveness of the treatment and of placebos. The expectations of physicians, researchers, staff and patients are all important in this regard. The research shows that placebo effects can be strong and enduring, although many scientists erroneously believe that placebo effects are small and short lived. In fact, an implicit belief held be many researchers is that if a treatment consistently produces dramatic improvements in a particular condition, then it cannot be working purely through a placebo mechanism. However, the only scientific demonstration of incremental effectiveness for a treatment is comparison with a placebo condition. Furthermore, that placebo condition must be as identical as possible to the "active" treatment, to equate the non-specific factors and expectations which can be so powerful. The same attention, enthusiasm, and effort

should be applied to the placebo treatment as to the active treatment.

Placebo Response Rates Are Variable

What's Wrong with These Statements?—
"A pure placebo effect rather than a specific effect of the light is an unlikely explanation because the degree of improvement was similar to that shown in other studies of bright light treatment and clearly superior to previous placebo control conditions."

"The response rate of about 30% for this bright light treatment seems to represent a greater benefit than a placebo response. But a placebo response rate for SAD patients is still unknown."

"We question whether the response rates for bright light treatment X, which are in the 30-40% range, exceed expected placebo response rates for depressed patients."

"Although this study did not include a placebo condition, the magnitude of response is similar to that found in other studies of bright light treatment."

"Antidepressant response to bright light treatment X is high, with about 80% of patients showing clinical remission within about a week, a rate that equals or exceeds most prior bright light treatment studies."

"SAD patients do not have high placebo response rates as shown in studies using placebo medication or dim light boxes."

"Our SAD patients do not appear to have high placebo response rates."

We have seen how placebo response rates can be inflated or diminished depending on the design of the study and on the expectations of the researchers and patients. It is not surprising, therefore, to see widely varying placebo response rates, even for the same disease and same treatment (Ross and Olson, 1981; Shapiro, 1971; Shapiro and Morris, 1978). In the review by Greenberg and Fisher (1989), which will be discussed more fully below, placebo response rates in antidepressant drug studies varied from 0 percent to 91 percent. They cite differences among results obtained from sites of multicenter antidepressant drug studies to further highlight this point. Thus, bright light treatment research studies should always include a control treatment. Borrowing placebo response rates or treatment response rates from another study, or using the average response rates from a review of studies is not acceptable.

The Search for Consistent Placebo Responders

There is no evidence that placebo responders are stupid or gullible. Attempts to identify placebo responders with personality tests, measures of intelligence, tests of suggestibility, and demographic variables such as sex and age have been unsuccessful (Brown et al., 1988; Buckalew et al., 1981; Honigfeld, 1964a, b; Merin, 1973; Shapiro, 1971; Shapiro and Morris, 1978). This general failure is probably because placebo effects depend on the patient's expectations for relief, and thus are likely to be specific to certain situations (Jones, 1977). In other words, an individual who has a placebo response in one situation, may not have a placebo response in another situation.

Do Placebo Effects Wear Off?

What's Wrong with These Statements?—
"Results of the present study in which patients were followed up for several weeks suggest that light therapy can benefit patients with winter depression. Although the effects of placebo may have contributed to the initial responses, this factor is unlikely to have had a continued influence over several weeks."

"If the beneficial effects of light therapy are due to patient expectations or other nonspecific factors, they should be transient."

Clinical lore is that placebo responses may occur in the initial phase of treatment, but then wear off with time. However, long-term studies usually show that patients maintained on placebos continue to improve, although perhaps not as much as with active treatment. Graphs showing the increasing effectiveness of placebos over time can be seen in a 6-week antidepressant drug study (Stark and Hardison, 1985), a 4-week electroconvulsive therapy study (Johnstone et al., 1980), and a 6-week antipsychotic drug study (Davis, 1980).

We must conclude that it is difficult to find evidence supporting the common notion that placebo effects wear off.

What's Wrong with These Statements?—
"Light therapy for SAD is probably not just a placebo because patients relapse on withdrawal of the lights."

"One argument for the specific antidepressant effect of bright light treatment is the observation of relapse during withdrawal."

