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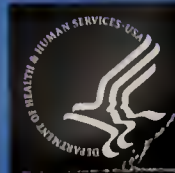
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**U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES**

National Institutes of Health

National Heart, Lung, and Blood Institute

National Center on Sleep Disorders Research

Trans-NIH Sleep Research Coordinating Committee

NIH Publication No. 03-5209  
July 2003



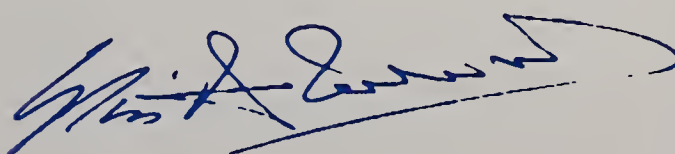
## FOREWORD

**T**he National Center on Sleep Disorders Research (NCSDR) was established within the National Heart, Lung, and Blood Institute (NHLBI) via a provision of the National Institutes of Health (NIH) Revitalization Act of 1993. The NCSDR was mandated to:

- Conduct and support research, training, health information dissemination, and other activities with respect to a basic understanding of sleep and sleep disorders, including research on biological and circadian rhythms, chronobiology, and other sleep-related topics.
- Coordinate NCSDR activities with similar activities of other Federal agencies, including other components of the NIH, and similar activities of other public and nonprofit entities.

The legislation further provided for establishment of a Sleep Disorders Research Advisory Board and for development of a National Sleep Disorders Research Plan. The Plan called for strengthening existing sleep research programs, creating new programs to address important research gaps and opportunities, applying state-of-the-art techniques and technologies to the study of sleep, and developing strategies for better understanding daytime sleepiness and reducing its negative impact on society.

Much has changed since 1996. Stimulated in significant part by the 1996 Plan, sleep research funding by NIH has doubled. New research and new knowledge have vastly expanded the array of questions to be addressed, and new technologies have yielded new tools and mechanisms for a highly interdisciplinary broad-based approach to sleep research. It is in this context that revision of the 1996 National Sleep Disorders Research Plan was deemed necessary. The 2003 Revision summarizes the specific sleep research achievements since the 1996 Plan, identifies present gaps in our knowledge and understanding, and concludes with prioritized recommendations for future research. As with the 1996 Plan, the 2003 Plan is envisioned not as a blueprint, but as a dynamic springboard for the creativity of individual scientists, whose insights and initiative underlie research progress. We are confident that these recommendations will contribute in substantial ways to advancing the frontiers of biomedical knowledge related to sleep, enabling timely diagnosis and effective treatment, and improving the health of our Nation through community-based public health education and intervention programs.



Elias Zerhouni, M.D.  
Director, National Institutes of Health





## PREFACE

The 1996 National Sleep Disorders Research Plan, developed under the leadership of the NCSDR and the Trans-NIH Sleep Research Coordinating Committee (SRCC), has been an important resource and stimulus for progressive expansion of sleep-related programs within NHLBI and NIH (see Appendix C). Indeed, since 1996 sleep-related initiatives totaling more than \$110 million have been funded, and the total for all sleep-related research grants within NIH has doubled.

To build on the achievements of the past 6 years and identify new opportunities for progress, we embarked on a comprehensive revision of the 1996 Plan, reviewing accomplishments, remaining knowledge gaps, promising new scientific directions, and unforeseen new challenges. A Task Force, consisting of 14 basic science and clinical research scientists representing a broad interdisciplinary range of biomedical expertise, was appointed to undertake this task. Its members are:

David P. White, M.D., *Chair*  
Thomas Balkin, Ph.D.  
Gene Block, Ph.D.\*  
Daniel Buysse, M.D.  
David F. Dinges, Ph.D.  
David Gozal, M.D.

Steve Henriksen, Ph.D.  
Hannah C. Kinney, M.D.  
Carol A. Landis, D.NSc., R.N.\*  
Emmanuel Mignot, M.D., Ph.D.\*  
Judith A. Owens, M.D.  
Jerry M. Siegel, Ph.D.  
Esther Sternberg, M.D.  
Debra E. Weese-Mayer, M.D.

*\*Member, 2002 Sleep Disorders Research Advisory Board*

The 2003 Revised Sleep Disorders Research Plan, submitted by this Task Force and approved by the Sleep Disorders Research Advisory Board (SDRAB), summarizes the dramatic expansion in interdisciplinary sleep-related research and resulting new knowledge achieved since the original 1996 Plan. The sleep research recommendations should serve as a valuable stimulus and guide to researchers in many disciplines for prioritizing and planning future research directions that will lead to expanding knowledge of the interrelationships between sleep, health maintenance, and disease prevention.



Claude Lenfant, M.D.  
Director  
National Heart, Lung, and Blood Institute





## INTRODUCTION

**S**leep-related problems affect 50 to 70 million Americans of all ages. Sleep-related problems have the same clinical relevance in women as men, and some sleep problems are more common in women. Important disparities in prevalence and severity of individual sleep disorders have been identified in racial and ethnic minorities and underserved populations. Sleep problems and disorders have major impacts on society, but have not received sufficient attention in clinical practice, in the education of health care providers and future biomedical researchers, or in public health education and intervention programs.

The three broad categories of sleep problems include:

- *Sleep Restriction:* This results from imposed or self-imposed lifestyles and work schedules. Many children, adolescents, and adults regularly fail to get sufficient sleep to function effectively during waking hours.
- *Primary Sleep Disorders:* More than 70 types of sleep disorders chronically affect people of all ages. Fifty percent or more of patients remain undiagnosed and therefore untreated.
- *Secondary Sleep Disorders:* People having a chronic disease associated with pain or infection, a neurological or psychiatric disorder, or an alcohol or substance abuse disorder often experience poor sleep quality and excessive daytime sleepiness.

The end result can be exacerbation of the primary medical condition and further impairment in health and safety, mood and behavior, and quality of life.

As part of the authorizing legislation establishing the National Center on Sleep Disorders Research (NCSDR) within the National Heart, Lung, and Blood Institute, a Sleep Disorders Research Advisory Board (SDRAB) was established to provide a primary source of advice on matters related to planning, conduct, support, and evaluation of research in sleep and sleep disorders. The SDRAB consists of 12 non-Federal members appointed by the Director, NIH, 8 of whom are representatives of health and scientific disciplines related to sleep disorders and 4 of whom represent the interests of individuals with a sleep disorder (see Appendix B). The Director, NCSDR, serves as Executive Secretary of the SDRAB.

The Trans-NIH Sleep Research Coordinating Committee (SRCC) was established in 1986 by the Director of NIH for the purpose of facilitating interchange of information on sleep and sleep-related research. When the NCSDR was established in 1993, responsibility for the Trans-NIH SRCC was transferred to the NCSDR and its Director serves as Chair of the Trans-NIH SRCC. The Trans-NIH SRCC in 1993 was comprised of only five NIH Institute representatives, but membership has progressively increased in parallel with increasing interdisciplinary scope of sleep research and especially since release of the first Sleep Disorders Research Plan in 1996.

Ten NIH Institutes/Centers are now members of the Trans-NIH SRCC:

Heart, Lung, and Blood (NHLBI)

*Carl E. Hunt, M.D.; Michael Twery, Ph.D.*

Aging (NIA)

*Andrew Monjan, Ph.D., M.P.H.*

Arthritis, Musculoskeletal, and Skin Diseases (NIAMS)

*Deborah Ader, Ph.D.*

Alcohol Abuse and Alcoholism (NIAAA)

*Ellen Witt, Ph.D.*

Child Health and Human Development (NICHD)

*Marian Willinger, Ph.D.*

Drug Abuse (NIDA)

*Harold Gordon, Ph.D.*

Mental Health (NIMH)

*Israel Lederhendler, Ph.D.*

Neurological Disorders and Stroke (NINDS)

*Merrill M. Mitler, Ph.D.*

Nursing Research (NINR)

*Mary Leveck, Ph.D., R.N.*

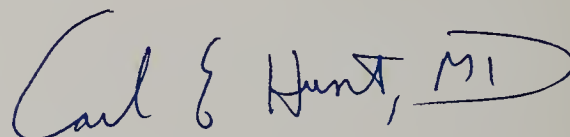
Complementary and Alternative Medicine (NCCAM)

*Nancy Pearson, Ph.D.*

The Task Force appointed to revise the Sleep Disorders Research Plan was assisted by the NCSDR and the Trans-NIH SRCC. A draft of the updated plan was broadly circulated to solicit comments from biomedical professionals involved in sleep-related research and clinical practice, and from relevant professional and public organizations representing individual scientific disciplines and sleep disorders.

Many comments were received and were carefully considered by the Task Force in completing the 2003 National Sleep Disorders Research Plan.

This Plan fully represents the deliberations and recommendations of the Task Force, summarizes the dramatic advances in knowledge since 1996, and identifies current gaps in our knowledge base. The recommendations for future research will not only guide prioritization of future sleep research within NIH and other Federal and non-Federal entities, but should also be helpful in identifying opportunities for new investigators from an ever-increasing diversity of scientific and clinical disciplines. The recommendations regarding training of sleep research scientists, the education of health care professionals, and community-based public education programs should also stimulate much-needed progress in these areas.



Carl E. Hunt, M.D.

Director

National Center on Sleep Disorders Research

National Heart, Lung, and Blood Institute

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NCSDR Web site: <http://www.nhlbi.nih.gov/sleep>

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# EXECUTIVE SUMMARY

## PROCEDURE

The first National Sleep Disorders Research Plan was released by the National Institutes of Health (NIH) in 1996. Considerable scientific and clinical growth of the field has occurred since then, necessitating a reassessment and update of research opportunities and recommendations. This 2003 revision of the National Sleep Disorders Research Plan summarizes the new knowledge acquired since the 1996 Plan and provides an updated and expanded guide for scientific research on sleep and its disorders.

The sections selected for inclusion in this revised Plan provide a broad perspective on the field of sleep and sleep disorders, and highlight the crosscutting and highly interdisciplinary evolution of this field. Each section provides:

- A brief overview of the topic.
- The major research accomplishments since release of the 1996 National Sleep Disorders Research Plan.
- The research recommendations for the future, including a listing of the two top recommendations, in italics, followed by a listing of any additional recommendations.

This executive summary presents the Task Force's highest recommendations for future research. *All the recommendations highlighted in this Executive Summary are considered*

*relatively equal in importance and are therefore not listed in any prioritized order.*

Several specifics of the overall process of the Task Force merit further comment. First, there was considerable discussion on how to address pediatric sleep science, since some developmental processes are only encountered in infants and children, while others represent a continuum from infancy to old age. Reflecting this continuum, the adult and pediatric sections were combined whenever possible (e.g., insomnia, sleep, and breathing). Separate sections focusing only on pediatric science were developed where there was no direct adult relevance.

Second, there was considerable discussion of how sleep and its disorders relative to women's health should be addressed in this document. It was decided to both create a specific section on sex differences and women's health in sleep, to emphasize scientific content unique to women, and to include in other sections, wherever appropriate, information as to how a particular disorder or physiologic process might differentially affect women and men. In this way, there would be adequate emphasis of all the diverse ways in which sleep concerns impact on maintenance of health and prevention of disease in women. Similarly, there is a separate section in this revised Plan devoted exclusively to racial and ethnic disparities in sleep and health, and relevant content is also included in other sections wherever appropriate.

## PROGRESS SINCE THE 1996 NATIONAL SLEEP DISORDERS RESEARCH PLAN

The years since release of the original National Sleep Disorders Research Plan in 1996 have been remarkably eventful not only in terms of progress in the sleep sciences but also in terms of lifestyle and activities of daily life that impact on sleep habits and behaviors. America is increasingly becoming a 24-hour per day society with constantly escalating expectations for around-the-clock services, information, and entertainment. After the events of September 11, 2001, we have also become a much more vigilant society. All these lifestyle changes directly impact not only the number of hours Americans sleep each day but also when during the 24 hours that sleep occurs.

We are now beginning to understand the impact of chronic sleep loss or sleeping at adverse circadian times on our ability to function optimally and on our physical and mental health. How sleep loss, sleep displacement (e.g., shift work, jet lag), and a wide range of sleep disorders affect one's ability to maintain health and healthy functioning, however, remains relatively poorly understood. Thus, despite the scientific progress made since 1996 in both clinical and basic science related to sleep and its disorders, there remains the challenge and the need to discover the functions of sleep, to understand and develop better treatments for the many disorders affecting sleep, and to explain the nature of human physiology during wakefulness and the individual stages of sleep. Without progress in these areas, countless millions will continue to suffer the consequences of dysfunction and abuse of this most basic regulatory process. Progress in every area cannot be included in this Executive Summary, but the most important gains in knowledge and understanding will be discussed to provide a context for the research recommendations that follow.

*Sleep Neurobiology:* The discovery in 1998 to 1999 of hypocretin/orexin and its role in the development of narcolepsy in animal models and in humans revolutionized our understanding of this debilitating disorder and promises important advances in the diagnosis and therapy of human narcolepsy. Discovery of the neuromodulatory role of hypocretin/orexin also greatly improved our understanding of the basic neurobiologic processes that control sleep and wakefulness. Anatomic areas promoting sleep, such as the ventrolateral preoptic (VLPO) area of the hypothalamus, have also been characterized. New anatomical and physiological approaches have led to advances in our understanding of the location and interconnections between hypothalamic and brainstem circuits controlling rapid eye movement (REM) sleep, non REM sleep, and wake states. Factors regulating the activity of these sleep-controlling neurons have been identified. Circuitry and neurotransmitter mechanisms controlling muscle tone across the sleep cycle, of relevance to numerous sleep pathologies, have also been identified.

*Circadian Biology:* A growing number of "clock genes" have been identified since 1996 that play a critical role in mammalian circadian timing. In addition, there is clear evidence that non-suprachiasmatic nucleus (SCN) tissues have clock genes and can demonstrate circadian rhythms. Thus, circadian modulation is now established to occur both centrally and peripherally, further emphasizing the importance of circadian chronobiology in the timing of sleep and waking as well as a wide variety of physiologic functions. Now these genetic studies are also being applied to humans, in particular patients with advanced sleep phase syndrome.

*Sleep-Disordered Breathing (SDB):* The consequences of SDB (obstructive sleep apnea, sleep apnea) in both adults and children have become increasingly clear over the last few years. In adults, the contribution of sleep



apnea to the development of systemic hypertension is becoming more evident, and data are accumulating that other adverse cardiovascular outcomes (stroke, congestive heart failure, myocardial infarction) may result from this disorder. In children, there is increasing evidence that sleep apnea may contribute to behavioral problems as well as learning and cognitive deficits. Thus, the diagnosis and treatment of this disorder is important from a variety of perspectives and across all ages.

*Pediatrics:* The recognition that having infants sleep supine (on their back) can substantially reduce the incidence of Sudden Infant Death Syndrome (SIDS) is now appreciated as a profoundly important early infant intervention that has saved thousands of lives. Recent research regarding the physiologic, psychological, and developmental aspects of sleep in infants, children, and adolescents has contributed to an increased understanding of the unique aspects of sleep and development. The study of pediatric disorders such as Congenital Central Hypoventilation Syndrome and Rett Syndrome has led to a better basic understanding of autonomic regulation and respiratory control. Recent findings regarding the complex relationship between sleep patterns and hormonal changes in adolescence have broadened our understanding of pubertal influences on sleep and circadian biology. The extent of sleep restriction and sleep disturbances among children and adolescents is now recognized to be much greater than previously believed, and the consequent impact on mood, neurobehavioral and academic functioning, safety, and health is considerable. Recognition of the link between sleep disturbances and neurobehavioral disorders in childhood, such as attention deficit hyperactivity disorder (ADHD), has profound public health implications for both the treatment and prevention of psychiatric comorbidity.

