Light Treatment and Biological Rhythms

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MELATONIN MADNESS

Jug-ger-naut; 1. an incarnation of the Hindu god Vishnu, whose idol, it is said, so excited its worshipers when it was hauled along on a large car during religious rites that they threw themselves under the wheels and were crushed...
—Webster's New World Dictionary of the American Language (1966)

Doctor who treats himself has a fool for a patient.
—Anonymous

Melatonin supplementation in humans has recently emerged from biomedical *esoterica* to become a widely self-administered, over-the-counter treatment for a variety of conditions including aging itself. Coincident with this development has been the publication of several popular books on the subject, the most seductive of which were co-authored by melatonin researchers writing for lay audiences. The books must be judged on their individual merits, only one of which is their likely effect on an ever remedy-hungry public. But by this criteria, one is left pining for the bad old days when mere "...press releases and press reports [had] become [the] effective and frequently employed means of making mountains out of scientific molehills" (LTBR 1995; 7:48-49).

This issue includes entries intended to provide both comment on and counterweight to this juggernaut. Dr. Morin provides a detailed and coherent history of 40 years of work on melatonin, evoking the counterpoint between circadian rhythms and pineal physiology research as well as the gradual and painstaking process of investigation. Following this are overviews and critiques of the state of "claims" of clinical effects of exogenous melatonin in humans, first in an essay by Dr. Lewy and then in a review, by Dr. Hughes, of two recently published influential books on the subject by Pierpoli & Regelson and Reiter & Robinson. Following is a draft of a Melatonin Fact Sheet, written by Josephine Arendt and slated for eventual availability through the SLTBR publications office. For a more definitive review of melatonin research findings, readers are referred to Dr. Arendt's recently published book, not reviewed here but cited in Hughes' piece. Taken together, these pieces support the impression that publicity more than real understanding has pushed recent melatonin sales to surpass those of vitamin C in the United States (Lancet 1996; 347:184).

A clinician's role is not merely to explain or advise patients about treatment but also to prescribe or administer it. Paternalistic though it may seem, such authority derives, in part, from the recognition that fears and wishes, as much as lack of information, cloud rational efforts at self-healing. Thus, those suffering from either real or imagined ills are well-served by a dispassionate clinician who, simply by being other, helps to reconcile claims and disclaimers and serves a useful gatekeeper role. That such a gatekeeper role is undermined by lay-directed solicitations for longevity, cancer prevention, AIDS therapy, and sexual potency, atop an even longer list, is unfortunate and likely dangerous. One can only hope that such publicity is as successful in providing impetus for further research.

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THE HISTORY OF BIOLOGICAL CLOCK RESEARCH: INTERWOVEN STUDIES OF MAMMALIAN PINEAL FUNCTION AND CIRCADIAN RHYTHM REGULATION

In the early 1960's, there were two research areas that were being vigorously, but separately, pursued. On the one hand, the pervasive nature of the phase response curve was being uncovered by investigations evaluating formal properties of circadian rhythms. On the other hand, great strides were made toward the understanding of pineal physiology. In the literature, the two areas of research became linked by the fact that critical events in pineal physiology (melatonin regulation, in particular) are rhythmic in the circadian domain and under phase control by light. The results of the extensive studies into rhythmic pineal activity were directly incorporated into the experimental and theoretical framework guiding investigations of photoperiodic time measurement. Full comprehension of photoperiodism has depended upon an understanding of both the neural pathways regulating pineal physiology and those controlling circadian rhythms. At some levels of analysis, the two are identical in form and function. Similarly, full comprehension of photoperiodism has required extensive research into melatonin's function as a regulator of gonadal activity. The circadian phase-specificity of this action contributed to the discovery that melatonin might also act as an entraining agent. The broad scientific contributions from biological rhythm research are likened to an elegant woven fabric in which the warp consists of pineal physiology studies and the weft is made of investigations into circadian rhythm regulation with common mechanisms shared by each. All areas of biological rhythm investigation have employed extensive inter-species comparisons which form a strong foundation of fact, theory and rationale for current research directed toward understanding the rhythmic regulation of human physiology and behavior.

The history of mammalian biological rhythm research is a fine fabric woven with a warp compiled of studies designed to elucidate mechanisms regulating pineal physiology. The weft of this fabric consists of investigations into the mechanisms generating and controlling circadian rhythms. Although the warp and weft are each individually identifiable components of the whole, they are inextricably linked. Similarly, at some levels of biological rhythm analysis, pineal regulation is also inseparable from regulation of circadian rhythmicity because common mechanisms are utilized for each function. This presentation emphasizes the interdependent historical relationships between studies of mammalian circadian rhythmicity and pineal physiology that have been woven into the scientific fabric of the past 40 years.

The phenomenon of reproductive seasonality in animals has been known for many centuries. Relatively recently, seasonality in some species has been determined to be a consequence of photoperiodic time measurement (PTM). PTM requires an internal, "circadian" clock with a natural period of about 24 hr which is used to interpret day length, the most reliable predictor of time of year. The study of circadian rhythms, endogenous self-sustained oscillations with periods of about 24 hr, gained enormous momentum in 1958 with the publication of Bunning's book, *Die Physiologische Uhr* (the most recent edition is Bunning, 1973). This was followed by three very influential symposia publications (The

Cold Spring Harbor symposium on *Biological Clocks* (1960); Aschoff, J., ed. (1965) *Circadian Clocks*. Amsterdam: North Holland; Menaker, M., ed. (1971) *Biochronometry*. Washington, D.C.: Natl. Acad. Sci.). These books sketched the field of biological rhythms not only in terms of understanding about formal properties of circadian clock regulation, but also in terms of circadian clock function for such things as seasonality. The early history of circadian rhythm study is summarized well by Pittendrigh (1974) in another influential publication.

Phase Response Curves

One early and most important development in the study of circadian rhythmicity was the discovery of phase response curves (PRCs). This discovery showed that when an organism is stimulated at a particular phase of its circadian rhythm, a perturbation occurs in the rhythm which varies in magnitude and direction according to the phase at which the stimulus is applied. When the stimulus is applied at different circadian phases and the corresponding perturbations plotted as a function of phase of application, the result is a PRC. The ability of investigators to generate PRCs illustrates a point at the historical foundation of all research into circadian rhythmicity. Without the physiological mechanisms providing the capacity of phase response to an environmental stimulus (usually light), the endogenous, self-sustained oscillator that is the circadian clock cannot become entrained to that stimulus.

PRCs are indispensable tools for the understanding of mechanisms of entrainment and circadian rhythm generation. The first published complete PRCs were demonstrated by Pittendrigh and Bruce (1957) with the fly, Drosophila pseudoobscura, and by DeCoursey (1959,1960) with Glaucomys volans, the flying squirrel. The first hamster PRC was published in 1964 (DeCoursey, 1964). It is widely accepted in the field of circadian rhythms that every eukaryotic organism, whether plant or animal, expresses circadian rhythmicity and has a PRC. The pervasive interest in phase response curves has been acknowledged by the recent publication of an atlas (Johnson, 1990) with the sole function of showing the great variety of PRCs (there are presently 343 in the atlas) for plant and animal species under many conditions.

Aschoff's (1965) summary of the literature from vertebrates and invertebrates discusses the role of light duration, intensity, light/dark transitions and several technical issues concerning modes of light presentation when generating PRCs. A seminal presentation and discussion of PRCs and their role in entrainment came in a series of 5 papers by Pittendrigh and Daan (Daan and Pittendrigh, 1976a,b; Pittendrigh and Daan, 1976a,b,c). They emphasized species differences in PRCs and several effects of photoperiod history on circadian rhythm expression. The PRC shape itself has been shown to be dependent on prior photoperiodic history (Pittendrigh, 1981).

"Non-parametric" entrainment is typically considered the product of a discrete time-giving stimulus (Zeitgeber) interacting with the physiological mechanisms of the endogenous circadian clock (Pittendrigh, 1981). The non-parametric model of entrainment has two essential elements: the pacemaker period and the PRC (Pittendrigh and Daan, 1976a). The latter is generally obtained without regard to the importance of Zeitgeber intensity, quality or duration. Thus, most of the characteristics of entrainment to natural photoperiods can be mimicked by the use of simple white light pulses. Pittendrigh and Daan have shown how the non-parametric model of entrainment can be applied to several vertebrates in species-specific ways. In the extreme, hamster circadian wheelrunning rhythms will entrain to a "skeleton" LD 14:10 photoperiod consisting of two 1 sec light pulses bracketing the 14 hr dark interval (Earnest and Turek, 1983). The flying squirrel will entrain to a single daily 1 sec light pulse (DeCoursey, 1972).