On the other hand, withdrawing the placebo can produce relapse just as after drug withdrawal (Berg, 1977; Lasagna et al., 1958).

What's Wrong with These Statements?—
"Light therapy has been used throughout the winter without any loss of efficacy, which would be unusual for a placebo effect."

"A placebo mechanism alone is not a plausible explanation for the antidepressant effect of light therapy because it has been effective repeatedly and for prolonged periods of time within individuals, whereas placebos generally decrease in efficacy over time and with repeated use."

Although our literature search did not produce evidence that placebo effects wear off over time, we did find numerous examples of specific treatments falling from popularity over time, being replaced by the latest technique. When this happens the old treatment loses much of its placebo effect because the enthusiasm and interest are attached to the new treatment (Honigfeld, 1964a; Shapiro, 1959, 1971; Shapiro and Morris, 1978; Wolf, 1959). Thus, we can expect continuing benefits from a placebo treatment as long as it remains popular and enthusiastically approved by the medical community.

One of the arguments often used for evidence that phototherapy for SAD is not merely a placebo is that it can be effective throughout the winter months and can produce reliable effects repeatedly in the same individual at different points in the winter as well as in successive winters. The literature suggests that a good placebo could produce similar long-term and reliable effects.

End of Excerpts

As I stated previously (LTBR, 5, 30-31, 1993), patients should not be overly concerned over whether any light treatment device they are using is entirely a placebo. As long as the treatment works well for them, it is worthwhile. Scientists, however, must continue to try to tease apart placebo effects from specific treatment effects, in order to learn more about the causes of SAD and to develop new treatments.

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CIRCADIAN CLOCKS IN THE MAMMALIAN EYE: A COMMENTARY

As a new graduate student in Michael Terman's lab, my first research project was a study examining circadian rhythmicity in the visual detection performance of rats. This study, already ongoing when I arrived in the lab, combined Michael's earlier interest in the behavioral analysis of animal sensory processes with his more recent interest in circadian rhythms. We found that rats displayed free-running circadian rhythms in detection accuracy when allowed continuous access to a self-paced psychophysical task in the home-cage environment (Rosenwasser et al., 1979). In this task, rats initiated trials by a lever-press, and then triggered the presentation of a brief, dim visual stimulus by a nose-poke response, ensuring that the head would be pointed toward the stimulus. The trialwise probability of stimulus presentation was 0.5, and the animal was trained to report detection or non-detection of the stimulus by pressing one of two alternate levers. Correct detections and correct rejections were both reinforced by electrical stimulation of the lateral hypothalamus, maintaining sufficient behavioral output throughout the circadian cycle for analysis of detection rhythms. When it eventually became time for me to present a dissertation proposal, Michael thought that it would be most interesting to determine whether these novel visual detection rhythms persist after destruction of the suprachiasmatic nucleus (SCN), but I felt certain that this study would only lead to the identification of yet another SCN-dependent rhythmic function and so pursued a different research direction.

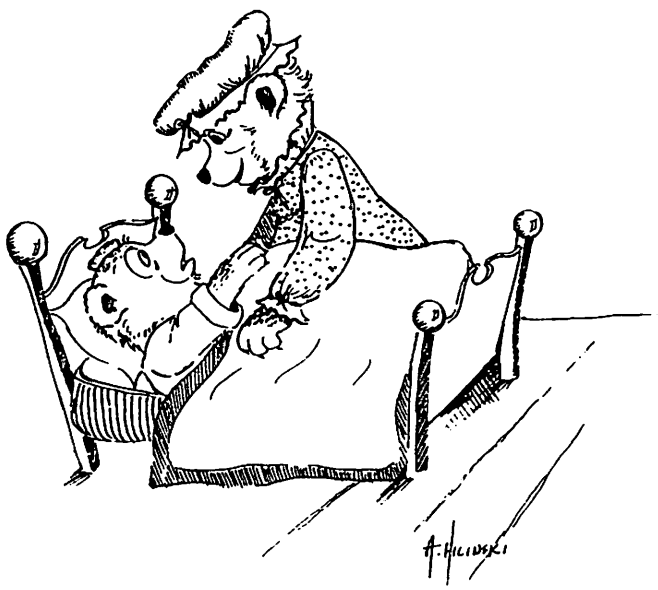
In part, our different predictions reflected different opinions regarding the nature of the visual detection rhythm itself. Despite our use of a detectability index (d') derived from Signal Detection Theory and thought to be relatively free of contamination by motivational factors; and despite our finding of a consistent phase-difference between free-running rhythms in the *accuracy* of performance and in the *vigor* of performance (i.e., the number of self-initiated test trials per hour); I never felt confident that the rhythms we were measuring reflected temporal variation in sensory processing. Instead, I believed that rhythmic visual detection performance was just that—a performance rhythm, rather than a visuosensory rhythm. In contrast, Michael always seemed more confident that this novel rhythm in fact represented oscillating visual sensitivity, and was thus fundamentally different from the behavioral and physiological rhythms already known to be dependent on the integrity of the SCN.