*Insomnia:* The high prevalence, risk factors, and consequences of insomnia have been

increasingly recognized since 1996. Insomnia has been identified as a risk factor for the onset of subsequent depression, anxiety, and substance use disorders. In addition, the efficacy and durability of behavioral therapies for insomnia have been demonstrated in controlled clinical trials.

*Sleep Deprivation:* Although previous studies have demonstrated many of the ill effects of total sleep deprivation, the impact of chronic partial sleep deprivation (restriction) had not been extensively investigated even though it is a much more common phenomenon. However, recent studies indicate that 4 to 6 hours of sleep per night yields a progressive, cumulative deterioration in neurobehavioral function including vigilance, neurocognitive performance, and mood. This reduction in performance is also associated with changes in cerebral activation during cognitive tasks. Physiologic changes (insulin resistance and increased sympathetic activation) appear to occur as well. Both the neurocognitive and physiologic effects of chronic sleep loss suggest there is optimal sleep duration and that there is a cost for failing to achieve it. However, the exact duration of sleep required at different periods of life remains poorly understood, as do the mechanisms driving these neural and metabolic processes.

*Sleep Education:* There is now broad recognition of the curriculum inadequacies regarding sleep and its disorders within most medical schools and residency training programs. A Sleep Academic Award Program was established by NIH in 1996 to address these educational gaps, and this program has led to the development of undergraduate and postgraduate sleep curricula, educational tools, and methods to enhance sleep knowledge. The awardees, working with national professional societies, have also begun to address sleep and fatigue in medical training. There have also been several public health education initiatives, including an effort to establish lifelong healthy sleep habits in

school-age children begun in 2001 with Garfield, the “Star Sleeper” as the “spokescat” for healthy sleep. A high school biology curriculum on sleep, sleep disorders, and biological rhythms has also been created, as have programs to combat drowsy driving. Thus, a variety of educational activities have recently been implemented that may have substantial impact on knowledge and public health behaviors.

We need to consolidate and extend the research progress made to date and to translate new knowledge and discoveries into effective therapies and improved lifestyle behaviors for all Americans (as described in the Department of Health and Human Services “Healthy People 2010” initiative). Sleep-related research must continue across the full spectrum from basic science to clinical investigation to community-based translational programs in order to apply what is known to improve public health and quality of human life. The scientific areas most important in extending and translating the research gains made to date are summarized in the following paragraphs. The order in which they are listed does not reflect any prioritization; indeed, these individual recommendations are all important and of equivalent high priority.

## RESEARCH RECOMMENDATIONS

- ▶ ***An improved understanding of all aspects of the neurobiology and functions of sleep is needed. These aspects include:***

The neurocircuitry whereby the previously described and yet-to-be-identified cellular systems that modulate state are connected to each other and to other neural systems needs to be characterized. In addition, the neuropharmacology and neuromodulators that mediate neural signaling in sleep and wakefulness, and their hierarchy in this process, need to be better understood. The genetic and proteomic mechanisms involved in the generation of sleep and

wakefulness also need elucidation. Finally, the phylogeny of sleep needs to be further investigated to help define the functions of sleep.

The neurobiologic basis of the two-process sleep system (homeostatic and circadian) needs to be better characterized regarding the anatomical, physiological, and functional links between the two systems and the contribution of each to altered sleep quality and timing.

Further research is needed to better understand how developmental maturation from the fetus to the adult influences all of the neurobiologic processes described above. This would include studies addressing how sleep itself influences neural development and how such development affects sleep at the neurobiologic level.

Investigation is needed of the neurobiological function of sleep as a whole and the independent functions of NREM and REM sleep. Without some grasp of the functional role of sleep in the behavior and survival of an organism, it remains very difficult to understand the development, neurobiology, and importance of sleep to physiologic function.

- ▶ ***Enhance our understanding of the impact of reduced or restricted sleep on behavior, and neurobiologic and physiologic functions across the age spectrum from childhood through old age. Studies in this area should address:***

The neurobiologic processes mediating sleepiness, state instability, and decrements in specific aspects of neurocognitive performance and alertness: this includes identification of brain structures, proteins, and genes that mediate the neural basis of sleepiness and the neurocognitive performance changes resulting from sleep loss. Also, the neurobiologic processes mediating the restoration of stable wakefulness, alertness, and performance require further investigation.



A systematic delineation is needed of the processes involved in, the mechanisms underlying, and the developmental aspects of acute and chronic sleep deprivation on non-neural systems. These systems include endocrine, cardiovascular, immune, hematopoietic, renal, gastrointestinal and muscle.

The effects of sleep loss on behaviors that diminish the safety of both the individual and society in general need to be studied. This includes but is not limited to the transportation industry, the armed services, the space industry, health care, law enforcement, and at-risk jobs in the construction, manufacturing, and service sectors.

- ▶ ***Improve our understanding of the processes that lead to specific sleep disorders in children and adults. The following disorders are included in this summary due to both their prevalence and their impact on afflicted patients:***

*Insomnia, defined as difficulty initiating or maintaining sleep:* Studies should include the development of animal models of insomnia, the study of specific insomnia phenotypes, and the application of neurophysiologic, neurochemical, neuroanatomic, and functional neuroimaging approaches to the study of insomnia in humans. Understanding why women are at higher risk for insomnia should also be a goal. Finally, genetic, genomic, and proteomic studies are also needed.

*Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD):* Studies should address the role of altered central dopaminergic mechanisms and abnormal iron metabolism in the pathogenesis of these conditions. Further development, refinement, and validation of animal models of RLS and PLMD are also needed. The use of neuropathologic techniques in the evaluation of brains and spinal cords of affected patients is also likely to be useful.

*Sleep-Disordered Breathing (SDB), including sleep apnea and disorders of ventilatory control:* Studies should address the processes that control both upper airway patency and ventilation itself with a particular focus on the influence of sleep on these biologic processes. The neural connections, neuromodulators, and molecular events mediating these state-dependent processes affecting respiration during sleep need to be studied.

*Primary disorders leading to hypersomnolence:* The neural mechanisms leading to hypersomnolence in conditions such as narcolepsy or primary central nervous system hypersomnolence need to be investigated. The focus of these studies should be how the neurobiologic causes of hypersomnolence differ from or resemble the effects of sleep loss.

- ▶ ***An assessment of normal human sleep phenotypes and the normal range of variation in this phenotype in adults and children (including racial and ethnic differences) is needed, not only to establish normative standards but also to serve as a model for recommended sleep behaviors. This assessment should include sleep duration, sleep stage distribution, sleep timing, sleep disruption, sleep quality, and other variables by which sleep and sleepiness can be quantitatively evaluated.***

Once normal sleep phenotypes are defined, the associated genotypes should be fully evaluated.

Abnormal sleep phenotypes should subsequently be recognizable, and genotyping of these individuals should then be pursued to define the genetic underpinning of abnormal sleep or altered circadian rhythm profiles. The impact of single nucleotide polymorphisms (SNPs) on normal sleep phenotypes should be testable as well.

The phenotype of patients with specific sleep disorders should be carefully defined in order to set the stage for subsequent genetic testing.

Methods to define normal and abnormal phenotypes through questionnaires or simple non-invasive testing should be a goal. Population surveillance and assessment of associated morbidities will then be possible on a large scale.

- ▶ ***New treatments for sleep disorders are needed. Adapting these therapies to individual patients, using pharmacogenetic and other approaches, is an important research priority. The outcomes of such treatments, including complementary and alternative medicine (CAM) therapies, need to be assessed at all levels including adherence, effectiveness, morbidity, quality of life, health care costs, safety, and performance/productivity. Such studies will likely require carefully designed and appropriately powered clinical trials in order to yield evidence-based guidelines for improved management and treatment of sleep disorders and hence substantial public health benefit:***

*Sleep-Disordered Breathing (SDB)—Adult and Pediatric:* Continuous positive airway pressure (CPAP) devices have improved substantially and remain an effective form of therapy for adult SDB. However, they are cumbersome and have achieved only moderate acceptance by patients. Other approaches, such as oral appliances and upper airway surgery, have relatively limited success rates for more than mild to moderate SDB. Therefore, current forms of therapy need to be improved, and novel therapies need to be developed. In children, the indications for surgical intervention need to be better defined. In addition, new surgical and nonsurgical treatments for SDB in children are also needed, including those that address major risk factors such as overweight and obesity.

*Insomnia:* Although the efficacy and durability of behavioral therapies have been demonstrated for primary insomnia, long-term trials evaluating the efficacy and safety of hypnotic medications have not been conducted and are a high priority. The development of novel pharmacologic and nonpharmacologic therapies, as well as complementary and alternative medicine therapies, for insomnia of all types (including insomnia in high-risk populations) remains a priority as well. Finally, the effectiveness of behavioral, psychological, and popular mind-body approaches and treatments should be evaluated in routine care settings.

*Narcolepsy:* The neurobiology of narcolepsy is now better understood, and the role of hypocretin is well recognized. Exciting possibilities for new research worthy of exploration include therapies involving hypocretin peptide supplementation, the development of hypocretin receptor agonists, cell transplantation, and gene therapy.

*Restless Legs Syndrome (RLS):* Without a better understanding of the etiology, pathogenesis, and neurophysiology of RLS, treatment strategies are limited and not effective in all patients. RLS and Periodic Limb Movement Disorder (PLMD) can have profound negative impacts on quality of life including daytime functioning, work performance, and social and family life. Therefore, methods to determine the extent of nocturnal sleep disturbance and daytime sleepiness both in children and adults with RLS can potentially enhance opportunities to develop novel and effective treatments.



- ***Further investigation is needed into the relationship between the processes of sleep and the development and progression of diseases of both neural and non-neural tissues. How sleep and its disorders contribute to the development of disease processes and alter their natural history is minimally understood. Conversely, the impact of various diseases on sleep should also be studied. The interaction between sleep and a variety of disease processes therefore needs to be studied at the epidemiologic, behavioral, physiologic and basic neurobiologic levels. Examples of these potential interactions include:***

*Medical Conditions:* Many medical disorders can impair sleep quality and can, in turn, be adversely affected by poor sleep. Common examples include congestive heart failure, pain, and obstructive lung disease. Congestive heart failure, for example, can lead to a cycling respiratory pattern resulting in sleep fragmentation and decrements in both quality of life and performance. The recurrent arousal from sleep secondary to the intermittent hypoxia associated with this respiratory pattern can potentially lead to a progression of heart failure and hence to reduced survival.

*Neurological Disorders:* Neurological conditions such as neurodegenerative disorders (Alzheimer's disease, Parkinson's disease), head trauma, encephalitis, stroke, and epilepsy are associated with insomnia, somnolence, motor activity during sleep, and/or breathing abnormalities during sleep. Studies should evaluate whether sleep disorders predispose to specific neurological conditions, whether neurological conditions can produce sleep disorders, and whether sleep disorders impair recovery for selected neurological disorders.

*Psychiatric, Alcohol and Substance Use Disorders:* The complex relationships and causal pathways linking insomnia and sleep deprivation to these disorders require further investigation. The impact of sleep disturbances on treatment outcomes and recurrence risk is also significant. Specific examples include the risk for subsequent depression among individuals with insomnia, the importance of sleep and dream disturbances in the development of post-traumatic stress disorder, and the role of insomnia and sleep deprivation in increasing risk for relapse to alcoholism and drug addiction.

*Pediatric Genetic and Neurodevelopmental Disorders:* Several genetic and neurodevelopmental disorders have associated sleep and/or SDB abnormalities. These include both rare syndromes and more frequent conditions such as Attention Deficit Hyperactivity Disorder (ADHD). Specific areas for further investigation include: (1) understanding the pathophysiology of autonomic nervous system (ANS) dysregulation in order to better understand maturation of the ANS and the abnormalities that occur in SDB; (2) investigating the anatomical contributions of the upper airway to the obstruction found in children with craniofacial malformation in order to better understand etiology of the more common causes of SDB; and (3) understanding how genetic disorders produce primary insomnia, daytime somnolence, or movement disorders during sleep. Rare genetic disorders associated with sleep abnormalities provide unique models that may facilitate exploration of novel pathophysiologic mechanisms and the discovery of new sleep-related genes that may be relevant to other, more common sleep disorders.

► *The education of health care providers and the public about the role of healthy sleep habits as an important lifestyle behavior and about sleep disorders is important. Current evidence suggests minimal learning opportunities at all levels (undergraduate, postgraduate, and continuing education). The development and implementation of sleep educational programs needs to encompass all relevant health professionals, including physicians, nurses, dentists, pharmacists, nutritionists, psychologists and other mental health practitioners). Furthermore, since many individuals use dietary supplements and other natural products as sleep aids, research findings regarding the effectiveness and safety of such products should be widely disseminated to health care providers and the public. In addition, a rigorous evaluation of the impact of these educational programs is needed to assess their efficacy in changing:*

- Professional knowledge, attitudes, skills and behavior
- Clinical practice
- Patient and health care providers health and quality of life

Public education programs about healthy sleep and sleep disorders should continue with an emphasis on culturally, ethnically and racially appropriate materials. These efforts should include school-based programs for both elementary and high school students as well as adult educational programs. An assessment of the impact of these programs on knowledge, attitudes, and sleep practices of children and adults should be a component of this process.

► *Recent scientific advances have led to the development of new technologies and methodologies, but these new approaches have not been systematically applied to the sleep sciences. In addition, new methods and approaches not currently available are needed in the sleep field to answer scientific questions and to better diagnose and manage patients. Prominent examples include:*

Mechanisms needed to study the neurobiology of a variety of sleep disorders, possibly including the development of relevant human brain banks. Examples include SDB and RLS/PLMD, sleep disorders in which little is known neuropathologically.

Animal models of normal sleep as well as individual sleep disorders would be highly useful in understanding not only normal sleep physiology, but also the pathogenesis of a variety of disorders and their behavioral and physiologic consequences.

Functional neuroimaging techniques (e.g., PET, fMRI, MRS, MEG, NIR, SPECT) are increasingly available to study sleep, sleep deprivation, and sleep disorders, thereby providing insights into the patterns of regional brain activity that characterize both normal and abnormal sleep/wake states. Application of these techniques to the study of sleep and sleepiness should be continued and expanded as further improvements and refinements become available.

Sleep monitoring in rodents, although currently utilized in a few laboratories, needs to be standardized and then made more broadly available so that mouse/rat sleep phenotypes can be easily defined in genetically altered animals.



New methods to measure and quantify the structure of sleep in humans are greatly needed. Such methods should be outcome focused, such that what is measured predicts not only the restorative processes of sleep but also the consequences of disrupting this process. Methods to relatively easily define circadian phase are also needed.

Effective new measures and methods to quantify sleep and other relevant physiological signals (such as respiration) in the home are greatly needed to facilitate both large epidemiologic investigations and the broader evaluation of patients with potential sleep disorders.