The effects of continuous Zeitgeber effects on entrainment have not received as much attention as the effects of discrete stimuli. However, both the Drosophila eclosion rhythm (Pittendrigh and Minis, 1964) and the hamster running rhythm (Pickard, 1989) entrain to sinusoidal light presentation, a continuous "parametric" effect (Pittendrigh, 1981). "Velocity response curves" describe parametric effects of constant light on circadian period (Daan and Pittendrigh, 1976a). Period may either increase or decrease according to the prevailing light intensity (Daan and Pittendrigh, 1976a; Aschoff, 1979; Nelson and Takahashi, 1990). As stated above, many of the parametric effects of light had received earlier attention (for example, Menaker, 1968; Chandrashekaran and Loher, 1969) in birds and flies. In 1973, the rat body temperature rhythm was shown to entrain more effectively to certain wavelengths than others (McGuire et al., 1973), but it was not until 1984 that spectral sensitivity for photic entrainment was described in a mammal (Takahashi et al., 1984). As early as 1972, spectral sensitivity for suppression of the pineal enzyme, hydroxyindole-O-methyl transferase (HIOMT), was demonstrated (Cardinali et al., 1972). In 1991, an important article appeared (Nelson and Takahashi, 1991a) showing that the hamster circadian system essentially counts photons in order to determine the magnitude of phase response. A companion article in the same year (Nelson and Takahashi, 1991b) described differences between visual system sensitivity to phase shifting and visual sensitivity to suppression of pineal melatonin by a single wavelength of light.

Neural Circadian Clock

Anatomical research (Hendrickson et al., 1972; Moore and Lenn, 1972) demonstrated a direct projection from the

retina to the suprachiasmatic nucleus (SCN) of the rat hypothalamus. The entraining effects of light are retinally mediated in mammals, yet no lesions of previously known visual projections were able to disrupt entrainment (Moore et al., 1968). Therefore, as a direct and immediate consequence of the anatomical discovery, several investigations (Stephan and Zucker, 1972; Moore and Eichler, 1972; Rusak, 1977) used lesion methods to establish the SCN as the likely site location of the circadian clock mechanism of rodents. Subsequent studies of *in vivo* (Inouye and Kawamura, 1979) and *in vitro* (Schwartz and Gainer, 1977; Green and Gillette, 1982; Groos and Hendriks, 1982; Shibata et al., 1982) SCN rhythms, as well as SCN stimulation (Rusak and Groos, 1982) and transplant investigations (Drucker-Colin et al., 1984; Lehman et al., 1987; Ralph et al., 1990), reinforced the anatomical implications of the lesion studies. The circadian clock in the SCN receives direct photic input from the retina (Groos and Mason, 1978; Sawaki, 1979; Groos and Mason, 1980). This retinohypothalamic tract is necessary and sufficient for circadian rhythm entrainment (Johnson et al., 1988). Elaboration of these basic observations continues at present with a large research effort devoted to the understanding of the organization and function of the suprachiasmatic nucleus.

Light Control of Pineal Physiology

Studies of circadian rhythmicity paralleled investigations of rat pineal gland function. These began with the observation by Fiske in 1960 that when animals were exposed to long term constant light, their pineals weighed less than those of rats in constant darkness or diurnal lighting (Fiske et al., 1960). Other investigators confirmed this result in rat and hamster (Quay, 1961) and showed further that short term exposure to light reduced pineal weight (Wurtman et al., 1963b) and that weight varied across the day (Axelrod et al., 1965).

A series of studies at this time began to link the pineal with photic control of reproductive phenomena in the rat (reviewed in Wurtman et al., 1968). These included demonstrations that treatment of rats with pineal constituents could modify the reproductive variables being measured. One such constituent was melatonin (Lerner et al., 1958; Lerner et al., 1959). There was soon speculation that melatonin or a similar substance from the pineal might be a hormone mediating the reproductive effects of short photoperiod (Quay, 1963; Wurtman et al., 1963b). Wurtman et al., (1963a) injected melatonin into rats in constant light and reduced the incidence of light-induced persistent estrus from 85% to 45%. Subsequent studies of melatonin's effects on rat reproductive variables were inconclusive (for reviews, see Reiter and Fraschini, 1969; Reiter and Sorrentino, 1970). However, melatonin was shown to have reliable effects on reproductive variables in weasel (Rust and Meyer, 1969), ferret (Herbert, 1971) and Djungarian hamster (Hoffmann, 1972; Hoffmann, 1973).

It was determined early on that melatonin content of the pineal varied with time of day (Quay, 1963; Wurtman et al., 1963b). In human plasma, a clear rhythm in a "melatonin-like substance" was demonstrated in 1973 (Pelham et al., 1973). In their 1980 review, Reppert and Klein (1980) list 8 species of mammals for which melatonin was known to increase during the night. The pattern is similar for both nocturnal and diurnal animals.

Suppression of Pineal Melatonin-Regulating System by Light

Much of the ensuing investigation into the physiologic control of melatonin was performed with rat pineal, a very useful model system for the study of pineal biochemistry (see Wurtman et al., 1968 for a review). The initial work (Wurtman et al., 1963b) demonstrated that light suppressed HIOMT, thought at the time to be the rate limiting step for melatonin synthesis. Further, enucleation blocked the suppressive action of light and equated HIOMT levels with those found in animals exposed to constant darkness (Wurtman et al., 1964b; Wurtman et al., 1964a). Removal of the superior cervical ganglion also was able to eliminate the daily rhythm in HIOMT (Wurtman et al., 1968). The ability of ganglionectomy to block actions of light had been suggested much earlier from work with the ferret (Abrams et al., 1954; Donovan and Van der Werff ten Bosch, 1956) although the mechanism had not been postulated to include the pineal.

Despite the fact that the initial studies evaluated light-suppression of HIOMT, this assay was not entirely reliable. A rhythm of HIOMT could not always be found (Quay, 1967; Lynch and Ralph, 1970; Reiter and Klein, 1971) although prolonged exposure to light did depress the enzyme (Wurtman et al., 1963b; Axelrod et al., 1965; Klein and Moore, 1979). Another pineal enzyme, N-acetyltransferase (NAT), was shown to fluctuate with robust rhythmicity that persisted in blind or constant dark-housed animals, but was suppressed by constant light (Klein and Weller, 1970).

Anatomical Control of Rat Pineal

Investigation of the neural pathways mediating photic control of the pineal began in the mid-1960's but did not proceed smoothly. There were two serious problems. First, the anatomical description of the visual pathways thought to transmit photic information to the pineal was incorrect. Specifically, the inferior fascicle of the accessory optic tract was thought to be fully crossed, but was later shown to be only partially crossed. Second, neither the SCN as circadian clock nor its innervation by a direct retinohypothalamic tract was known. Nevertheless, a series of well-designed experiments was published beginning in 1966 (Axelrod et

al., 1966; Wurtman et al., 1967; Moore et al., 1967; Moore et al., 1968; Moore and Klein, 1974; Klein and Moore, 1979). The studies utilized the same basic design strategy to partition the visual system into a set contributing to pineal regulation and a set with no role in pineal regulation.

In retrospect, two important results emerged from the initial work. The primary visual pathways could be excluded from further consideration as regulators of pineal function, and rhythmicity of the pineal could be blocked by lesions of the medial forebrain bundle placed in the lateral hypothalamus (Axelrod et al., 1966; Wurtman et al., 1967; Moore et al., 1967; Moore et al., 1968). Re-analysis of the functional anatomy subsequent to discovery of the retinohypothalamic tract and the SCN circadian clock showed that loss of the SCN blocked pineal rhythmicity (Moore and Klein, 1974). Further, the SCN regulated both pineal HIOMT and NAT levels, but neither primary nor accessory optic tracts mediated the effects of light on these enzymes (Moore and Klein, 1974; Klein and Moore, 1979). The earlier results indicating that medial forebrain bundle lesions would block pineal activity were no longer attributed to disruption of a visual pathway but to interruption of an SCN-efferent projection descending to the lower brainstem or spinal cord (Klein and Moore, 1979).

A proposed retino-pineal route by which pineal function is photically regulated was shown by Wurtman et al. (1968). The route included a fully crossed inferior accessory optic tract projection to the nucleus of Bochanek, an unknown path to the medulla, a third-order connection to the upper thoracic spinal cord, a fourth order connection to the superior cervical ganglion and a final projection from ganglion to the pineal. This route has been modified to exclude the projection to the nucleus of Bochanek but to include an SCN efferent path to the tuberal hypothalamus with the caveat that "details concerning the precise localization of hypothalamic connections regulating autonomic innervation of the pineal gland are not well known..." (Klein and Moore, 1979). The present status of the retino-pineal connection is much as it was in 1979. It is not yet clear how the SCN efferent projections exit the hypothalamus or how many synapses are in the descending pathway to the cervical spinal cord (see discussion below concerning the neuroanatomical regulation of photoperiodic time measurement).

