BIOLOGICAL RHYTHMS BULLETIN

Published Jointly By

The Society for Light Treatment and Biological Rhythms

and

The Society for Research on Biological Rhythms

Volume 1, Number 1 **Spring 1999**

With the inauguration of this Bulletin I am pleased to see completed one of the goals we had set out for this two year period in the operation of our Society. As we noted in our previous letter announcing the creation of this joint Bulletin, we have high hopes that it will provide a regular informal forum for information and discussion-- announcements for job searches such as the JBR editorship found in this issue, dates for meetings, useful information for teaching, and eventually position pieces written by administrators from granting agencies--in general, the professional issues that drive our scientific lives.

Several additional initiatives remain on the table. One of these, acquiring the ability to pay for dues and meeting registrations by credit card, is now largely in place due to excellent work by SRBR Treasurer Terry Page. With this in place, we will initiate a drive to expand our membership, both within North America and overseas. Financial development to promote long term stability of the Society remains a real goal.

Ultimately the success of any scientific society, including the SRBR, must be measured by the extent to which it promotes its discipline and improves the lives of its members. We expect this Bulletin to promote the study of biological rhythms, and hope it will in concrete ways contribute to your scientific life. Larry Morin as editor for this Bulletin has worked hard to make this issue both interesting and useful and I trust you will find it so. As always, I'll be interested in your feedback.

Jay C. Dunlap
SRBR President

The editors of this Bulletin have kindly invited me to submit some thoughts for your consideration concerning the role of the Society for Light Treatment and Biological Rhythms, this Bulletin, the place of our work, and a perspective on its future. On the occasion of a trial period of a cooperative publication with the Society for Research on Biological Rhythms, such consideration is particularly opportune.

After ten years the role of the SLTBR remains clear: it has provided an intellectual forum for exploring the role of light and biological rhythms, particularly as they affect the mind and behavior. It has provided an arena, perhaps the only arena, where human studies of this aspect of physiology have been at the fore. This Bulletin has played a no-holds-barred role in the Society's struggling with scientific issues and in linking us together. The value that the membership places on this Bulletin is reflected by the lacuna that many of us feel during those times when it might have arrived late! For academics SLTBR has provided a fellowship of scholars and friends with parallel intellectual interests. Given the peripheral place of light and biological rhythms in most medical schools or University departments, such a collegial opportunity can not be minimized. For our valued corporate, clinical, and lay members SLTBR has also provided a critical outlet for effectively and authoritatively transforming academic data from obscure jargon to real world usefulness.

The science of the Society's membership has been meaningful. Members have performed groundbreaking work that has solidly documented the efficacy of light as a treatment for some kinds of depression and the importance of melatonin in biological clock functions in humans. Members have developed the psychological tools that allow such research to meet the highest standards of the fields of psychology and psychiatry. Members have developed the devices that are now commonly used for phototherapy in depression, and members have tested in humans the proposed models of light and biological rhythms that animal research has uncovered. In the spirit of optimal science being a two-way dialogue between disciplines and optimal clinical research being a two-way dialogue between bench and bedside, members have also proposed new models for basic scientists to pursue as well. Reflecting its international contributions, the work of the SLTBR has recently been recognized in *JAMA*. (Nov. 11, 1998; vol. 280: pp. 1556-1558).

Where do we go from here? Most of the middle age-to-senior researchers among us are avidly pursuing some scientific question

In This Issue

or two or three that is fundamental to our work. Finding ways to fund junior colleagues so that we will have successors and future partners is a difficult problem. We have historically demanded and encouraged rigorous science and thinking. Our challenge remains to find the funding that will support such rigor.

I hope that the publication of a joint Bulletin of the SLTBR and SRBR will spur scientific and clinical cooperation and investigation between the membership of our societies. Given the increasing evidence of science crossing interdisciplinary boundaries and the need for furthering such work, this opportunity for "cross-pollination" of ideas and efforts has much potential for the evolution of our fields. Many of the readers of this Bulletin might find value in being members of both societies. The more clinicians and clinical researchers understand of basic science and the more basic scientists understand of the clinic, the more that each of us can be helpful to the other.

The clinicians and commercial interests among us have the challenge to make light therapy available to more people, when indicated. And I would pose a dual challenge to lay people who are among our membership. First, to tell the researchers and commercial interests among us what you need from the academicians in the way of practical science. And second, to act as advocates with public and private foundations to support studies of the effects of light and biological rhythms in humans.

I would like to invite each of our members to become involved in any appropriate way. SLTBR is a community as much as we are a Society—open to all who wish to join, and eager for all to contribute. Since its founding, this Bulletin has provided thoughtful and distinguished commentary on our field. Our annual meetings have been intellectually stimulating, challenging, and dare I say, even fun. This Bulletin and the annual meeting need your input, and their qualities affect our collective capacity.

In that vein, I would like to use this space to make a special plea to your kindness. I am quite aware that too many of us lack the funding to do anything approximating the research or clinical work we would like to do. I am painfully aware that our scientific colleagues in Russia are in even more dire straits associated with their nation's economy. Following in the footsteps of Drs. Daniel Kripke and Anna Wirz-Justice, I would like to invite each reader of this Bulletin to consider making a personal donation of US $50 (or whatever you can afford) and each corporate member to make a donation of US $200 to support research efforts in Russia. If we can even raise US $5,000 it might help run a lab for an entire year! Leading work by Russian researchers has previously included studies of light for depression and light for resetting menstrual cycles. If you would send a tax-deductible contribution made out to the SLTBR and send it to SLTBR Russia Fund, 842 Howard Avenue, New Haven, CT 06519 USA we shall use the full amount raised for scientific purposes. (An international committee would be appointed to assign the donated monies to the specific research projects with the most promising potential.) I hope you will give this request your sincere and urgent consideration.

I invite SRBR and SLTBR members to send me an e-mail with your comments on any aspect of SLTBR (dan.oren@yale.edu) or to contact the new SLTBR executive director Stephanie Argraves (SLTBR@yale.edu) with administrative questions.

Dan Oren
President, SLTBR

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Opinions expressed in the Bulletin are those of the author and do not necessarily represent the views of the SRBR or the SLTBR or of the Board of Directors of either organization.

Unsolicited manuscripts, letters to the editor, announcements or other contributions are welcome. They should be submitted to either of the editors at the addresses listed below. Please submit one double-sided hard copy, together with a disc containing a WordPerfect or Microsoft Word file. Alternatively, manuscripts may be sent as email attachments. Please use the publication style of the Journal of Biological Rhythms. The editors reserve the right to edit and condense letters to the editor.

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A RENEWAL OF COMMUNICATION

The 1998 meeting of the Society for Research on Biological Rhythms (SRBR) convened in Amelia Island along with colleagues from the Society for Light Treatment and Biological Rhythms (SLTBR). Numerous rhythms investigators are members of both societies. The Amelia Island meeting was jointly organized to provide attendees the opportunity to browse through non-human circadian rhythm research offerings, as well as through research efforts by colleagues studying human circadian rhythm regulation or clinically-oriented rhythm issues. The joint effort was a great success and has, as explained in a fall letter from Jay Dunlap, SRBR President, led to another joint enterprise in the form of this Bulletin.

The Bulletin originated in 1988 as a scientific news and comment organ of the SLTBR with Michael Terman as editor. The first issue contained notes from Dave Hudson and Ben Rusak inviting SLTBR members to pursue their rhythm-related interests by joining the SRBR and contributing to the Journal of Biological Rhythms. With the current issue, the Bulletin initiates a new phase in its history and becomes a publication of the two societies. Support for its printing and distribution is being received from the NSF Center for Biological Timing and from the SLTBR.