Quantifiable, noninvasive, relatively rapid methods to measure sleepiness in children and adults are greatly needed to scientifically understand its causes and consequences, and to predict performance such that the safety of the individual and society can be protected.

Informatics can be directly applied to clinical, neurophysiologic, imaging, and genetic questions as they apply to sleep and its disorders, but are not currently widely utilized in this field. Thus, the use of these methods should be expanded.

► ***Women, from adolescence to post menopause, are underrepresented in studies of sleep and its disorders. Enhanced efforts are needed to better understand the neurophysiology of sleep and the neuropathology of sleep disorders in women. These efforts should include:***

- Basic and clinical studies to establish how sex-related differences in sleep and its regulation influence the risk for, and mechanisms of, sleep disorders.
- Longitudinal studies in women including both subjective and objective sleep indicators before and during menarche, in women of childbearing age including pregnancy and the postpartum

period, and in women during the menopausal transition.

- Studies of how sleep disturbance in pregnancy affects fetal development and health both acutely and postnatally.

► ***Racial and ethnic minorities have significant health disparities. Improved data are needed to develop and implement effective prevention, intervention, treatment, and other sleep-related programs and services for racial and ethnic minorities. Elimination of disparities in sleep disorder outcomes should address not only social and environmental factors, such as education and access to health care, but also relevant gene-environment interactions. Relevant studies should include:***

- Identifying the neurophysiological and neuroanatomical correlates and gene-environment interactions contributing to racial and ethnic disparities in prevalence and severity of individual sleep disorders.
- Developing effective strategies to reach racial and ethnic minorities in public health education programs for sleep-related conditions.

## RESEARCH TRAINING

Although clinical activities and opportunities in the sleep field are expanding, a larger and more interdisciplinary scientific work force is needed if we are to fully address the scientific questions discussed above. Attracting new basic and clinical investigators to this field represents a major challenge for the field if we are to meet the expanding research needs and opportunities. Some of the potential barriers include:

- The perceived difficulty of defining sleep phenotypes in mice/rats, thereby making molecular and genetic studies more difficult.

- The perceived difficulty of studying a “state” in very reduced preparations or cell lines.
- The challenges posed to clinical research by the need for objective measurement of sleep-wake physiology and behavior, using cumbersome and expensive technology, and the need to control a wide range of factors, limit effective measurement of sleep-wake processes in naturalistic environments.
- “Sleep science” does not have Division or Departmental status at most medical centers. As a consequence, designated space, faculty positions, access to graduate students, and potential for collaboration are all limited.

Novel strategies to increase the number and scope of sleep investigators need to be identified and implemented. There is an acute need for additional dedicated Sleep Medicine training programs and for investigators in other training programs (e.g., neurobiology, genetics, aging, pulmonology, neurology, psychiatry, pediatrics, and neuropathology) to train sleep scientists. Sleep is a highly interdisciplinary field, and successful sleep centers therefore require scientific and clinical expertise from multiple disciplines, with a sufficient critical mass of investigators focused on sleep in order to achieve scientific progress. The association between basic sleep investigators and clinical scientists at these sleep centers also promotes translational research that can yield results more immediately applicable to patient care and public health interventions. Due to a lack of a critical mass of sleep investigators at most medical centers, this goal may demand a more regional or national approach than is needed for most other disciplines. This may also require an iterative process by which integrated, multidisciplinary sleep centers are carefully developed with substantial training programs and the increasing dispersal of well-trained program graduates

can then contribute to development of new sleep centers.

In addition to attracting new investigators to the sleep field, there is a need to expand the number of trained scientists from other relevant disciplines electing to focus on sleep-related research. These disciplines include informatics, epidemiology and genetic epidemiology, clinical trials, functional imaging, genetics, and molecular biology. Without collaborators demonstrating these specific skills, sleep science will not be able to utilize currently available technologies and methodologies and hence will have diminished potential for progress. Ongoing training and expanded collaborative opportunities are needed, as is a comprehensive plan to attract, train and retain new scientists, and to continue expanding the skills of current investigators.

## CONCLUSION

Considerable progress has been made since release of the original National Sleep Disorders Research Plan in 1996. Resources expended by the National Institutes of Health (NIH) to study sleep and its disorders have steadily increased (see Appendix C). New scientific techniques that facilitate research discovery are being applied to sleep questions, and have led to an improved understanding of normal sleep physiology and the pathogenesis of a variety of sleep disorders. As a result, both access to care for patients with sleep disorders and the quality of care are substantially better. However, many research questions remain unanswered, and new questions need to be addressed; therapy for a number of sleep disorders remains suboptimal; and the research workforce addressing sleep science is inadequate. This Revised National Sleep Disorders Research Plan presents a comprehensive summary of focused research, training, and education recommendations that addresses these opportunities and needs.



## SECTION I BASIC SLEEP SCIENCE

- Circadian Biology
- Sleep Neurobiology
- Pharmacology and Pharmacogenetics of Sleep and Waking

1





# CIRCADIAN BIOLOGY

## BACKGROUND

Circadian oscillators are critically involved in the regulation of the sleep/wakefulness cycles, although the relationship is complex and not fully understood. It is generally recognized that the sleep/wakefulness rhythm is not driven directly by the circadian clock, but rather emerges from an interaction of the circadian clock located within the suprachiasmatic nucleus (SCN), and a distinct sleep-wake homeostatic process (e.g., the “sleep homeostat”) in which the drive or need for sleep depends upon the prior amount of wakefulness and sleep. Sleep disorders may arise from dysfunction at several levels within these two timing systems. Alterations in the circadian pacemaker within the SCN, changes in the sleep homeostat, and alterations in the coupling between the two timing systems may each be causal in sleep disturbances. A complete understanding of the origins of normal and abnormal sleep will require a detailed understanding of both the circadian and sleep/wakefulness systems.

## PROGRESS IN THE LAST 5 YEARS

- Identification of the first mammalian clock genes. Within the past 5 years, eight “clock genes” have been identified that play a critical role in mammalian circadian timing. A recent study indicates that alterations in the *hPer2* gene are associated with advanced sleep phase syndrome. In addition, mutations of

the murine clock gene affect both sleep duration and the response to sleep loss, indicating that some genes may be involved in both the timing and pressure to sleep.

- Confirmation of the multi-oscillatory, distributed nature of the mammalian timing system: Dynamic measurements of molecular rhythms from several clock genes reveal that many organs and non-SCN regions of the brain express circadian rhythms, although not as robust as the rhythm generated by the SCN. These observations raise issues about the role of non-SCN rhythm generators in the control of the sleep/wakefulness cycle and the development of sleep disorders.
- Discovery of temporal complexity within the SCN. Recent experiments reveal regional specialization in the capacity to express circadian rhythms. It is evident that not all SCN neurons enjoy the same phase relationship to one another. Molecular rhythms of the right and left SCN appear out of phase in behaviorally split animals, and phase differences among SCN neurons may be responsible for encoding day-length information.
- Discovery that circadian photoreception is functionally and anatomically separate from vision and that this nonvisual system may affect many physiological and behavioral systems. These findings are important because sleep/wake rhythms are regulated

by photoreception via the SCN, and the sleep/wakefulness cycle can influence photoreception (e.g., eye closure during sleep). These photoreceptors may be linked directly to sleep centers in the brain, since there are retinal afferents of unknown functions that project directly to these centers.

- Discovery of new neurotransmitter systems and anatomical areas of the brain, especially the hypothalamus, and in particular discovery of the orexins/hypocretins in the regulation of rapid eye movement (REM) sleep. These anatomical and neurochemical targets are linked to the SCN and provide new avenues for studying the interactions of the circadian clock and sleep-waking timing systems.
- Discovery that chronic partial sleep loss for as little as 1 week can lead to metabolic and endocrine changes that are precursors for specific disease states (e.g., obesity and diabetes) and are also relevant to aging. Decreased total sleep time is often associated with circadian dysfunction either on a voluntary basis (e.g., shift work) or involuntary basis (e.g., aging), making it imperative to determine the importance of circadian factors that lead to decreased sleep and the health consequences associated with chronic sleep loss.
- Discovery that the rest phase of the rest-activity cycle of the fruit fly shares many behavioral and pharmacological features associated with sleep. This should allow this model organism to be used to further explore the molecular and genetic basis of sleep and the adverse effects of sleep deprivation.

## RESEARCH RECOMMENDATIONS

- *Recognition of the importance of the neurobiological basis of the two-process sleep system and these two separate timing processes controlling sleep rhythmicity will continue to provide an important conceptual framework for the dissection of altered sleep regulation. The anatomical, physiological, and functional links between the two systems are virtually unknown. The search for the neurobiological basis of these two processes and their interaction should remain at the center of basic research in this area. A more complete characterization of the contribution of these two processes to altered sleep timing and quality, particularly in relation to development and aging, is important.*
- *The circadian physiology of sleep disorders and the pathophysiology of certain disorders of the timing of sleep remain to be fully characterized and understood at a fundamental level. Circadian desynchrony is considered to be at the core of certain disorders that involve both insomnia and sleepiness (e.g., delayed sleep phase syndrome; shift work sleep disorder). Given the number of people affected by these disorders and the behavioral debilitation, it is important to determine whether any of the key circadian parameters (e.g., free-running period [ $\tau$ ], phase-response curve [PRC], light sensitivity, internal coupling between sleep and other circadian-mediated physiology, etc.) are altered in these disorders. It will also be important to search for linkages between circadian rhythms and sleep disorders not normally associated with circadian timing (e.g., Restless Legs Syndrome).*



- The availability of clock gene mutations in mammals will allow study of the effects of alterations of the circadian pacemaker on the sleep/wakefulness rhythm. In addition, these genes may have effects on sleep that are independent of the SCN. It will be important to determine how these genes act to regulate sleep, independent of the central pacemaker, and to assess the effects of circadian period, phase, and amplitude on the sleep/wakefulness rhythm.
- Although the free-running period ( $\tau$ ) of the human circadian rhythm may not change during aging, animal studies suggest an impact on other circadian parameters (e.g., amplitude). It will be important to explore the effects of aging on central and peripheral circadian generators and how age-related changes in circadian function affect sleep.
- How circadian dysregulation and sleep loss interact to affect health is an important but poorly understood topic. This issue is of particular importance to the aged and to disadvantaged populations. Multiple jobs and unusual work cycles can lead to circadian disruption. It will also be important to understand the long-term effects of chronic sleep loss in adolescents. Good model systems and more sophisticated long-term data collection will be essential.
- Development of a methodology for non-invasive *in vivo* measurement of human circadian phase is needed. This may require the identification of new markers and/or the development of novel detection systems.
- Quantitative modeling of a mammalian circadian clock is needed. The molecular processes and interactions that appear to generate rhythmicity will need to be described in a mathematically rigorous fashion. The central clock mechanism has grown in complexity with an attendant loss of conceptual clarity. Modeling may allow for a better focus on critical processes.
- Although it is clear that there are significant sleep problems associated with adjustment to shift work and transmeridian flight, our understanding about entrainment kinetics is very limited. In particular, little is known about entrainment kinetics in older individuals who have more difficulty in maintaining stably entrained biological rhythms. Recent research indicating that different circadian rhythm generators within the brain and other organs reset with different kinetics suggests that the physiology of internal and external synchronization is important. Molecular and neurophysiological tools are now available in several animal model systems to address these problems.
- Animal research indicates that circadian photoreception enjoys distinct photoreceptors within the retina and specialized neural pathways. A full functional and molecular characterization of this system in humans is required.

# SLEEP NEUROBIOLOGY

## BACKGROUND

Sleep time is defended by an accumulation of “sleep debt”—the need for more sleep that results from sleep restriction. Recent study findings in animals and humans suggest that a complete and sustained loss of sleep can result in death. It is likely that an understanding of the effects of sleep loss will reveal basic principles of brain function relevant to a broad spectrum of neurological and behavioral disorders. Sleep is known to strongly affect the activity of most brain neurons.

Modern sleep neurobiology research has not yet achieved consensus as to the function of sleep. What determines the brain’s memory for sleep loss? What is the neurological deficiency being regulated by the sleep debt memory? Does rapid eye movement (REM) sleep have different functions than non-REM (NREM) sleep?

Functional significance of the marked differences in the amount of sleep within the animal kingdom is unknown. Similarly, the considerable variation in the duration of the sleep cycle (Wake-NREM-REM) in different species of mammals from a high of 2 hours to as little as 15 minutes is poorly understood, as are the determinants and health significance of the variations of sleep duration within the human population.

## PROGRESS IN THE LAST 5 YEARS

- Molecular biological approaches have contributed to understanding sleep control mechanisms. These approaches have led to one of the greatest achievements of sleep research since the discovery of REM sleep; the identification of the hypocretin (orexin) system and its central role in narcolepsy and behavioral control.
- Genetic expression studies of sleep in *Drosophila* (fruit flies) have produced important discoveries about the genetic basis of sleep. Moreover, they have established this species, with its well-documented and readily manipulated genome as a valid model of sleep genetics, making further rapid progress likely. Studies of murine mutants have progressed along the same lines. A better understanding of the populations of genes activated by sleep, waking, and sleep deprivation, and the time course of this activation has been made possible by the application of recent developments in simultaneous assessment of the activity of large numbers of genes.
- Studies using polymer-encapsulated suprachiasmatic nuclei (SCN) and related studies of diffusible factors released by the SCN have identified some of the major mediators of circadian-sleep relations.
- Less progress has been made in elucidating, at a molecular level, the phenomenon of sleep debt. The functional and biochemical regulation of changes in sleep time, REM

and NREM amounts, and sleep morphology (e.g., delta power, eye movement intensity) with development remains mysterious, although some progress has been made in characterizing the neurophysiology and neurochemistry of sleep changes across the lifespan.

- Progress has been made in the electrophysiology of sleep at the neuronal level. The mechanisms responsible for generating and synchronizing rhythmic neuronal activity in NREM sleep have been localized to thalamic regions, and the ionic currents mediating rhythmic discharge have been identified. Cell groups in the hypothalamus and basal forebrain critical in the control of NREM and REM sleep have been identified with anatomical and electrophysiological techniques. Some recent evidence suggests that localized brain mechanisms may mediate sleep debt.
- Important roles of amino acid and monoamine mechanisms in regulating muscle tone at the motor-neuronal level across the sleep cycle have been demonstrated. The circuitry controlling neurotransmitter release has been clarified. These advances are important in understanding numerous sleep disorders, including Sleep-Disordered Breathing (SDB), cataplexy, REM sleep behavior disorder (RBD), and other parasomnias.
- The neurochemical phenotypes of major groups of neurons contributing to REM and NREM sleep regulation have been identified. Previously appreciated monoaminergic (serotonin, norepinephrine, epinephrine, dopamine, histamine) mechanisms have been shown to interact with amino acid (glutamate, GABA, glycine) neurotransmitter systems at forebrain and brainstem levels. Anatomical connections between the neurons critical to REM and NREM sleep have been traced. Hypocretin/orexin has been identified as an important modulator of activity in

sleep-control systems. Other peptides important in the control of sleep states have been described and localized to brainstem and forebrain sleep control regions.

- Limited progress has been made in understanding the phylogeny of sleep. REM sleep has been found in primitive mammals. Some birds may show inter-hemispheric asymmetry during sleep based on electroencephalogram (EEG) recordings. Unihemispheric sleep and unihemispheric sleep debt have been found in marine mammals.

