

FINAL REPORT
to the
Canadian Institutes of Health Research

HEALTH EFFECTS OF DISRUPTED SLEEP

AND CIRCADIAN RHYTHMS

New Frontiers Workshop

December 8 and 9, 2001

Halifax, Nova Scotia

Sponsors:

Institute of Circulatory and Respiratory Health

Institute of Neurosciences, Mental Health and Addiction

Institute of Population and Public Health

Servier Laboratories

ICN Pharmaceuticals

Submitted, March 1, 2002

FINAL REPORT

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A. Background

This workshop was sponsored jointly by three CIHR Institutes and two pharmaceutical companies, indicating the breadth and variety of the topics covered. It addressed aspects of sleep and circadian rhythms research ranging from molecular mechanisms to public policy, and spanning basic research, clinical research and population health issues. The aim of the workshop was to document the significance of these research areas to human health, to evaluate the current state of research and training in these areas in Canada, and to identify mechanisms to promote future development of these areas.

Sleep disorders are increasingly recognized in the popular press as pervasive and highly disruptive of normal functioning and health. The topics of which the public is mostly aware are: insomnia, sleep disruption related to shift work or jet travel, and sleep disruptions due to nightmares/sleepwalking, especially in children. There is more limited public awareness of sleep-disordered breathing, sleep abnormalities in neurological and psychiatric conditions, and less common syndromes such as narcolepsy. Sleep disorders medicine (broadly defined to include psychological interventions) is the clinical specialty that addresses these disorders.

Sleep research, however, extends far beyond these clinical issues to the study of fundamental aspects of human physiology that are closely tied to sleep. These include: the mechanisms of learning and memory; the causes and treatments of depression; the basic regulatory mechanisms controlling cardiovascular and respiratory function; the aging process; and the nature of human consciousness. The breadth of sleep research reflects the fact that sleep is a universal feature of the life of mammals (perhaps of all animals), and occupies a third of the lives of humans. A fundamental problem is that our historic ignorance of the nature and functions of sleep has allowed it to be generally neglected in the training of physicians and other health care professionals, and to be poorly supported through funding agencies in Canada. Research on the physiology, behaviour and mental activity of humans during the one-third of our lives that we sleep does not receive anything close to proportional attention or support from funding agencies. This imbalance is predicated on the erroneous assumption that almost everything of significance to human health, well-being and happiness occurs during waking hours and is largely independent of what happens during sleep. The workshop reviewed in some detail convincing evidence that contradicts this view.

Research on circadian (“about a day”) rhythms is historically separate but functionally very closely linked to sleep research, and the two fields are becoming increasingly intertwined. The fundamental temporal structure of human physiology and behaviour (and, indeed, that of essentially all living things on this planet) is the daily or circadian rhythm. Circadian rhythmicity pervades every aspect of our physiology, from cell replication to cognitive functions, and provides an organizing structure on a par with that of the principle of homeostasis. The temporal structure of the circadian day is the product of a genetically programmed, internal pacemaker system that is normally synchronized by light and other signals to environmental time cues. Progress in analysing this system over the last decade has placed circadian rhythms research at the leading edge of systems and molecular neuroscience. Indeed, the ‘molecular genetics of circadian clocks’ has been identified as one of the major scientific stories of the past decade by the journal *Science* (and was its runner-up Story of the Year in 1998).

The existence of circadian rhythmicity has profound and generally unrecognized implications for diagnosis and treatment of a wide variety of clinical conditions, including

cardiovascular/respiratory illnesses, cancer, and of course sleep disorders. Disruption of normal circadian rhythmicity is reflected in the symptoms of jet lag, in the physiological disorganization that accompanies shift work, and in several clinical conditions, including abnormal sleep-phase disorders. Sleep-wake cyclicity and circadian rhythmicity are fundamental regulatory mechanisms, as important to the health of the organism as are the mechanisms regulating cardiovascular function, respiration, thermoregulation and metabolism.