The editors of the Bulletin welcome the joint readership and emphatically invite to all submit items for publication. We believe the Bulletin will serve the useful role of enhancing communication among all folks in the field of biological rhythm research. Toward this end, one goal will be to publish pertinent announcements about forthcoming meetings, job openings, post doc positions available, etc., as well as general rhythm-related news, humor and comment. We encourage you to submit anything that might be of interest to the world rhythm research effort, including articles or *commentaries* that might be worthy of re-printing, with permission, from other publications. Just remember that the Bulletin will explicitly avoid competition with the Journal of Biological Rhythms and not use items which are more appropriate for publication there.

We look forward to hearing from you.

Larry Morin, Editor for the SRBR
Alexander Neumeister, Editor for the SLTBR

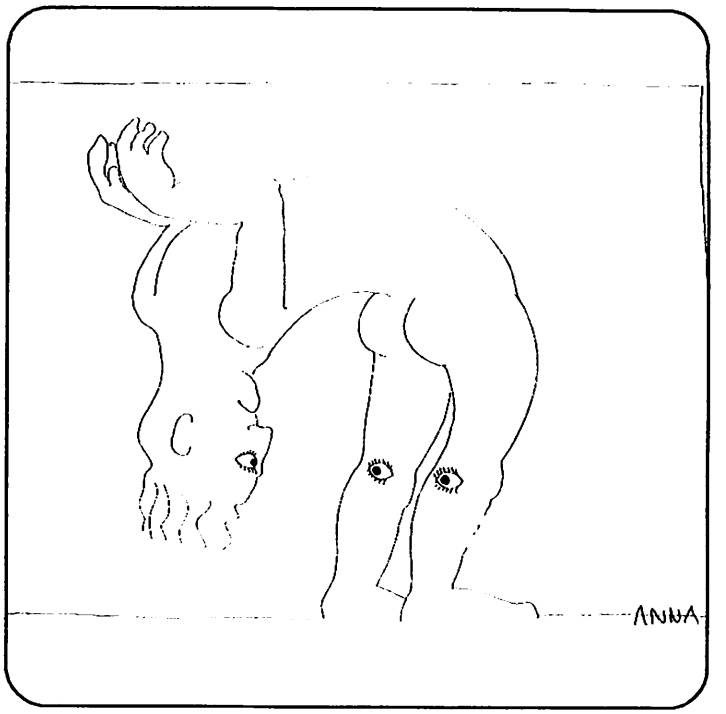
BREAKTHROUGH OF THE YEAR

First Runner-Up: A remarkable year for clocks.

Nineteenth-century philosophers proposed that God was a clockmaker who created the world and then let it run. Modern biologists might in part agree, for it's clear that evolution has carefully crafted clocks that allow almost all organisms to follow the rhythm of the sun. In 1998, a volley of rapid-fire discoveries revealed the stunning universality of the clock workings: Across the tree of life, from bacteria to humans, clocks use oscillating levels of proteins in feedback loops to keep time. Perhaps more amazing, fruit flies and mice – separated by nearly 700 million years of evolution – share the very same timekeeping proteins. Now that they better understand the cellular clock, scientists can begin to manipulate it, with applications from curing jet lag to brightening winter depression.

Clocks made the Runner-Up list in 1997 too, after researchers identified the first two mammalian clock genes, *Clock* and *per*. This year a prodigious amount of work from the clock research community filled out the story dramatically. For example, work in fruit flies showed that during the morning hours, CLOCK binds to a protein partner and together they turn on genes for proteins called PER and TIM (Timeless). These two proteins eventually shut down their own genes. But to keep the proteins on a 24-hour cycle, PER and TIM's turnoff must be delayed. This year researchers found the cause of that delay in flies: a protein called DOUBLE- TIME (DBT) that destabilizes PER, keeping its levels low until enough TIM accumulates to pair with PER and shield it from l3BT. Only then do PER and TIM enter the nucleus to turn off their genes, causing levels of the two proteins to wane until morning, when CLOCK and its partner turn on the genes once again. Discovering all this in one organism would be breakthrough enough, but researchers found the same proteins or close variants playing the same roles in mice, too. As reported in June, a negative feedback mechanism appears to power plant clocks as well, albeit with different genes. And in September, a Japanese team showed that the single-celled cyanobacteria's clock is based on the same theme.

Despite this elegant molecular machinery, circadian clocks are imperfect timekeepers: Left on their own, their daily cycles run longer or shorter than 24 hours. Light keeps them in line, like a daily adjustment of a watch. In July re- searchers showed how: Light causes the rapid destruction of TIM, at least in flies. Researchers thought that, in mammals, eyes are required for the light signal to reach the clock: But in January a U.S. team made the shocking discovery that light shone on, of all places, the back of the knees seems to reset the clock in humans; several groups have now repeated that finding. Capping a year of dramatic discoveries, in November researchers fingered three plant pigments that capture light and pass its signal to the clock; one seems to play the same role in animals. For clock researchers already pleased with the pace of findings in 1997, this year's double-quick barrage of discoveries has exceeded all expectations.



RELEASE of CANADIAN CLINICAL GUIDELINES for SAD

Clinical guidelines for the treatment of seasonal affective disorder (SAD)were recently released by the Canadian Consensus Group on SAD. Drs. Raymond W. Lam (University of BC) and Anthony J. Levitt (University of Toronto) spearheaded the effort by a panel of 14 clinical researchers representing major mood disorders centers at Canadian universities and institutes. The guidelines resulted from a standardized, rigorous review of over 600articles in the scientific literature, consensus clinical opinion from thepanel, and external review by Drs. Dan Oren, Michael Terman, and Anna Wirz-Justice. The full guidelines are written in an accessible question and answer format with major sections on Diagnosis, Epidemiology and Pathophysiology; Light Treatment; Medication Treatment; and Management Issues. A full reference list of articles to February, 1999, is included. The guidelines were partly supported by an unrestricted educational grant from Pfizer Canada.

The full guidelines are in press and will soon be available from the editors and from SLTBR. A summary of the guidelines was published as a supplement in the Canadian Journal of Diagnosis in November, 1998, and is available on the web at http://www-fhs.mcmaster.ca/direct/sad.html

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Photopigments and clock responses to light

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1. Introduction

In order for a circadian clock to provide useful temporal information, it must be synchronised (entrained) to environmental time as determined by the solar cycle. A large variety of environmental variables show predictable periodic changes over the solar cycle making them suitable as potential entraining agents for circadian clocks. However, under most circumstances, by far the most influential of these is the diurnal change in quantity (and perhaps quality) of light (Roenneberg and Foster 1997).

In mammals, the primary circadian clock resides in the hypothalamic suprachiasmatic nuclei (SCN). Light information is thought to reach the SCN via the retinohypothalamic tract (RHT), a dedicated monosynaptic projection from the retina. This anatomical organisation, combined with reports from multiple mammalian species that removal of the eyes abolishes photoentrainment (Foster 1998), suggests that the task of circadian photoreception is the responsibility of retinal elements. However, although the mammalian retina is among the most comprehensively described animal tissues, the precise nature of these photoreceptive elements remains unknown.