## RESEARCH RECOMMENDATIONS

- *Determine the function of sleep as a whole and of the differential roles of REM and NREM sleep. It will be helpful to study genetic mutant murine and invertebrate models with unusual sleep properties. A resource that can be better utilized is the variation in sleep time and quality in the animal kingdom. As the cost of sequencing continues to be reduced, it becomes practical to sequence the genomes of diverse species to determine the genetic basis of these differences. Advances in technology have made it practical to better record and characterize the great differences in sleep duration and quality between species. Recent work demonstrates that sleep is present unihemispherically in some mammals. In other animals, REM sleep appears to occur without the low-voltage activity seen in most mammals. In still other mammals, blood pressure, heart rate, respiratory changes, eye movements, erections, and other phenomena characteristic of human sleep do not occur. These variations in mammalian and in nonmammalian species, particularly if understood in an ecological context and at the cellular level, can provide a major insight into the functions of sleep.*



- *Bridge the gap between what is now known about the anatomy and neurochemistry of sleep, wake and waking arousal-generating systems, and the nature of the information processing that occurs at the synapses within these systems. Identification of the functional role played by each neurochemical link and the analysis of neurotransmitter interactions would, for example, facilitate the development of drugs to control muscle tone over the sleep-wake cycle.*
- The pathophysiology and neurochemistry of sleep disorders needs to be better understood. How abnormal operation of sleep regulatory systems results in sleep disorders needs to be clarified. The anatomical and pathophysiologic causes of RBD, SDB, periodic limb movements during sleep, and parasomnias are poorly understood. Although major advances have occurred in our understanding of narcolepsy (see Section V), further work is needed to clarify the cause of narcolepsy without cataplexy, and how disorders of the hypocretin/orexin system and other systems produce the multiple symptoms of narcolepsy. Studies in this area represent a great opportunity for clarifying basic issues of sleep control and sleep pathology.
- An understanding of sleep debt at the biochemical and genetic level is needed, building on the new knowledge of sleep control at the neuronal level. The biochemical and genetic substrates of waking and arousal during waking and of REM sleep and NREM sleep debt need to be understood.
- Interactions between sleep states and thermoregulatory, metabolic, cardiovascular, and respiratory regulation at all levels of the neuroaxis need to be better described and understood. The roles of sex, sex hormones, sexual maturity, pregnancy, and lactation in sleep control need to be investigated at a mechanistic level.

# PHARMACOLOGY AND PHARMACOGENETICS OF SLEEP AND WAKING

## BACKGROUND

The use of sedative/hypnotic and psychostimulant drugs to treat medical conditions such as Attention Deficit Hyperactivity Disorder (ADHD), insomnia, heart disease, narcolepsy, Restless Legs Syndrome (RLS), and other medical disorders (see Section V) can result in profound effects on normal sleep/wake architecture and perceived sleep quality. In addition, over-the-counter and herbal remedy markets exist to cater to the need to either stay awake or to fall asleep. The two most common substances employed in this capacity are caffeine and ethanol.

Self-medication can lead to dose-related impairments in sleep/wake architecture and in other physiological parameters that indirectly impair sleep/wake quality. The use and misuse of other prescription and recreational drugs—including psychostimulants (methamphetamine, cocaine), sedative/hypnotics (barbiturates, benzodiazepines), opiates (heroin, oxycodone), androgenic steroids, and so-called “club drugs” (e.g., MDMA)—can be accompanied by adverse physiological consequences, including significant alterations in circadian rhythms and sleep/wake architecture.

In addition to these drug-induced effects on normal sleep/wake rhythms, individual differences (including important gender and age factors) in the pharmacological response to drugs are also important. In addition to gender and age effects, these differences

also result from genetic differences in pharmacodynamic effects and drug metabolism. However, a wide gap still exists in understanding the potential role these diverse factors play in sleep/wake pharmacology. Future insights into the pharmacology of arousal states must include greater focus on pharmacogenetic-based studies, both in humans and in appropriate animal models of sleep/wake and circadian rhythm disorders.

## PROGRESS IN THE LAST 5 YEARS

The original 1996 Sleep Disorders Research Plan provided no explicit recommendations regarding the specific investigation of the pharmacology and pharmacogenetics of sleep and arousal. Implicit in the recommendations, however, was an appreciation of the impact and scope that drugs have on normal sleep/wake processes. Conversely, both primary and secondary sleep disorder phenotypes can be triggers for prescription and nonprescription drug use that may, as a side effect, exacerbate disturbances in sleep. Building on existing knowledge regarding the effects of a wide spectrum of drugs on sleep and waking behavior, the 1996 Plan has resulted in important, incremental progress in several relevant areas.

- The increase in the number of investigator-initiated applications and responses to NIH-sponsored initiatives has led to funded research bearing directly on pharmacologic perturbations of the sleep/wake cycle.

Relevant areas of research have included: (1) efficacy of caffeine on sleep inertia and cognitive performance, (2) pharmacotherapy for sleep/wake disorders in aging, (3) rational pharmacotherapy of primary insomnia, (4) treatment of hypnotic dependence, and (5) the effects of hormone replacement therapy on sleep measures in postmenopausal women. Results from these and other studies have led to a better understanding of drug efficacy in several medical conditions as well as the extent of individual differences in drug effects on sleep/wake measures.

- We now have a better understanding of the effects of prenatal and postnatal cigarette smoke exposure in Sudden Infant Death Syndrome (SIDS) (see Section VI), the effects of opioids on rapid eye movement (REM) sleep suppression, the effects of leptin on ventilatory and respiratory control, and the effects of psychopharmacological therapy on sleep in the major mental disorders. Furthermore, there have been important advances in our understanding of the effects of the major drug classes on sleep disorders in animal models and the brain circuits where these drugs are believed to act.
- Preclinical neuroscience research has provided new insights into the complex circuitry, neurotransmitters, and neuromodulatory substances involved in sleep/wake regulation and their interaction with brain circuits involved in circadian rhythm control. Findings from research in fruit flies, animals, and humans have added considerably to our knowledge of the complex regulation of behavioral state. Because of these findings, greater opportunity exists to better understand the actions of drugs on the brain, and also to investigate novel classes of drugs that have nontraditional mechanisms of action on receptor systems within these newly refined brain circuits.
- Research has delineated the molecular basis of narcolepsy and circadian rhythm disorders (see Section V). Genes responsible for these disorders have been positionally cloned and found to code for specific proteins, some of which are receptors for other small molecules that could be targets for chemically synthesized drugs. These might be effective for sleep/wake pharmacology. Indeed, the clinical utility of drugs such as modafinil and gammahydroxybutyrate (GHB) for narcolepsy, and selective dopamine receptor agonists for treatment of RLS, has been demonstrated. In addition, while short-term pharmacologic treatment for insomnia has been demonstrated to be efficacious, most insomnia is chronic, not short-term. No carefully conducted studies have examined the longer-term pharmacologic treatment of insomnia, including issues such as efficacy, safety, or the relative advantages of different agents.
- Genome screening and single nucleotide polymorphism (SNP) analysis have been initiated in Sleep-Disordered Breathing (SDB), RLS, Alzheimer's disease, and fatal familial insomnia (see Section V). These diseases have major sleep/wake disruptions and are potentially subject to new forms of pharmacotherapy. Individual differences in the response to such treatments may relate to genetic differences.
- New knowledge has been achieved regarding the pharmacotherapy of insomnia in alcoholics, the physiological correlates of chronic alcohol ingestion in both basic and clinical studies, and the interactions between adolescent sleep, life-style and alcohol use. In addition, sleep and the effects of alcohol in alcohol-dependent subjects are now better understood, although more work needs to be done. Alcohol has been shown to alter circadian clock function when exposure takes place in the early postnatal period in rat pups. Studies on selectively bred mice and rats have




demonstrated both ethanol-related metabolic variations as well as wide variations in ethanol-induced narcosis, indicating strong genetic regulation of ethanol pharmacology. Ethanol appears to have sensitive, pharmacological actions primarily on brain NMDA (N-methyl-D-aspartate) and GABA (gamma-aminobutyric acid) receptor subtypes, offering the possibility of novel pharmacotherapy. In human studies, virtually every type of sleep problem has been observed in alcohol-dependent patients. Their sleep patterns are fragmented and typical encephalographic (EEG) rhythms are altered. Sleep changes persist for months or even years of abstinence, and alterations in sleep architecture appear to be predictive of relapse to alcoholism. Other studies indicate that alcohol aggravates SDB and further increases the decrements in cognitive performance resulting from sleep deprivation. Both gender and ethnic differences in the response to ethanol and other abused drugs have been studied, but additional research is needed. Future studies should include studies of sleep/wake measures during drug withdrawal and during relapse to drug taking.

- Morphine and similar opioid drugs cause selective decreases in REM sleep through actions on brainstem cholinergic neurons, neurons known to participate in the initiation of this sleep state. This may have relevance for the treatment of pain as well as for understanding treatment efficacy of opioids in RLS.
- Sleep effects of therapeutic psychostimulant treatment in ADHD in both adolescents and adults have received some attention, but results are so far inconsistent. Also, gender differences have not been adequately studied. Particularly in adults, underlying sleep/wake abnormalities have been reported in ADHD patients that can be exacerbated with medication, particularly dextroamphetamine.

## RESEARCH RECOMMENDATIONS

- *Consolidate the recent gains made in the descriptive anatomy and neurochemistry of sleep/wake generating systems by investigating the hierarchies of neurotransmitter interactions within these complex circuits. These studies would facilitate the development of drugs to treat sleep and waking disorders and also lead to a better understanding of the neuropharmacology of behavioral states.*
- *Encourage studies of the relative efficacy, safety, and long-term effects of psychostimulants (e.g., methylphenidate, d-amphetamine, modafinil, and caffeine), and hypnotics (particularly benzodiazepine receptor agonists and antidepressants) related to sleep/wake measures in animal models and humans, including appropriate patient populations. These pharmacological assessments should also be assessed with regard to potential interactions and efficacy of behavioral and hormonal therapies.*
- In both basic and clinical populations, study interindividual, gender, racial/ethnic, and age-related differences in baseline sleep, circadian physiology, and responses to both prescription and nonprescription pharmacological agents.
- Investigate acute and long-term sleep/wake consequences of all classes of abused drugs (including ethanol) as unique, self-administered pharmacological agents. Both clinical and basic studies are needed.
- Encourage pharmacological studies of genetically/molecularly engineered animal models for sleep disorders. Existing genome databases can be used to elucidate sleep/wake-related response to drug effects and to facilitate the discovery of new targets for sleep/wake disorder medications.

- Encourage development of state-of-the-art technologies to measure the effects of drugs on sleep, circadian physiology, and alertness in animal models and human subjects (e.g., genomics, expression arrays, proteomics, neurochemical, chemical, imaging, encephalographic analysis, etc.).
- Evaluate whether the identification and treatment of sleep disturbances can improve the clinical course of patients with alcoholism and other substance use disorders.



## SECTION II

### RESTRICTED SLEEP: NEUROBEHAVIORAL AND PHYSIOLOGICAL EFFECTS

- Sleep Deprivation in Adults
- Sleep Deprivation in Children and Adolescents

1





# SLEEP DEPRIVATION IN ADULTS

## BACKGROUND

Studies on the effects of sleep loss on neurobehavioral functions, especially neurocognitive performance, have two primary emphases: (1) specification of the properties of tasks (e.g., cognitive versus physical; long versus short duration) that make them sensitive to sleep loss; and (2) specification of the aspects of performance (e.g., cognitive processing speed versus accuracy, declarative versus implicit memory processes) that are impacted by sleep loss. There has been controversy regarding the likely nature of sleep loss-induced performance deficits (e.g., whether they reflect true deficits in physiological function of the brain, a motivational effect reflecting reprioritization of the reinforcement hierarchy, an initiation of sleep onset mechanisms in the face of waking performance, or some combination of these processes). This controversy remains unresolved due to lack of understanding of the function(s) of sleep, the physiological processes affecting recuperation during sleep, and the neurobiology of sleepiness.

Implicit in this research has been the assumption that total and partial sleep deprivation produce qualitatively similar decrements in brain function and/or motivation levels that differ only in degree. As a result, the overwhelming majority of studies in which the relationship between sleep and performance has been explored have utilized the more efficient total sleep deprivation procedures, and very few studies have examined the effects of chronic sleep restriction. Furthermore, of

these few studies only a very small subset have included adequate and objective verification of compliance with the sleep restriction regimen being studied.

Nevertheless, partial sleep deprivation is more pervasive than total sleep deprivation. Epidemiological studies suggest that mean sleep duration has decreased substantially as proportionally more people are awake more of the time. These decreases are due, in part, to expanded possibilities for nighttime activities that accompanied the introduction of electric light and other technologies and to the more recent trend toward expansion of both manufacturing and service sectors to 24-hour-per-day operations. Sleep restriction appears to be an almost inevitable consequence of nighttime shift work.

Because of the scarcity of chronic sleep restriction experiments despite a wealth of total sleep deprivation/performance studies, theoretical and practical questions remain:

- What are the physiological processes mediating neurobehavioral performance deficits resulting from sleep loss?
- What accounts for the wide individual differences that emerge in the ability to maintain performance during sleep loss?
- Do the physiological and neurobehavioral responses to chronic partial sleep loss differ from those resulting from total sleep loss?
- Relative to the adverse neurocognitive and physiological effects of sleep loss,

is there habituation/adaptation or potentiation/sensitization to repeated exposure to sleep loss?

- Are there physiological and/or behavioral adaptations or dysfunctions in sleep or circadian physiology in response to chronic sleep restriction (e.g., a change in sleep itself or the brain's recovery response to chronically inadequate sleep)?
- Are the neurobehavioral and physiological effects of chronic partial sleep loss different at different circadian phases?
- What are the physiological processes that affect restoration of cognitive performance capacity during recovery sleep, and are these processes reflected in any currently measured sleep parameters?
- How much recovery sleep is required following chronic partial sleep loss versus total sleep deprivation?
- What are the effects on neurobehavioral functions of long-term (weeks, months, years) exposure to a typical work or school schedule of 5 or more days of sleep restriction followed by 2 days of recovery?

Research on sleep loss countermeasures in healthy adults, including pharmacological and nonpharmacological interventions, such as napping strategies, has practical and theoretical relevance. Studies on the efficacy, long-term effectiveness, and safety of repeated use of traditional stimulants (e.g., caffeine, d-amphetamine, methylphenidate) and novel wake-promoting agents (e.g., modafinil) for maintenance of performance in healthy adults engaged in emergency and/or continuous operations are needed. Complementary studies of sleep-inducing and/or phase-shifting drugs (e.g., benzodiazepine agonists, melatonin) to enhance sleep and subsequent alertness/performance (e.g., shift work, transmeridian travel, or recovery from continuous operations) will

also continue to expand from the clinical to the operational realm.

Napping strategies and sleep scheduling will constitute at least part of any comprehensive strategy to maintain alertness and performance during extended continuous operations. Cell phones, beepers, and other communication devices can put some workers in a perpetual "on-call" status in which sleep might be interrupted by need for rapid decisions and/or other duty-related tasks. Studies of sleep inertia (and sleep inertia countermeasures), therefore, will be of increasing relevance and importance. Finally, exploration into the physiological effects of acute and chronic sleep loss in vital organ systems other than the brain has only just begun.