Photoperiodic Time Measurement in the Hamster

The hamster proved to be a very valuable species for study because insufficient daily light causes reproductive collapse (Hoffman and Reiter, 1965), an effect that is robust and easily measured. A "short photoperiod" was determined to be <12.5 consecutive hours of light/24 hr day in the hamster (Gaston and Menaker, 1967). Enucleation results in a 0 hr daily light period and induces loss of reproductive function (Reiter and Hester, 1966) equivalent to that occurring during a short photoperiod. "Resonance" experiments (Elliott et al., 1972), patterned after previous work with plants and birds (Hamner, 1960; Hamner, 1963) demonstrated a photosensitive phase of the circadian day. If short pulses of light are administered to hamsters any time during this phase, the ability of prolonged daily darkness to inhibit reproductive function is blocked (Elliott, 1976). The effects of short photoperiod could also be blocked by removal of the pineal gland or the superior cervical ganglia (Reiter and Hester, 1966; Reiter, 1969). On the other hand, melatonin administered at the correct daily time induced gonadal collapse in long day housed hamsters (Tamarkin et al., 1976; Tamarkin et al., 1977a; Tamarkin et al., 1977b) which is similar to that seen if the animals are maintained in short photoperiod.

Central Pathways Controlling Hamster PTM

Demonstration that the SCN is the clock controlling circadian rhythmicity triggered studies of the SCN as a requirement for PTM. Thus, destruction of the SCN revealed loss of capacity for PTM in the hamster (Stetson and Watson-Whitmyre, 1976; Rusak and Morin, 1976). This discovery instituted a basic difference *in principle* between the ensuing research on central nervous control of hamster pineal and that which had been performed earlier with rats. The hamster strategy acknowledged the existence of a central circadian clock that, in some sense still unknown, controls the timing of synthesis and release of certain pineal constituents including melatonin. The SCN projects to numerous sites in the hypothalamus (Swanson et al., 1974; Berk and Finkelstein, 1981; Stephan et al., 1981; Watts et al., 1987; Morin et al., 1994), but the connecting pathways to spinal cord that mediate pineal function have not been elucidated in this or any species. Nevertheless, the most complete summary concerning the functional neuroanatomy of the path from the eye to the pineal was presented by Reiter (1980) based on results from the hamster. It is debatable whether the paraventricular hypothalamus is part of the pathway mediating PTM (reviewed in Smale et al., 1989).

Toward Integration of Rat and Hamster Literatures

Research on PTM was a driving force that eventually implicated melatonin as an effector hormone in the system controlled by circadian clock mediation of day length. However, the extensive parallel body of literature concerning the biochemistry of pineal gland physiology had been developing for many years. In 1974, Axelrod (1974) presented the understanding of pineal function in an important review paper titled, "The pineal gland: A neurochemical transducer." In it he summarized the metabolism of melatonin and rhythmicity of pineal constituents including NAT, HIOMT, and melatonin. They vary as a function of time of day with essentially none being synthesized during the daylight hours. Because the two enzymes regulate synthesis of melatonin, their rhythmic

fluctuations and their response to light have been considered to be indices of melatonin levels (see Wurtman et al. 1968; Axelrod, 1974; Reppert and Klein, 1980 for reviews). Axelrod's review also summarizes the literature of the early 1970's showing that nocturnal exposure to light causes an abrupt, complete drop in an animal's pineal NAT. This effect can be mimicked by pharmacological manipulations that block â-adrenergic innervation of the pineal. To quote the author:

> A brief exposure to light reduces or shuts off the release of noradrenaline from sympathetic nerves, and a rapid fall in enzyme activity ensues. The action of light on the retina is a stimulating event, yet it inhibits the release of the neurotransmitter from sympathetic nerves in the pineal. This would indicate that, somewhere in the brain between the retina and the superior cervical ganglia, a stimulatory signal is converted to an inhibitory signal. [...] The circadian rhythm in pineal amines appears to arise from a biological clock present in or near the suprachiasmatic nucleus in the hypothalamus. (Axelrod, 1974, p. 1348)

In fact, several studies have demonstrated the circadian nature of the rat and hamster pineal melatonin rhythm and its correlation with expression of the locomotor rhythm (Ralph et al., 1971; Tamarkin et al., 1978; Pohl and Gibbs, 1978).

Suppression of Melatonin by Light

The demonstration that melatonin could be suppressed by light was a natural outgrowth of a long term, vigorous scientific effort to understand the biochemistry and physiology of the rodent pineal. The Axelrod laboratory at NIMH emphasized the biochemistry. Others focussed on the physiology. In Czechoslovakia, Illnerova initially demonstrated that acute nocturnal light would rapidly increase the normally low levels of pineal serotonin (Illnerova, 1971). Shortly thereafter, the usually high levels of nighttime pineal NAT were shown to abruptly decline after photic stimulation (Deguchi and Axelrod, 1972; Klein and Weller, 1972). The two, seemingly opposing phenomena, were reconciled in accordance with the known biochemistry and the proposal "that the circadian rhythm of serotonin in the pineal gland is regulated by the inverse rhythm of N-acetyltransferase, which causes an increased removal of serotonin by N-acetylation at night and a decreased rate of removal during the hours of daylight" (Klein and Weller, 1972). The inverse daily relationship between pineal serotonin and melatonin was well enunciated by 1968 (Fiske and Huppert, 1968), but the work by Klein and Weller (1972) set the stage for the exuberant investigations of light and pineal melatonin that continue at the present time:

> The physiological importance of a rapid change in N-acetylation of serotonin may be related to the secretion of melatonin, the putative antigonadotrophic hormone of the pineal gland. The findings of organ culture experiments indicate that large changes in the production and "secretion" of melatonin by the pineal gland are regulated by the activity of N-acetyltransferase... Perhaps the rapid effect in vivo of light on the activity of N-acetyltransferase would be transferred into a similar large and abrupt decrease in melatonin production and secretion, thus increasing the precision and accuracy of the pineal gland acting as an "endocrine transducer" that changes information about the daily dark period into an endocrine signal, that is, the duration of melatonin secretion (Klein and Weller, 1972). [Several references cited in this text have been omitted.]

The accuracy of the foregoing speculation has been borne out. Illnerova and colleagues (1978) demonstrated that light would, in fact, suppress nocturnal pineal melatonin. The time course correlated well with that for light suppression of NAT (Deguchi and Axelrod, 1972; Klein and Weller, 1972). In addition, melatonin in serum was shown to be rapidly suppressed in rats and ewes by acute light exposure (Rollag and Niswender, 1976; Illnerova et al., 1978). Illnerova and colleagues then proceeded to describe the parallel, precipitous decline of both NAT and melatonin upon exposure of rats to only 1 min of photic stimulation during the middle of the night (Illnerova et al., 1979). This study also showed that neither melatonin nor NAT began to recover toward normal nocturnal levels during the remainder of the night.

Measurement of melatonin in the blood of rodents was relatively difficult in the early 1970's. Klein began research with rhesus monkeys which had the advantage of being large enough to provide many blood samples throughout the day in quantities sufficient for measurement of melatonin. In small rodents, most experiments were restricted to measuring pineal melatonin content (but see Illnerova et al., 1978). Using pineal or blood measures, the Klein lab at NIH published a series of papers demonstrating in the hamster (Tamarkin et al., 1979) and rhesus monkey (Perlow et al. 1978; Perlow et al., 1980; Perlow et al., 1981; Reppert et al., 1981) that light could suppress the normal nocturnal rise in melatonin. At nearly the same time, Rollag et al. (1980) published similar data from hamsters, as did Lewy et al. (1980) from humans. The latter study included the observation that, unlike all other species, high intensity light might be necessary to obtain the melatonin suppression effect in humans. However, the relative insensitivity of humans to the melatonin suppressing effects of light may not be as great as initially described (Bojkowski et al., 1987; McIntyre et al., 1989).

Initial investigations of light-induced suppression of melatonin in the hamster showed it to be much more sensitive than for phase shifting of locomotor rhythms (Hudson and

Menaker, 1984). This has been confirmed by subsequent investigation (Podolin et al., 1987; Nelson and Takahashi, 1991b). Approximately 1 lux of white light will fully suppress melatonin within 30 min (Brainard et al., 1982). Sensitivity of the rat to photic suppression of NAT has also been tested (Vanecek and Illnerova, 1982). It is now presumed that loss of reproductive capacity by hamsters in short days is the direct result of the light-induced change in pattern and quantity of circulating nocturnal melatonin from the pineal gland (Bartness et al., 1993). The precise characteristics of the nocturnal melatonin release that are essential for loss of reproductive function and the manner in which light regulates these characteristics are actively being studied.