The workshop reviewed the importance to human health of sleep and circadian rhythms research and addressed the issue of funding mechanisms for this research. Research on sleep and circadian rhythms and its application to medical and workplace conditions can provide the opportunity to develop better treatment regimes for many clinical conditions, and can link researchers, business and government in order to facilitate translation of existing and developing knowledge essential to maintaining population health and reducing risks of injury and disease. The absence of a single Institute at CIHR devoted to these areas means that multiple Institutes or CIHR 'central' must be responsible for their support. This is fitting in that the subject matter of these research areas transcends traditional ways of organizing research; i.e., by disease entity, organ system, target population, level of analysis, or methodology, as reflected in the Institute structure of CIHR. The risk, however, is that CIHR will not contribute appropriately and adequately to the development of research and training in these areas because of the absence of a single disease focus for its advocacy, and the lack of a single Institute to champion this research.

There is little appreciation among either the public or most health professionals of the impact on health and safety of sleep disorders, circadian rhythm disruption and, in general, of the temporal structure of human physiology. Appropriate training programs for the next generation of health-care providers and researchers are clearly needed in order to develop a cadre of trained personnel to conduct and disseminate research in these areas. Two equally important tasks for the future are to integrate the existing and emerging knowledge in these areas into the training programs of health-care professionals, and to disseminate this knowledge effectively to the general public, regulatory agencies, business and government.

B. The State of Knowledge in the Field

It is not possible to summarize in the space available the state of knowledge in the diverse areas represented in this workshop, but some highlights are described below.

Circadian Mechanisms

Circadian physiology involves a central, neural pacemaker system, synchronized to external cues associated with the day-night cycle, traditionally, the light-dark cycle itself. Our understanding of this mechanism has advanced rapidly in the last decade with the identification of several families of clock genes that regulate circadian timing in different taxonomic groups, including mammals. Altered expression of one of these genes has been linked to a human circadian sleep timing disorder – advanced sleep phase syndrome. The gene transcription-translation feedback loops that constitute the core of the clock, and the intracellular links between clock cell inputs, cycling clock genes, and clock cell outputs have yet to be fully specified. Molecular and cellular mechanisms involved in the mediation of light effects on circadian systems have also been elucidated, and the expression of cycling clock genes and their protein products has been identified in peripheral tissues, as well as in the brain pacemaker system.

The circadian pacemaker receives information about internal physiological state (e.g., related to arousal and behavioural activity) as well as information about light, the primary synchronizing cue. Arousal-related cues can also have very potent synchronizing effects on circadian systems, and some neurochemical and molecular mediators of this phenomenon have been described. But how photic and non-photoc signals are integrated to maintain or adjust the timing of circadian rhythms in natural environments is not well understood at either the phenomenological or cellular levels. Recent studies of human circadian rhythms have focussed on identifying the role of light, exercise and the hormone melatonin in regulation of circadian

rhythms, and evaluating their utility as phase-shifting agents in simulated or actual shift-work situations.

Effects on the circadian clock of acute or chronic sleep loss (such as occur as a result of shift work, jet travel and biobehavioural disorders; e.g., depression), has hardly been explored. Quite recently, sleep loss per se in an animal model has been shown to cause shifts of the circadian system of rodents, reinforcing a growing interest in the physiological and functional links between the central circadian pacemaker and the distributed neural systems regulating sleep-wake cyclicity. Some neural and endocrine output signals from the circadian pacemaker have been identified, but specific pathways regulating most rhythmic processes, including the sleep-wake cycle, are not well characterized.

Animal studies have suggested links between aging and circadian organization. Aged rodents have been shown to have disorganized circadian rhythms, which can be restored to more normal amplitudes by transplantation of the neural circadian pacemaker from a young animal. Disruption of circadian organization by lesions or repeated shifts of environmental cycles has been demonstrated to reduce life span.

While there remains considerable controversy around these issues, some evidence suggests that aspects of circadian system responses to environmental stimuli can be modified by prior experience. The use of circadian time information as a modulator or attribute of cognitive processes such as learning and memory, and the neural mechanisms linking learning, brain plasticity and the circadian system remain very poorly understood.