Apparently, Michael was right and I was wrong. At a subsequent conference on photobiology and photomedicine, Terman and Terman (1985) reported that robust circadian rhythmicity in visual detection persists after lesions of the SCN that abolish other behavioral rhythms in the same animals. These results strongly implied that the visual *detection* rhythm was in fact a visual *sensitivity* rhythm, functionally and anatomically dissociable from circadian modulation of drive, arousal, and other performance factors. Further, this rhythm could be photically entrained, reentrained, and phase-shifted after SCN lesions (Terman and Terman, 1985; Reme et al., 1991). Although the locus of the driving pacemaker was not known, Terman and Terman (1985) speculated that oscillating visual sensitivity depends on "a specialized pacemaker for circadian sensitivity, possibly within the eye..." (p. 156).

This hypothesis seemed plausible given that several aspects of retinal morphology and physiology display circadian variation in both mammalian and non-mammalian vertebrates (Reme et al., 1991; Cahill and Besharse, 1995). Direct evidence for intraocular circadian oscillators controlling melatonin synthesis in cultured *Xenopus laevis* eyecups was presented as early as 1983, while subsequent studies have localized the intraocular oscillator in *Xenopus* to the retinal photoreceptor layer (Cahill and Besharse, 1995). Though somewhat less conclusive than tissue culture studies, rhythmic retinal melatonin synthesis in Japanese quail

persists after pinealectomy, sympathectomy, and optic nerve section, creating a kind of *in vivo* culture system (Underwood et al., 1990). In rats, similar experiments have shown that circadian rhythmicity of rod outer segment disk shedding—like the visual sensitivity rhythm—is unaffected by SCN lesions, and that disk shedding rhythms also persist after pinealectomy, optic nerve transection, and sympathectomy (Reme et al., 1991); Cahill and Besharse, 1995). On the other hand, Bobbert and Brandenburg (1982) reported that sympathetic denervation abolished circadian rhythms in electroretinographic sensitivity in rabbits, and Teirstein et al. (1980) found that optic nerve transection altered phase-shifting of the disk shedding rhythm in rats. These results indicate that optic nerve and/or sympathetic efferents may allow for reciprocal influence between retinal and central oscillators.

Now, Tosini and Menaker (1996) have reported the first successful demonstration of sustained circadian rhythmicity in a mammalian retinal culture preparation. In this study, hamster retinas were cultured at lowered temperature (27°C) revealing rhythmic melatonin synthesis that was apparently masked under more typical 37°C conditions. As in *Xenopus*, elevated retinal melatonin synthesis was seen at night under light-dark conditions and during subjective night under constant darkness. This rhythm persisted with undamped amplitude for at least five cycles, and could be reentrained by exposure to phase-shifted light-dark cycles *in vitro*. Remarkably, retinas collected from wild-type hamsters and from hamsters homozygous for the circadian clock mutation, *tau*, showed melatonin rhythms with free-running periods identical to those seen in the locomotor activity rhythms of the two phenotypes (i.e., about 24 hours in wild-type and about 20 hours in *tau* mutants), indicating that the *tau* mutation affects a molecular clock "gear" shared by circadian oscillatory mechanisms in the hamster SCN and retina. This groundbreaking study provides the first direct evidence for autonomous, self-sustaining circadian rhythm generation by mammalian neural tissue outside the SCN. Of course, it remains to be determined whether the retinal clock generating melatonin rhythms is also related to visual sensitivity, disk shedding, or other retinal rhythms. Such relationships do seem plausible, since melatonin appears to act as a paracrine mediator imparting circadian organization to several other aspects of retinal function in *Xenopus*, and given that the hamster *tau* mutation also shortens the period of the disk shedding rhythm (Grace et al., 1996).