Site of Melatonin Action

The discussion concerning the linkages between studies of circadian rhythmicity, pineal function, photoperiodic time measurement and neuroanatomical regulation of circadian rhythmicity or pineal function becomes ever more recursive when considering the site(s) of action by pineal melatonin. In the white-footed mouse, timed, intra-hypothalamic injections of melatonin diminish reproductive function (Glass and Lynch, 1982), and the SCN may be the specific target of these injections (Glass and Lynch, 1982). Both lesion and infusion studies indicate that the SCN of Siberian hamster is a target for regulation of seasonal reproduction by melatonin (Bartness et al., 1991; Badura and Goldman, 1992). Limited information suggests that the thalamic paraventricular and reuniens nuclei may also be targets in this species (Badura and Goldman, 1992). It is not yet clear where melatonin normally acts to induce the large anti-gonadal effects seen in short photoperiod housed Syrian hamsters although the SCN do not seem to be a necessary target (Bittman et al., 1979; Maywood et al., 1990). In both ram and Syrian hamster, the mediobasal hypothalamus may be the critical site of melatonin action on reproductive variables (Lincoln and Maeda, 1992; Lincoln, 1992; Lincoln and Maeda, 1992; Maywood and Hastings, 1995).

In addition to its role in photoperiodism, melatonin is known to regulate circadian rhythmicity in some species. The pineal is well known as a circadian clock in birds (Gaston and Menaker, 1968; Menaker and Binkley, 1981). Continuous release melatonin implants in birds results in the loss of the locomotor rhythm (Turek et al., 1976). Melatonin also appears to act as an entraining agent in some vertebrates (Redman et al., 1983; Underwood, 1986; Cassone et al., 1992; Heigl and Gwinner, 1992; Chabot and Menaker, 1992; Margraf and Lynch, 1993). In others, including the Syrian hamster and mink (Hastings et al., 1992; Bonnefond et al., 1993), it has no entrainment effect. As indicated above, whenever entrainment to a particular stimulus occurs, there must *de facto* be a PRC. PRCs to melatonin have been published for three species: lizard (Underwood, 1986), rat (Armstrong, 1989) and human (Lewy et al., 1992). As might be expected from the wide variety of PRCs to light or chemical stimulation (see Johnson, 1990; Morin, 1991; Smith et al., 1992), there are substantial species differences in the melatonin PRC shapes. There is a question whether any mammal can entrain to melatonin given in physiological amounts (Bittman, 1993).

The advent of methods for determining the presence of melatonin receptors (Vanacek et al., 1987; Dubocovich and Takahashi,1987) has permitted identification of multiple neuroanatomical candidates at which melatonin might act to modify the photoperiodic response or circadian rhythms (for an extensive list of sites across 9 mammalian species, see Colwell et al., 1993). The one site common to all 9 species is the pituitary pars tuberalis. The SCN has been identified as a melatonin binding site in rabbit (Stankov et al., 1991), rat (Vanacek et al., 1987), Syrian hamster (Weaver et al., 1989; Williams et al., 1989), Djungarian hamster (Weaver et al., 1989; Duncan et al., 1989), mouse (Weaver et al., 1990), and human (Reppert et al., 1988) but not in 3 species of ungulates (Bittman and Weaver, 1990; Helliwell et al., 1991; Deveson et al., 1992) or ferret (Weaver and Reppert, 1990).

Summary

As new information from circadian rhythm, pineal or photoperiodic time measurement research has been uncovered, it has been incorporated into the larger framework consisting of all available data from all species studied. Results from mammals exist within that larger framework, only a small fraction of which has been mentioned here. The general presumption has been that, although details may vary from one species of mammal to the next, the same basic mechanisms govern rhythmicity in all. This conceptualization has been obvious in the Klein lab, for example. There, biochemical exploration of melatonin rhythmicity in rat was extended to simultaneous studies of both rodent and primate and eventual emphasis on the latter. More recently, the Reppert lab has intensively studied the melatonin receptor and its genetic control in rodent, monkey and human tissue (Rivkees and Reppert, 1991; Weaver et al., 1993). Novel strategies for investigation of circadian rhythm entrainment and melatonin function will almost certainly become available now that the melatonin receptor gene has been cloned (Ebisawa et al., 1994).

Research directly into primate or human issues pertaining to rhythmic control of melatonin theoretically could have proceeded without the antecedent work on hamster circadian rhythms and photoperiodic time measurement. Similarly, it could have proceeded without the antecedent research on rat pineal biochemistry. However, it did not develop independently any more than did the areas of hamster rhythm or rat pineal biochemistry research. Each field of investigation has grown through repeated reference to, and

influence by, the product of many other areas of scientific endeavor. Thus, the threads of a very large number of research projects on invertebrates, birds, reptiles, rodents and primates, among others, are being woven into an intricate fabric. The detail of this fabric is well-established in some places, but is constantly being augmented and clarified in others as research on specific topics flourish. The result is an elaborate, complex image of the research into the topic of biological time.

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CLINICAL USE OF MELATONIN IN HUMANS

I have been asked to write a short monograph, *sans* references, about the recent flurry of publicity over melatonin. Although there may be as many as 40 use patent applications for melatonin, I will not attempt to describe these or name their inventors; much of this information should be in the public domain. However, I would like to disclose that I am co-inventor of an approved patent for melatonin which is held by my university and teaches how to use low (physiologic) doses of melatonin to shift circadian phase position.

In recently published books by lay, medical and scientific authors, claims for human use rarely have been substantiated. While it would be wonderful to help patients with AIDS, increase longevity and cure hypertension, it is premature to recommend melatonin for these indications at the present time. (This is not to say that the more promising in *vitro* and *in vivo* findings should not be followed up with human studies.) Regrettably, some of our scientific colleagues have maintained that we should not wait. They reason that if melatonin has a certain effect in animals, it must work this way in humans. Logic, however, is no substitute for verification of speculations such as these, particularly since melatonin is notorious for having opposite effects in different species.

Even with regard to the uses that are most substantiated by human studies, phase shifting and sleep induction, what is the rush to exhort people to take melatonin? Although we have some idea about the optimum timing and dosing parameters when using melatonin to reset circadian phase, these parameters need to be simplified and better communicated to physicians. The direct soporific effect, in my opinion, appears to be a side effect of melatonin that is dose- and time-dependent and varies somewhat among individuals (that is, not everybody becomes sleepy on melatonin). As with most side effects the higher the dose, the more likely an individual will have this response. However, the higher the dose, the more concern there is for safety, not to mention the risk of a morning "hangover."

It has been suggested that melatonin has this direct soporific effect even at low physiologic doses. Sleep enhancement has been demonstrated mainly as a decrease in sleep latency that occurs when melatonin is given at times that would, according to the melatonin phase response curve, result in a same-day phase advance. Thus, a decrease in sleep latency in the afternoon nap studies and evening sleep studies could be the result of a phase advance in sleep propensity that peaks near these times. In my opinion, melatonin's direct soporific effect appears to be dose dependent, and sleep induction shown at physiological doses in all studies to date is due to a phase shift of the sleep propensity rhythm until proven otherwise.

Aside from purity issues and possible unknown effects, concerns over safety also relate, at least in part, to these recognized actions of melatonin in humans. The wrong time of administration could result in a phase shift opposite of that desired, thus making jet lag worse, for example. Furthermore, when melatonin is taken during the day for phase shifting, pharmacological doses that might cause sleepiness should be avoided. Therefore, even for these indications, there is still more research to be done before melatonin's clinical use can be recommended with impunity.

Although there is general agreement that melatonin is probably safe over the short term for most people, long-term studies are relatively lacking, or at least have not been made publicly available. One example of a long-term use for which there are no human studies is the claim of increased longevity. There are only rodent studies in this area. As mentioned above, it is inappropriate to extrapolate human use recommendations from such studies. The anti-aging rodent studies, in particular, are problematic. In particular, one of the most cited is a study in which pineal glands were cross-transplanted between old and young mice. However, melatonin was not measured. Not only is it questionable that the pineal can produce melatonin under such experimental conditions, it is even more doubtful that production would occur at 12-hour intervals, which in other studies by the same authors was shown to be critical. What is even more disturbing is that at least one of the strains of mice in these studies does not produce melatonin.

If and when melatonin is ready for clinical use, should this be by prescription? If not, should a clinician be consulted before using it? Certainly, in serious conditions such as AIDS, cancer and hypertension, patients should not take melatonin in place of a more established treatment. In some cases, melatonin might make patients worse. For example, if melatonin is eventually shown to enhance immune function in humans, melatonin might be contraindicated in patients with auto-immune disease (perhaps even rheumatoid arthritis).

Therefore, at the present time, I recommend that individuals consult their physicians before taking melatonin. If someone is going to experiment on themselves before clinical studies are completed, have a physician as a co-investigator. In any event, more research needs to be done and the findings

better communicated before melatonin can be recommended for general use. Of most concern is that the results of long-term studies be properly evaluated before recommending daily usage. Finally, it is hoped that the current craze, spurred by the many books published on melatonin this year, will result in more funding for basic and clinical research, from both government and private sources.

—Al Lewy, M.D., Ph.D.