#### PROGRESS IN THE LAST 5 YEARS

- Functional brain imaging studies and electroencephalographic (EEG) brain-mapping studies show that the patterns of functional connectivity between brain regions, evident during performance of specific cognitive tasks, are altered by sleep loss. This suggests that maintenance of performance during sleep loss may depend upon regional functional plasticity.
- Recent experiments have documented precise dose-response effects of chronic sleep restriction on waking neurobehavioral and physiological functions, suggesting that the cumulative waking neurocognitive deficits and state instability that develop from chronic sleep loss have a basis in a neurobiological process that can integrate homeostatic pressure for sleep across days.
- There have been increased efforts to determine the roles of rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep in memory consolidation, although definitive evidence for such relationships remains elusive.



- Plasticity in visual cortices during a critical period in some animal studies is NREM sleep-dependent. This suggests that one function of sleep is to facilitate the functional organization of the brain, and that there are sleep-dependent aspects of putatively related processes such as long-term potentiation (LTP) and DNA repair.
- Genetic array techniques have identified the patterns of gene expression that characterize and differentiate sleep and wakefulness. This information will help in understanding the most basic cellular processes mediating performance and alertness deficits following sleep loss, and the restoration of performance capacity and alertness during subsequent sleep.
- Studies have identified those aspects of performance that are most susceptible to sleep inertia, their differential time courses, and have begun to identify sleep inertia countermeasures (e.g., caffeine).
- Discover the physiological processes mediating restoration/recovery of alertness and performance by sleep. This includes elucidation of the basic mechanisms that contribute to the time course of recovery within and between days, as well as determining whether there are longer-duration time constants for reversal of the cumulative neurobehavioral deficits that accrue during chronically restricted sleep.
- Determine whether and how factors such as cognitive activity/workload and physical activity/work modulate sleepiness.
- Identify factors accounting for individual differences in sleep need and in the apparent differential vulnerability among people with similar sleep needs in their neurocognitive and physiological responses to sleep deprivation. Once the stability and reliability of these individual differences are established, a search for stable and reliable biological and behavioral predictors to establish a phenotype can then be investigated.

## RESEARCH RECOMMENDATIONS

- *Determine the physiological and behavioral processes mediating the state instability (manifested as increased variability in alertness and neurobehavioral performance) that result from acute versus chronic sleep loss. Compare these processes with those mediating the alertness and performance deficits that characterize pathologies such as narcolepsy, Sleep-Disordered Breathing (SDB) (see Section V), and closed head injury.*
- *Identify the full range of psychological, behavioral, and physiological (e.g., endocrine, immune, cardiovascular, liver, muscle, etc.) consequences of long-term cumulative partial sleep deprivation and their underlying mechanisms.*
- Determine the physiological basis and behavioral characterization of sleep inertia effects, and study the comparative effects of possible countermeasures for sleep inertia.
- Assess the physiological modulation of sleepiness by stimulant and wake-promoting pharmacological agents, focusing on their sustained efficacy and safety for acute and chronic sleep deprivation, the impact of repeated dosing, and the effect of these agents on recovery sleep homeostasis and on the "recycle rate" (the speed with which full recovery from sleep loss is achieved, preparing the individual for initiation of another episode of sleep restriction/deprivation).

# SLEEP DEPRIVATION IN CHILDREN AND ADOLESCENTS

## BACKGROUND

Many fundamental questions regarding basic physiologic processes mediating sleepiness and alertness and the neurobiological processes underlying the cumulative neurobehavioral effects of chronic and intermittent sleep restriction are important in understanding their effects on the developing brain. Very little is known about the extent to which the relative plasticity of neural systems in children affects their vulnerability to adverse neurobehavioral, cognitive, emotional and physical consequences of sleep loss, and how sleep restriction affects a variety of neurodevelopmental processes.

Compared to adults, little is known about the magnitude and distribution, causes, consequences, and assessment of sleep loss and sleepiness in children and adolescents. Because the neurobehavioral manifestations of sleepiness in children may differ substantially from those of adults, the first challenge is to operationally define sleepiness in children. Objective, reliable, and cost-effective measures of sleepiness and alertness in children are lacking—particularly measures that could be applied to large epidemiological samples. In addition, subjective self-report data regarding sleepiness are largely unavailable in children, and behavioral manifestations of sleepiness not only vary with age and developmental level but also are often not reliably interpreted by parents and other caretakers.

Empirical studies involving both normal and sleep-deprived pediatric populations (e.g., children with sleep disorders, adolescents) have described the extent and consequences of inadequate or disrupted sleep in children. A few studies have examined mood, behavior, and performance changes resulting from acute sleep loss in children in experimental settings, but results have been inconsistent. Profiles of neurobehavioral and cognitive deficits related to chronic sleep loss and cumulative sleep debt in children are even less well defined, and little is known about the functional impairments that can develop in “real world” activities such as school performance, social relationships, behavior at home, and extracurricular and safety-sensitive activities (e.g., sports, driving).

Furthermore, few studies have attempted to use neuroimaging or metabolic techniques in children and adolescents to correlate changes secondary to sleep loss with alterations in specific brain functions known to occur in adults, e.g., complex tasks modulated by the prefrontal cortex. Despite potentially important adverse effects of sleep loss on neuroendocrine, metabolic, immunologic, cardiovascular, and other physiologic systems in the developing organism, the relationship between sleepiness and these physiologic parameters in children is largely unexplored.

An additional challenge is to examine variables that may serve as relative risk-promoting or protective factors for the effects of sleep loss in children, including those that may be genetically determined. These variables may yield important information about the development of interindividual differences in vulnerabilities to sleep loss that extend into adulthood. In addition, understanding these variables will allow definition of vulnerable populations, including racial and ethnic minorities and underserved children, in whom early intervention may be necessary for maintenance of health and prevention of long-term sequelae.

### PROGRESS IN THE LAST 5 YEARS

- Epidemiologic studies have begun to explore selected relationships between chronic partial sleep deprivation and sleep disruption related to primary sleep disorders, mood and performance deficits in children and adolescents, and academic failure. Studies of sleep in children with primary behavior and learning problems have further supported an association between sleep restriction and performance impairments. Evidence indicates that children experience significant daytime sleepiness as a result of disturbed or inadequate sleep, and most studies suggest a strong link between sleep disturbance and behavioral problems.
- Studies delineating the neurobehavioral, cognitive, and emotional effects of sleep loss in experimental settings in adolescents and older school-aged children have broadened our understanding of the similarities and differences that exist between adults and children and between children of different ages. Decreased positive mood in association with sleep disturbance is a consistent finding.

Neuropsychological profiles of impairment have been less consistent, however, with more reliable effects on attention/response inhibition, and variable effects on motor skills, memory, verbal creativity, problem solving, and general cognitive abilities.

### RESEARCH RECOMMENDATIONS

- *Establish the incidence and prevalence of chronic sleep loss and sleepiness in children using objective, standardized, and cost-effective methods of assessing sleepiness and/or its functional consequences at all stages of maturational development. Specific vulnerable and at-risk populations for adverse consequences of sleep loss and sleepiness should be identified, as well as relative risks and protective factors for the expression of sleep-deprivation effects. The biological and behavioral factors that result in sleep loss in children and adolescents also need to be identified.*
- *Identify deficits in specific neuropsychological domains and patterns of impairment resulting from acute and chronic sleep loss in children at various developmental stages, including higher level cognitive processes, such as attention, motivation and emotional regulation. Neuroimaging and other novel techniques should be utilized to examine the neurophysiologic effects of sleep loss on cognition and performance in the developing human.*
- Examine the bidirectional effects of sleep loss and sleepiness on the immune, neuroendocrinologic, metabolic, cardiovascular, and other physiologic systems, and identify developmentally appropriate biologic markers for the effects of sleep loss.





## SECTION III ENABLING TECHNOLOGY

- Analysis of Sleep-Wake States
- Genetics and Proteomics: Phenotype Issues and Methodological Approaches
- Functional Neuroimaging of Sleep and Wake States
- Post Mortem Brain Analysis in Sleep Disorder Patients

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# ANALYSIS OF SLEEP-WAKE STATES

## BACKGROUND

The monitoring of sleep states is accomplished using several electroencephalographic (EEG) leads in combination with electrooculographic (EOG) and submental electromyographic (EMG) signals. These variables are scored in combination using a system described by Rechtschaffen and Kales (R and K) in the early 1960s to yield non rapid eye movement (NREM) stages 1 to 4 sleep and rapid eye movement (REM) sleep. Although this system has been useful, it also has weaknesses. The principal weakness is the inability to easily detect and quantify microarousals or subtle disruptions of sleep. Thus, the full impact of many sleep disorders on sleep architecture cannot be meaningfully quantified. In addition, measures of sleep staging, sleep continuity, and sleep disruption do not accurately predict subsequent performance. Although there are several possible explanations for this poor relationship, the limitations of the R and K, despite new definitions applied to it, preclude measurement of sleep micro-architecture and its disruptions. Therefore, new methods are needed to monitor and quantify sleep.

The quantification of breathing abnormalities during sleep also presents a unique challenge. Until recently, there were no standard definitions of apneas, hypopneas, or the clinical syndromes associated with these events. However, even after the standardization of equipment, measurement techniques, and definitions, the current methods of assessment of Sleep-Disordered Breathing (SDB) seem to predict little regarding associated

adverse outcomes such as neurocognitive impairment or cardiovascular disease). As a result, new methods to both measure and quantify SDB and its consequences are needed.

Currently utilized methods for recording sleep and breathing not only have the quantitative problems described above but are also cumbersome and expensive. They do not allow for the evaluation of large populations suspected of having potential sleep disorders or for the completion of substantial epidemiologic evaluation of normal or at-risk populations. Simple, noninvasive methodologies to directly or indirectly monitor sleep, respiration, and other physiologic variables thus need to be developed both for the screening and diagnosis of sleep disorders and for epidemiologic investigation.

## PROGRESS IN THE LAST 5 YEARS

- Meaningful standardization of the methods, equipment, and definitions for SDB and associated syndromes has been accomplished.
- Numerous studies, ranging from a single signal (generally oximetry) to full polysomnography, have investigated simplified systems to measure sleep and respiration in the home, but have yielded varied results. However, none of these approaches has been sufficiently effective to be commonly utilized in routine clinical practice.

- New assessments of EEG signals (primarily frequency analyses) and heart rate variability have provided new insight not only into sleep itself, but also into the consequences of sleep disruption.

## RESEARCH RECOMMENDATIONS

- *New methods are needed to measure and quantify the structure of sleep. These methods should be outcome focused such that what is measured predicts not only the restorative processes of sleep, but also the results of disrupting this process. Sophisticated, computer-based signal-processing methodologies should be applied, using both linear and nonlinear dynamic approaches. The result should be a quantitative assessment of both the macro and micro structure of sleep.*
- *New approaches are needed for the measurement, assessment, and quantification of physiologic/biologic variables during sleep. Such methods should be easily accomplished to permit broad applicability, quantitative, and predictive of the consequences of the sleep disorder under assessment. The focus should be on novel, noninvasive approaches that do not require labor-intensive, expensive scoring, perhaps including microtechnology, should be.*
- Portable ambulatory systems to measure sleep and other physiologic variables (respiration, leg movements, etc.) reliably in the home environment are needed. These systems should be inexpensive, easy to use both for screening and for diagnosis of sleep disorders, and be applicable for large-scale epidemiologic studies. Furthermore, these systems should measure variables that are outcome-focused such that the results can be utilized to both predict consequences and define the need for therapy.
- New methods are needed to define circadian phase in the clinical setting such that the role of circadian abnormalities in disorders such as insomnia can be determined. Such methods would also allow for more precise manipulation of circadian phase when appropriate.

# GENETICS AND PROTEOMICS: PHENOTYPE ISSUES AND METHODOLOGICAL APPROACHES

## BACKGROUND

Sleep behavior is extremely variable across and within animal species, suggesting the importance of genetically based differences. Limited genetic epidemiological data indicate that many sleep disorders have a strong genetic component. Advances in genetics and genomics have been spectacular and include sequencing the genomes of various organisms and high-throughput studies using genetic arrays and polymorphic markers. Animal models of sleep and circadian disorders with selected genetic alterations are now being generated. Similar developments in the area of protein characterization and the more general field of proteomics are now rapidly developing. The field of sleep disorders medicine is now well-positioned to take advantage of these new technologies.

A solid foundation in the area of phenotyping sleep and its disorders in both animals and humans is needed before proceeding with genetic analysis. The discovery of new methods and improvements in existing sleep recording techniques in humans are also needed. When performing genetic studies, it is important to consider potential study design limitations. The strength and location of linkage regions identified, for example, depends on the strength and precise phenotype selected. Thus, linkage regions may not be identified if the power of the study is insufficient, and large numbers may be required for such studies to be successfully accomplished. Even if linkage regions are identified, these may be large and contain

many candidate genes. Sequencing of candidate genes may not yield mutations or may identify mutations that are not relevant to the phenotype. In this case, the use of complementary approaches such as DNA expression arrays and proteomics to identify novel genes of interest may be a powerful approach to identify relevant candidate genes.

Molecular correlates of sleep and diurnal rhythms would be important for a wide range of clinical studies. Much human research relies on blood samples, which are easily obtained, but often there is little knowledge about chronobiologic variations in the parameters being measured, and no regard for the time of day or the sleep history of the subject when the sample is taken. The impact of sleep and diurnal variation on other systems is exemplified by blood coagulation and thrombotic tendencies. Myocardial infarctions or strokes occur more often in the morning, and blood properties such as platelet aggregation may change during the day. It would be useful to have molecular markers to assess chronobiologic and sleep history variability.

## PROGRESS IN THE LAST 5 YEARS

- There have been advances in technology development in the area of sleep phenotyping in mice. In the clinical arena, sleep recording devices have been made more portable and easier to use. Similar progress has been made in automated sleep scoring



algorithms that utilize concepts such as neural networks, fuzzy math, and wavelet fitting, allowing for more rapid analysis and the possibility of high-throughput sleep phenotyping.

- Eight genes that significantly contribute to the generation of circadian periodicity have been isolated in mammals. Recently, studies in humans have shown, for the first time, a correspondence between human and animal sleep phenotypes. Most strikingly, a mutation in the gene *HPER2*—a gene known to be involved in the regulation of circadian rhythmicity in mammals—was demonstrated to cause Familial Advanced Sleep Phase Syndrome (FASPS) in a human family. Additionally a polymorphism in *CLOCK*, another gene involved in the generation of circadian rhythmicity, was found to influence morningness-eveningness tendencies in humans. These studies are likely to be extended and lead to discovery of other human mutations and polymorphisms affecting circadian regulation.
- Similar progress has been made using a genetic approach in narcolepsy (see Section V). Using a positional cloning approach, mutations in the hypocretin receptor 2 gene) have been isolated in a canine model of narcolepsy. The knocking-out of *preprohypocretin*, a gene initially believed to be involved in appetite regulation, led to the establishment of a murine model of narcolepsy. These findings were found to be directly applicable to human narcolepsy-cataplexy, as it has been now shown that most patients have a hypocretin deficiency. This last finding is remarkable as the disorder in humans is genetically complex and HLA-associated. These results demonstrate the importance of careful phenotyping of human sleep disorders to reduce disease heterogeneity and the importance of animal models.