MOTHER ARE YOU TELLING ME THE TRUTH ABOUT THIS SUPRACHIASMATIC NUCLEUS THING? WILL I REALLY WAKE IN THE SPRING?

As reviewed by Morin (1994), the circadian visual system in mammals comprises a distinct neural system largely separate from the circuits and pathways subserving visuoperceptual function. This parallelism probably begins in the photoreceptive elements (Garcia-Fernandez et al., 1995), and continues through the ganglion cells (Moore et al., 1995) and into the brain. Despite this anatomical segregation, circadian modulation of visual sensitivity may represent a common form of functional "handshaking" between the circadian and image-forming visual systems. Such handshaking could occur both peripherally—where an intraretinal oscillator could cause increased nighttime sensitivity to both perceptual and chronobiological effects of light—and centrally, where SCN efferents could modulate several aspects of visual processing. While the specific mechanisms generating visual sensitivity rhythms remain unknown, Tosini and Menaker's report may spur renewed interest in their identificaion.

In nonmammalian vertebrates, both circadian pacemaking and circadian photoreceptive functions are distributed within a retino-hypothalamo-pineal system comprising the circadian neuroendocrine axis (Cassone and Menaker, 1984; Rosenwasser, 1988), and considerable species diversity is seen in the relative importance of retinal and pineal mechanisms for maintenance of behavioral activity rhythms, the *sine qua non* of pacemaker identification. In contrast, mammalian pacemaking function appears to be localized to the SCN while mammalian circadian photoreception appears to be entirely retinal. Nevertheless, and perhaps surprisingly, circadian melatonin rhythms are seen in cultured pineals from a wide variety of nonmammalian vertebrates, whether or not

pinealectomy alters behavioral rhythms in that species. Such observations remind us that existence of a self-sustained pineal *oscillator* does not imply existence of a pineal *pacemaker*. The same is certainly also true of retinal oscillators, since robust rhythmicity persists after enucleation in hamsters and other mammalian species.

On the other hand, this logic does not rule out the possibility that a retinal clock contributes in some subtle fashion to the organization of the mammalian circadian system. Indeed, the mammalian pineal neither serves as a circadian pacemaker nor contains a self-sustaining circadian oscillator, but pineal melatonin nevertheless does appear to influence the hypothalamic pacemaker and thus contribute to rhythmic expression under some conditions (Thomas and Armstrong, 1988; Cassone, 1992; Yanovski et al., 1990). Even in constant darkness, a retinal clock could generate circadian variation in retinohypothalamic tract activity by modulating the frequency of spontaneous dark discharge, and one could imagine that this low-level rhythmic input could subtly influence central clock function; for example, by altering free-running period. While direct comparison of the effects of constant darkness and blinding on circadian behavior in nocturnal rodents is lacking, Bobbert and Riethoven (1991) have suggested that oscillating retinal dark discharge may alter substantially the free-running period in rabbits. In this species, free-running period is longest in constant darkness, shorter in constant light, but shortest in blinded animals! In addition, identification of a circadian clock in the mammalian retina provides the beginnings of an anatomical foundation for the concept of a distributed multioscillatory circadian timing system. Despite considerable functional complexity suggestive of multiple oscillators (e.g., splitting, transients, etc.; cf., Rosenwasser and Adler, 1986), the only previous direct evidence for redundancy of oscillator function in mammals has been at the intra-SCN (e.g., Welsh et al., 1995) rather than extra-SCN level. The notion that uncoupling between anatomically distributed oscillators partially underlies the functional complexity of the circadian timing system appears at least somewhat more plausible in the context of Tosini and Menaker's findings.

