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Suprachiasmatic Nucleus or Nuclei What's in a name?

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Juliet knew "that which we call a rose by any other name would smell as sweet." Likewise, the primary mammalian circadian oscillator located in the anterior hypothalamus, the SCN, would still be an oscillator no matter what we call it. But how do we as a field define SCN? A Medline search of the term "suprachiasmatic" in papers published from 1997 to present pulled out 337 papers in which SCN was defined in the abstract (plus an additional 224 papers in which SCN was not defined in the abstract). Interestingly, about two thirds of these abstracts (n=228) defined SCN as suprachiasmatic nucleus whereas SCN was defined as the suprachiasmatic nuclei in 92 abstracts. It might be argued that the SCN, like all nuclei in the central nervous system is bilaterally represented and therefore SCN = suprachiasmatic nucleus. However, since the output of the circadian oscillators located in each suprachiasmatic nucleus[1] is measured as a unitary circadian rhythm, then functionally the SCN, our biological clock, is represented by the suprachiasmatic nuclei. On the other hand, SCN was also defined simply as suprachiasmatic, suprachiasmatic region, and suprachiasmatic hypothalamic area in a handfull of abstracts. In the title of the "SCN" book, "Suprachiasmatic Nucleus: The mind's Clock"[2], the singular form (nucleus) is used whereas when SCN is defined in the text, it is suprachiasmatic nucleus in 9 chapters and suprachiasmatic nuclei in 10 chapters! Some even prefer to call the suprachiasmatic nucleus the SCh, similar to its description by Krieg in his classic 1932 paper "The hypothalamus of the albino rat[3]." It would appear however, that no matter how we define the SCN, if the pace of exciting discoveries regarding our biological clock continues as it has in the recent past, we will all come out smelling like roses.

[1]Pickard, GE and Turek, FW (1983) The suprachiasmatic nuclei: Two circadian clocks? Brain Res 268:201-210.

[2]Suprachiasmatic Nucleus: The Mind's Clock. DC Klein, RY Moore, and SM Reppert, (editors), Oxford University Press, New York, 1991.

[3]Krieg, WJS (1932) The hypothalamus of the albino rat. J Comp Neurol 55:19-89.

P.S. I prefer nucleus.

THE MORE THINGS CHANGE, THE MORE THEY REMAIN THE SAME

The flame has burned brightly! But, with this issue the Biological Rhythms Bulletin comes to an end. The editors thank all of you who have contributed to it for making the Bulletin a success. We have had some very good feedback which indicates, at least, that it was being read by a few of you. We would like to thank Mary Herndon, in particular, and the staff at the Center for Biological Timing for their extremely capable assembly and printing of the 4 issues of the Bulletin.

We even thank those of you who have promised material and who have not delivered it. Do not despair! Someone will seek you out because there will be alternate sites in which to present your viewpoint. As most of you know, the Journal of Biological Rhythms has a new editor-in-chief, Dr. Marty Zatz. One of his goals is to make readers of the Journal more aware of the vitality in our field of biological rhythm research. Toward this end, he expects to incorporate much of the material that would otherwise have been published in the Bulletin. One of the Bulletin editors (LPM), joined by Anna Wirz-Justice, will move to the Journal to assist Marty with the solicitation and editing of Bulletin-equivalent material. Alex Neumeister, a member of the SLTBR and also a Bulletin editor, will now become Editor, along with Robert Levitan of the University of Toronto, of a newsletter explicitly for the SLTBR members.

We have an answer to that important question:
How many chronobiologists does it take to screw in a light bulb?
Can't guess? Well, good authority has it that the answer is one, provided the person is relatively coordinated. (The authority is Joe Miller who says it's his original joke previously published years ago without attribution in the SLTBR newsletter). Joe further suggests the establishment of a regular "ChronoHumor Column," the first contribution to it being melatonin. Get it?

In This Issue

(Editor's note: The SLTBR supports research by Russian scientists and makes monetary awards based upon competitive application for the funds. The following briefly describes the history of the research problem and the proposed study by Drs. A. Putilov and K. Danilenko that recently received funding from the SLTBR.)

SLTBR Russian Research Support Fund

"Waking EEG power density in winter depression treated with bright light"

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The hospital of our medical research center in Novosibirsk (West Siberia) provides an unique opportunity to investigate non-pharmacological antidepressants in lifetime drug-naive patients. Our group was the first to study Seasonal Affective Disorder (SAD) and light treatment in Eastern Europe, and, over a 10-year period, we tested clinical and physiological effects of bright light, physical exercise, and their combination with one night of sleep deprivation (N=224 subjects). In particular, the response of sleep regulatory systems to bright light has been studied in two experiments. A previously suggested deficiency of slow-wave sleep in depressed SAD (Anderson et al., 1994) was replicated (N=21 SAD, 10 controls) and reversed after successful light therapy (Palchikov et al., 1997). A pilot study (N=8 SAD, 6 controls) followed slow-wave activity (SWA) during nighttime sleep and daytime and nighttime naps (Putilov et al., 1998). The decay of SWA during sleep was less prominent in SAD than controls (Putilov et al., 1998). However, no differences between patients or controls was found in sleep onset latency in naps at any time of day, independent of light treatment (Danilenko et al., 1996). SWA in the first 8 min of non-REM-sleep increased from the first (morning) to the last (nighttime) 20-min sleep attempts in both patients and controls, in agreement with the quantitative predictions of the buildup of SWA in somnostat models (Daan et al., 1984; Putilov, 1995) and with the response of SAD patients to a total sleep deprivation (Brunner et al., 1996). Recent studies have described waking EEG theta-alpha activity as an index of sleep pressure accumulation during the wake phase (Cajochen et al., 1999). SAD patients showed a rapid saturation of sleep pressure during the first 10 hours of wakefulness, whereas in controls the buildup followed an exponential function over 35 hours.