MELATONIN: MIRACLE OR MYTH

What if I told you that there was a new drug that can treat or decrease your chances of getting the following diseases: cancer high blood pressure, coronary heart disease, Alzheimer's disease, Parkinson's disease, and AIDS. In addition, by taking this drug you will sleep better, have better sex, have more vivid dreams and live to be 120 years old—all these benefits with virtually no side effects. Sounds like a bad Infomercial doesn't it? Nevertheless, these are some of the claims being made about the pineal hormone melatonin from recent books published last year in the popular press. At the time of this writing there have been five books and one pamphlet published on the topic, but I will review only the two best selling and most "scientific" books: *The Melatonin Miracle: Nature's Age-Reversing, Disease-Fighting, Sex-Enhancing Hormone*, by Walter Pierpaoli and William Regelson and *Melatonin: Your Body's Natural Wonder Drug*, by Russell J. Reiter and Jo Robinson. These two books have scientists (Dr. Walter Pierpaoli & Dr. Russell Reiter) as lead authors. As a favor to Dr. Reiter, I reviewed an advance copy of his book. However, I have no financial interest in any of these books or in melatonin as a drug.

The Melatonin Miracle: Nature's Age-Reversing, Disease-Fighting, Sex-Enhancing Hormone Walter Pierpaoli and William Regelson with Carol Coleman. Simon & Schuster, New York, 245 pages, 1995, $21.00 U.S.

The number of inaccuracies in this book was distracting. For instance, Dr. Pierpaoli and Dr. Regelson at one point inaccurately attribute one of the roles of oxytocin to vasopressin and another time claim that prolactin is a pineal compound. Perhaps less innocuous is their recommendation of optimal doses for long-term treatment. These authors recommend that "to restore levels to their youthful peaks" individuals 75 or older should take "3.5 to 5 mg at bedtime" (pg 204). This dose would yield blood levels a hundred times higher than physiological levels. They also claim that endogenous melatonin induces REM sleep and dreams, which is contradictory to the literature (Birkeland, 1982; Claustrat, Brun, Garry, Roussel & Sassolas, 1986). Easily the most amusing quote from this book, however, is, "If you have ever been sexually aroused, you should be grateful to your pineal gland" (p. 161).

Most of the book is an account of Pierpaoli's controversial research on the potential of exogenous melatonin to prolong life in mice. Pierpaoli claims that he has indisputably demonstrated that the pineal gland is the aging clock and that long-term melatonin administration can slow down or even reverse the aging process. It is no wonder that the public is excited about claims that melatonin will extend their lives to 120 years and that they will be rollerblading with their great grandchildren in their nineties with "the strength of a 35 or 40 year old," no less (p 24). The evidence behind these amazing claims comes from several experiments by Pierpaoli and his colleagues. In the most dramatic of these experiments, pineal glands were cross-transplanted between young and old mice. The old mice receiving the young pineal glands lived longer than expected, and the young mice receiving the old pineal glands died sooner than expected (Lesnikov & Pierpaoli, 1994). In his book, Pierpaoli presents these data as the "final word," proving that the pineal gland is the location of the "aging clock." In other studies he and his colleagues reported that long-term melatonin administration could extend the lives of mice by as much a 20% to 30%. From his research, Pierpaoli concluded tha in these mice the decline in endogenous melatonin was caused by an aging pineal gland and that the lack of youthful melatonin was responsible for the aging and eventually the deat of the animals. He then concluded that melatonin administration in humans will have the same positive effects. By a indications this is the heart of the so called "melatoni miracle."

Pierpaoli and his co-authors make a great leap of faith i assuming that the effects of melatonin on mice can be d rectly applied to humans. They also make a great leap math in concluding that extending the lives of mice by 30' means that humans will live to be 120 years old, a 60% i crease over the current life expectancy. Considerably wor than embellishing their results, however, is their failure disclose that all of the mice (NZB, BALB/cJ, C57BL/6 for which melatonin administration was shown to prolo life (Pierpaoli, Dal'Ara, Pedrinas & Regelson, 199 Pierpaoli & Lesnikov, 1994; Pierpaoli & Maestroni, 198 lacked one or both of the enzymes (HIOMT & SNAT) ne essary for pineal glands to synthesize melatonin endo enously (Ebihara, Hudson, Marks & Menaker, 1987; El

hara, Marks, Hudson & Menaker, 1986). One of these mutant strains (BALB/cJ) was even used in the pineal cross-transplantation experiment. Thus it is incorrect to conclude that endogenous melatonin played any role in the effects of their pineal cross-transplantation studies, or that the cause of the aging in any of these mice was a decline of endogenous melatonin. These mutant strains of non-melatonin producing mice were also used in their investigation of young-to-old pineal implantation into the thymus (Pierpaoli et al., 1991) and in their pinealectomy studies (Pierpaoli et al., 1991; Pierpaoli and Lesnikov, 1994). Pierpaoli also failed to mention that in one investigation of female mice that do synthesize melatonin (C3H/He), melatonin supplementation "induced a high number of tumors primarily affecting the reproductive tract" (Pierpaoli et al., 1991).

It should be noted that the only investigation to replicate Pierpaoli's melatonin administration findings outside of Pierpaoli's laboratory reported that a melatonin antagonist extended the life of mice as well (Oaknin-Bendahan, Anis, Nir & Zisapel, 1995). These findings suggest an alternative explanation to the proposed direct life extending effects of exogenous melatonin, that daily melatonin (and apparently the melatonin antagonist) serve as zeitgebers, facilitating circadian entrainment and circadian stability. Preserving the circadian system later in life could have health benefits (Armstrong & Redman, 1991) that are independent of a direct effect of melatonin as either an immunomodulator or as an antioxidant.

Melatonin: Your Body's Natural Wonder Drug, Russell J. Reiter and Jo Robinson. Bantam Books, New York, 290 pages, 1995, $22.95 U.S.

This book cannot be reviewed without first considering the source. No individual knows more about the pineal gland and melatonin than Dr. Reiter. He is the best at integrating data across species and from in vitro studies to in vivo studies to make a cohesive case for the potential effects of melatonin in humans. Consequently, Reiter's book is informative, even at times to the melatonin researcher. It contains more detailed and more accurate descriptions of the topic, including an interesting interview with the discoverer of melatonin, Dr. Aaron Lerner.

Given the thrust of his recent research, it is not surprising that Reiter's book gives more emphasis to the antioxidant effects of exogenous melatonin, evidence primarily coming from in vitro research. From the promising results of these studies, Reiter concludes that endogenous melatonin is a free-radical scavenger. Since melatonin declines with age, theoretically leaving humans more susceptible to various diseases associated with oxidative damage, Reiter concludes (like Pierpaoli) that long-term melatonin administration will prolong the number of years we are healthy. As yet though, only high doses of melatonin have been shown to yield antioxidant effects which in no way suggests a role for endogenous melatonin. This kind of speculation about the roles of endogenous melatonin based upon demonstrated effects of pharmacological doses of exogenous melatonin is characteristic of this book.

Reiter's speculation also goes the other way, predicting what exogenous melatonin might do based upon relationships among endogenous melatonin and other physiological states. In this type of speculation, these authors ignore the axiom that correlation does not mean causation. The fact that melatonin levels decline with advancing age, for instance, is not evidence that melatonin has a causal role in the aging process. This same point can be made for speculation that melatonin may eventually treat coronary heart disease, PMS, schizophrenia, reduce suicide rates and speed up slow sperm. While it may be interesting that these conditions correlate with low melatonin levels, it is not enough evidence to then suggest that melatonin can treat these conditions. In further speculation about what melatonin might do, this book really goes out on a limb by suggesting that melatonin may increase the firmness and frequency of erections (p. 129). In humans, the only well-documented effects of exogenous melatonin are circadian phase-shifting and sleep. Most of the other purported effects of exogenous melatonin in humans have been based upon successful combination therapy. For instance, the trial of melatonin as an oral contraceptive in women includes a dose of progestin (0.3mg). Similarly, the most successful melatonin treatment of cancer has been done in combination with IL-2. Although this book presents the ability of exogenous melatonin to potentiate the efficacy of these drugs, it does not mention that melatonin may change the efficacy of other drugs as well, with accompanying consequences that are not, a priori, good.

Reiter and Robinson list more than a dozen effects that melatonin may have on the immune system (pg. 56-57). It seems unlikely that any drug with such apparently robust effects on human physiology could really be "free of negative side effects?" For instance, if the effects of exogenous melatonin are beneficial to someone with a compromised immune system, melatonin administration may pose a threat to those whose immune systems are the problem. Indeed there is evidence that melatonin may stimulate the immune system and cause exacerbation of autoimmune collagen II arthritis in mice (Hansson, Holmdahl & Mattsson, 1993).