2. Candidate circadian photoreceptors

The most obvious candidates for any photoreceptive task in mammals are the retinal rod and cone photoreceptors. These cells form the basis of visual photoreception and remain the only mammalian cell types known to be directly light sensitive. It may well be that these classical photoreceptors contribute to photoentrainment (David-Gray et al. 1998). However, observations in both mice and humans that circadian photo-responsiveness can survive a loss of photoreceptor capacity sufficient to induce visual blindness, has lead to speculation that circadian photoreception may not be restricted to these classical photoreceptor cells (Foster 1998).

Rod and cone photoreceptors absorb light using a vitamin A-based (11-*cis* retinal) chromophore bound by an opsin protein and, traditionally, the search for non-rod, non-cone photoreceptors has centered on attempts to identify previously unknown opsin-like proteins. Over the last several years, a number of novel opsins have been identified in non-mammalian vertebrates (Soni and Foster 1997; Provencio et al. 1998; Soni et al. 1998). To date, mammalian homologues of these genes have not been published, but the search for novel opsins in mammals has intensified.

On a less conventional theme, several non-opsin based putative photopigments have been discussed in the context of circadian photoentrainment. It has been suggested that light absorbing heme moieties such as haemoglobin and bilirubin might be capable of acting as functional photoreceptors (Oren and Terman 1998). These could provide the circadian system with photic information through an as yet unidentified humoral transduction mechanism. Finally, genes encoding two putative vitamin B2 based photopigments, termed "cryptochromes" have been identified in mice and humans (Hsu et al. 1996; Kobayashi et al. 1998). Despite the plethora of candidate circadian photoreceptors most of the recent excitement in this area of research has centered on the mammalian cryptochromes and these form the subject of the remainder of this review.

3. Cryptochromes

The cryptochrome genes of mice and humans represent a distinct branch of the photolyase/cryptochrome family of light sensitive proteins. In terms of sequence similarity, they are most closely related to a subset of the photolyase proteins found in non-vertebrate species (Lucas and Foster 1999). Photolyase proteins bind a flavin and pterin as dual cofactors in order to absorb near UV/blue light and repair UV induced damage to DNA through a redox-type reaction (Todo et al. 1993; Hearst 1995). Despite this sequence similarity, the mammalian cryptochromes do not have an apparent DNA repair function, and consequently were named after the more distantly related cryptochromes of higher plants (Hsu et al. 1996). The plant cryptochromes are the only members of this family previously shown to have a photoreceptive function (Cashmore 1998).

The confusion surrounding the nomenclature of these genes has recently been confounded by description of a novel photolyase/cryptochrome gene in *Drosophila*. This gene does not encode one of the recognised *Drosophila* photolyases and has been termed cryptochrome, although in terms of sequence similarity it is not strictly homologous to either mammalian or plant cryptochromes (Emery, So et al. 1998).

Members of the cryptochrome/photolyase family in *Arabidopsis* (*cry1* and *cry2*), *Drosophila* (*dcry*) and Mus (*mCry2*) have recently been implicated in the circadian photoentrainment pathway (Emery et al. 1998; Somers et al. 1998; Stanewsky et al. 1998; Thresher et al. 1998). The results in *Drosophila* and *Arabidopsis* are beyond the scope of this short review and are discussed elsewhere (Lucas and Foster 1999). Below we consider the roles that the cryptochromes might play within the circadian system of mammals.

4. Evidence that cryptochromes are involved in mammalian photoentrainment

Explicit speculation that cryptochrome proteins might form the basis of circadian photoentrainment in mammals originated with the report that, in mice, their pattern of expression includes (amongst other tissues) both the retina and the SCN (Miyamoto and Sancar 1998). In order to test this hypothesis, Thresher and co-workers recently reported an examination of circadian rhythmicity in mice lacking *mCry2* (Thresher et al. 1998). The loss of *mCry2* has several interesting effects on circadian organisation. *mCry2*-less mice show a marked increase in free-running circadian period under constant darkness and substantially increased phase shifts to a 6-hour light pulse starting around CT17. However, despite the prediction that this gene is involved in photoentrainment the only evidence presented of a decreased sensitivity to light was a reduction in the photo-induction of the putative clock gene *mPer1* in the SCN. Interpretation of this last result is complicated by the lack of an appropriate control group (no light pulse) with which to assess the relative induction of this gene in the two genotypes.

Perhaps the single most important observation regarding the *mCry2*-less mice is that they exhibit apparently normal photoentrain-ment to a 12:12 light:dark cycle. This result confirms that *mCry2* does not represent an essential component of the photoentrainment pathway in mice. There are two possible explanations for this finding: (a) *mCry2* does not perform any function in the process of photoentrainment, or (b) *mCry2* is a component of one of several, parallel photoreceptive inputs to the circadian clock, in which entrainment survives the ablation of any single pathway. Thresher and co-workers interpret the various effects of the *mCry2*-knockout on circadian phenotype as support for the second of these hypotheses. However, other conclusions are equally valid on the basis of the data published.

The circadian phenotype of *mCry2*-less mice provides a convincing argument for the involvement of this protein in the circadian system (Thresher et al. 1998). However, the nature of its involvement remains unclear. The fact that *mCry2*-less mice retain functional circadian rhythms argue that *mCry2* is not a state variable of the rhythm generating oscillator itself. However, the data would be consistent with practically any other role in the development, maintenance or regulation of the circadian system. The precise involvement of cryptochromes in the mammalian circadian system therefore remains a fascinating question, one which may require the successful lesion of both *mCry1* and *mCry2* genes to adequately address. In the meantime, a direct experimental examination of the hypothesis that cryptochromes act as circadian photoreceptors would be appropriate.

5. Demonstrating a role in the photoentrainment pathway.
As yet, the analysis of *mCry2*-less mice has fallen short of definitively assigning a role for *mCry2* in the photoentrainment pathway. What, then, would constitute convincing evidence for such a role? The minimum prediction for a member of this pathway is that its removal be associated with a decrease in sensitivity of at least one clearly defined aspect of photoentrainment. In mice the accepted experimental assay of circadian photosensitivity is the circadian phase shift induced by a single light pulse presented under conditions of constant darkness. This experimental paradigm has the advantages of being extensively characterised and well suited for distinguishing changes in sensitivity from changes in the amplitude of response (Figure 1).

The fact that *mCry2*-less mice retain functional photoentrainment indicates that if mCRY2 is a circadian photopigment, it must form one of several photoreceptive inputs to the clock. Consequently, it may be that any reduction in circadian photosensitivity associated with its ablation is restricted to specific wavelengths of light or may only be observed when the *mCry2*-knockout is combined with other photoreceptor lesions. Thus, a very detailed analysis of photosensitivity in *mCry2*-less mouse may be required before such convincing evidence is unearthed.

6. Photoreceptor or phototransducer?
The approaches that could be used to identify *mCry2* as part of the photoentrainment pathway are relatively straightforward (see above). However, a protein may perform a multitude of tasks in such a pathway. Demonstrating that it acts as a circadian photopigment requires that the protein's function is defined by its light absorbing properties. Spectral analysis is the accepted approach to address this issue (Takahashi, DeCoursey et al. 1984).

Classically, the assignment of candidate photopigments to specific light responses is achieved by matching action and absorption spectra (Lythgoe 1979). Photopigments have defined spectral sensitivities (absorption spectra) which may be experimentally determined. By necessity, the responses which rely on these photoreceptors share this spectral sensitivity. Thus an action spectrum (a measure of the sensitivity of a given response to different wavelengths of light) showing the same shape and position of maximum sensitivity as an absorption spectrum has been previously regarded as a prerequisite to linking a photoreceptor to a specific light response.