The main purpose of the project is to further test disturbances of sleep regulation in SAD. In particular, we will try to replicate and extend the result of the Cajochen et al. study. Subjective sleepiness and the waking EEG will be recorded several times in at least 15 SAD subjects when depressed, and 15 controls during daytime, and in some of them, throughout a 38-hour period of wakefulness, as a part of a more extensive study on the effects of sleep deprivation on SAD. The procedure will be repeated after a week of light treat-ment. Depressive symptoms will be rated with the SIGH-SAD. We will compare baseline differences and effects of light treatment on mood and sleep homeostasis (indexed by the time course of waking EEG theta-alpha) in subjects with SAD and in controls.

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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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FROM: "Ronald E. Becker, MD" <becker@massmed.org>

I was asked yesterday whether vertigo was a known side effect of melatonin use.

A (non-sleep) colleague has an adult male patient (mid 50's) with no other known medical concerns. He had complained of disrupted sleep, which improved on melatonin, 3 mg taken nightly. However, he began having vertigo on rising in the morning. When he decreased his dose to approximately 1 mg (by cutting the pill!) the vertigo went away, but sleep became 'disrupted' again. He went back to 3 mg and once again had the vertigo. There is no past history of vertigo, and the vertigo is experienced only on rising in the morning after taking 3 mg melatonin the night before.

I tried several Internet literature and database searches. There are several reports to the FDA about "dizziness" and "dysequilibrium," but few details are given. I have not heard of this side effect in my patients (mostly pediatric).

I would appreciate hearing if anyone else has encountered this side effect.

Ron Becker, MD, Children's Hospital, Boston

AAMCC ANNOUNCEMENT

The American Association for Medical Chronobiology and Chronotherapeutics (AAMCC) was organized in 1998 as a forum for physicians, medical scientists and other health care providers interested in applying chronobiology and chronpharmacology to patient care. In 1999 theAAMCC organized the 8th International Conference on Chronopharmacology and Chronotherapeutics together with its first national meeting in Williamsburg, VA, August 24-28, and abstracts were published as a supplement to Volume 16 of the journal *Chronobiology International*. Beginning January 2000, the AAMCC has joined the International Society for Chronobiology in sponsoring *Chronobiology International* as its official journal which will be available at a greatly reduced rates to its members. Submission of papers on medical chronobiology and chronotherapeitucs are invited (Chief co-editors: Michael Smolensky (msmolensky@sph.uth.tmc.edu) and Ludger Rensing (rensing@uni-bremen.de). AAMCC current activities consist of educational presentations in the USA and participation on invitation in a chronobiology course organized by the newly emerging Mediterranean Society on Chronobiology in fall 2000 in Turkey.

Do No Harm

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The first ethical principle of medicine is: do no harm. Our Society for Light Treatment and Biological Rhythms (SLTBR) has "treatment" in its title: the goal of helping people, not harming them. Indeed, the great majority of scientific material presented at our meetings is concerned with understanding human illnesses and the means for alleviating illness. Tests of treatments which help people have been our primary focus.

At the current time, the American psychiatric community and an interested press and public are focusing increasing attention on ethical issues which must concern SLTBR. Of first concern are studies which are intended to do harm. Some studies of this type have been presented at our meetings. Of second concern are studies which are intended to allow spontaneous disease progression when effective treatment is available. Placebo-controlled trials are frequently presented at our meetings. An interacting concern is whether psychiatric patients should be considered competent to consent to non-beneficial studies which may do harm or foster disease progression. Related is the question of whether any competent person would agree to studies which do harm or foster disease progression, if the real risks-benefits ratio were clearly and adequately explained.

Our society does allow people to consent to donate blood, for example, although it hurts and involves some minor risk. We allow people to play professional football, although most are eventually going to be injured. Sports are fun and the professionals are highly paid. We even allow people to climb high mountains for the thrill, although a reliable percentage die in the attempt. Evidently, our free society allows people to volunteer for unnecessary risks.

In harmful studies such as drug challenge studies, the situation is a bit different, since the risk falls on the psychiatric patient, but the thrill goes to the investigator. If a patient is an inpatient, especially, the illness is probably disabling and costly and probably there is some urgency about relieving it. To make such patients worse goes in the wrong direction from what physicians have been trained to do. Nevertheless, there is a good argument that psychiatric patients, like other free people, should have the right to decide to take risks, when the risks are clearly explained and the patient has the capacity to freely consent. My concern is that harmful studies have sometimes been proposed with inadequate disclosure to patients with impaired capacity to consent, so that the combination is poison.