Although this book includes a list of who should not take melatonin (including people with autoimmune disorders), there are times when it almost dares others to take it. For instance, early in the book the authors write, "should you acquiesce to the natural aging process?" What is not included in this choice is the potential risk of taking a drug with no regulations to control its manufacturing process.

Conclusions

Both books succeed in their attempts to capture the reader's attention and to increase interest in melatonin as a new and exciting area of research. In trying to appeal to the lay audience, however, these books (to different degrees) have compromised the presentation of scientific material. These books also downplay the complete absence of published chronic toxicity studies, banking solely on preliminary (and largely unpublished) results from ongoing clinical trials of melatonin as an oral contraceptive, a trial that likely includes no elderly subjects. To date, most of the placebo-controlled melatonin investigations in humans have used acute or subchronic administration of melatonin to extremely healthy people. While it is clear that melatonin has little or no acute toxicity, without controlled chronic toxicity studies it is ill-advised to recommend long-term melatonin therapy to people. There is also general concern about the lack of regulation in the manufacturing process of over-the-counter drugs sold as food supplements (Benjamin, 1992). In fact, the FDA has already begun to recall some of these melatonin pills for containing less than the advertised amount of melatonin. Although these two are clearly the most informative of the popular-press books, they should not be used as a substitute for informed medical advice. Furthermore, optimistic speculation, however theoretically sound, is no substitute for the scientific process. Those wanting to learn more about melatonin, should read Dr. Josephine Arendt's book, *Melatonin and the Mammalian Pineal Gland* (Arendt, 1995). This is a scholarly contribution that, in addition to presenting most of the research on melatonin, more objectively presents some of the research suggesting the potential health benefits of exogenous melatonin. Arendt's book, however, contains surprisingly little on melatonin and sleep. For this information, I would recommend Drew Dawson's 1993 review (Dawson & Encel, 1993). If you just must know what all the fuss is about, then clearly Dr. Reiter's book is the better (if not the funniest) of those published in the popular press.

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INFORMATION ON MELATONIN

The following is a working document, written by Dr. Josephine Arendt in collaboration with SLTBR, intended to provide current and concise guidelines on indications, dosing, and adverse effects of melatonin supplementation in humans.

What is Melatonin?

Melatonin is a natural hormone produced by the pineal gland in the brain. It is normally made at night and is thought to signal darkness to the body. It appears to serve similar functions in all life forms so far studied and act as a time signal for the organization of daily and annual rhythms. In some species, especially some lower vertebrates and birds, melatonin is essential for the organization of daily (circadian) rhythms. In mammals it appears to reinforce behavior associated with darkness, such as sleep in humans.

Melatonin has rapid, transient, mild sleep-inducing effect and lowers alertness and body temperature during the 3-4 hours following low doses. It is able to shift the timing of the internal "body clock" both to later and earlier times when administration is appropriately timed. The appropriate timing can be predicted from a "phase response curve," but only in people whose body clock phase is known. Thus, in people synchronized to a normal 24-hour environment, timing is relatively simple and can to some extent be judged by their habitual sleep times. However, optimal timing is not so simple after time zone travel and in shift workers. In such people the body clock is often out of its normal timing.

Uses of Melatonin

Melatonin has been used successfully in more than 500 subjects during the last 8 years in experiments on the alleviation of jet lag and for helping some night shift workers to adapt their sleep, alertness and melatonin rhythms. Its primary effects are improvement of sleep and faster adaption of daily rhythms to the new time-zone or work schedule.

It has also proven useful in certain other types of sleep problems. Most is known about sleep disturbance related to disturbed body rhythms, for example, delayed sleep phase syndrome, non-24-hour sleep wake cycle (often seen in the blind) and insomnia of the elderly. However, it also appears to help the sleep quality of normal healthy adults in recent studies. There is some evidence in a small number of people that in certain unusual environments (living continuously in dim light) sleep can become fragmented when using melatonin.

With a fast release preparation, the dose used is usually 2-5 mg daily by mouth (slow release formulations may be available shortly). These doses give blood levels of melatonin much higher than the normal physiological night time rise. Lower doses have been shown to shift the body clock and to induce sleepiness. However, dose-response studies suggest that 5 mg is more effective than lower doses, at least in young adults. The only side effects reported more than once to date in extensive field studies of jet lag are sleepiness (8.3%), headache (1.7%), nausea (0.8%), feeling fuzzy/giddy (1.4%).

Questionable Claims

Melatonin is claimed to have anti-oxidant and anti-cancer effects. It is also claimed to extend lifespan (in mice). The evidence for these latter claims is sparse and controversial. For example, pro-oxidant and cancer-inducing effects have also been reported. More research is needed and there is no evidence at all that it will extend human life. It has been investigated as a potential contraceptive in high doses (75-300 mg) combined with a progestin mini-pill in humans. The most frequent side effects noted were in diarrhea, abdominal pain and non-migraine headaches. Curiously, no effects on sleep were reported in these investigations. There is no published long term toxicology of low doses (<1-10 mg).

It is not yet a registered medication but is available in health food shops and pharmacies. The quantity of melatonin stated to be present per capsule/pill varies but is usually less than 10 mg. It is difficult to comment on the quality of the various products. **However, any product derived from animal tissue (for example, cow pineal gland extract) should be treated with caution.** It has recently been banned from sale in health food shops in the United Kingdom, Canada and many European countries.

To use melatonin we advise that you be over 18 years old, healthy, not pregnant, free of medication other than minor analgesics and oral contraceptives and have no personal or family history of psychiatric disorder. If you have any doubts about your state of health or if you experience side effects, you should consult your personal physician. You are advised not to drive or use heavy or dangerous machinery or do equivalent tasks requiring alertness for 4-5 hours after taking a pill. Long haul aircrew or shift workers are advised not to self-medicate as the timing of melatonin administration can be critical in these subjects.

How to Use Melatonin

For mild insomnia 2-5 mg of melatonin is taken at bedtime (10-11 p.m.). Its use in shift work and in the elderly requires much further evaluation. Its use in non-24-hour sleep-wake disorder requires specific instructions. It is impossible at present to evaluate the success rate in any of these applications except for jet lag, where overall 50% reduction in subjective symptoms is found. Insufficient numbers of subjects have been studied in other applications. In particular its effects on work-related performance require evaluation. Combination treatments with timed bright light and melatonin will probably prove most efficacious in many applications

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Using Melatonin to Alleviate Jet Lag

Melatonin is able to help shift your body clock to earlier or later times. For example, when traveling eastward you need to sleep, eat and work earlier than in your home time zone and when traveling westward you need to sleep, eat and work later. It also reinforces the effects of darkness; melatonin increases sleepiness, decreases alertness and lowers your body temperature slightly.

To help alleviate jet lag, you must take melatonin at a particular time of day. Taken at other times it could have undesirable effects. **It is not worth using melatonin for westward time zone transitions of less than 5 hours.**

Eastward Travel

When going east, take one capsule (2-5 mg) on departure day, on the flight if necessary, between 6 and 7 p.m. local time. On arrival take a capsule at local bedtime, 10 to 11 p.m., for 4 days.

If your stopovers are less than 4 days, on the evening preceding your next departure do not take a capsule at bedtime, but at 6 to 7 p.m. local time. On arrival take a capsule daily at local bedtime, 11-12 p.m., for 4 days.

Westward Travel

When going west, take a capsule daily at a local bedtime, 11 p.m. or later for 4 days after arrival at each stopover and at your destination. If you wake in the very early hours of the morning (before 4 a.m.) you may take another capsule. Do not take capsules pre-flight if going west, unless your stopover is less than 4 days and you will be taking them at bedtime the night before departure.

Precautionary Notes

Melatonin can induce sleepiness and lower alertness in sensitive individuals. You are advised not to drive, operate heavy or dangerous machinery, or do equivalent tasks requiring alertness for 4-5 hours after taking your pill.

If you are a long-haul pilot or air crew, we do not advise you to use melatonin. This is due to potential difficulties with timing the dose. If you or a close blood relative suffer from psychiatric conditions or migraine you are advised not to use melatonin. If you are under 18 years old or know (or suspect) that you are pregnant you are advised not to use melatonin.

Possible side effects of melatonin treatment are sleepiness (desirable), headache (infrequent) and nausea (very infrequent).

Always check with your physician before taking any new medication.

REVIEW AND SUMMARY OF RECENT MEETINGS

WFSRS Second International Congress

The World Federation of Sleep Research Societies, incorporating sleep researchers from Australia, Canada, Europe, Japan, Latin America and the United States, met for the Second International Congress in Nassau, The Bahamas, Sept. 12-16, 1995. The theme designated for this meeting was "The Mystery of Sleep".

Although the title for this meeting suggests singularity, the aim of this meeting was to discuss, argue, theorize, and try to uncover many of the "mysteries of sleep." This was possible due to the diversity of research currently being undertaken in the area of "sleep," and the presence of researchers at all levels from sleep labs worldwide.