Sleep Mechanisms

Our understanding of the physiology of sleep regulation has advanced rapidly with the characterization of neural, endocrine and immune regulators of sleep cycles. A large body of work has analysed the links among cortical and subcortical structures in regulating the cyclicity of sleep and the changes in information processing and consciousness that accompany sleep. The recent identification of a genetic defect giving rise to the sleep disorder narcolepsy in animal models led rapidly to the identification of related genetic and neurochemical defects in humans with narcolepsy. This newly identified neurochemical agent (orexin or hypocretin) also provides a novel avenue to a better understanding of the mechanisms underlying normal sleep regulation. Classical neurotransmitters such as acetylcholine and noradrenaline have been known to play major roles in regulating the cycles of sleep and waking, and the mechanisms involved continue to be a major focus for sleep researchers. It is now critical to begin to investigate how the novel neuropeptides that have recently been identified as sleep regulators interact with these classical neurotransmitters to control behavioural state.

The timing of sleep is regulated by both the circadian clock, as described above, and by homeostatic factors that signal sleep need or sleep debt. The molecular substrates that represent the homeostatic component of sleep regulation are still not known, but there is considerable interest in the role of endogenous changes in adenosine levels in key brain areas as a candidate mechanism. This is a topic of active investigation.

Other studies have examined links between sleep and learning. Sleep has been suggested to be critical to the process of storing and making permanent some kinds of newly acquired skills and memories. There are vigorous debates currently being waged in leading scientific journals about the roles of different sleep stages in memory formation and consolidation.

Recent studies have demonstrated that age has a dramatic effect on sleep organization and quality, and on the amplitude of circadian rhythms. Studies have also shown that endocrine factors, especially those associated with reproductive cycles in women, can modulate sleep and lead to serious sleep disorders. Sleep architecture and efficiency can change dramatically with endocrine status and age, and these changes are reflected in different patterns of use of drugs to regulate sleep patterns. Much remains to be learned about how endocrine and other factors modify sleep and circadian rhythmicity during adolescence, pregnancy, menopause and aging, and how these may impact on health and longevity.

Clinical Populations

Studies on clinical populations have focussed on a number of issues. One is the role of sleep and circadian organization in major psychiatric disorders such as major depression, seasonal affective disorder (SAD) and schizophrenia. Sleep disruption has long been known to be a feature of major depression, and manipulations of sleep duration and timing can alleviate depression transiently in many patients. In addition, seasonal changes in the patterns of melatonin secretion are abnormal in patients with SAD, and treatments that affect the circadian system can have dramatic therapeutic effects. Finally, abnormal circadian and sleep-wake organization were recently characterized in a patient with schizophrenia.

Because of the close pharmacological relations between mechanisms affecting mood in depressed patients and those affecting sleep, many treatments for depression also alter sleep parameters, but this issue has not been investigated thoroughly and requires a great deal more study. In particular, newly developed treatments for depression, schizophrenia, and dementing illnesses need to be assessed thoroughly for their effects on sleep. Both beneficial and harmful effects of pharmacological treatments may be mediated indirectly by their effects on sleep, but these effects are often not studied thoroughly in the course of drug development. New drugs to aid sleep regulation have recently been released to market, including arousing agents such as modafinil and short-acting, non-benzodiazepine sleep promoters. Successful behavioural, therapeutic interventions for insomnia have also been developed based on applications of learning theory.

The rhythmic sensitivity of physiological systems to pharmacological agents has been well documented for many drug and target combinations. The clinical impact of this rhythmicity is obvious in some conditions that are themselves robustly rhythmic; e.g., daily rhythms of risk for cardio- and cerebrovascular incidents, and symptoms of arthritis and asthma. A few tentative steps have been taken in the design of drug treatment schedules or of drug formulations (e.g., Chrono-Vera™) to match their levels to the rhythmic intensity of symptoms in some conditions. Another line of research has documented rhythms in the sensitivity of cancerous cells to antineoplastic agents in both rodent models and humans. This rhythmicity may be related to well-documented rhythms of cell replication. A number of clinical trials have demonstrated fewer side effects and fewer reductions in drug dosage attributable to such side effects when drug timing was optimized with respect to tumour and host sensitivity. Additional clinical trials are under way to assess these findings in other conditions, but this area of research has received little attention from most physicians treating patients with drugs or radiation therapies for cancer.