For example, it is well known that intravenous stimulants produce cerebrovascular damage.[1] One summer, a medical student worked in my lab to show that a single dose of intravenous methylphenidate can produce cerebrovascular lesions in rats. We could never get that study published except in abstract.[2] People who are interested in making schizophrenics more psychotic still do intravenous stimulant challenge tests. I would be quite surprised if investigators clearly inform their schizophrenic volunteers that their brains might be permanently damaged. Does the potential value of such studies to society really outweigh their potential for harm to the individual? I remember an involuntarily-hospitalized schizophrenic who was given an intravenous methylphenidate challenge after she signed consent while in a seclusion room. If she was fully competent at the time, why was she locked in the seclusion room? Are we confident there was no element of coercion, when the consent was obtained by the doctor who was locking her up?

Another example was a recent article by very distinguished authors, using alpha-methylparatyrosine to make depressed patients relapse.[3] The patients were euthymic outpatients when the study began, so one would presume they were competent to consent, but the challenge made them quite severely depressed. In my opinion, this would be a fair summary of what the consent form should have said:

> There is an abundance of information that low norepinephrine transmission is somehow a factor in depression. Further, it is already known that alpha-methylparatyrosine (a drug which reduces norepineph-rine) can cause depression and make depression much worse. Acute depression is the expected result of receiving alpha-methylparatyrosine in this experiment, and it would not be anything new. Indeed, alpha- methylparatyrosine can cause very severe depression and desperate suicidality. Also, it is known that people with prior depression, such as yourself, are more likely to relapse into depression than people who have never had depression. There is a fair chance that participating in the experiment will make you grievously depressed. Many experts believe that each relapse of depression increases the risk of future depression, perhaps through a neurologic mechanism called brain kindling. Therefore, this experiment might tend to make you more depressed and despondent throughout your life. One young volunteer whom the investigators supposed was healthy died during a study of alpha-methylparatyrosine, but because of special aspects of that incident, the investi-gators believe that the chance that you will die as a result of this experiment is much less than one percent. Participating in this experiment will have no medical benefit for you, the volunteer. Because of sometimes horrible effects of alpha-methylparatyrosine, it is unlikely this investigational drug will ever be used clinically, but this experiment might make a minor addition to what is already known about the mechanisms of depression.

Presuming that competent patients did volunteer, it would be amazing if the benefits and risks had been presented quite this

frankly. It is hard to understand how such studies could be consistent with the current version of the Declaration of Helsinki [http://www.wma.net/e/policy/17-c_e.html], which states that for non-therapeutic research, "The subject should be volunteers - either healthy persons of patients for whom the experimental design is not related to the patient's illness." I believe that some experiments are being done in our field where the risk to benefit ratio is too unfavorable for the individual, and they could not be done if the consent process were as open as it should be.

As a member of an Institutional Review Board, I am concerned that consent documents should fully, frankly, and plainly disclose the risks of human experiments. There are frequent occasions when investigators fall short. As a medical community, researchers must insist on full disclosure of the risks of experiments, and we should not approve experiments where harm is likely. Second, we are concerned that competent consent be obtained. Whereas psychiatric patients should not loose their rights and freedom when they need treatment, it is obvious that some psychiatric patients (and medical patients) have diminished capacity to consent. The question of competence becomes of more concern for inpatients and for patients with certain conditions such as Alzheimer's disease. Institutional Review Boards must increasingly scrutinize who judges competence (i.e., the investigator or a disinterested professional) and what criteria are used. In instances where full capacity to consent is uncertain, good judgement will require consent both by the patient and by a responsible family member or caregiver. It is also necessary to recognize that involuntary patients and those with legal guardians present special ethical problems because of their diminished capacity to consent. Such patients should be included in beneficial human research only when there are specific scientific reasons for including persons with diminished capacity and special precautions taken to protect their interests. Perhaps patients with diminished capacity to consent should never be included in harmful research.

Another issue is the problem of placebo treatment. Since testing new treatments is important, when there is no accepted (evidence-based) treatment for a condition, it is ethical to test a new treatment versus placebo. Also, when a new treatment may be better than the accepted treatment, it is ethical to compare the new treatment with an accepted treatment. An ethical problem arises when a study is designed to compare a new treatment with placebo, when an accepted evidence-based treatment is available. The study may do harm to the patients placed on placebo by delaying available treatment. At one time, it was considered ethical for NIH investigators to monitor untreated depressed patients until they committed suicide. This probably would not be considered ethical today with our extensive knowledge of the efficacy of antidepressant treatments. Indeed, many observers think it is no longer ethical to treat depressives or schizophrenics with placebo, if substantial distress is likely to occur which could be alleviated by treatment. The current version of the Declaration of Helsinki states, "In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method." [http://www.wma.net/e/policy/17-c_e.html] Here again, also, the questions of competence and full disclosure arise, for why would any competent patient agree to risk being assigned to placebo and suffer serious symptoms, if the patient fully understood that effective alternative treatment is available?

Sometimes the FDA or NIH review committees insist on placebo arms of clinical trials. I have had grants refused because the proposed trial had no placebo arm, only a comparison between light treatment and standard treatment. Many observers feel that it is time to improve the ethical outlook of review committees.