- Genome screening and genetic association studies have been initiated in Sleep-Disordered Breathing (SDB) and Restless Legs Syndrome (RLS) (see Section V). Significant linkage results have been reported and await confirmation. In the candidate gene area, an association between *APOE e4* and sleep apnea has been reported and will need to be replicated.

## RESEARCH RECOMMENDATIONS

- *Develop new methods to measure sleep, circadian physiology, and sleepiness in large numbers of animals and human subjects. One goal is to develop and validate surrogate measures. Another goal is to define normal sleep-pattern variation in the general human population. Normative data will also be critical to define and validate existing or novel sleep disorder phenotypes. These data will be needed to elucidate corresponding genetic factors.*
- *Continue the study of animal models, such as the fruit fly, zebra fish, and mice to enhance our understanding of physiology and circadian biology. Use of these models to study sleep or the regulation of rest/activity should be a priority, as this may lead to the discovery of novel sleep-regulatory pathways. Powerful new genetic approaches, such as those used to discover circadian clock genes (e.g., mutagenesis screens), can be used to find new genes that are involved in the homeostatic need to sleep and in interactions between the circadian and sleep-wakefulness systems. Other approaches, such as "quantitative trait loci," should be considered insofar as true "sleep knockouts" may be not viable in mutagenesis screens.*
- Identify new disease phenotypes, including rare familial sleep disorders or subtypes of current sleep disorders based on treatment

response or other characteristics. The study of multiplex families where sleep disorders appear to be segregating as a single gene could lead to the positional cloning of novel sleep disorder-related genes. This may facilitate our understanding of other, more common sleep disorders, as well as increase our understanding of the normal physiology of sleep.

- Study interindividual differences in baseline sleep, circadian physiology and response to sleep deprivation in a large number of subjects to better define normal and pathological conditions. Recent results indicate large interindividual differences in how people react to sleep deprivation. Additionally, subjective sleepiness varies significantly in patients with equivalent degrees of SDB and sleep fragmentation. The study of these interindividual differences has both clinical and basic research relevance.
- Twin prevalence and segregation analysis studies need to be conducted for all sleep disorders across various populations in order to estimate heritability and environmental contributions for each sleep disorder. This will help prioritization and design of further genetic studies.
- Genome screening studies using classical family design and candidate gene-based research should be continued and extended. Since most sleep disorders are genetically complex, large numbers will be needed and there is a need to encourage the blending of epidemiological and genetic designs. Ethnic variation in the expression and the genetic basis of various sleep disorders has been identified and will require further exploration. Studies of SDB, RLS, and other disorders such as hypersomnia will benefit from this approach.
- Genetic array and proteomic studies in selected tissue samples or protein-protein interaction experiments should be encouraged. These new techniques can be extremely useful to discover novel components within a molecular or a disease pathway.
- Mouse models are increasingly used in genetic and behavioral studies, and have been created but not yet widely utilized in narcolepsy. A large number of mice with various genetic alterations are being created in multiple laboratories but are rarely tested for sleep abnormalities. Finding sleep abnormalities in some of these models could lead to the discovery of novel sleep regulating pathways that may be involved in selected sleep disorders. To remedy this situation, there is a need for developing and distributing genetically determined animal models for sleep disorders. Collaborative efforts should be explored to phenotype sleep in mice models for investigators that are working outside of the field of sleep research.

# FUNCTIONAL NEUROIMAGING OF SLEEP AND WAKE STATES

## BACKGROUND

Although the physiological and adaptive functions of sleep remain to be clarified, it is clear that sleep and wakefulness are neurologically mediated. Sleep researchers have employed behavioral observations, clinicopathologic observations, correlative studies with polysomnographic measures, and extrapolations based on invasive research in non human subjects in order to characterize and understand the brain processes mediating and constituting sleep and wakefulness. Each of these approaches continues to yield new knowledge about sleep and the brain, and each provides a unique view, or "level of analysis," of sleep and brain functioning ranging from the behavior of single neurons to the behavior of the entire organism. The ultimate result of this multifaceted approach is likely to be a comprehensive and coherent understanding of sleep.

Functional brain imaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), Magnetic Resonance Spectroscopy (MRS), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), and near-infrared optical imaging (NIR) have enabled new and unique analyses in the study of sleep and waking. These techniques allow measurement of metabolic and neurochemical activity throughout the brain, and can discern dynamic patterns of regional cerebral activity during various brain states, including stages of sleep and levels of alertness during wakefulness or

during functional challenge. Furthermore, these techniques are likely to enhance identification of both normal and abnormal sleep/wake processes.

## PROGRESS IN THE LAST 5 YEARS

- Functional neuroimaging techniques (primarily PET) reveal that non-rapid eye movement (NREM) sleep is associated with deactivation of centrencephalic regions (brainstem, thalamus, basal ganglia) and multimodal association cortices (e.g., prefrontal and superior temporal/inferior parietal regions). Rapid eye movement (REM) sleep is characterized by reactivation of all centrencephalic regions deactivated during NREM sleep except the multimodal association areas. Thus, deactivation of the multimodal association areas has been shown to be a defining characteristic of sleep.
- PET studies during sleep-deprived wakefulness reveal regional cerebral deactivations that are especially prominent in prefrontal and inferior parietal/superior temporal cortices, and in the thalamus. These patterns are similar to that found during NREM sleep, but the deactivations are of lesser magnitude than during NREM sleep. This pattern is consistent with, and helps explain, the nature of cognitive performance deficits that occur during sleep loss. Considered together with results of sleep studies, this pattern suggests that NREM sleep initiation and sleep-deprived wakefulness in healthy individuals are manifestations of related neurobiological processes.



- Relative activation/deactivation patterns revealed by fMRI techniques during performance of cognitive tasks suggest that maintenance of performance following sleep loss may be a function of the extent to which other cortical brain regions can be recruited for task performance in the sleep-deprived state. This is one of a number of possible ways that individual differences may occur in the ability to maintain alertness and performance following sleep loss.
- PET, SPECT, and fMRI studies reveal that a subset of depressed patients show initially elevated activation in anterior cingulate and medial orbital cortices. In these patients, sleep deprivation reduces this regional hyperactivation, and improvements in mood are a function of the extent to which this activity is reduced. These studies suggest possible mechanisms by which antidepressant drugs may exert their effects.
- PET scans reveal that the midbrain reticular activating system remains relatively active during stage 2 sleep—a finding that may account for the relatively heightened arousability that characterizes this stage of sleep.
- PET scans taken at 5 versus 20 minutes after awakening suggest that reemergence of conscious awareness upon awakening occurs as a function of centrencephalic reactivation, and reestablishment of a specific pattern of functional interconnectivity between brain regions. These data also suggest that restoration of alertness (e.g., dissipation of sleep inertia effects) occurs as a function of reactivation and reestablishment of functional interconnectivity patterns involving prefrontal cortices. These findings could constitute an important first step toward specification of the physiological basis of post-sleep waking cognitive capability.

## RESEARCH RECOMMENDATIONS

- *Perform neuroimaging studies that measure absolute as well as relative changes in brain metabolic activity and neurotransmitter levels. Such studies are needed to: (1) determine the effects of sensory and cognitive demands on subsequent levels and patterns of regional brain activity during both sleep and wakefulness and as a function of state changes, and (2) to establish the functional neuroanatomy of sleep, wakefulness, alertness, and cognitive capability.*
- *Apply the enhanced capabilities afforded by improved functional neuroimaging, including greater temporal and spatial resolution, to study sleep and sleep disorders. These applications will help to determine the physiological correlates of phasic events like eye movements during REM, sleep-dependent changes in activity levels of specific thalamic nuclei, and brain changes subserving microsleeps and lapses of attention.*
- Utilize functional neuroimaging techniques to determine the functional neuroanatomy of REM sleep, NREM sleep, and waking in patients in sleep disorders such as narcolepsy, REM behavior disorder, and Restless Legs Syndrome. Such studies will yield insight into the pathophysiology of these disorders. Similar studies in patients with other disorders known to impact sleep processes (e.g., depression, chronic pain conditions) will yield insight into the pathophysiology of these disorders.
- Determine the effects of sleep and alertness-promoting pharmacological agents on patterns of regional brain activation/deactivation and on occupancy/activation at specific receptor sites. Such studies will elucidate the mechanisms by which these agents impact sleep/wake processes, and will facilitate the development of new

agents that might more specifically target sleep/wake-relevant sites and receptors.

- Develop new approaches to obtain polysomnographic measures and other physiological signals during MRI scanning to facilitate the study of sleep and alertness unaffected by electromagnetic interference from the MRI scanner.

# POST MORTEM BRAIN ANALYSIS IN SLEEP DISORDER PATIENTS

## BACKGROUND

The post mortem study of brains of patients with sleep disorders has significantly contributed to our understanding of human sleep regulation and its dysfunction. Human brain analysis at autopsy in sleep disorders is important for two major reasons: (1) it generates hypotheses from observations directly in human tissues about the cellular and molecular mechanisms of human disease for testing in animal models, cell culture systems, and genetic models; and (2) it tests the relevance to human disease of observations made in animal models and cell culture systems by examining specific cellular and molecular markers in human tissue samples.

Currently, human neuropathology involves analysis at the structural, neurochemical, cellular, and molecular levels, and its modern tools hold promise of much-needed insights into central and autonomic mechanisms in sleep disorders. A potentially revolutionary tool for human brain analysis is microarray analysis of gene expression in autopsied tissues. The potential of this genomic technology in human neuropathology to uncover critical molecular abnormalities is illustrated by its recent application to post mortem brain analysis in schizophrenia. With cDNA microarrays, altered gene expression was found in the frontal cortex in schizophrenic patients compared to autopsy controls. The most changed gene, which was never before linked to schizophrenia, was a regulator of G-protein signaling 4, suggesting schizophrenia is a disease of the synapse and thus providing an opportunity to better understand

a devastating disorder whose basic mechanism(s) has been elusive.

Sudden Infant Death Syndrome (SIDS) represents a sleep disorder in which neuropathologic examination with modern neurochemical techniques suggests abnormalities in a specific brainstem region and neurotransmitter system, namely the medullary serotonergic system). These findings from human infant brains will generate hypotheses to be tested in animal models. Narcolepsy, on the other hand, represents a sleep disorder in which seminal observations in genetic animal models resulted in subsequent delineation of the neuropathology in affected human patients, e.g., deficiencies in the hypothalamic hypocretin system.

These two examples underscore the critical need to analyze the human brain at autopsy in patients with sleep disorders. National autopsy networks and brain tissue banks may be needed to collect brain tissues from patients with common, rare, or non-lethal sleep disorders, and to disseminate affected and control brain samples to interested sleep researchers. Some national, NIH-supported brain tissue banks are well established, and have proven vital to the success of human brain research in neurodegenerative disorders such as Alzheimer's disease and genetic disorders such as Rett syndrome). An informal survey of national brain tissue banks, however, reveals virtually no accrual of brains from patients with any primary sleep disorders except SIDS. Specialized training of neuropathologists in the neuroanatomy, neurochemistry, and neuropathology of sleep will be needed, however, to make optimum use of this new research resource.



## PROGRESS IN THE LAST 5 YEARS

- The neuropathologic post mortem evaluation of brains in patients with narcolepsy confirmed observations from animal models that the major lesion is in the hypocretin neurons of the lateral hypothalamus. A reduced number of hypocretin neurons, associated with gliosis, was reported in the hypothalamus of human patients with narcolepsy, as well as, in a separate study, the absence of hypocretin mRNA in the hypothalamus and lack of hcrt-1 and hcrt-2 levels in the cerebral cortex and pons (target sites).
- The neuropathologic post mortem evaluation of brains in patients with Fatal Familial Insomnia (FFI), a prion disorder, established that the major lesions are in certain subnuclei of the thalamus that are interrelated to the limbic system, and suggested a specific role for these thalamic regions in sleep and autonomic control that can now be tested in animal models.
- Neuropathologic insights from analysis of SIDS and control brains at autopsy revealed that a substantial subset of SIDS victims have abnormalities in serotonergic receptor binding in regions of the medulla involved in chemoreception, respiratory drive, blood pressure responses, and upper airway control. Dysfunction of serotonergic neurotransmission in the medulla in affected infants may put them at risk for sleep-related sudden death when stressed by hypoxia and/or hypercarbia in a critical developmental period.
- Neuropathologic post mortem analysis in patients with dementia and REM Behavior Disorder (RBD) revealed an association between Lewy body dementia and RBD. Lewy bodies were present in affected patients in regions of the brainstem involved in arousal, REM sleep, and autonomic control.

## RESEARCH RECOMMENDATIONS

- *Utilize established national brain tissue banks for increased accrual and dissemination of brain samples and associated histories from patients affected by both primary and secondary sleep disorders (see Section V). The spinal cord should be likewise stored in certain cases in which spinal cord involvement is postulated, e.g., Restless Legs Syndrome. The accrual of central nervous system (CNS) samples from control cases without sleep disorders will also be needed.*
- *Establish a National Autopsy Network for Sleep Disorders, and perhaps Centers for individual sleep disorders, in order to assure accrual of brains from patients with sleep disorders, including those that are rare and/or non-lethal. Such a network, for example, would alert pathologists that the brain of an individual with Sleep-Disordered Breathing (SDB) or insomnia dying of an unrelated cause is of interest to sleep scientists and should be obtained and processed as needed for neuropathologic analysis. Blood, cerebrospinal fluid (CSF), and brain and spinal cord tissues should be collected in addition to a detailed sleep history.*
- Apply state-of-the-art neurochemical, cellular, and molecular markers to the study of sleep disorders in human brain tissue, especially those without a pathologic correlate at the light microscopic level. Techniques should include gene expression microarray technology, protein analysis with mass spectroscopy, tissue receptor autoradiography, in situ hybridization for mRNA in tissue sections, immunocytochemistry with single and double labeling, stereological cell counting, and electron microscopy combined with immunological markers.

- Apply state-of-the-art genomic approaches to post mortem brain analysis for novel gene discovery and gene expression profiling in sleep disorders. Possible approaches include microarrays, quantitative real-time PCR assays, and serial analysis of gene expression (SAGE). These methods, among many others, provide information about normal and abnormal gene expression in a tissue or cell. Details must be refined regarding applicability of this technology in human brain tissues with variable agonal conditions (e.g., pH changes) and post mortem intervals. The methods for relating expression data to disease-model databases and gene sequence databases (e.g., single nucleotide databases) will also require refinement. Multifactorial and multilevel analyses will need to combine massive gene expression datasets with the clinical diagnosis, medication, family history of the illness, and genetic heritage of each subject.
- Ensure neuropathology limbs to large, multi-institutional studies of human sleep disorders for analysis and storage of specimens (e.g., brain, CSF, blood), and for correlation of neurochemical, cellular, and/or genetic markers with clinical pathophysiology.
- Analyze the spatial and temporal profiles of sleep-related molecules across development including aging in relevant brain regions (e.g., hypothalamus, basal forebrain, brainstem, thalamus, cerebral cortex) in human post mortem brain.