The condition that leads to the largest numbers of consults and sleep studies in most sleep clinics is obstructive sleep apnea (OSA), the most common form of sleep-related breathing disorder. Although the majority of patients remain undiagnosed, excessive daytime sleepiness, a history of loud snoring, and sometimes witnessed cessation of breathing during sleep are the major indications leading to investigation. The characteristic daytime sleepiness puts OSA patients (and others in their vicinity) at very high risk while driving or operating heavy machinery; falling asleep while driving is a common pattern in OSA patients. Because many members of the work force involved in commercial transportation and in industrial activity have significant risk factors for OSA, there is an enormous risk to public health and safety associated with this condition. Important risk factors include being male, obese and middle-aged or older. OSA has also been independently linked to many serious health problems, including hypertension, cardiovascular disease and stroke. Few studies have examined whether successful treatment for OSA reduces the risk of cardiovascular or cerebrovascular disease in patients. OSA patients often have a long history of medical consultation and treatment before they are accurately diagnosed, placing a very large burden on the health-care system. The costs associated with untreated OSA have been documented, and have been shown to drop dramatically with successful treatment.

While several treatment modalities for OSA are available, continuous positive airway pressure (CPAP) delivered usually via a nasal mask is the most common treatment, with a strong record of success where compliance is adequate. There is a very uneven distribution of sleep

laboratories and clinics capable of diagnosing and treating OSA across the country, with little coverage in many poorer provinces.

Because a separate New Frontiers workshop was organized to address the many features of sleep-related breathing disorders, our workshop included only minimal coverage of this extremely important clinical condition. It is clear, however, that major research opportunities exist related to the mechanisms underlying OSA, the relations of this condition to other medical conditions, and the public health impact of inadequate diagnostic and treatment capacity for this condition.

Shift Work and Fatigue

A major applied research thrust is related to fatigue and shift work-related disorders. Because of extended hours of work, work during non-traditional hours, and rotating shift schedules, a very large proportion of the work force is exposed to the risks associated with lost sleep and disrupted circadian rhythms. These risks have proved to be very large. Many studies have demonstrated that shift workers have increased risks for cardiovascular and gastrointestinal disease and a few have demonstrated increased breast cancer risks, but there remain nagging issues related to self-selection and confounding variables that need to be resolved. More clear-cut is the evidence that those working at night, whether driving or flying commercial vehicles, operating machinery, working in health care or protection services, or acting as flight traffic controllers, are at increased risk of falling asleep on the job. They are also at increased risk of accidents when traveling to and from work, depending on the timing of their shift changes. One approach to capturing the varied consequences of shift work is to evaluate them in terms of changes in quality of life measures. These take into account factors such as domestic role stresses, social isolation, marital and social conflicts, use of drugs and alcohol, and other factors that are not captured by accident statistics or counts of unintended naps.

Excess fatigue and other shift-work related problems constitute an enormously complex issue involving economics, personal work preferences, unions, business profitability, domestic stresses, occupational health and safety, and changing societal demands for services. It is further complicated by the fact that the very real and very costly problems associated with shift work do not have uniform solutions, as there are very substantial differences in work load, risk and potential solutions for each work environment and worker cohort. While a good deal of research has been done, it is rare to find studies that are well-controlled, prospective in design and capable of yielding unambiguous answers. The profound economic and social costs associated with work-related fatigue and sleep loss demand continued efforts to identify solutions to these problems.

The evidence that repeated shifts in lighting schedules may shorten lifespan in animal models suggests that the immediately observable consequences of shift work on physiology and behaviour (serious as these are) may only hint at the damage caused by chronic disruption of the circadian system. A recent Workers' Compensation adjudication in Nova Scotia (to be appealed) has made national headlines by supporting a worker's contention that repeated exposure to rotating shifts caused him permanent injury in terms of disrupted sleep and circadian rhythm regulation. Industries have stressed that the spread of such claims could so disrupt productivity as to render non-competitive all Canadian companies using shift workers. This would correspond to companies employing about one-quarter of the Canadian work force. Yet the state of our scientific understanding of the issues underlying the validity of these claims is rudimentary.