Many light treatment trials historically have used a placebo arm with adequate rationale. First, for studies lasting only 1 week, the amount of perhaps-unnecessary illness or relapse in the placebo-treated patients would be small, indeed, placebo SAD patients do tend to improve. Second, until recently, the evidence that light treatment was better than placebo was not considered sufficient even for SAD. Today, the short-term effectiveness of both light treatment and antidepressant drugs has been demonstrated for SAD and for nonseasonal depression, but a need for longer-term trials is recognized. Leaving depressed patients (SAD or nonSAD) on placebo for months will be difficult to justify ethically in most situations. One good alternative will be to compare light treatment with antidepressant drugs. Another good alternative, already used for light trials in nonseasonal depression but not yet for SAD, will be to compare light plus antidepressant drug with antidepressant drug alone. Trials of light plus psychotherapy versus psychotherapy alone will also be appropriate.

As a society, SLTBR should encourage its members to focus on beneficial research and to turn away from studies which may cause significant harm.

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Comments on Kripke's Article, "Do No Harm"

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Dr. Kripke's Do No Harm is the latest in a series of vitriolic attacks on certain types of psychiatric investigations: the challenge study and off-medication research. He urges the Society to associate with the goal of helping people, not harming them. He divides investigations into either good or evil, and makes it clear that some investigators are designing studies with the intent to harm subjects or to allow spontaneous disease progression when it could be prevented. The allegations continue as he asserts that these experiments are done with either incompetent subjects and/or with deceit. Dr. Kripke doubts that any competent person would agree to studies which do harm or foster disease progression, if the real risks were clearly and adequately explained. He follows this provocative introduction with simple

declarative statements. "...harmful studies such as drug challenge studies...the risk falls on the psychiatric patient, but the thrill goes to the investigator." "...harmful studies have sometimes been proposed with inadequate disclosure to patients with impaired capacity to consent, so that the combination is poison." The lack of scholarly or sophisticate analysis continues when he suggests that a study which he could not get published is a basis for warning any subject receiving a CNS stimulant that they may get permanent brain damage.

It is not possible to respond to all Dr. Kripke's allegations, for he does not identify the study that followed untreated patients until they suicided, nor can we evaluate his story about the use of seclusion to coerce consent. I select three areas for brief comment:

1. Allegations of deceit and malevolence. Dr. Kripke's statements of harm, deceit, non-valid consent, withholding of evidence of significant risk of permanent brain damage, and malevolent intent of thrill-seeking psychiatric investigators constitute a condemnation of our field and of many of us as investigators. He provides no documentation of any of these remarkable assertions. Negative and distorted media attention has been given to similar allegations directed at UCLA and the University of Maryland Baltimore. But in each case the NIH office for Protection from Research Risks found no unethical research protocol and no harm to any subject. Is it proper for a polemic devoid of documentation to be given space in a professional publication? Reckless allegations and poor scholarship do a disservice to the serious discussion research ethics. Dr. Kripke continues a tradition of allegation without documentation coupled with the most remarkable misunderstanding of facts (Hilts PJ, 1994; Hilts PJ, 1998; Lehrman NS and Sharav VH, 1998; Shamoo AE and Keay TJ, 1996; Whitaker R, 1998; Whitaker R and Kong D, 1998).

2. Withholding medication causes disease progression. The problem of accepting comparability between treatments as sufficient evidence for efficacy has been considered elsewhere (Kane JM and Borenstein M, 1997; Temple R, 1997). Denouncing the placebo without considering the purposes, safety, and actual effect on clinical course is unwise. The proposition that withholding standard treatment is unethical in any circumstance fails a common sense standard of ethics as soon as one equates a week without aspirin in an arthritis study (with clinical rescue procedures) to withholding insulin in a diabetic study or chemotherapy in a cancer study. A continuous evolution of optimal approaches for assessing efficacy with procedures which minimize risk and enhance benefits is essential. There is an extensive literature with which to test the proposition than placebo controlled studies in schizophrenia cause disease progression (Carpenter WT, Schooler NR and Kane JM, 1997; Gilbert PL, Harris J, McAdams LA, Jeste DV, 1995), reinforced by recent analysis (Johnstone EC et al, in press). The evidence is solidly against the disease progression hypothesis, and it appears that the time periods and clinical monitoring associated with clinical research provide a relative safe framework for medication-free research (Wyatt RJ, 1997; Carpenter, WT 1997). Examination of actual facts leads to an emphasis on procedures which minimize risk and enhance benefits, as outlined elsewhere (Carpenter WT, Schooler NR and Kane JM, 1997), rather than condemnation of medication-free research.

3. Challenge studies cause harm. Miller and Rosenstein (1997) have recently reviewed this area. A timely example involves the ketamine challenge in schizophrenia which has involved about 56 schizophrenia subjects who have received ketamine in about 120 challenge studies. Data from all these subjects is in press (Carpenter WT, in press), and suggest minimal distress and modest symptom increase. Effects quickly subside after infusion discontinuation, with no disease progression. There is no indication that any subject was misinformed or harmed. The suggestion by Dr. Kripke that investigators place patients at risk for thrills is reprehensible.