Finally, as Tosini and Menaker point out, the existence of a mammalian retinal circadian oscillator suggests that self-sustained oscillatory function may be found wherever circadian photoreceptors are found, in both mammalian and nonmammalian vertebrates: both functions are found in the mammalian retina, but neither (so far as we know) are found in the mammalian pineal. It would not be surprising if both functions are shared by the same retinal cellular population, as appears to occur in at least some nonmammalian vertebrates (i.e., *Xenopus*) and invertebrates (i.e., *Bulla*).

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TIME BANDITS

It is odd, as a bilingual chronobiologist, how normal seem to me the German words that have infiltrated circadian diction. It is only when I found the following sentence on the Internet (SLEEP-L), did I realize that the nuances between the various Zeit-words are more delicious when one can be amused by the connotations in both languages.

"I ... would imagine clinical intervention should probably concentrate on developing other zeitgeist stimuli to their fullest potential. "

So: zeitgeist stimuli. After years of studying mundane zeitgebers, the mind boggles at this new dimension to our research. I wonder what such stimuli could be.

I sent the above to Our Editor, who replied: "I looked in my German dictionary to see what's in there under Zeit--. Someone knowledgeable in the language (hint, hint) could write a whole essay on chronobiology using "Zeit" words. Such as Zeitabschnitt, Zeitabstand, Zeitangabe, Zeitaufnahme, Zeitaufwand, Zeitbeduerfnis, Zeitbehelf, Zeitbestimmung, etc. Zeitgeber is absent, although Zeitnehmer might suffice in a pinch. Frankly, I like Zeitschrift as a pun meaning "periodical" and Zeitlichkeit has a hallowed ring to it. All kept pace by a Zeitmesser. I'm sure a clever Swiss wordsmith with good Zeitsinn could go on for a long zeitraubend Zeitraum on this!"

It must have been early morning mania that inspired him. The words don't even need translation, because you can intuit their meaning, or at least, fantasize one (go get your German dictionary). I didn't take his hint, hint. But perhaps this is the opportunity to share a wonderful list of thirty-three alternative spellings of zeitgebers given by Biology students in a final exam:

Zeigers
Zetgerbers
Zeitgeists (aha!)
Zeitagibers
Zetibergs
Zeitgerers
Zeitebergers
Zetiebers
Zeitglibers
Zeitengebers
Zetigebers
Zeitigebers
Zeiterberg
Zietgeibers
Zetebergers
Zeiterburgs
Zitegers
Zeitgeibers
Zeightgebers
Zetgiebers
Zeitgerbers
Zeitberge
Zetibers
Zeitgibers
Zeitegebers
Zetigebegers
Zeitibergs
Zeiterbars
Zietbergurs
Zeitinburgers
Zeiterbers
Zietgieters
Zetegerbers

This list, compiled by a graduate student at the University of Washington, was sent to Colin Pittendrigh in 1982 who forwarded it to Juergen Aschoff with the comment "Zeitebergers and Zeitinburgers are good with Zwiebeln." Zeitinburgers, of course, are THE as yet unresearched primary zeitgeber for food intake.

One could start getting carried away. Zeiterbars are where you can spend lots of time (on zeiterbeers). Zietgieters are the dutch version, to be consumed with an iced glass of oude genever (modelled by Daan & Beersma). Zeitgerbers are used only to entrain gerbils (not hamsters). Zeitberge and Zeitibergs are mountains of time (another way of free-running). Zeitgibers are nasty people who say gib gib gimme...