At its simplest this is almost a platitude, thus blue color vision is reliant upon photoreceptors capable of absorbing blue light. However, in the case of the *mCry2*-less mouse it makes a powerful prediction. If mCRY2 is a circadian photopigment then one would expect a change in the photosensitivity of *mCry2*-less mice matching the absorbance spectrum of mCRY2 (Figure 2). Such a result would represent strong circumstantial evidence that it is the light absorbing properties of mCRY2 which define its role in photo-entrainment. In other words it acts as a photopigment. Conversely, until such time as a detailed absorption spectrum of mCRY2 is described and compared with detailed action spectra for circadian phase shifting in wild type and mCRY2-less mice, it will be difficult to make a convincing case that mCRY2 acts as a circadian photopigment.

7. Conclusions
The identification and preliminary investigation of genes bearing some sequence similarity with the cryptochromes of higher plants in mice, humans and *Drosophila* has rightly generated a great deal of excitement at the possibility that mechanisms of photoentrainment in such diverse species might have a common phylogenetic root.

However, while the recent examination of mice lacking *mCry2* suggests that this gene encodes an important component of the circadian system, further examination of these animals is required before we can be sure whether or not it functions as a circadian photopigment. This analysis should include a demonstration that the sensitivity of photoentrainment is changed by the loss of this gene in a manner predicted by the absorption spectrum of the protein.

Note: The experimental measurement of action and absorption spectra will be described in detail in the next issue of this Bulletin.

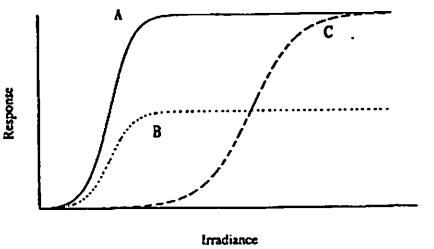

Figure 1
Alterations in irradiance responsiveness may be characterized as changes either in photic sensitivity or in the amplitude of response. In this cartoon, comparison with the wild type (**A**) indicates a decrease in the amplitude of response in mutant strain **B**, and a true decrease in photosensitivity in strain **C**.

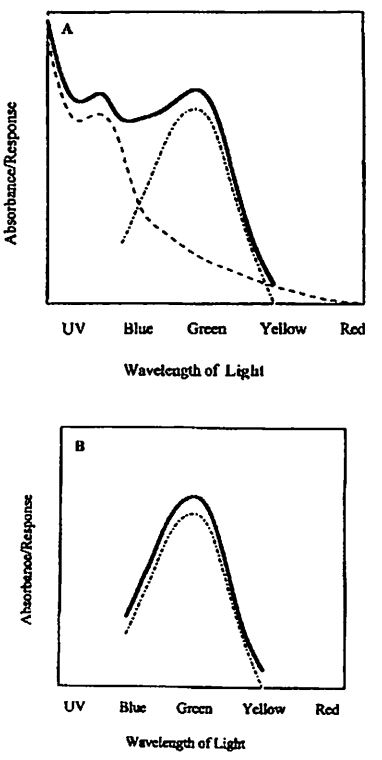

Figure 2
The classical method of assigning photoreceptors to a defined biological function is by matching the absorption spectrum of the candidate photopigment with the action spectrum of the biological response. In this cartoon depiction (**A**), the action spectrum of photoentrainment (solid line) is defined by the absorbance spectra of two photopigments (dotted black lines). Following genetic ablation of one of the photopigments, the action spectrum is altered in a predictable manner (**B**).

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A Reaction to Lucas and Foster:

Pluralitas non est ponenda sine neccesitate

Dan A. Oren
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Occam's seven century old principle that entities should not be multiplied unnecessarily has served mathematics and physics quite well.[1,2] That some of the most controversial debate in photo/chrono/biology in recent years has turned on this apparently razor-sharp axiom reflects that we are wrestling with a fundamental issue: the identification of mammalian chronobiological photoreceptors.

Surprisingly, given our current inadequate understanding of these receptors, the biological effects of light on organic chemical molecules are fairly well characterized. As formulated by Theodor Grotthus (1785-1822) and John William Draper (1811-1882) in what is now termed the First Law of Photochemistry, for light to produce a chemical reaction, it must first be absorbed by or act upon a molecule. The fact, therefore, that we struggle to identify the molecule or molecules that mediate the chronobiological (and antidepressant and energizing) effects of light in mammals represents an anomaly in the immense garden of photobiology that photochemists have illuminated.

Foster and colleagues have engaged this challenge wholeheartedly. And his team's elegant, thorough work has provided much of the empirical data that inform our current understanding.

Lucas and Foster employ the principle of parsimony that their countryman William of Ockham posited and state above that "the most obvious candidates for any photoreceptive task in mammals are the retinal rod and cone photoreceptors." But, to be fair to the ancient logician, Occam's principle does not advocate parsimony at all costs, merely thoughtful and careful consideration in the proclamation of parsimony. It is not that entities should not be multiplied: rather there must be a necessity for doing so. Such generosity in the practice of parsimony is wise, indeed, because depending upon one's perspective and training, what is parsimonious to one observer may seem tortuous to another.

The well-established principles of photochemistry thereby collide with the anomalous circadian photoreceptor pigments characterized in the landmark work of Takahashi, Menaker and others[3] and the seemingly resilient pigments that regulate timing of the biological clock in Foster's rodent models[4] and in humans with light-responsive chronobiological systems despite significant visual impair-ment.[5-7] On a parallel track, the inability to observe disturbed visual function in winter seasonal depression[8] also challenges the logical proposal that the visual pigments are the same chromophores that transduce the energizing and phase-shifting effects of light in humans.

The "humoral phototransduction"[9] model was developed in response to these and other difficulties in reconciling a visual-based theoretical construct with empirical results. It embraces the principle of parsimony, but considers it from a molecular and evolutionary approach rather than from an organ-based perspective. The model stands on parallel foundations of parsimony in plants and animals: highly conserved chronobiological responses to light[10] and highly conserved tetrapyrrole chromophores produced by parallel molecular pathways. The model unites these observations and proposes that similar light-sensitive chromophores across the kingdoms play critical roles with regard to the regulation of biological time. The published

thesis focuses specifically on the circular tetrapyrrole-containing hemoglobin and the linear tetrapyrrole bile pigments, but explicitly leaves room for the consideration of other tetrapyrrole and non-tetrapyrrole chromophores as well. The role of tetrapyrroles in absorbing energy and in mediating time signals in plants is well described.[11] That their mammalian chromophore counterparts have varying ambient-light-dependent interactions with gaseous neurotransmitters creates a potent impetus for considering their energy-regulating, time-keeping potential as well. The novel chronobiological photoreceptors observed by Takahashi and Menaker's team had the remarkably non-vision-like capacity to have a high threshold of light required for stimulation and the capacity for integration of both intensity and duration of light exposure in producing a chronobiological effect.[3] Tetrapyrrole chromophores provide a ready mechanism to fulfill both of these criteria by virtue of the light intensities required to stimulate light's effects upon heme binding to various gases[12] and the light intensities required to promote the breakdown of bilirubin.[13] Humoral photoreceptors would allow for ready integration of the intensity vs. dose signals by circulation of the blood. Demonstration of rhythm-shifting effects of light applied to human skin offers further consistency with (but not yet proof of) a humoral model.[14]