Dr. Kripke's commentary does not merit an attempt to rebut each issue, or to provide a comprehensive review of each study category. I do not assert that all studies using placebo or pharmacologic challenge are essential science or risk-free. I do assert that these studies are usually serious science conducted by serious investigators and reviewed by serious IRB's. I believe each must be considered on its own subject risk/benefit considerations and scientific merit, and categorical condemnation is not supported by scholarly and dispassionate review of evidence. The Society will be ill-advised to follow Dr. Kripke's simple template for distinguishing beneficial from harmful research, and good from bad investigators. The proposition that science address society's moral obligation to its ill citizens by abandoning non-therapeutic research in favor of therapeutic research denies the hope that new knowledge of disease will lead to new and better therapeutic hypotheses. Society will have failed the future person with schizophrenia if new treatment developments are limited by the part-way therapeutics and limited pathophysiologic knowledge of today.

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Comments on Kripke's Views on "Do No Harm"

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> "For every complex problem, there is a solution that is simple, neat, and wrong." - H.L. Mencken

First, I entirely agree with Will Carpenter's critique. My statement is a supplement to his substantive points. [quotes from Kripke's article are in *italics*]

The first ethical principal of medicine is: do no harm. It is a common rhetorical device to appeal to authority when historical and logical analysis fails. This supposed Hippocratic dictum dates from about 400 BC (Even the thrust of the original is in doubt since John Morrison (jdmorrison@fuse.net) notes "never do harm to anyone" from the Hippocratic oath translates into Latin as, "aut ne offendas," a different verb from "noceo.").

In historical context the medical practice of the time consisted almost entirely of placebos and toxic interventions, e.g. purging. Hippocrates was sensibly advising the doctor to stick with the placebos and rely on the healing power of nature. Further, since Hippocrates antedates the scientific experimental evaluation of treatments, as well as the development of powerful specific agents, by a few millennia, it would be remarkable if any of his statements applied within our current context. Does Kripke suggest that anti-cancer drugs be foresworn?

The World Medical Association (Geneva 1948) pointed out, "In its most compelling portions, it emphasizes the profundity of the medical covenant, patient dignity, the confidentiality of the transaction, and the physician's responsibility to guard against abuse or corruption of his knowledge and art" Their suggested modernization omits the supposed "first principle" entirely.

Another classical rhetorical device is the ad hominem attack. By implying unworthy motivation one can avoid the inconvenient necessities of factual documentation and logical analysis.

Of first concern are studies which are intended to do harm. Some studies of this type have been presented at our meetings. Of second concern are studies which are intended to allow spontaneous disease progression when effective treatment is available. Placebo-controlled trials are frequently presented at our meetings... Our society does allow people to consent to donate blood, for example, although it hurts and involves some minor risk. ... Evidently, our free society allows people to volunteer for unnecessary risks. In harmful studies such as drug challenge studies, the situation is a bit different, since the risk falls on the psychiatric patient, but the thrill goes to the investigator." Thrill? Apparently this motivational aspersion is all that is necessary for Kripke's argument since there is no further analysis of the real complexities of challenge studies (which Will Carpenter addresses).

My concern is that harmful studies have sometimes been proposed with inadequate disclosure to patients with impaired capacity to consent, so that the combination is poison. Kripke fails to document this claim. It is of interest that the recent NBAC report raised similar concerns (and made similar recommendations) while clearly stating that they had gathered no relevant facts and that fact-gathering would be a good idea. Indeed, evidence first and judgement after (outside of Alice in Wonderland) is generally considered the correct scientific and legal method.

An ethical problem arises when a study is designed to compare a new treatment with placebo, when an accepted evidence-based treatment is available. The study may do harm to the patients placed on placebo by delaying available treatment.... Indeed, many observers think it is no longer ethical to treat depressives or schizophrenics with placebo, if substantial distress is likely to occur which could be alleviated by treatment. Here again the questions of competence and full disclosure arise, for why would any competent patient agree to risk being assigned to placebo and suffer serious symptoms, if the patient fully understood that effective alternative treatment is available? Kripke does not note that this has been extensively discussed in the scientific literature (Laska et al. 1994; Klein 1995; Klein 1997) or that the FDA does not accept this line of argument. The critical issue is that simply comparing a new to standard treatment may yield a fallacious judgement of effectiveness because in this sample neither may be working. This is referred to as the need for assay sensitivity.

At one time, it was considered ethical for NIH investigators to monitor untreated depressed patients until they committed suicide." I would appreciate some documentation for this remarkable claim.

Sometimes the FDA or NIH review committees insist on placebo arms of clinical trials. I have had grants refused because the proposed trial had no placebo arm, only a comparison between light treatment and standard treatment. Many observers feel that it is time to improve the ethical outlook of review committees. Many observers feel that it is time to improve the scientific rigor of some investigators.

Leaving depressed patients (SAD or nonSAD) on placebo for months will be difficult to justify ethically in most situations. Correct.

One good alternative will be to compare light treatment with antidepressant drugs. Not correct because of lack of assay sensitivity.

Another good alternative, already used for light trials in nonseasonal depression but not yet for SAD, will be to compare light plus antidepressant drug with antidepressant drug alone. Trials of light plus psychotherapy versus psychotherapy alone will also be appropriate. Neither correct on same basis.

Strangely, the answer to the problems posed by long term parallel placebo maintenance lies in precisely the sort of study that Kripke decries- randomized placebo substitution in maintained improvers with close blind monitoring for signs of relapse. To sum up, the issues of ethical experimentation and scientific rigor require both documentation and logical analysis. The problems of a lack of ethical consensus remain and are not resolved by dubious appeals to ancient authorities.