For the many new researchers present, the meeting started with Student Day. This day was designed to allow new researchers a look at questions being posed by other novice researchers, as well as questions under investigation by other more established research groups. Student Day also allowed an insight into an essential part of research: *funding*. Helen Baghdoyan presented a proposal for projects requiring funding, which she had previously presented to the NIH. Another important part of Student Day was the examination, discussion and presentation of several classical, theoretical papers. This exercise enabled groups of new researchers to communicate their understanding of the paper and integrate knowledge from their area of sleep research with others in their group and then present this to the entire group.

At the end of Student Day a special symposium entitled "The Pharmacology of Hypnotics and the Therapy of Insomnia" was presented for all participants of the congress. The panel for this symposium included Thomas Roth, Malcolm Lader, Elio Lugaresi and Wallace Mendelson, who presented discussions on the treatment of insomnia with benzodiazepines and other hypnotic agents, the pharmacology of such treatments, the prevalence of benzodiazepine use across the population of a country and future directions for the treatment of insomnia with hypnotic agents.

The title symposium for this congress, "The Mystery of Sleep," was held on the second morning. This symposium provided four well known scientists the opportunity to present their thoughts on the mysteries of sleep. The symposium was chaired by William Dement, and the four speakers were Allan Rechtschaffen, Michel Jouvet, Rodolfo Llinas and Pier Luigi Parmeggiani.

For this and the following days of the conference, time and communication was divided between symposia, poster sessions, debates, workshops and focus groups. As with all meetings of this size, the poster sessions provided an excellent means for the presentation of a wide range of studies and new data by a large number of people. Over 500 posters were presented across three days.

Symposia were run concurrently to allow for the distribution of as much information as possible, on as wide a range of areas as possible. Symposia topics included molecular biological and cellular aspects of sleep and circadian rhythms, pathological aspects of sleep related disorders and the relationship sleep has with various pathological states, circadian rhythms and sleep, and treatment of sleep disorders using bright light. In addition to the information conveyed in these symposia, presentations of this style provided an excellent opportunity for researchers, especially new researchers, to observe and understand the art of oral presentation, which is an important tool in science.

The great debates held during the meeting also provided audience members with the opportunity to learn another requisite skill of science: how to argue your point of view convincingly. The debates posed a number of questions, including "Snoring is dangerous to your health" and "We do not need more sleep" and gave two researchers on the pro team and two on the con team the opportunity to present their side of the argument, using published data and theories both for and against the question. Teams then had the chance to refute the arguments of the opposing team, present their closing statements and answer any questions from the audience before the audience voted, and a winning team was declared.

A popular format throughout the congress was that of the focus groups. The focus groups were designed to get a number of prominent researchers in a particular area together to sit around a table and generate discussion into current trends, findings and unanswered questions in their area, rather than just present data. This format worked well in most instances, and although no burning questions, such as "Is melatonin an hypnotic agent?" were conclusively solved, focus groups provided a good base for future discussions of such burning and controversial issues in a less structured and more accessible environment than symposia.

This meeting was very well organized, thanks to the efforts of Dr. Michael Chase, Judy Franzblau and the powers that be behind the scenes in organizing a meeting of this size. In addition to the symposia, workshops, posters, debates and focus groups held throughout the day and into the night, participants were able to mingle on a less formal basis during the welcome reception, the cruise to Blue Lagoon Island, the Gala Dinner, and the numerous informal satellite symposia held into the early hours of the mornings.

Naomi Rogers, Centre for Sleep Research, University of South Australia, Adelaide, SA.

The WFSRS meeting in the Bahamas provided a tropical setting for the sleep research societies' four-yearly meeting. Perhaps as a response to the relaxed context of the meeting, the participants were faced with an innovative program format that featured focus groups and debates in addition to the more traditional and didactic "chalk and talk" format of the workshops.

The Symposium on bright light addressed theoretical and clinical uses of bright light in the treatment of insomnias related to sleep-wake timing disorders. Dr. Kronauer presented a parametric model of the theoretical effects of bright light on the circadian system. Of particular interest was the suggestion that high intensity bright light may not be essential to achieve effective phase control of the circadian system. This was an interesting shift in theoretical direction by the Boston group and suggests that appropriately timed light treatments may be possible in situations where high intensity lighting is impractical (e.g. in space).

Clinical studies showing the effectiveness of bright light in the treatment of phase disturbed and age-related sleep disorders were presented by the other participants. Dr. Okawa presented data showing that early morning bright light improved sleep consolidation in Alzheimer's (AD) patients more than in patients diagnosed with multi-infarct dementia (MID). The study suggests that circadian disregulation of the sleep-wake system may be important in AD and bright light treatment may be effective in consolidating the sleep period. Drs. Campbell and Lack reported data on clinical trials of bright light treatment for age-related sleep disorders. Both of these studies showed significant clinical efficacy for bright light treatments. However, Campbell's subsequent studies investigating longer-term maintenance of improvement showed more equivocal results. Bright light treatment was often less effective after several months and the correlation between circadian and clinical effect more tenuous. Taken together, these results suggested a more complex relationship between circadian pathology, bright light treatment and sleep disorders.

In my view, the new format for the meeting was a welcome change. The debates and focus groups encouraged a more dynamic and interactive approach to sleep. The "moral relativism" expressed in the debates seemed particularly useful. By directly acknowledging competing theories and perspectives in a dialectic format, students were presented with a less prescriptive view of sleep research. The focus groups also have considerable potential. The format encourages frank discussion and dialogue. Many of the students commented on how useful they found these groups and how the groups helped them more easily to approach researchers subsequently.

While many of the groups were dynamic and provided an active and fruitful dialogue, some of the groups were less useful. The format is highly dependent on the skills of the group leader and some groups were marred by inadequate preparation or a failure to adapt to the format. Some of the groups used the format only to present their research data in a traditional format without the benefit of audio-visual aids.

While I hope the new format is continued, I would suggest that more guidelines and support are provided to help participants with the transition to a more demanding and dynamic format. All in all a good conference and the organizers are to be congratulated on innovation and location.

Drew Dawson, Ph.D., Centre for Sleep Research, University of South Australia, Adelaide, S.A.

FLASHLIGHT POLL

What's In a Name?

Modern day professional societies probably got their start one day when a group of cave dwellers acknowledged a common interest (star gazing, fire making, nit picking...) and began meeting to exchange ideas. Over the centuries, such groups became more formalized, developing into trade guilds that not only shared common interests but also common concerns. Guilds gradually became powerful mechanisms for defending the rights and interests of their members. In this regard, it was critically important for the town fathers (and mothers) to know with whom they were dealing when, for example, the Street Sweepers Guild staged a strike. As such, identity—*identifiability*—was everything. Thus, the adoption of formal names. (An added benefit, of course, was that creation of such formalized organizations helped to legitimize the collection of membership dues...)

It is likely that from the very start, the process of adopting a Society designation carried with it certain unwritten rules. To wit—

1) The Society's name shall be descriptive, but not complex; self-important and exclusionary, but not pompous or magisterial;

2) The Society's name shall not exceed four words (excluding conjunctions, of which two shall be permitted);

3) The initials of the Society's name shall form a spiffy acronym;

4) The acronym should, under no circumstances, form a word or phrase open to sexual innuendo;

5) In lieu of a spiffy acronym, the initials of the Society's name shall roll off the tongue in an agreeable manner.

There may be more rules, but since they are unwritten, who's counting?

So, let us see how we, as a Society, measure up...namewise.

1) Our name is descriptive for sure; excruciatingly so. What other Society is named after a treatment modality? There is no Prozac Society (though there *is* a Hemlock Society...), or an Association for Flu Shot Vaccines. By its very descriptiveness, our name is certainly exclusionary. It suggests that if you don't engage in Light Treatment, perhaps you ought to find another club to join. By the same token, you can't really say our name is pompous or magisterial. To the contrary, it's downright pedestrian. On rule No. 1, then, we break even.

2) We clearly violate this rule. With five words and two fillers, we're bigger violators than mouthful societies like the Society for Prevention of Cruelty to Animals, and almost as bad as the Mother of all violators, the American Federation of Labor and Congress of Industrial Organizations (and these guys had to merge to get this bad!).

3 & 4) There is nothing spiffy about the acronym SLTBR, and on some lips ("slut-bar"), violation of rule No. 4 clearly hangs in the balance.

5) Nor do we earn redemption by complying with this very liberal final rule. Perhaps due to its lack of vowels, S-L-T-B-R rolls off the tongue as agreeably as a dislodged tooth.

In summary, our Society fails miserably the Test of Unwritten Rules. So what? Is this sufficient reason to consider a name change? As detailed in the Flash(light) Poll results below, our ranks are divided on this question. And a reasonably good case can be made for either position.