Lucas and Foster note that the cryptochromes are the molecules of the hour as possible candidates for a photoreceptive role in plant and mammalian chronobiology. Yet, as they point out, empirical testing of cryptochromes (and for that matter of other putative photoreceptors) along time-tested photobiological lines is required. The headlines elsewhere that cryptochromes are THE sole chronobiological photoreceptors clearly take parsimony further than Occam would have permitted. Since—within the visible spectrum—cryptochromes are primarily blue-light absorbers, even if they are part of the photoreceptive system in mammals, they do a poor job of accounting for effects of green light in suppressing melatonin production in humans[15] or in having an antidepressant effect in humans[16] or in shifting biological rhythms in hamsters.[3]

Whatever the outcome, whether the cryptic process of mammalian and human phototransduction turns out to be humoral or neuronal or both or other, better understanding of that process will open new directions of investigation and point in new directions toward human health. A few of us who were wrestling with the First Law of Photochemistry as it applied to psychiatry and chronobiology were in an intellectual funk just a few years ago when our hard-earned data seemed to be leading us into darkness. But, with 20/20 hindsight, it seems that it was our and our field's parsimonious focus on the first words of Occam's principle—without considering it in toto—that left us in a lurch. Fortunately, the tide has turned. With novel theoretical- and empirical-based directions to pursue, it seems reasonable to hope that within a few years some of the critical philosophical and photoreceptive questions that we face today will be answered.

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Djungarian Hamster and/or Siberian Hamster: Who is who?

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Colleagues keep asking me about the correct common name of *Phodopus sungorus*. Is it the Djungarian hamster or the Siberian hamster or the Striped hairy-footed hamster? And what about *Phodopus campbelli*, is it the Djungarian hamster or Campbell's hamster, or what? In fact, there is considerable confusion also in the literature concerning the common names for two of the now recognized three main species of the genus *Phodopus*, namely *Phodopus sungorus* (Pallas, 1773) and *Phodopus campbelli* (Thomas, 1905). The third species, *Phodopus roborovski* (Satunin, 1903), the "Desert hamster", is rarely used as a laborarory animal and is so different in its habitus from the two other *Phodopus* species that it cannot be mistaken (Ross 1994). In contrast, *P. sungorus* and *P. campbelli* looking similar to the unexperienced eye and I have visited several labs in which colleagues claimed to have a colony of *P. sungorus* but instead it turned out to be *P. campbelli*. And in publications - even from the same

laboratory - one can find both common names "Djungarian hamster" and "Siberian hamster" for *P. sungorus* as well as for *P. campbelli*.

In the late 1960s a Czech scientist, Dr. J. Figala, came to the laboratory of Prof. J. Aschoff at the Max-Planck-Institute Andechs (Germany) on a "von Humboldt stipend". He brought with him two breeding pairs of *Phodopus sungorus*, started a colony and in collaboration with G. Goldau and K. Hoffmann made inital observations on seasonal changes in body weight, fur color and the occurrence of torpor in this dwarf hamster (Figala et al. 1968). Dr. Hoffmann soon realized the great potential of *Phodopus* and he deserves the merits of having introduced this hamster species as a very valuable animal model for pineal research (for a review see Steinlechner and Niklowitz 1992). Dr. Hoffmann was generous enough to give hamsters away to colleagues and by 1980 there were many laboratories all over the world working with *Phodopus* from Hoffmann's stock or other sources.

At the time Hoffmann started his work, *Phodopus sungorus* was considered to exist in two different geographical races: the nominate form of *Phodopus sungorus sungorus*, a north-western subspecies which turns white in winter, and *Phodopus sungorus campbelli* in the south-east of the distrubution range which does not change its fur color in winter (Argyropulo 1933, Veselovski and Grundova 1964, Flint 1966). The generic name *Phodopus* was introduced by Miller (1910) and is derived from *phodos*, the genitive case of the Greek *phos*, meaning blister, and the Greek *pous*, meaning foot. It refers to the large coalesced pad on the plantar surface of each foot (Ross, 1994, 1995). The species name given by Pallas (1773) refers to the region "Sungaria" (different spellings exist: Dsungaria or Djungaria or Zungaria, see map), south of the Altai mountains. The literal translation of the nominate form therefore is: "the blister-footed (D)Sungarian (hamster)". Since Hoffmann clearly worked with the nominate form, he consequently called it (as did most others before him, e.g. Veselovski and Grundova 1964, Flint 1966) the Djungarian hamster. The alternative name existing in the (English) literature at that time was the "Hairy-footed hamster" (Ellerman and Morrison-Scott, 1951). Never (at least to my knowledge) was it called the "Siberian hamster". The other subspecies *P. sungorus campbelli* was named in honour of W.C. Campbell, who collected the type specimen in Inner Mongolia in 1902 (Ross 1995).

By 1967, Vorontsov et al. had reported differences in chromosome morphology of both hamsters and in 1979, Yudin et al. showed that cross breeding produced sterile male offspring (however, female offspring often are fertile; Stetson, pers. comm.). The papers by Vorontsov et al. and Yudin et al. were written in Russian and hence did not receive due attention for a long time. *Phodopus campbelli* received its present taxonomic status as a separate species in 1984 (Corbet, 1984). All those who have worked with both species of *Phodopus* will certainly agree that there are major behavioral and morphological differences meriting the separation. Dr. K.W. Wynne-Edwards sucessfully trapped both hamster species in the (at that time, i.e. early 1980s) U.S.S.R. and worked with both species in the field as well as in the lab. To my kowledge, Wynne-Edwards and Lisk (1984, 1987) were the first to name *Phodopus sungorus* the Siberian hamster and *Phodopus campbelli* the Djungarian hamster. Subsequently, many (especially American) colleagues and even the American Society of Mammalogists (see Ross 1995) and the British Museum of Natural History (Corbet and Hill, 1986) followed this suggestion.

Although there are no strict rules of nomenclature for common names, the choice of "Siberian" and "Djungarian" for the common names was, in my view, very unfortunate and has let to the present major confusion. Admittedly, *Phodopus campbelli* has its center of distribution south-east of the Altai mountains (Region of Djungaria) but especially Mongolia, whereas *Phodopus sungorus* originates from south-west Siberia and north-east Kazakstan, making the common names quite logical. Even more so would have been "Mongolian hamster" for *P. campbelli*, and "Kasak hamster" for *P. sungorus*, if the type locality (see below) played a role. On the other hand, I think it is terribly misleading that a former subspecies is now called by the common name of the nominate form. I am convinced that much confusion would have been avoided if the nominate form *Phodopus sungorus* had retained its original common name, i.e. Djungarian hamster. It is the newly acknowledged species which should get a new name. Another logical name would have been "Campbell's hamster". I have used the common name Djungarian hamster for *Phodopus sungorus* in all my publications since 1977 and I see no good reason to change this habit.

As I said before, there are no strict rules for the use of common names. However, there are indeed strict rules for the use of scientific names. No editor should accept papers in which only the common name is given. The use of only the common names has led to misunderstanding, misinterpretation and even awful mistakes. Therefore, I highly recommend, and strongly urge, all colleagues to use the scientific name which designates the species beyond all doubt. This requires, of course, that you know for sure the species with which you are working. The following short characterization of each species may help to achieve this certainty:

Phodopus sungorus:

This is the preferred species for studies on circadian and seasonal rhythms and for pineal research! During summer (i.e., long photoperiod), the pelage of *P. sungorus* is dark greyish brown on the backand head with a black mid-dorsal stripe. The fur on the underside is whitish to light grey. In winter (short photoperiod), *P. sungorus* turns more or less completely white, except for the mid-dorsal stripe. This color change is by far the best identifying characteristic of *P. sungorus*.