> "Say what you will about the Ten Commandments, you must always come back to the pleasant fact that there are only ten of them. " - H.L. Mencken

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TIME AND TIMING IN BIOLOGICAL SYSTEMS: A Meeting Report

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Feedback is perhaps the most often utilized form of regulation in nature. Feedbacks do not necessarily lead to oscillations, but, given the right conditions, they can. They are accomplished by diverse mechanisms (for instance, Ca^{++} fluxes, transcriptional loops, predator/ prey relationships), and their oscillations can range from milliseconds to multiples of years. Most of us in the SRBR investigate oscillations in relatively long time constants, specifically elucidating their mechanism or their effects on an organism. Although divergent mechanisms underlie long versus short oscillations, they possess common features. Based on the potential of these common features, an unusual meeting was convened in Southern Germany from November 5 to 8, 1999. Long-term (circadian) and short-term (nervous system) timing researchers came together for 2 days of talks and discussion. In the end, a working group was formed to attempt to build a platform or network to strengthen interactions between all rhythm researchers.

The meeting started with overviews of the respective fields by the co-chairmen (T. Roenneberg and E. Pöppel, U. Munich, Germany). The circadian system was discussed from a comparative and evolutionary perspective (M. Menaker, U. Virginia, USA), as well as for its role in enhancing reproductive fitness (C. Johnson, Vanderbilt U., USA). Neural substrates of the mammalian circadian system were highlighted by talks that implicated non-classical photopigments in photo-entrainment (R. Foster, Imperial College, England), a two-component oscillatory structure of the SCN (W.J. Schwartz, U. Mass. Med. School, USA), synaptic communication between cultured SCN neurons (S. Honma, Hokkaido U. School of Med., Japan), and the involvement of CRY proteins in the negative limb of the core transcriptional/ translational feedback loop (S. Reppert, Mass. General Hospital and Harvard Med. School, USA). A strategy applying classical T-cycle protocols to the *Neurospora* model system was also presented, suggesting that a canonical clock gene functions to transduce environmental signals (M. Merrow, U. Munich, Germany). Practical or clinical topics included studies of chrono-chemotherapy involving substantial numbers of patients (F. Levi, Inst. d. Cancer e. Immunogen., France), assessment and consequences of shift work (J. Arendt, U. Surrey, England), and differential entrainment of the sleep-wake rhythm (K. Honma, Hokkaido U School of Med, Japan).

The themes characterizing neurological timing indicated broad possibilities for cross-talk between the two groups. They included neural regulation of rhythmic motor programs (K. Sillar, U. St. Andrews, Scotland), cognitive processing in developmental dyslexia (R. Hari, Helsinki U. Tech., Finland), temporal and spatial coordination among cortical regions throughout the brain (W. Singer, Max Planck Inst. Brain Res., Germany), oscillatory cortical responses to repetitive sensory stimulation (M. Pastor, U. d. Navarra, Spain), subjective time perception (Zakay, Tel Aviv U., Israel), and the neuropharmacology of sleep and depression (Drucker-Colin, Fac. Med. UNAM, Mexico). A model of cortical function and learning was also presented, with the results resembling oscillations seen in animal studies (J. Kropotov, Russ. Acad. of Sci., Russia).

Final talks included a review contrasting the historical, physical and biological concepts of time (E. Rhunau, U. Munich, Germany), and an approach to understanding and treating clinical apneas as disorders of oscillatory state (D. Paydarfar, U. Mass. Med. Sch., USA).

Time and Timing was sponsored by the SmithKline Beecham Foundation, the philanthropic leg of the company. It was dedicated as a commemoration to Ivan Pavlov, whose life and accomplishments were warmly recounted (L. Pickenhaim, Leipzig, Germany). It is the second of such symposia, which are specifically planned as an opportunity to bring together scientists from different fields and increase opportunities for interdisciplinary and international collaborations. Philosophically, critical components of the meeting were the outstanding discussants from throughout central Europe and the poster presenters, primarily students, who were invited to participate based on their excellence. The wonderful Bavarian food and free-flowing weißbier were appreciated by all! Interspersed throughout the weekend were numerous art events and exhibits, all pertaining to time--and also on time. Many of these were incorporated--almost hard-wired--into the program, under the mistaken assumption that scientists who work on time would be cognizant of their allotted time. Ha!

So, in the end, what is the potential for cross-talk between the two fields of rhythm research? Basic properties such as entrainment, phase response curves and differential phase-locking will be useful for any dissection of oscillatory behavior. While these tools have been much more widely utilized by circadian biologists, the neurobiologists can share their more concrete approaches to multiple oscillator systems. There is rich potential in complementary interactions between the short and long term time domains. For instance, it is widely recognized that there are substantial circadian rhythms in vigilance (or something experimentally defined as such), memory, and sensitivity to external stimuli. What happens when these functions, undoubtedly mediated by short term oscillations, become asynchronous? Is this when accidents occur in the middle of the night on autobahns or during shift work, or when cognitive processes suffer? Perhaps Stephan Michel summed it up best: "The implications of the domain 'time' in so many different physiological processes struck me as a fundamental property of maybe all cells and functions. The 'sampling' of sensory input as a way to very efficiently reduce the enormous data flow without losing critical information is one of these examples...This conference started a process" To that end, a working group was established specifically to serve as a Resource Center for rhythm researchers concerned with all time domains.