Quality of Life and Health Status Impacts

Assessing the impacts of sleep and circadian disorders on people is complicated by the fact that changes in physiological parameters generally correlate weakly with subjective assessments of sleep-related impacts on quality of life. Quality of life –the parameter often of primary concern to patients– has received inadequate attention in studies of sleep disorders. In a call for proposals in 2000, the US National Institutes of Health stated that “*inadequate sleep is such a pervasive problem that it appears to be accepted as a normal part of life*”, and observed

that “*little is known about the consequences of sleep deprivation on quality of life and measures of behavioral, cognitive and psychosocial function*”.

One reason for this lack of information is that there have been few well-validated and responsive quality-of-life measures for use with sleep patients. One of the two now used most widely internationally for assessing sleep-related quality of life issues is a Canadian product (Flemons & Reimer, 1998), the Calgary Sleep Apnea Quality of Life Index (SAQLI). When quality of life has been assessed specifically, patients with sleep disorders show levels of deterioration similar to those of individuals with other chronic diseases, such as hypertension and chronic obstructive pulmonary disease. Standard treatments may not reverse these values to population norm levels, suggesting that currently available treatments for common sleep disorders are not fully effective.

Health Systems and Population Impacts

Our knowledge of the physiological mechanisms regulating sleep and circadian systems and of the clinical consequences of related disorders far outstrips our knowledge of the consequences for population health and the health care system. Very little research has been done on the impacts of untreated sleep disorders on health system costs, nor on the costs of lost productivity and accidents. While some research has been done on this topic related to sleep apnea, other disorders have hardly been addressed. One Canadian study has documented that sleep apnea patients use health-care resources to a much greater extent than unaffected individuals for a ten-year period before diagnosis, and reduce their use after treatment.

The impact of sleep and circadian disorders on productivity has been difficult to quantify because of a lack of instruments with appropriate sensitivity that can be used in natural workplace situations. In one narrowly focussed study, however, there was a difference of 13% observed in productivity between workers treating their allergic rhinitis with sedating versus non-sedating antihistamines. The undoubtedly much larger impacts of sleepiness and fatigue from clinical disorders still need to be documented.

As mentioned above, access to diagnostic and treatment facilities for sleep disorders varies widely across provinces. Yet there has been little or no health-systems level research done to compare the consequences for provincial health systems of these differences. Nor has there been any research in Canada on alternative modes of delivery of services that may address the discrepancies in access and the costs associated with diagnosis and treatment, as well as the very substantial economic costs and human suffering associated with a lack of treatment.

C. Workshop Activities

Our central activity was a two-day intensive workshop held in Halifax on December 8/9, 2001. During this workshop, 19 invited speakers from across Canada, and Dr. Torbjorn Åkerstedt of the Karolinska Institutet in Stockholm reviewed a number of issues for an audience of approximately 29 invitees, including individuals from three Halifax universities and the Capital Health District. Two of the invited speakers were members of the Executive Committee of the Canadian Sleep Society, a professional association of clinicians, scientists and technologists. Among the topics addressed were: the current state of knowledge related to sleep regulation and circadian rhythms; Canadian strengths and weaknesses and funding mechanisms for these research areas; economic, social and medical consequences of disorders of sleep and rhythmicity; the need for a training program and alternative models of its development; and the potential role of CIHR and its Institutes in facilitating the future development of research in this area.

A Web page was created to facilitate communication and organization of the meeting, and it has since been updated to include a number of the presentations, which are available for download (<http://www.dal.ca/~rusak/workshop/>). A representative of the Organizing Committee (Dr. Debra Morrison) attended the Toronto meeting of New Frontiers Program grantees and presented a summary of the workshop activities and conclusions, since Dr. Rusak was unable to

attend. The availability of the Web page should facilitate future interactions among those who attended the workshop and others interested in these research areas.