Body mass: in summer 35 g - 45 g, in winter 25 g - 30 g

Distribution: E. Kazakstan and S.W. Siberia, the Baraba Steppe (see map).

Type Locality: E. Kazakstan, 100 km west of Semipalatinsk, near Grachevsk.

Phodopus campbelli:

Similar in size to *P. sungorus*. Pelage is darker brown and the underside is slate grey. There is a suffusion of yellow or buff on the dividing line between the dorsal and ventral pelage. The mid-dorsal stripe is narrower and more sharply defined (see Ross 1995, for a complete description). There is no color change in winter (short photoperiod)! Usually it is more aggressive than *P. sungorus*.

Distribution: Steppes and semi-deserts of central Asia: Altai Mountains, Region of Tuva, Transbaikalia, Mongolia.

Type Locality: "Shaborte" N.E. Mongolia (about 42°40' N; 116°20' E). The reported coordinates are approximate and vary between authors because "Shaborte" is not a geographic locality but a Mongolian name for a mud lake that dries out periodically (Argyropulo, 1933).

Figure 1. Map of Inner Asia showing the home land of *Phodopus sungorus* and *Phodopus campbelli* (details and names see text). Adapted from Ellermann and Morrison-Scott (1951).

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Reprinted from an unknown newspaper:

St. John's Wort plus sun may harm nerves

NEW YORK (Reuters) – St. John's Wort, a popular over-the-counter herbal remedy for depression, may cause temporary nerve damage in people who use it and are then exposed to sunlight, a US researcher reports in the October 3rd issue of The Lancet. Increased sensitivity to sunlight is associated with use of the herb.

Dr. Geoffrey M. Bove of Beth Israel Deaconess Medical Center, Boston, Massachusetts, describes the case of a 35-year-old who developed temporary nerve damage after taking the herb.

Four weeks after the woman started taking daily 500 milligram doses of St. John's Wort, she began to feel "stinging pain" on her face and the backs of her hands – areas exposed to the sun.

"Spontaneous pain was mild but worsened during and after being in the sun," Bove writes. "Pain was provoked by minimal mechanical stimuli such as light touch or air movement."

Bove reports that following sunbathing, the woman began feeling pain on the sun exposed parts of her arms and legs, She then sought medical attention. On physical examination, no skin burns were found. Even so, light touching, gusts of air, and cold caused "acute" pain in areas that had been exposed to sunlight, Bove writes. The pain lasted for a few seconds after the brushing, gusts of air, and cold exposure were terminated.

The woman's symptoms suggested nerve damage, or "subacute toxic neuropathy." She stopped using the herb and her symptoms began to improve. Over the following 2 months, her symptoms gradually disappeared, according to Bove.

Compounds known as "photoactive hypercins" are among the active ingredients in St. John's Wort. When exposed to light, these compounds produce substances that can damage cells. Myelin, the fatty insulation that wrap around nerves, is particularly vulnerable to this damage, Bove writes. If the myelin is damaged, symptoms appear similar to this patient's.

"Photosensitivity after St. John's Wort ingestion has previously been reported only in terms of pigment changes," Bove comments. "Photosensitivity manifesting as toxic neuropathy has not previously been reported, but clinicians should be aware of such symptoms after St. John's Wort ingestion and exposure to the sun," he concludes.

SOURCE: The Lancet 1998; 352:1121-1122.

SLTBR 11th ANNUAL MEETING
May 16-18, 1999

This year's meeting will be held in Alexandria, VA just before the American Psychiatric Association meets in Washington, DC. Sunday afternoon begins with a continuing medical education course directed by Raymond W. Lam, MD (Vancouver), cosponsored by the University of California-San Diego. Anthony J. Levitt, MD (Toronto) will present and discuss the new clinical practice guidelines for the treatment of seasonal affective disorder (SAD), recently issued by the Canadian Consensus Group. Alfred J. Lewy, MD (Portland, OR) will discuss clinical strategies for melatonin administration in circadian rhythm and mood disorders. Daniel F. Kripke, MD (San Diego) will discuss the application of light therapy in nonseasonal major depression, and Ray Lam will discuss the application for premenstrual depression and bulimia nervosa.

SLTBR's Young Investigator Award will be presented on Monday to Marc Hébert, PhD (Chicago). He will readdress the persistent question, "Does Retinal Sensitivity Have Anything to Do with SAD?" with a discussion of recent electrophysiological and psychophysical data.

Christopher Thompson, MD (U.K.) will deliver the keynote address (including a workshop discussion), with presentation of a new meta-analysis of light therapy trials that compares treatment efficacy in nonseasonal and seasonal depression. This year's Symposium celebrates two decades of seminal research by Norman E. Rosenthal, MD and his colleagues at the Clinical Psychobiology Branch of NIMH, work that has sparked an unprecedented international research effort in clinical chronobiology. Speakers include Frederick K. Goodwin, MD, former Director of NIMH, Siegfried Kasper, MD (Vienna), Bengt Kjellman, MD (Stockholm), Masako Okawa, MD (Chiba, Japan), Susan Swedo, MD (Bethesda), Thomas A. Wehr, MD (Bethesda), and Anna Wirz-Justice, PhD (Basel).

Tuesday's highlight is the First Annual ALPCO/Bühlmann Distinguished Lecturer presentation by Charlotte E. Remé, MD (Zürich): "Retinal Gene Expression, Cell Death, and the Spectral Distribution of Visible Light."

Abstracts have been received, and Michael Terman, PhD (New York), Program Chair, sends word of provocative contributions, including: strong benefit of a noradrenergic drug for treatment of SAD; a major confound in salivary melatonin assessment under a popular sampling protocol; melatonin phase shifts in subjects receiving light exposure during sleep; marked improvement of depressive symptoms in pregnant patients given light therapy; a potential photoperiod effect on suicide rate in the southern hemisphere; a potential effect on spontaneous bright light exposure on depression in nursing home patients; and more. . . .

For registration and hotel information, check www.websciences.org/sltbr or contact sltbr@yale.edu. Volume 11 of the *SLTBR Abstracts* will be available after the meeting.

HUMAN FRONTIER SCIENCE PROGRAM
10th Anniversary Workshop

May 31 to June 2 1999
European Parliament, Strasbourg, France

The Regulation of Sleep

Organizers: A. Borbély (Zurich), O. Hayaishi (Osaka), T. Sejnowski (La Jolla)

Topics include:

Neurophysiology, neurochemical meidators, molecular genetics, circadian rhythms, functional brain imaging.

Speakers include:

Peter Achermann, University of Zurich, Switzerland
Joelle Adrien, INSERM, Paris, France
Michael J. Berridge, The Babraham Institute, UK
Alexander A. Borbély, University of Zurich Switzerland
Derk-Jan Dijk, Harvard Medical School, USA
Martha Gillette, University of Illinois, USA
J. Christian Gillin, University of California, San Diego, USA
Osamu Hayaishi, Osaka Bioscience Institute, Japan
Craig Heller, Stanford University, USA
Michel Jouvet, Université C. Bernard, Lyon, France
James M. Krueger, Washington State University, USA
Fernando H. Lopes da Silva, University of Amsterdam, The Netherlands
Pierre Maquet, University of Liege, Belgium
Robert W. McCarley, Harvard Medical School, USA
Bruce McNaughton, Arizona Research Labs., USA
Emmanual Mignot, Stanford University, USA
Ferenc Obal, University Medical School, Szeged, Hungary
Terrence J. Sejnowski, The Salk Institute, USA
Mircea Steriade, University of Laval, Canada
Irene Tobler, University of Zurich, Switzerland
Giulio Tononi, The Neurosciences Institute, San Diego, USA

In addition to the workshops, a ceremony will be held in honour of the 10th Anniversary of the Human Frontier Science Program, which will include a round-table discussion on perspectives in the life sciences in the next century.