For your ideas, comments, or questions contact Martha Merrow <martha@imp.med.uni-muenchen.de>

MEETING REPORT, V LATIN AMERICAN SYMPOSIUM OF CHRONOBIOLOGY

Diego Golombek, President, Organizing Committee, V LASC, Tigre, Buenos Aires, Argentina, 1999

The V Latin American Symposium of Chronobiology took place in Buenos Aires, Argentina, from September 30th to October 3rd. This was the fifth meeting of a series bravely started by a group of enthusiastic Brazilian chronobiologists in 1991, and that has taken place in Brazil and Mexico since then. About 70 participants from Argentina, Brazil, Chile and Mexico, as well as guests from the US, Canada and Spain attended the meeting, which was held in an island in the Paraná de las Palmas river (just to make sure it wouldn't be easy to leave the place) about 2h away from the city of Buenos Aires. Just before the meeting we had a graduate course co-organized by the universities of Buenos Aires and Quilmes, which was very successful.

The main focus of the Symposium was to discuss every single detail of our work and to allow Latin American researchers and students to interact with each other and with our guests. With this aim in mind, the main activities of the meeting were thematic roundtable discussions (including academic and educational aspects of chronobiology, memory and behavior, entrainment, molecular biology, retina, SCN, sleep and human rhythms) and poster presentations. We also had an important session for discussion of student projects (for people to go, flatter, compliment and maybe even criticize speakers). Keynote lectures were delivered by Michael Menaker (A history of chronobiology), Bill Schwartz (The suprachiasmatic nucleus as a pacemaking tissue), Carla Green (In vivo manipulation of the vertebrate circadian clock) and Marcelino Cereijido (Life, time and death). Our late night activities were meant for even more informal discussions of general topics of broad interest, including a marvellous tango lesson (yes, your next-door chronobiologists dancing some real tango). After a quite improbable trip, Gene Block joined us for the final day of the meeting, and was greeted by many SRBR members present at the place. It is said that Greg Cahill did not change clothes during the Symposium (actually, his luggage was lost somewhere in Bolivia and was returned to his home address about 2 months later!).

The symposium was funded by grants from the National Agency for the Promotion of Science and Technology (ANPCyT, Argentina), the National University of Quilmes (UNQ, Argentina), the International Brain Research Organization (IBRO) and the National Science Foundation (NSF, USA).

We really had a great time (and a lot of Argentinean beef) at the Symposium, with lots of fruitful discussion and participation during the roundtables and poster presentations. The student projects session was particularly enthusiastic, and all of our guests had the chance to interact closely with Latin American researchers and in many cases, plan future collaborations. As an Argentine writer has put it, "in spite of store windows, in spite of fluorescent tubes, in spite of all light strategies men have invented to scare themselves away, at last there is an hour when it is night in Buenos Aires". Maybe we found it.

ANNOUNCEMENTS

The **Seventh Meeting of the Society for Research on Biological Rhythms** will be held at Amelia Island Plantation, Jacksonville, Florida, USA, May 10-14, 2000. A meeting announcement including detailed information, instructions, and forms for registration, abstract submission, and housing reservations will be mailed to SRBR members in January. Deadline for abstract submission is March 1. Downloadable forms and meeting information updates will be available on the Internet at http://www.srbr.org.

The **Gordon Conference on Pineal Cell Biology** will be held at Queens College, Oxford University, UK August 27-September 1, 2000. Further information is available at the Gordon Conference website http://www.grc.uri.edu/programs/2000/pineal.htm.

The **12th Annual Meeting of the Society for Light Treatment and Biological Rhythms** will be held at the Evanston Holiday Inn, Evanston, IL May 7-9, 2000. The meeting notification and registration form can be accessed at http://www.sltbr.org/annual.htm.

The Argentine Society for Neurochemistry will organize a **Symposium on Circadian Rhythms** at the next meeting of the American Society for Neurochemistry (Chicago, March 25-29, 2000). The Symposium will take place on Monday, March 27th from 6.30 to 8.30 PM. Special emphasis in the latest findings concerning the generation, regulation and synchronization of vertebrate circadian rhythms. Please contact Diego Golombek (dgolombek@unq.edu.ar) or Mario Guido (mguido@dqbfcq.fcq.unc.edu.ar) for more information, or visit the ASN homepage at http://www.tmc.edu/asn/2000asn.htm.

A **Summer School for Chronopharmacology** will be held at Heidelberg University during August 1-11, 2000. The lectures in general will be held in German; foreign speakers will present their lecture in English. Details and updates can be found on the homepage of Heidelberg University at http://www.ma.uni-heidelberg.de/inst/phar. Direct requests for further information to Dr. Björn Lemmer, bjoern.lemmer@urz.uni-heidelberg.de.