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## SECTION IV

### SLEEP AND HEALTH

- Normal Sleep, Sleep Restriction, and Health Consequences
- Sleep, Sex Differences, and Women's Health
- Racial and Ethnic Disparities
- Sleep and Aging
- Sleep and Safety
- Sleep in Medical Conditions

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# NORMAL SLEEP, SLEEP RESTRICTION, AND HEALTH CONSEQUENCES

## BACKGROUND

Government publications, such as "Healthy People 2000" and its sequel "Healthy People 2010," contain recommendations for adequate nutrition and physical fitness for healthy functioning, but no recommendations or standards for normal sleep duration and quality. Epidemiological data have never been obtained defining normal sleep and wakefulness as measured systematically by both subjective and objective indicators in infants, children, adolescents, young adults, middle-aged and older adults. Only limited electroencephalographic (EEG) sleep data as a function of age and gender are available from laboratory studies published more than 25 years ago. Data used to describe "normal" EEG sleep from infancy to old age were based on 1 or 2 nights of sleep recordings in a small number of subjects in a laboratory setting. Most of these studies were conducted prior to the establishment of accepted sleep monitoring and scoring standards. In fact, the most widely used reference of "normal" human EEG sleep is based on studies in which EMG recordings were not used in the scoring of rapid eye movement (REM) sleep.

Despite beliefs about the importance of sleep for health and normal growth and development, there are no standards of sleep physiology based on current polysomnographic criteria. Furthermore, there is no comprehensive database defining normal sleep-wake behavioral patterns by age or sex across the life span. Thus, health care providers have no normative reference for comparison with an individual's sleep pattern alone or as it relates

to good health, and public health agencies have no way of knowing whether there are population shifts in the quality and quantity of sleep obtained by different age groups.

Descriptions of sleep phenotypes and definitions of normal sleep patterns and requirements must incorporate the wide range of normal developmental and physical maturational changes across the life span. Although cross-sectional studies yield important information regarding sleep in discrete age groups, they do not address the evolution and persistence of sleep/wake patterns across time. There is a need to understand the complex reciprocal relationship between sleep and cognitive/emotional development from the prenatal period through adolescence and through adulthood. Prospective longitudinal studies utilizing validated screening and assessment tools are thus needed to delineate the development of sleep patterns and behaviors and to generate predictive models.

## PROGRESS IN THE LAST 5 YEARS

### *Sleep and Environment*

- Sensory stimulation resulting from environmental noise, light, motion, temperature, and even odors can produce activation at levels antithetical to the initiation and maintenance of sleep. Thus, sleep environments in which sensory stimulation is minimal (e.g., dark, quiet, comfortable temperature) tend to be preferred subjectively and tend to enhance sleep initiation and maintenance.



- Recent efforts by some hotels to offer rooms that are especially conducive to sleep, and by some transportation industries to improve the sleep environments of both customers and employees, reflect recognition of the importance of sleep and a sleep-conducive environment.
- Despite knowledge of the importance of environmental variables for sleep quality and duration and of considerable variations in sleep environments across ethnic and socioeconomic strata, there has been little scientific investigation of environmental factors potentially critical for healthy sleep and waking. Subjects requiring scientific investigation include:
  - *Cosleeping or bed-sharing (sleeping with one or more other persons in the bed)*: Although evidence suggests that the somesthetic stimulation resulting from bed-sharing can have a negative effect on sleep continuity and architecture, the relative benefits and adverse consequences of this practice have not been adequately explored.
  - *Sleep location*: Sleep at home versus sleep in public places in which control over environmental stimulation is minimal (e.g., on an airplane), or in the work environment (e.g., sleeper berths on trucks, trains, and planes).
  - *Sleep position*: This has been determined to be important in Sudden Infant Death Syndrome (SIDS) and in modulating the severity of Sleep-Disordered Breathing (SDB), but sleep position has not been studied relative to the potential for sleep fragmentation (e.g., sleeping semi-recumbent versus fully recumbent).
  - *Sleep surface*: Virtually ignored in sleep science, many consider optimal sleep surface to be crucial to obtaining a good night's sleep.
- *Environmental noise/light*: Ambient noise and vibration have occasionally been studied as factors improving or impairing sleep quality, but little is known regarding the extent to which various types of noise and vibration affect sleep. A few experiments have found that light at night can enhance alertness, and that properly timed light exposure can hasten phase shifts of circadian biology (e.g., shift workers). There have been no studies, however, to determine whether turning on room lights at night adversely affects sleep quality or quantity.
- *Health disparities and vulnerable populations*: Socioeconomically disadvantaged populations may be more likely to sleep in environments that are hot, humid, cold, noisy, and/or crowded. There has been no systematic study of the effects of these factors on sleep quality and quantity either alone or in combination, and no study of potential effects of these factors on waking functions including school and work performance. Children and adolescents, the elderly, and shift workers are populations who may be especially vulnerable to the adverse effects of environmental variables on sleep quantity and quality.

It is important to determine the extent to which each of these environmental factors affect sleep quality and contribute to sleep loss, sleep pathology, daytime sleepiness, and daytime functioning. Scientific data in these areas would be fundamental to answer questions regarding the determinants of a good night's (or day's) sleep.

### *Health Consequences of Insufficient Sleep and Chronic Sleep Debt*

- Adequate sleep is essential for healthy functioning and survival. Inadequate sleep and unhealthy sleep practices are common, however, especially among adolescents and young adults. In the 2002 National Sleep Foundation annual survey, nearly 40 percent of adults ages 30 to 64, and 44 percent of young adults ages 18 to 29 reported that daytime sleepiness is so severe that it interferes with work and social functioning at least a few days each month. Excessive daytime sleepiness is a major public health problem associated with interference with daily activities, including cognitive problems, motor vehicle crashes (especially at night), poor job performance, and reduced productivity. Optimum daytime performance with minimal sleepiness in adolescents and young adults appears to require at least 8 to 9 hours of sleep at night with few interruptions. A majority of adolescents and adults, however, report habitual sleep durations of fewer than 7 hours per night during the week and fewer than 8 hours of sleep each night on weekends.
- The beneficial effects of healthy sleep habits and the adverse consequences of poor or insufficient sleep have not been well studied. Sleep is essential for survival, yet only in the last decade has scientifically credible, experimentally based data from humans been gathered on dose-response relationships between chronic restriction of sleep by 1 to 4 hours a night and accumulating daytime sleepiness and cognitive impairments. Most individuals develop cognitive deficits from chronic sleep debt after only a few nights of reduced sleep quality or quantity, and new evidence suggests additional important health-related consequences from sleep debt related, for example, to common viral illnesses,

diabetes, obesity, heart disease, and depression. Findings from a recent study of young adult men placed on a restricted sleep schedule of 4 hours each night for 6 consecutive nights showed altered metabolism of glucose with an insulin resistance pattern similar to that observed in elderly men. The implications from this study, if replicated, are that chronic sleep loss may contribute to obesity, diabetes, heart disease, and other age-related chronic disorders. As promising as these data are for providing solid scientific evidence of the health consequences of chronic insufficient sleep, most people report habitual nighttime sleep in the range of 6 hours. Data are needed to determine the extent to which habitual sleep durations of 6 to 8 hours are associated with increased disease risk in men and in women.

### *Sleep Duration and Quality: Relationship to Morbidity and Mortality*

- The relationship between sleep (quantity and quality) and estimates of morbidity and mortality remains controversial. Data from epidemiological studies suggest that a habitual short sleep duration (less than 6 hours of sleep per night) or long sleep duration (more than 9 hours of sleep per night) is associated with increased mortality. A recent epidemiological report found that self-reported sleep duration averaging either less or more than 7 hours of sleep daily was associated with higher mortality. It is not clear how sleep duration increases risk. Moreover, although such epidemiological studies have used very large convenience samples, they have relied on retrospective self-report, the least accurate index of sleep.
- There have been no epidemiological prospective studies examining the relationship between sleep and health outcomes (morbidity and mortality) that included



estimates of sleep based on both subjective and objective measures. Past practices of adding questions about habitual sleep duration to large epidemiological studies designed to answer questions about, for example, the relationship between nutrition and risk for heart disease or between smoking and cancer risk are not sufficient. Although studies of sleep patterns and behavior would be prohibitively expensive and require multiple sites with subjective and objective measures of sleep in a very large sample, important questions regarding the relationship between sleep duration and quality and morbidity and mortality can only be addressed through such large studies. Furthermore, recent studies have shown that sleep duration of at least 8 hours is necessary for optimal performance and to prevent physiological daytime sleepiness and the accumulation of "sleep debt." Findings from these and other studies can only be reconciled with data suggesting that habitual sleep durations of eight hours are associated with higher mortality by a large comprehensive study of the effects of sleep on health and risk for disease.

Without knowledge of what needs sleep fulfills or what sleep patterns (duration and quality) best predict health (or morbidity and mortality), it is very difficult for sleep researchers and clinicians to answer questions such as:

- What are normal sleep patterns?
- How much sleep is needed by infants, children, teenagers, adults, and the elderly for healthy functioning?
- What is the minimum amount of sleep required for optimal functioning and for health?
- How much of the patterning of sleep is genetic and how much is environmental?

- How are patterns of growth and development from infancy to adolescence and from adolescence to adulthood negatively impacted by insufficient sleep?
- What is the influence of prematurity on the development of sleep patterns? Do infants considered "poor" or "problem" sleepers develop insomnia as children and/or adults?
- What sleep patterns in young and middle-aged adults predict good quality sleep in the elderly? Is the amount of sleep more important than the time of day when sleep occurs?
- Do daytime naps make up for lost sleep at night?
- What are the health consequences of long-term exposure to chronic sleep restriction such as those imposed by a typical work or school schedule of 5 or more days of sleep restriction followed by 2 days of partial recovery?
- Does the duration of recovery sleep, or the timing of recovery sleep in the daily cycle, or both, determine the benefits of sleep for healthy functioning?
- How much recovery sleep is required following exposure to chronic sleep restriction in order to restore physiological and neurobehavioral capability to baseline?
- Does habituation/adaptation in the body's physiological systems develop to sleep loss or chronic sleep restriction and at what cost to one's health?
- How important are environmental variables, such as sleep surface and light, in affecting sleep quality and quantity?



## RESEARCH RECOMMENDATIONS

- *Epidemiological longitudinal studies to define normal sleep behavior (timing, duration, quality) and phenotypes using state-of-the-art objective and subjective technologies. Such studies are needed across the life span and especially in vulnerable populations, and should focus on the transition from infancy to adolescence, adolescence to middle age, and middle age to advanced age. Prospective studies representing the diversity of human cultures are needed to define normal sleep phenotypes across cultures and in different ethnic and socioeconomic groups.*
- *Epidemiological longitudinal studies to prospectively assess the relationships among sleep duration (short and long), sleep quality (good and poor), and health outcomes (morbidity and mortality). There is a need to determine the incidence and prevalence of "sleep debt" in vulnerable populations including children, adolescents, young adults, shift workers, new parents, those exposed to prolonged work hours, those of low socioeconomic status. There is also a need to determine the functional and health-related consequences of sleep debt on increased disease risk, such as related to depression, obesity, diabetes, and cardiopulmonary diseases.*
- The genetic, environmental, and psychosocial factors that impact children's sleep, and the relative contributions of each, need to be identified.
- Identify how sleep disturbances in early childhood impact cognitive and social development, behavior and performance, as well as subsequent development of sleep disorders in adolescents and adults.
- Studies to identify and evaluate countermeasures and novel approaches to prevent sleep deprivation in children and adults. Countermeasures to improve the sleep of shift workers, especially daytime sleep after the night shift, are needed. Practical methods need to be developed to phase shift circadian rhythms to align with daytime sleep. Factors in need of study include: work and sleep schedule combinations, light exposure during night shifts (intensity, timing, duration, wavelength), and daylight exposure following completion of the night shift.
- The effects on sleep physiology and daytime functions of relevant environmental variables (in isolation and combination) need to be investigated, especially in vulnerable populations such as children, adolescents, the elderly, the socioeconomically disadvantaged, and shift workers. Factors to study include sleeping alone versus sleeping with one or more other persons in the bed (including children), sleep position, sleep surface, personal risk, and environmental stimuli such as noise, vibration, light, temperature, and humidity.

# SLEEP, SEX DIFFERENCES, AND WOMEN'S HEALTH

## BACKGROUND

Women, from adolescence to postmenopause are underrepresented in studies of sleep and its disorders. Although sleep complaints are twice as prevalent in women, 75 percent of sleep research has been conducted in men. More sleep studies in the past 5 years have included women, but small sample sizes prohibit meaningful sex comparisons. Thus, sex differences in sleep and sleep disorder characteristics, in responses to sleep deprivation, and in sleep-related physiology remain unappreciated. Furthermore, findings from studies based primarily in men are often considered to be representative of "normal" even when it is recognized that there are important sleep-related physiological differences in women, including timing of nocturnal growth hormone secretion and differential time course of delta activity across the night.

Sexual dimorphism in the central nervous system has been well documented but the functional implications of sex differences in the neurotransmitter and peptide systems that modulate sleep and wake are unknown. There is a need to study sex differences in sleep and homeostatic regulation across species to more fully understand the role that sleep plays in normal development, maturation, adaptation, aging, and disease propensity. Sex hormones influence sleep and circadian rhythms, and sleep affects neuroendocrine functioning, in particular the episodic secretion of gonadotropin hormones. There are potentially different effects of endogenous sex hormone cycling on neuronal groups involved in regulating behavioral

states and circadian rhythms. It is important to understand how sex-related differences in sleep and its regulation influence the risk for and mechanisms of sleep disorders and other diseases.

Evidence from animal studies supports the presence of sex-related differences throughout the lifespan in susceptibility to disease in general and to sleep disorders in particular. As classic examples of sexual dimorphism, both the long-term neurobehavioral consequences of sleep-associated intermittent hypoxia, as occurs in Sleep-Disordered Breathing (SDB), and the consequences induced by early life maternal separation stress exposures, are reduced in female animals when compared to male littermates. The mechanistic roles of sex-related hormones and their receptors and signaling pathways in mediating the emerging sex-dependent differences in susceptibility to specific neural insults are only now beginning to be explored, and the new insights achieved should have major implications for the development of novel therapeutic interventions.

Physiologic changes in neuroendocrine hormones, body temperature, mood, and emotional state during puberty, the menstrual cycle, pregnancy, and menopause have profound effects on sleep quality, daytime functioning, and well-being in adolescent girls and adult women. It generally has been assumed that sleep prior to puberty is similar in girls and boys, and that sex differences first emerge during this developmental transition. The validity of



this assumption, however, and the extent of sex differences in sleep and sleep disorders in children and adolescents are not known. There have been no cross-sectional or longitudinal studies of subjective and objective measures of sleep coupled with measures of neuroendocrine functioning during and after puberty. Despite the propensity for mood disorders to emerge during adolescence and the greater prevalence in girls compared to boys, little is known about how changes in sleep, sex hormones, and sleep deprivation affect mood and emotional problems in this age group.

Although being female is a risk factor for insomnia, and insomnia is a risk factor for depression, little is known about how changes in sex hormones during the menstrual cycle impact sleep physiology and mood in adolescent girls and women. In fact, most of what is known about sex hormones and sleep is derived from studies of exogenous hormones in adult rodents and humans. Little is known about endogenous sex hormones, changes in sleep physiology, and the development of dysphoric mood and dysmenorrhea during the menstrual cycle. There have been only a few sleep laboratory studies in small samples of adult women during all phases of the menstrual cycle. Findings show wide individual variation, with no consistent relationships between menstrual phase and changes in sleep physiology.