Attendance at the workshops is open to interested scientists. There will be a registration fee of US $160, and registrants will be expected to pay their own travel and accommodation expenses. Further information and registration forms can be obtained from the web sit or by writing to the address below, giving your name, address, e-mail address, telephone and fax numbers, and specifying that you are interested in the "Regulation of Sleep" workshop.

Human Frontier Science Program,
Bureaux Europe, 20, place des Halles,
67080 Strasbourg Cedex, France
E-mail: smetzger@hfsp.org, Fax: +33 3 88 32 54 47, Web: http://www.hfsp.org

GORDON RESEARCH CONFERENCE ON CHRONOBIOLOGY

Il Ciocco, Barga, Italy
June 13 - 19, 1999

Eberhard Gwinner, Chair
Nicholas Mrosovsky, Vice-Chair

Sunday Evening, June 13
Opening
Adaptive and Evolutionary Aspects of Circadian Rhythms
Serge Daan (University of Groningen, Netherlands): Discussion Leader
Carl Johnson (Vanderbilt University, USA): Adaptive significance of circadian rhythms in photosynthetic organisms
Gerhard Heldmaier (University of Marburg, Germany): Circadian rhythms in daily torpor and hibernation
Nicholas Mrosovsky (University of Toronto, Canada): Masking: understanding rather than excluding it
Monday Morning, June 14
Human Circadian Pathologies and their Treatment
Anna Wirz-Justice (University of Basel, Switzerland): Discussion Leader
Eus van Someren (Netherlands Institute of Brain Research): Circadian rhythms in dementia
Tom Wehr (NIMH, USA): Rhythms and blues: Role of circadian and seasonal rhythms in pathogenesis and treatment of mood disorder
Makoto Uchiyama (National Center of Neurology and Psychiatry, Japan): Human circadian rhythm disorders: pathology in circadian and homeostatic sleep regulation
Jürgen Aschoff Memorial Lecture
Michael Menaker (University of Virginia, Charlottesville, USA): Toward a complete understanding of circadian organization
Monday Evening, June 14
Molecular Mechanisms I
Jay Dunlap (Dartmouth College, USA): Discussion leader
Steven Reppert (Harvard, USA): Comparative Analysis of Clock Genes
Steve Kay (Scripps, USA)Transcriptional control and circadian timekeeping
Till Roenneberg (University of Munich, Germany): Light and temperature effects on the circadian system of Neurospora with and without FRQ
Tuesday Morning, June 15
Molecular Mechanisms II
Discussion Leader to be nominated
Hajime Tei (University of Tokyo, Japan): Molecular mechanisms for circadian expression of the mammalian Per1 gene
Chuck Weitz (Harvard, USA): Molecular analysis of the mammalian circadian clock
Elaine Tobin (UCLA, USA): The CCA1 protein and its involvement in circadian rhythms of Arabidopsis
Susan Golden (Texas A&M, USA): New loci that affect circadian rhythms of gene expression in cyanobacteria
Deborah Bell-Peddersen (Texas A&N, USA): Molecular analysis of circadian output pathways in Neurospora crassa
Tuesday Evening June 15
Pineal and Retinal Rhythms
Michael Menaker (University of Virginia,USA): Discussion Leader
Roland Brandstaetter (Research Center for Ornithology, Germany): Distinct patterns of circadian rhythm expression in the avian pineal gland
Greg Cahill (University of Houston,USA): Pineal, retinal and behavioral rhythms in Zebrafish
Carla Green (University of Virginia): Xenopus transgenics shed light on the retinal circadian clock
Gianluca Tosini (Morehouse School of Medicine, USA): Melatonin circadian rhythm in the retina of rodents and primates
Wednesday Morning, June 16
Circadian Photoreception and Photoentrainment
Michael Terman (New York Psychiatric Institute, USA): Discussion Leader
Domien Beersma (University of Groningen, Netherlands): Phase and frequency responses to light and their role in stabilizing entrainment
Robert J. Lucas (Imperial College, UK): Novel photoreceptors mediate the effects of light on the mammalian circadian system
Jeff Hall (Brandeis University, USA): Circadian photoreception on Drosophila
Paul Devlin (Scripps, USA): Genetic analysis of circadian photoreception in Arabidopsis
Wednesday Evening, June 16
The SCN as a Pacemaker
Rae Silver (Barnard College, USA): Discussion Leader
Erik Herzog (University of Virginia, USA): The role of clock and tissue organization in period determination of SCN neurons
Patrick Card (University of Pittsburg, USA): Functional dissection of the retino-hypothalamic tract with neurotropic viruses
Helena Illnerova (Prague, Czech Republic): Regulation of the spontaneous SCN rhythmicity
Larry Morin (SUNY, USA): Midbrain contributions to circadian timing
Thursday Morning, June 17
Multiple Oscillators, Multiple Pacemakers
Gene Block (University of Virginia, USA): Discussion Leader
Ueli Schibler (University of Geneva, Switzerland): Control of circadian gene expression in peripheral organs and tissue culture cells
Andrew J. Milllar (University of Warrick, UK): Multiple autonomous circadian clocks in higher plants
Charlotte Helfrich-Foerster (University of Tuebingen, Germany): Multiple pacemaker neurons control locomotor activity in Drosophila: evidence for a hierarchical organization
Chen Liu (Harvard, USA): GABA as an internal synchronizer of SCN neurons
Sato Honma (Sapporo, Japan): Coupling mechanism of multiple oscillators in the master clock, SCN
Thursday Evening June 17
Sleep
Irene Tobler (University of Zürich, Switzerland): Discussion Leader
Craig Heller (Stanford University, USA): Circadian and homeostatic regulation of sleep
Eve van Cauter (University of Chicago, USA): What is sleep good for?
David F. Dinges (University of Philadelphia, USA): Neurobehavioral effects of sleep loss: homeostatic and circadian dynamics

Chair
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INTERNATIONAL CONGRESS on CHRONOBIOLOGY

Dates: August 28 (evening reception) until September 1 noon (total 3.5 days). There will be a banquet dinner on the evening of Aug. 31. The meeting location is in the lovely Mayflower Hotel, near the White House in Washington, DC.
Abstract and meeting registration deadline: Friday, May 14, 1999.