But it was important to return to the source of all this trouble, to ask Aschoff why he had had the presumption to introduce such obscure terminology in the first place. He replied immediately (tongue in cheek), and so we now have the ultimate historical explanation): "The enormous fuss arising around the word 'zeitgeber' can be traced back to a printing mistake in the proofs of my first article on this theme. There it should not have been called 'Zeitgeber' (with an i), but Zeltgeber (with an l). The word 'Zelt' (tent) can be traced back to the old-norse 'tjald' (curtain), from which is derived the french verb 'taudir' (seek shelter). Zeltgeber, then, are those signals that exhort the organism to seek shelter or leave it. Unfortunately, this printing mistake was only recognized long after the word 'Zeitgeber' (a totally meaningless neologism) had established itself in the literature."

Our Editor still complained, "but I don't see on the list the word for yesterday's entraining agent. Shouldn't it be some-

thing like Zeitgegebener? Maybe "time giver" is a misnomer altogether since the clock already has circadian time. Maybe Zeitdampfungsflosse or Zeitfestigkeit would be more appropriate and germanic? Perhaps we can solicit further input in a Zeitpunkt poll to temporarily replace the Flash-Light poll."

So I asked around in a very non-representative e-mail. There were many non-replies. To the question, "What are zeitgeist stimuli?" Marty Zatz provided the definitive definition: "Don't you know? They come in over the Internet. Specialty of a jointly owned subsidiary of Microsoft and Disney Corp." Dave Klein was less informative: "Stop the Zeitscheiss!" Tim Monk had a creative suggestion to end this teutonic dominance of the circadian vocabulary: "Of course, now that we all recognize the importance of light as an entraining agent of the human circadian system, perhaps we should rename them SIGHTGEBERS!"

Scott Campbell was meticulous in his definition "Zeitgeist stimuli: that class of inducement which, when given with the proper experimental fervor (i.e. 'spirit'), cause the biological clock to be entrained or reset." He also added a more typical campbellian definition, namely, "those stimuli that, when experienced by the entire experimental sample, take on an importance that cause them to be the subject of a *Time* magazine cover story."

A serious suggestion came from Alex Borbely: "It is time to drop the German term 'Zeigeist' and refer to it as 'time ghost'. " The importance of these ghosts for the circadian system becomes immediately evident, because ghosts are well known to appear after midnight and disappear with dawn. Their close relationship to darkness raises the question whether they are related to melatonin. In fact, there is an unconfirmed theory that time ghosts arise in the evening hours and are present, but invisible before midnight. If confirmed, this would strengthen the time ghost/melatonin association. Another important question is whether, under constant routine conditions, time ghosts start to free run or to "free float."

Then things began to turn cynical. Ben Rusak expressed the present zeitgeist quite concisely: "I think it is safe to assume that 'zeitgeist' stimuli suitable for entrainment would have the following characteristics: They would be outsourced, rather than produced in the clinic in which they are used. The outsource would certainly be in the private sector. Once arrived in the clinic, the stimuli would be downsized for greater efficiency. The staff applying the stimuli would be let go, and rehired under short-term contracts by a personnel agency providing services to the clinic under their own contract. For reasons no one would ever be able to trace, some extremely wealthy people, mostly bank shareholders, would get yet more extremely wealthy as a result of the entire process. The patients would have to wait three times as long as previously to get their treatments, and pay an exorbitant "facilities" fee to do so. The patients would not get any better, but no one would really care."

Irv Zucker was similarly despondent: " A zeitgeist stimulus captures the essential character of the society/culture at a fixed moment in time and serves to distinguish it from the previous 'era'. Some potent current zeitgeist stimuli are: pheromones distilled from the armpits of CEOs: when brought into proximity of executives of any large company, they cause these individuals to opt for a merger with yet another, even larger company, eventual 'downsizing' and casting adrift into unemployment thousands of individuals." As Ray Lam put it, "Perhaps a zeitgeist stimulus could be considered a chronotrend?"

There is indeed little in the current zeitgeist—forget about the stimuli—to please any reasonable person. But let us continue with the newest technique that appeared in Sleep-L: "Is anyone aware of any research relating to treatment of insomnia in blind people caused by a free-running circadian rhythm? I'm specifically interested in treatment through artificial stimulation of the suprachiasmatic nucleus." Here we go. Zeitgeist stimulation. Tickle your clock.

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