D. Specific Recommendations

Recommendation 1: Advisory Committee

A key issue motivating this workshop was the fact that the organization of the CIHR Institutes did not identify a single Institute with responsibility for the fields of research represented by this group. Sleep and/or circadian rhythms are mentioned as among the responsibilities of two Institutes: ICRH and INMHA, but they occur in the context of a long list of other responsibilities. And they do not appear as relevant to Institutes concerned with cancer, metabolism, aging, endocrine systems, women's health, child and adolescent health, etc, where they have clear relevance. Within the broad health mandate of CIHR, there is little reflection, for example, of the following issues:

- the integrated neural, endocrine and immune mechanisms regulating sleep and circadian rhythms
- the health, economic and social impacts of sleep-related breathing disorders
- the underlying neural/cardio-pulmonary causes of sleep-related breathing disorders
- the applications of sleep and rhythms research to medical treatments
- the applications of sleep and rhythms research to shift work disorders, and to other aspects of fatigue management
- the vulnerability of children and adolescents to fatigue and sleep loss, and the impact on academic performance
- the dramatic changes in sleep occurring during pregnancy, menopause, and especially aging
- the occurrence of fatigue and sleep disorders in many neurological conditions

Sleep and circadian rhythms research spans clinical and basic science, social and economic impacts, public policy and public health domains. It impacts on the mandates of virtually all of the CIHR Institutes, reflecting the full range of the CIHR mandate.

But the organizational structure of CIHR will encourage only piecemeal support of separate subtopics within these areas, because they fall in the periphery of the scientific agendas represented by the Institutes. Thus, there may be support to study sleep or circadian rhythmicity in relation to depression; to body weight regulation, diabetes and metabolism; to the timing of cancer chemotherapy; to circadian monitoring of blood pressure regulation; or to the impact on family function or on industrial and transportation safety of shift work schedules. Such support will likely arise incidentally in the course of initiatives aimed at other topics: understanding the mechanisms of depression, optimizing treatment of cardiovascular disease, etc.

This approach would fail to recognize the integrative nature of these fields and the interdependence of knowledge, theories and practice related to each of these topics. The net result will be a failure to adequately exploit the potential of these fields and of Canada's research excellence in sleep and circadian rhythmicity to better the health of Canadians.

To facilitate the development of research on the diverse aspects of sleep and circadian rhythmicity that affect human health, CIHR should appoint an advisor or, preferably, advisory committee, on this topic. Its role should be to provide Governing Council and the Institute Advisory Boards with information and advice with respect to developing initiatives integrated across Institutes in relation to sleep and circadian rhythms. The advisory group should also be mandated to develop approaches to improve the dissemination of knowledge of these research areas, and to facilitate knowledge translation.

Recommendation 2. National Training Program

Expertise and facilities for research and training in sleep and circadian rhythms are widely scattered across the country. There are major concentrations of researchers in Montréal and Toronto, as one might predict on a population-density basis. Montréal has a particularly strong representation because of a long history of support from Québec funding agencies, and through an MRC/CIHR Group grant. Expertise that is not duplicated in these centres is, however, also found in Halifax, Québec City, Winnipeg, Calgary, Vancouver, and Burnaby. As in many scientific areas, Canadian expertise may be of international standard, but it is often only one person deep nationally, much less in any one geographic location.

This geographic scatter of expertise (and specialized facilities) creates serious problems in the training of the next generation of researchers on sleep and circadian rhythms. Any one training centre can develop only a limited program and expose trainees to only a limited range of research experience and faculty expertise. This situation creates real limitations on the competitive quality of our trainees, however excellent the raw material. Their US competitors benefit from training programs funded by the National Institutes of Health and the National Science Foundation that create broad, integrative training environments ranging in some cases from molecular mechanisms to clinical and policy applications; e.g., at the University of Virginia (in a consortium with Rockefeller and Brandeis), at Harvard Medical School, at the University of Pennsylvania, at Stanford, and at Northwestern/University of Chicago, among others. They can offer not only breadth of training, facilities and faculty expertise that are not duplicated in any one location in Canada, but financial resources for trainee support and research that are not even approached within the Canadian context.