STUDENT PROGRAM: Organized by M. Marques and B Millet
Student lunch event with "Topic Tables" including:
- Methodology of biological rhythms (experimental design, data collection and analysis)
- Molecular, cellular and genetic aspects of biological rhythms
- Regulation of biological rhythms by environmental factors.
- Regulation of biological rhythms by hormones, melatonin and other substances

ADDRESSES
D. DINGES What is wakefulness? Sleep need and circadian control of neuro-behavioral functions (Introduction by K.-I. Honma)
A. LOUDON: A matter of life and death: Biological timing in seasonal environments (Introduction by M. Menaker)
J. TAKAHASHI Molecular genetics of mammalian circadian rhythms (Introduction by Dr. P. Pevet)

DATABLITZ SESSIONS:
Brief slide presentations submitted by participants.
Chairs: C. Green and M. Menaker (Univ. Virginia USA); M.-T. Romero (State Univ. New York, Binghamton, USA); W. Rietveld (Univ. Leiden, Netherlands)

SYMPOSIA AND WORKSHOPS:
Hormonal and Metabolic Response in Shiftwork. Chair: J. Arendt
- A. Knutsson (Umea, Sweden) Metabolic risk factors for major disease in shift work
- G. Brandenberger, (Strasbourg, France) Hormonal responses to simulated phase shift as a function of core body temperature and sleep
- R. Barnes & J. Arendt (Surrey, UK), Direction and rate of adaptation of the melatonin rhythm in different offshore shift schedules
- D. Ribeiro, L. Morgan, S. Hampton & J. Arendt (Surrey, UK) Pancreatic and metabolic responses in simulated and real shift work: risk factors for heart disease?
- E. van Cauter, Karine Spiegel (Chicago, USA) Effects of sleep deprivation on glucose tolerance

SCN structure and function Chair: F. Davis
- E. Herzog (Univ. Virginia) Circadian period is determined by molecular and intercellular events in the SCN
- S. Low-Zeddies (Northwestern University) Circadian behavior and SCN anatomy in clock chimeric mice
- W. Schwartz, (Massachusetts Med Sch) SCN as tissue: toward linking molecular and cellular studies to whole animal behavior
- C. B. Saper (Boston, USA) Mechanisms of circadian input to sleep regulation

Melatonin: Basic Aspects Chair: P. Pevet
- A. Kalsbeek (Amsterdam, The Netherlands) Nervous pathways and neurotransmitters involved in the SCN-driven daily rhythm of melatonin
- D.C. Klein (Bethesda, USA) Molecular and cellular mechanisms involved in the norepinephrine stimulation of melatonin synthesis
- V. Simonneaux (Strasbourg, France), The role of neuropeptides in the regulation of melatonin synthesis
- D. Weaver (Boston, USA) or P. Morgan (UK) Sites and mechanisms of action of melatonin

Entrainment of Human Circadian Rhythms: Photic v.s.Non-Photic
Chairs: K. Honma and H. Tokura
- K. Honma Non-photic entrainment of human circdian rhythms
- T. Wehr Photoperiodism and human circadian rhythms
- H. Tokura Propotional influence of bright and dim lights on human circadian rhythms
- M. Okawa Pathology of human circadian entrainment

Controversies in the Epidemiology of Seasonal Depression
Chair: R. Lam
- G. Murray (Melbourne, Australia) Construct validation of seasonality in Australia
- A. Magnusson (Iceland) Do populations at far northern locations adapt to the long winter?
- A. Levitt (Toronto, Canada) Epidemiology of seasonal depression in Canada
- P.P.A. Mersch (Netherlands) Epidemiology of seasonality and seasonal depression in the Netherlands

Physiology and Behavior of Entrainment Chair: L. Morin
- L. Morin (Stony Brook University, New York) Functional anatomy of the hamster circadian rhythm system
- M. Gorman (Michigan, USA) Probing the properties of constituent circadian oscillators
- L. Smale (Michigan State Univ.) Neural correlates of a diurnal pattern of entrainment
- B. Goldman (University of Connecticut, Storrs, CT) Circadian rhythms in subterranean mammals

Role of Photopigments in the Circadian Rhythm Regulation.
Chair: R. Foster
- R. Foster: Mammalian Photoentrainment: A role for both classical and novel photopigments?
- I. Provencio, A Candidate Mammalian Circadian Photopigment
- T. Furukawa, Attenuated circadian entrainment in mice carrying mutations in the photoreceptor-specific homeobox gene Crx
- A. Sancar, Cryptochrome in a mammalian circadian photoreceptor

Cardiovascular chronobio-/chronopharmacologic animal models
Chairs: B. Lemmer, G. Koren
- B.J.A. Janssen (Maastricht, NL) Mechnisms of blood pressure regulation in rats
- G. Koren (Boston, USA) Circadian variation in heart rate and QT-interval in conscious mice
- B. Bruguerolle (Marseille, France) Rhythms in heart rate, temperature and motility in rats: Effects of drugs
- K. Witte (Mannheim, Germany) Experimental chrono-pharmacology: Effects on blood pressure and target tissues

Rhythm Disturbances in Old Age Chairs: Y. Touitou, D. Weinert
- D. Weinert (Halle, Germany) Rhythm disturbances in old mice and their consequences
- Y. Touitou (Paris, France) Endocrine temporal structure in the aged
- T. Monk (Pittsburgh, USA) Psychophysiological aspects of biologic rhythms
- V. Someren (Amsterdam, The Netherlands) Treatment of rhythm alterations in the elderly

Common themes in the molecular basis of circadian oscillators
Chair: J. Dunlap
A. Sehgal (Univ. Pennsylvania) Timekeeping and light entrainment by the Drosophila circadian clock
J. Price (West Virginia University) The doubletime gene of Drosophila, a clock protein kinase
D. Bell-Pedersen (Texas A&M University) Circadian clock control in Neurospora
C. Weitz (Harvard Univ.) Molecular Factors in the Mammalian Circadian Oscillator

Chronobiology and Chronotherapy of Cardiovascular Disease
Chair: E. Haus
F. Portaluppi (University of Ferrara, Italy) Chronopathophysiology of cardiovascular events
W. White, (U.S.A.) Circadian profile in blood pressure--relationship to end organ damage
B. Lemmer (Germany) Effects of circadian timing of drug dosing on the 24-hour blood pressure profile
S. Willich (Germany) Epidemiologic study on the effect of dosing time of nitrates on angina pectoris

New Aspects of Serotonergic Regulation of Circadian Clock Systems Chair: S. Shibata
S. Shibata, Effects of serotonergic drugs on behavior and clock gene expression
G. Pickard , 5HT1B receptor-mediated presynaptic inhibition of retinal input to the suprachiasmatic nucleus
C.N. Allen, Presynaptic and postsynaptic mechanisms of 5-HT in the suprachiasmatic nucleus
D.J. Kennaway, Serotonin and the modulation of melatonin rhythms in the rat

POSITIONS AVAILABLE

EDITOR IN CHIEF, JOURNAL OF BIOLOGICAL RHYTHMS

Fred Turek's 5 year term as editor of the Journal of Biological Rhythms ends with the last issue of 1999. The SRBR announces a search for a new editor. Please send nominations to Dr. Rae Silver, Chair of the Search Committee (addresses below). Interested candidates are invited to send Rae Silver a c.v. with a brief outline of the strengths and weaknesses of the JBR and a proposal of how she/he would promote the journal.

Fred Turek will handle the arriving manuscripts through June-August, that is, until the 1999 volume is filled. He would then turn over the manuscripts to the new editor. Fred has generously offered to "take care of things" until there is a smooth transition. In fact, he would end up handling isolated papers for another 6 months, including second submissions, and manuscripts with unresolved issues. The Journal of Biological rhythms is published 6 times per year by Sage Publications. At the present time, $15,000/annum is provided by Sage Publications and SRBR to defer expenses associated with the position.

Dr. Rae Silver Chair, JBR Editor Search Committee Columbia University Mail Code 5501 1190 Amsterdam Ave. New York, NY 10027	Phone: Fax: Email:	212-854-5531 212-854-3609 qr@columbia.edu

POST DOCTORAL POSITION AVAILABLE

A post doctoral research position oriented toward basic and functional neuroanatomy of the mammalian circadian rhythm system is currently open in the laboratory of Dr. Larry Morin in the Department of Psychiatry and Graduate Program in Neurobiology and Behavior, Stony Brook University. Interested applicants should contact Dr. Morin by phone (516-444-1613) or by email (lmorin@epo.som.sunysb.edu).