Whimsical rules set aside, a Society's name *should* be representative of the interests of its membership. In the past several years, with continued growth of the Society, the research and clinical interests of our members have naturally become more diverse. Although a large majority of us continue to have a strong involvement in the study of light as a research tool and treatment modality, light treatment is no longer the only game in town. Alternative treatments such as melatonin administration, vitamin B12, and timed exercise have drawn the attention of many of us. Simply, we are no longer a society only for Light Treatment and Biological Rhythms. We have outgrown our name; ours is a *nomen nudum*.

On the other hand, there is an investment in our current appellation that should not be dismissed lightly. Some would argue that *removing* "Light Treatment" from our professional identity is as misleading as keeping it in. After all, the use of bright light in research and treatment remains our primary stock-in-trade. By the same token, the case could be made that the "...Biological Rhythms" that rounds out our identity is general enough to embrace our ever-expanding diversity. Add to this realization that we are recognized by both colleagues, and by the general public, by our current name (not

to mention the expense of getting all of that stationary changed) and you've got a pretty firm argument for maintaining the status quo.

So what's a Society to do? Well, a prudent beginning would be to poll the membership. Find out how they feel. Get some feedback. The problem here is that our membership, by and large, is un-pollable. Poll-nonresponsive. They are Poll poopers. Nevertheless, the 10% of the membership that does respond deserves to be heard. Herewith, then, are the results of our latest Flash(light) Poll:

"I believe that our society should change its name to better reflect the diversity of its membership"

We received responses from 39 of you. Of the respondents, 16 were researchers, 7 were clinicians, and 10 identified themselves as both researcher and clinician; we heard from 3 manufacturers/distributors, a patient/consumer, a student, and an "other." Responses came from 14 states in the U.S., one Canadian Province, 7 European and Asian countries and Australia. Eight people used e-mail to respond, 8 people faxed, and 23 of you used traditional mail.

If we assume that this sample is representative of the entire membership, then we need to change our name. Twenty-three of the 39 respondents (59%) favored a name change. Fourteen people voted "No", and two respondents abstained, but provided comments.

Here are some of the comments that accompanied "YES" votes, most in the form of suggestions for our new designation:

"Society for Treatment of Biological Rhythm Disturbances (STBRD)"

"Society for Applied and Clinical Chronobiology (SACC)"

"...we should not limit the society by suggesting that it is a group that exists solely to foster the development of light therapy as a treatment for biological rhythms."

"...if we MUST keep the same acronym: Society that Loves to Treat Biological Rhythms"

"shorten the name..."

"Society for Light and Biological Effects (SLBE)"

"Society for Research on Zeitgebers and Rhythms (SRZR)"

"A prominent animal researcher used to call us SPLAT (Society for the Promotion of Light as Treatment). But it is obvious that we are becoming interested in more than just light treatment....One possible name could be Society for Applied Biological Rhythms Research (SABRR, pronounced saber)."

"Society for Human Chronobiology (SHC)"

"1) Chronobiology Society, 2) Chronotherapy Society, 3) Society of Circadian Biology and Therapy (SCBT)."

"...the point is to keep the acronym to retain continued identity...Society for Light and other Treatments of Biological Rhythm Disorders"

"National Network of Light Experts (NNLE)"

"this is not a strong, compelling need—mostly it would be nice to be out from under our acronym "slut bar". No matter what, a new name should include the word 'light'".

Most "NO" responders chose not to comment. Those who did expressed the general opinion of, "if it ain't broke, don't fix it..."

"In the non-medical/patient community lots of people have (already) lost you due to the recent address change. Heaven knows what a name change will do."

"Defer changes until membership reaches 1000."

"...the name is adequate because 'biological rhythms' is a very broad term."

Well. There you have it. A wealth of suggestions but no resolution. Perhaps a committee needs to be formed. Let's see....the Committee for Analysis of Name Tags Designed to Ease our Current Identity Dilemma (CANT DECIDE). Yes. That's what we need. A committee. Any volunteers?

—SSC

BULLETIN BOARD

ANNUAL MEETING JUNE 2-4 IN BETHESDA, MD

SLTBR's 8th Annual Meeting is scheduled June 2-4 at the National Institutes of Health, Bethesda, MD, and in the nearby Ramada Bethesda, the meeting's host hotel. Dan A. Oren, M.D., Program Chief at the National Institute of Mental Health, is meeting chair.

A State of the Art CME course, "Practice and Science of Light Therapy and Melatonin," will be held from 1 to 5 p.m. Sunday, June 2, at the Ramada. Presenters include J. Christian Gillin, SLTBR president, welcome and introduction; Raymond Lam, "Optimal Light Treatment for Seasonal Depression;" Siegfried Kasper, "The Role of Serotonin in Light Therapy and SAD;" Scott Campbell, "The Use of Light to Help Shift Workers;" Josephine Arendt, "The Use of Melatonin for Sleep and Jet Lag," and Ellen Liebenluft, "Rapid Cycling Bipolar Disorder, Light, and Biological Rhythms."

The meeting will continue on Monday and Tuesday on the NIH campus. Symposium speakers include David Klein, NIH, "The Role of N-Acetyl Transferase;" Martin Zatz, NIH, "How Does the Pineal Gland Work?" Ignacio Provincio, USUHS, "The Hunt for the Circadian Photoreceptor;" Dan Oren, "The Physical Effects of Light on Biochemistry," and David Schlager, SUNY, "Is SAD an Adaptive Behavior?"

The Call for Abstracts may be requested from the SLTBR office. Deadline for receipt of abstracts is April 22, 1966.

Members will receive registration materials and other meeting information in the near future. Additional information can be obtained from SLTBR, 1020 W. 44th Ave., Suite 304, Wheat Ridge, CO 80033-2840, Tel (303) 424-3697, Fax (303) 422-8894, e-mail 5686814@mcimail.com.

JOURNAL AVAILABLE TO SLTBR MEMBERS

SLTBR members are invited to participate in a special membership benefit offer. The *Journal of Biological Rhythms* is available to SLTBR members at a special one-year courtesyrate of $55—over 30% off the regular rate of $79. Your subscription will start with Volume 11, No. 1, March 1996. International members please add airmail postage of $16; Canadian members please add 7% GST and airmail postage of $16.

If you would like to participate in this special program, please check the journal box on your dues notice and include the subscription fee with your dues.

Welcome New Members

Welcome to the following new members of the Society who have joined since publication of the October 1995 issue of *LTBR*.

Albert P. Bensusen
Willem J.T. de Man
Kenneth R. Gaarder
Hilbert A.C. Kamphuisen
Charles S. Mirabile Jr.
Adam Moscovitch
Baba P. Pendse
David Pierce
Frank Reis
Joel D. Rudinger
Kausar Suhail
Rita J. Brooks
Derk-Jan Dijk
Ronald L. Hoffman
Jeana B. Lindell
Jeanette Modrick
Samuel Moskow
Justine A. Petrie
Haleya Priest
John W. Ringwald
Robert Searfoss

MEMBERSHIP CATEGORIES CHANGED BY BOARD

In its Fall 1995 meeting, the SLTBR Board of Directors expanded the Regular Membership category to include all professionals in relevant fields with no requirement to submit publications with the application.

Regular Members are defined as degreed professionals psychology, medicine, chronobiology, etc., who are actively working in the field of light treatment or biological rhythms.

as evidenced by clinical work, research or publications in peer-reviewed journals. Annual dues for Regular Members are $75.

Associate Members are defined as individuals who are interested in the field, but are not professionals as defined above. Annual dues are $75.

Student Members are full-time students pursuing an advanced degree in relevant fields related to light treatment or biological rhythms. Annual dues are $25.

Corporate Members are manufacturers and distributors of light treatment apparatus and ancillary equipment, publishers of books and journals, light therapy clinics, etc. Annual dues are $600.

Membership renewal notices were mailed in mid-January. Members are asked to return their payments promptly. A late payment fee of $20 will go into effect after March 1.

AUTHORS ASKED TO USE *JBR* STYLE GUIDELINES

Authors contributing articles to *LTBR* are reminded that submissions should be written in the style consistent with the *Journal of Biological Rhythms*. This is especially true of references. Articles not submitted in the correct style may be returned to the authors for revision.

General guidelines for references include: Authors' given names are abbreviated as initials with no periods following surnames; volume numbers of periodicals are italicized with no space after the colon following the volume number, and journal titles are abbreviated as appropriate with no periods.

Examples of proper reference style are as follows:

Campbell SS, Dawson D, and Anderson M (1993) Alleviation of sleep maintenance insomnia with timed exposure to bright light. J Am Geriatri Soc *41*:829-836

Okawa M, Hishikawa Y, Hozumi S, and Hori H (1991) Sleep-wake rhythm disorder and phototherapy in elderly patients with dementia. In *Biological Psychiatry*, G Racagri and T Fukuda, eds, pp 837-840, New York, Elsevier Science Publishers.