We propose the establishment of a national training program in sleep and circadian rhythms for undergraduate, graduate and postgraduate (MSc, PhD and residents) students. It should include an integrated set of curricula adapted to the levels of trainees and including web-based instruction, videoconferencing, and local didactic course content. Trainees funded through the program would complete components of their training at multiple institutions, depending on their research needs and interests and availability of specialized facilities in different locations. A summer institute would be offered annually to which distinguished Canadian and foreign scientists would be invited to interact with groups of trainees in both formal and informal learning situations. Degree programs would be certified via appropriate university faculties, and students in some areas would be able to do work placements in industry or medical facilities related to their research and training programs.

We recommend that CIHR help to sponsor a national training program on sleep and circadian rhythms, as outlined above, and assist an organizing committee to make necessary institutional and industrial contacts to facilitate the development of the program.

Recommendation 3: Collaborative Network on Sleep Disruption and Fatigue

The areas of basic sleep and circadian rhythms research have important implications for many aspects of human health, both in medical contexts and in relation to critical public health issues. No mechanism exists on a national basis to facilitate translation of research findings into policies and practices to improve health and safety. In other health research areas, mechanisms such as an Institute Advisory Board can serve as a venue for these kinds of interactions, but no such mechanism exists in the absence of an Institute devoted to sleep and circadian rhythms. The economic impact of disorders associated with shift work, extended work hours and fatigue is enormous, and great potential exists for partnering to develop and commercialize better approaches to dealing with these issues.

We propose the establishment of a national Collaborative Network on Sleep Disruption and Fatigue. It would focus on the education of relevant groups as to the implications of sleep disruption and fatigue for health and safety, and provide a mechanism to facilitate translation of research into practice in industry, government and the clinic. Participants should include: researchers, clinicians, policy makers, educators, trainees, funding

agencies, pharmaceutical companies, Department of National Defense, shift work employers and employee groups, and patient support groups.

Recommendation 4: Future Workshops

Future workshops should be organized to follow up on the previous two recommendations. One would bring together a group to design and develop a formal proposal for a training program in sleep and circadian rhythms. A second would bring together the various partners required to design and begin to implement a national collaborative network on sleep disruption and fatigue.

Recommendation 5: Requests for Applications in Sleep and Circadian Rhythms

Since these research areas are not central to the mandates of any individual Institute and are not represented on Governing Council, there are few obvious avenues for the development of RFAs on important research topics in these areas. The level of support available for Canadian research on sleep and circadian rhythms is not internationally competitive. Potential topics of interest listed below include references to women's health, to rural and Northern health issues, and to avenues for potential commercialization and industrial benefits:

- **the relations of sleep-disordered breathing to other medical conditions, including cerebro- and cardiovascular disorders**
- **neural systems and molecular mechanisms linking sleep and circadian rhythms regulatory mechanisms**
- **the long-term impacts of currently utilized shift-work and school schedules on worker and student health, safety and quality of life**
- **animal and human laboratory models to assess pharmacological and behavioural treatment approaches to shift work and jet lag**
- **design and implementation of healthier shift-work and school schedules**
- **evaluating age-related changes in sleep and circadian organization, and developing age-appropriate mechanisms for treating related disorders**
- **sleep and rhythms issues specific to women: effects of menopause on sleep; pregnancy and risk of OSA; shiftwork-related increases in risk of breast cancer; pre-menstrual and post-partum mood disorders**
- **the impact of extreme Northern seasonal changes in daylength on human sleep, health, and adaptation to work schedules**
- **the economic, social and quality-of-life impacts of regional disparities in access to clinical sleep assessment and treatment**

On the basis of advice from the Advisory Committee (Recommendation #1), CIHR should introduce appropriate RFAs on sleep and circadian rhythms, either through Governing Council, or through a consortium of Institutes with overlapping interests related to particular topics.