Sunriver/Mini Mitter is pleased to announce **FDA clearance for Actiwatch®-Score**, a medical device that combines an actigraphy monitor with an LED system for subjective scoring of pain, nausea, anxiety, fatigue, hunger or any other parameter that can be graded on a scale of 1 to 10. An alarm, which can be pre-set to ring at either specified or random intervals, signals the wearer that it is time to score the parameter being documented by pushing the event marker. No response is recorded as a zero. The alarm function can be turned off. The software will note which scores are prompted and which are manual entries. Actiwatch-Score weighs 19 grams and measures 3.5 cm x 3.8 cm. For more information on Actiwatch-Score, contact the Mini Mitter staff scientists at 1-800-685-2999 or (541) 593-8639 or check the company's web site http://www.minimitter.com.

POSITIONS AVAILABLE

Two postdoctoral positions are available immediately to investigate cellular and molecular mechanism of vertebrate circadian rhythmicity. Ongoing projects include classical and molecular genetic analysis of the zebrafish circadian system, and cellular and biochemical studies of signal transduction pathways that regulate the circadian clock in Xenopus retinal photoreceptors. Candidates with strong backgrounds in cellular or molecular biology and/or zebrafish genetic technologies are preferred. Applicants should send a CV, a statement describing research interests and experience, and contact information for three references to: Gregory M. Cahill, Dept of Biology and Biochemistry, University of Houston, 4800 Calhoun Rd, Houston, TX 77204-5513. Tel: (713) 743-2694; Fax: (713) 743-2636 gcahill@uh.edu.

Senior Research Scientist/Senior Research Associate/ Research Assistant Professor in Photoreceptor Cell Biology. A senior, full time research position is available to conduct work in the relationship between clock driven regulation of gene expression and rhythmic physiology of photoreceptors such as membrane turnover. Candidates having prior post-doctoral experience in cell/molecular biology and a desire to play a leadership role in the research laboratory are invited to apply. Experience in photoreceptor cell biology or molecular/cellular aspects of circadian rhythms is helpful but not essential. Major current projects in the laboratory involve studies of i) the cytoskeleton in photosensitive membrane turnover, ii) gene regulation controlled by the photoreceptor circadian clock, and iii) the relationship between clock controlled gene regulation and cellular changes related to rhythmic membrane turnover. The laboratory currently uses biochemical, molecular and cell biological techniques including use of transgenic animals. Transgenic approaches including both Xenopus and zebrafish have been developed for these studies in the laboratory. Salary and title are negotiable based on experience. Send/FAX CV and references to: Dr. Joseph C. Besharse, Dept of Cell Biology, Neurobiology & Anatomy, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226-0509. Tel (414) 456-8261; Fax (414) 456-6517; jbeshars@mcw.edu; http://www.mcw.edu/cellbio.

Postdoctoral Fellow in Photoreceptor Cell Biology A postdoctoral position is available to study the relationship between clock driven gene expression in photoreceptors and photosensitive membrane turnover. Current work brings together the role of the cytoskeleton in rhythmic membrane turnover and the role of a photoreceptor based circadian clock that controls transcription of downstream genes. The work requires application of biochemical, molecular and cell biological techniques. The laboratory is currently conducting functional studies using transgenic techniques in mouse, Xenopus and zebrafish. Send/FAX CV, references and a description of research ideas and interests to: Dr. Joseph C. Besharse, Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509. Tel: 414-456-8261; Fax: 414-456-6517; E-mail: jbeshars@mcw.edu; http://www.mcw.edu/cellbio.

Two PhD Student Positions At the Department of Animal Behavior of the University of Groningen, directed by professor S. Daan, two PhD student positions are available on projects in human chronobiology. The salary varies from Hfl. 2374/month in the first year up to Hfl. 4037/month in the fourth year. For information on composition and activities of the group please visit http://www.biol.rug.nl/animal_behaviour or http://www.biol.rug.nl/zoolab/.
The first project is entitled "Ocular and Extra-ocular Effects of Light on the Human Circadian System" and will start in January 2000. It is based on intriguing reports that illumination of the skin affects the biological clock in humans. Ocular and extra-ocular (skin) light schedules will be varied in healthy human subjects and blind people to investigate the effects on the circadian rhythms of physiological and psychological variables. Applicants should send a letter, including a complete curriculum vitae to Dr. D.G.M. Beersma, P.O. Box 14, 9750 AA Haren, The Netherlands, before 26 January 2000. For more information contact Dr. D.G.M. Beersma, phone: #31-50 3632053, email: d.g.m.beersma@biol.rug.nl or Dr. M.C.M. Gordijn, phone: #31-50 3637658, email: m.c.m.gordijn@biol.rug.nl. The *second project is* entitled "Circadian and behavioral determinants of fatigue and EEG slow wave activity". This project starts in February 2000. Within the framework of sleep and mental alertness regulation the project aims at investigating the effects of mental, physical and visual workloads on fatigue and local brain recovery in healthy human volunteers. For more information contact Dr. D.G.M. Beersma, phone: #31-50 3632053, email: d.g.m.beersma@biol.rug.nl or Dr. A.M. Strijkstra, phone: #31-50 *3632073*, email a.m.strijkstra@biol.rug.nl.

Faculty Position for Research on Circadian Clock The Division of Biological Science at the Graduate School of Science, Nagoya University invites applications for a faculty position to study the circadian clock of cyanobacteria or plants, starting in April 2000. We are particularly interested in individuals who will work with the Research Group of Biological Rhythms (Drs T. Kondo and H. Iwasaki). Please visit http://www.bio.nagoya-u.ac.jp:8001/annE.html for more details.