E. Advice to Funders

The NFP workshop on Sleep and Circadian Rhythms was a unique opportunity for a subset of Canadian researchers in these fields. Members of the two major research groups represented at this meeting (sleep and chronobiology) have rarely had the opportunity to meet before in a Canadian context. Their primary (and limited) means of communication have been through international meetings covering both topics, which are themselves rare, and through the Canadian Sleep Society, which held its first scientific meeting in 2001. This workshop opportunity, therefore, allowed for exposure of these groups to each other's interests and concerns in reference to issues that affect us specifically as Canadian researchers. It was judged by participants to have been very successful in identifying core issues and concerns, in identifying key research areas for the future, and in building a broader community identity.

Given the late notification of funding for this workshop (which was not included in the initial funding round), there was very little time to organize the meeting in the context of the deadlines required by the New Frontiers program. There were necessary compromises made in terms of invitees, format and content that might not have been necessary with a more relaxed time-line for the organization of the meeting. As the funding organizations involved were themselves under time and budget constraints not of their design, this concern is not one that could have been corrected easily.

Another problem, however, was that no staff member from the three Institutes who sponsored the meeting attended it, despite having lengthy notification of its timing. The short time-lines involved for the entire program and the number of workshops sponsored through it might have been important factors. Since none of the CIHR Institutes are headquartered in Atlantic Canada, geography and travel time may also have been factors, as they are so often for Atlantic Canadian scientists. We are well aware of the extreme time pressures on staff from the Institutes during the inaugural year of organizing their structures and developing their programs. Nevertheless, the delayed funding and absence of any representation from Institute staff reinforced the concern of participants that the research areas represented at the meeting are not regarded as central to the missions of any of the Institutes involved. This concern strengthens our desire that the recommendations presented above actually be implemented.

APPENDIX I

WORKSHOP ORGANIZERS

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APPENDIX II
WORKSHOP AGENDA

Saturday, December 8, 2001

0900-0915	B. Rusak	Introduction, overview and goals
0915-0945	B. Rusak	Light effects on circadian and other neural systems
0945-1015	N. Mrosovsky	Nonphotic clock resetting: a personal history & thoughts on funding

1015-1030 Break

1030-1100	R. Mistlberger	Functional relations of sleep and circadian systems
1100-1130	K. Semba	Anatomy and physiology of sleep/circadian relations
1130-1200	M. Ralph	Molecular approaches to circadian systems

1200-1315 Lunch

1315-1345	D. Boivin	The human circadian system
1345-1415	J. Carrier	Sleep disorders across the lifespan
1415-1445	G. Bjarnason	Circadian systems and cancer chemotherapy

1445-1500 Break

1500-1530	H. Driver	Women's health and sleep research
1530-1600	R. Lam	Psychiatric illness and circadian rhythms
1600-1630	R. Lam et al.	Clinical trials in sleep disorders medicine

Sunday, December 9, 2001

0900-0930	D. Morrison	Obstructive sleep apnea: Health consequences and costs
0930-1000	A. Décarý	Cognitive consequences of OSA
1000-1030	M. Reimer	Quality of life and health status impacts of sleep/circadian disorders

1030-1100 Break

1100-1200	T. Åkerstedt	The costs and consequences of shift work
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1200-1315 Lunch

1315-1345	M. Dumont	Laboratory studies of shift work
1345-1415	R. Heslegrave	Field studies of shift work
1415-1445	V. Gil	Pilot studies of fatigue management in commercial transportation

1445-1500 Break

1500-1530	J. De Koninck	Sleep research and training needs and opportunities in Canada
1530-1545	R. Godbout	A proposal for a Canadian sleep/circadian training program
1545-1700	M. Reimer	General discussion and planning
	B. Rusak	

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APPENDIX IV
A SAMPLING OF CANADIAN
SLEEP AND CIRCADIAN RHYTHMS PUBLICATIONS

The list below is not meant to be an exhaustive, nor an entirely representative, list of Canadian research publications in the several areas reviewed in the workshop. It provides a biased sampling of publications in these areas, with a focus on conference organizers and participants. There was no specific attempt to cover the topic of sleep-disordered breathing, since this topic is covered through a separate workshop. It does provide examples of the kinds of research publications that have been and are being generated by Canadian researchers in these areas.

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