There are considerable methodological challenges in studying sleep across phases of the menstrual cycle. Without normative data based on ovulating and nonovulating women, however, neither the researcher nor the clinician have reference points to aid in the interpretation of menstrual cycle effects on sleep or its disorders. Although not all women of childbearing age experience premenstrual symptoms and secondary insomnia, insomnia and related symptoms may occur associated with onset of menses. Insomnia related to menses may be related to a fall in endogenous progesterone or a differential

sensitivity to endogenous hormone fluctuations, but these hypotheses require further testing. Potential health consequences or disease risk that are engendered by this repetitive "incident" insomnia that can occur every month for 40 years of a woman's life are not known. However, menstrual cycle symptoms and premenstrual dysphoria correlate with excessive daytime sleepiness. Women with significant dysmenorrhea may be at higher risk for developing insomnia and depression.

Hormonal changes and physical discomfort are common during pregnancy, and both can affect sleep. Although nearly all pregnant women will experience disturbed sleep by the third trimester, there have been only two longitudinal sleep studies of subjective and objective sleep measures during pregnancy. There have been no reports of intervention studies to improve sleep quality during pregnancy. Some have assumed that disturbed sleep is a "natural" consequence of pregnancy, labor, delivery, and postpartum that resolves over time, since few women seek assistance to improve sleep. Research has not shown a relationship between sleep quality and quantity and any perinatal adverse outcome, length of labor, or type of delivery. More studies are needed, however, to clarify the extent to which sleep-related problems during pregnancy may have adverse fetal, perinatal, or infant-related consequences.

Very little is known about the effects of late stage pregnancy sleep disturbances on labor and delivery, emotional distress, or postpartum depression. However, nighttime labor and a history of sleep disruption in late stage pregnancy are related to a higher incidence of postpartum "blues." Certain sleep disorders, such as Restless Legs Syndrome (RLS), Periodic Limb Movement Disorder (PLMS), SDB, or insomnia, may emerge during pregnancy, and the extent to which these disorders resolve or place women at higher risk for sleep disorders later in life is not clear. Pregnancy induces changes in the



upper airway and in functional residual capacity that predispose women to snoring, SDB, and reduced oxygen stores. Pregnant women who snore may be at risk for pre-eclampsia and/or SDB. The number of pregnant women with SDB may be substantial, but the prevalence has not been defined in either uncomplicated or complicated pregnancy. Women with pre-eclampsia and excessive weight gain during pregnancy are at greater risk for the development of SDB and pregnancy-induced hypertension, which have been associated with adverse perinatal outcomes, but few polysomnographic studies have been done in these women.

Many women during the menopausal transition (perimenopause, menopause, postmenopause) complain of sleep disturbances that are attributed to vasomotor symptoms (e.g., hot flashes and night sweats) rather than to menopausal status. Estimates of self-reported menopausal-related insomnia range from 33 to 51 percent, but the actual prevalence of sleep disturbances in midlife women, particularly as a function of race, ethnicity, and body size is not well defined. Although there have been only a few sleep studies with both subjective and objective measures, a majority of midlife women with self-reported poor sleep quality report high psychological distress without objective evidence of poor sleep efficiency. Whether these women are physiologically hyperaroused (e.g., increased hypothalamic-pituitary-adrenal axis or sympathetic activity) without significant impact on standard indices of laboratory sleep remains to be clarified.

Data on changes in sleep physiology in women during the menopausal transition are sparse and no longitudinal sleep studies have been conducted. Compared to placebo, short-term hormone replacement therapy (HRT) has shown beneficial effects on improving subjective and objective sleep quality in women with menopausal symptoms, but not all studies show the same effects. Menopause may be a significant

risk factor for SDB. It has been suggested that menopause-induced sex hormone deficiency might explain the increased prevalence of SDB in post-menopausal women and that women on HRT might be at lower risk. Given concerns about disease risk, such as related to thromboembolic events, cardiovascular disease, and breast cancer) associated with HRT for the treatment of menopausal symptoms, fewer women in the future may receive HRT. Hence, more women may experience menopause-related insomnia or HRT withdrawal symptoms that could exacerbate insomnia. Alternative and established therapies for insomnia need to be systematically evaluated in women during and after menopause.

In addition to perimenopausal and menopausal effects on sleep in women, surveys show that more than 80 percent of working women report fatigue and exhaustion, and half of them obtain inadequate sleep. Women shift workers with altered sleep and circadian rhythms are at increased risk for menstrual irregularities, infertility, miscarriage, and low birth weight infants. Women remain the main caregivers for children and elderly family members. These responsibilities may add a significant stress burden and increased vulnerability for sleep disturbances with negative impacts on health and quality of life. In addition, significant life events, such as spontaneous abortions, stillbirth, or death of a child or spouse, have been associated with development of post-traumatic symptoms, including sleep disturbances. Women who consume alcohol as a method of coping with work, family, and social demands are at increased risk for alcohol-induced sleep disturbances.

## PROGRESS IN THE LAST 5 YEARS

### *Sleep and the Menstrual Cycle/ Premenstrual Syndrome*

- Sleep architecture is unaffected by menstrual cycle phase. Body temperature

is elevated and circadian rhythm amplitude is reduced during sleep, however, in the high progesterone phase (luteal) of the menstrual cycle, but the underlying mechanism is not known. Compared to men, women have a blunted drop in body temperature and an earlier nadir of the circadian body temperature rhythm.

- Women on oral contraceptives have reduced slow wave sleep and REM latency. Body temperature throughout the menstrual cycle is similar to that of normal cycling women in the luteal phase.
- Dysmenorrhea is associated with significantly disturbed sleep quality prior to menses. Compared to control women, women with dysmenorrhea had altered sex hormones, body temperature, and sleep throughout the menstrual cycle.

### *Sleep in Pregnancy and Postpartum*

- Longitudinal studies indicate that age, combined with anemia, is related to first trimester fatigue and that reduced sleep time is related to fatigue during the third trimester. Both reduced sleep time and anemia are related to fatigue postpartum. Significant changes in sleep are evident in the first trimester of pregnancy, with increased total sleep time coupled with more awakenings, but postpartum sleep efficiency is lower than in prepregnancy. Slow wave sleep percentage is reduced throughout pregnancy compared to prepregnancy and postpartum. One study found that REM sleep was reduced during pregnancy, but was reduced in another longitudinal study, most notably during the third trimester.
- RLS occurs in about 20 percent of pregnant women and may be associated with reduced levels of folate.
- Thirty percent of pregnant women begin snoring for the first time during the second trimester.

- Pre-eclamptic women show evidence of SDB associated with increased blood pressure. Pregnant women who snore have a twofold greater incidence of hypertension, pre-eclampsia, and fetal growth restriction compared to nonsnorers.
- Self-reported sleep quality, derived from sleep diaries, shows considerable sleep disturbances in the early postpartum period. Sleep efficiency improves during the first year postpartum, but it is unclear whether sleep quantity and quality return to pre-pregnancy levels.
- There is a relationship between sleep and mood during pregnancy, and through the first 3 to 4 months postpartum. Increased disturbances in self-reported sleep and decreased reported total sleep time are associated with depressed mood postpartum.

### *Sleep and Menopausal Transition*

- Longitudinal studies of midlife women showed increased self-reported insomnia, night sweats, and hot flashes across the menopausal transition from late perimenopause to postmenopause. Self-reported sleep disturbance in middle-aged women also has been associated with worse mood, higher blood pressure, higher waist/hip ratios, and chronic dissatisfaction with sleep.
- The prevalence of self-reported insomnia is 17 percent in a community-based cohort of racially mixed perimenopausal menstruating women. Reduced estradiol, increased hot flashes, and psychosocial factors are all associated with poor sleep quality after controlling for current sleep medication use.
- Sleep quality, as measured by polysomnography (PSG), does not appear to be different in peri- or postmenopausal women compared to premenopausal women. Also, there do not appear to be any differences in PSG sleep quality in women who use HRT versus those



who do not. These observations imply that sleep disturbances in midlife women are not a "normal" part of the menopausal transition.

- HRT (estrogen preparations) is effective in reducing menopausal symptoms and self-reported sleep disturbances (insomnia and daytime sleepiness), and in increasing REM sleep and the amount of slow-wave sleep in the first third of the night. In one randomized trial, comparing two different forms of progesterone in combination with estrogen therapy, PSG sleep efficiency improved, with reduced wake after sleep onset in the group receiving micronized progesterone.
- The prevalence of SDB in postmenopausal women on HRT is significantly lower than in postmenopausal women not on HRT, indicating that menopause may be a significant risk factor for SDB in women, and HRT may reduce that risk. The hypothesis that healthy postmenopausal women not on HRT have more SDB compared to women on HRT has also been confirmed in a large population-based study.

## RESEARCH RECOMMENDATIONS

- *Establish how sex-related differences in sleep and its regulation influence the mechanisms and risks of developing disease and sleep disorders. Studies of sex differences in sleep and homeostatic regulation across species are needed to more fully understand the role that sleep plays in normal development, maturation, adaptation, aging, and disease propensity. Animal models of sleep disorders need to be developed that incorporate careful delineation of sex-related differences in susceptibility to development of these disorders and their consequences. Studies of the specific cellular and molecular mechanisms underlying sex differences in sleep disorders throughout the lifespan should be pursued.*
- *Conduct longitudinal studies of sleep during pregnancy and through the postpartum period that include both subjective and objective sleep indicators and include baseline measurements. Fuller description of the extent of sleep disorders developing during pregnancy and postpartum is needed so that novel and existing therapies can be instituted to reduce health risks to the mother and the fetus. The relationship between extent of disturbed sleep during the late stages of pregnancy and delivery and the development of postpartum depression warrants study as a basis for designing novel interventions. Effects of sleep disturbance postpartum on maternal-infant interactions also require further study.*
- Determine the extent to which the prevalence of insomnia and sleep disorders increases during the menopausal transition, identify factors that predict which premenopausal women are at high risk for developing insomnia, and evaluate alternative and traditional therapies for improving sleep in menopausal women.
- Obtain normative sleep data on girls before, during, and after puberty, as well as on women of childbearing age, to assess changes associated with different phases of the menstrual cycle, changes in endogenous sex hormones, and in response to exogenous hormones.
- Determine the extent to which adolescent girls and young women with significant dysmenorrhea are at risk for insomnia and depression.
- Study how sleep disturbance in pregnancy affects fetal development and health as well as the maturation of fetal physiology related to sleep, and the extent to which fetal effects may be associated with long-term pediatric consequences.



# RACIAL AND ETHNIC DISPARITIES

## BACKGROUND

Racial and ethnic minorities have significant health disparities compared to the rest of the population. To achieve the objectives of the “Healthy People 2010” initiative, there is a need for more consistent and reliable racial and ethnic data. Such data are needed to develop and implement effective prevention, intervention, treatment programs, policies, and services. For sleep disorders and for health status in general, efforts to eliminate disparities in health outcomes need to address not only social and environmental factors, such as education and access to health care, but also possible biological or genetic differences, including gene-environment interactions.

Many clinical conditions appear to contribute to racial and ethnic disparities in health outcomes. A few account for most of these disparities, including smoking-related diseases, hypertension, HIV, diabetes and trauma. The leading cause of death in African Americans and Hispanic Americans is heart disease. Sleep disorders, particularly Sleep-Disordered Breathing (SDB), may contribute to the increased prevalence and severity of heart disease, and may also contribute to these disparities through other mechanisms not yet clarified.

## PROGRESS IN THE LAST 5 YEARS

- Since release of the original Sleep Disorders Research Plan in 1996, studies across ethnically diverse populations have identified

significant differences in the prevalence of SDB in African Americans and have suggested distinct pathophysiological mechanisms. Among young African Americans, the likelihood of having SDB is twice that in young Caucasians. Frequent snoring is more common among African American and Hispanic women and Hispanic men compared to non-Hispanic Caucasians, independent of other factors including obesity.

- SDB appears to be in part genetic, with increased prevalence not only in African Americans but also Asians and Hispanics compared to Caucasians. African Americans appear to have a different maxillo-mandibular structure than Caucasians, which may contribute to increased risk for SDB. African Americans with SDB develop symptoms at a younger age than Caucasians but appear less likely to be diagnosed and treated in a timely manner. This delay may at least in part be due to reduced access to care. Additional studies are also needed to explore the extent to which ethnic disparities in other diseases, such as stroke and diabetes, are related to a sleep problem such as SDB.
- The adverse impact of low socioeconomic status (SES) on health status may in part be mediated by decrements in sleep duration and quality. Low SES is frequently associated with diminished opportunity for sufficient sleep or environmental conditions compromising sleep quality. Hispanic children have less Stage 3 and 4 sleep and more Stage 2 sleep than their Caucasian

counterparts, suggesting that there may also be racial/ethnic differences in sleep quality.

- Sleep loss has been shown to be associated with decreased glucose tolerance, elevated evening cortisol levels, and increased sympathetic activity. Sleep loss may thus contribute to increased risk for chronic conditions such as obesity, diabetes, and hypertension, all of which have increased prevalence in underserved, underrepresented minorities. Racial and ethnic disparities related to obesity may also contribute to disparities in health outcomes related to SDB. Obesity is more common in African Americans and Mexican Americans than in Caucasians.
  - African Americans are at increased risk for cardiovascular disease, diabetes, infections, certain cancers and alcoholism. Recent studies suggest that alcoholics of African American descent may have more profound sleep abnormalities and abnormal immune function than Caucasian alcoholics and healthy individuals. Disordered sleep and sleep loss may disrupt the maintenance of internal physiological mechanisms. Therefore, investigating the interrelationships between alcoholism, sleep loss and ethnicity and irregularities in hormonal, autonomic nervous, and immune systems may yield new insights regarding mechanisms for the increased mortality rate among African American alcoholics.
  - Blood pressure normally drops (dips) by about 10 percent during the night. African Americans, however, tend to be "nondippers" compared to Caucasians, independent of weight, gender and SDB. Studies in elderly African Americans and Caucasians suggest that for many older African Americans with hypertension, blood pressure does not fall the expected amount at night, and that this nondipping is associated with more severe SDB. Non
- dippers with high systolic blood pressure (SBP) during the day or high SBP or diastolic blood pressure (DBP) during the night were more likely to have more severe SDB. African Americans who are non dippers may therefore benefit from screening for SDB.
- Studies have also identified an increased prevalence of SDB in African American children compared to Caucasian children. African American children are also 50 percent less likely to have had their tonsils and adenoids removed (T&A) and more likely to have residual disease if a T&A has been performed. In children with sickle cell disease, there is not only a higher risk of SDB, but also higher prevalence and associated morbidity due to vaso-occlusive crises.
  - Racial and ethnic disparities also appear to exist in the prevalence of other sleep disorders. Non-Caucasian adults report an insomnia rate of 12.9 percent compared to only 6.6 percent for Caucasians. Genetic studies have shown a higher degree of genetic polymorphisms and lower linkage disequilibrium in some populations, especially African Americans. Narcolepsy studies conducted in African Americans have resulted in identification of specific HLA alleles that are involved in mediating HLA class II susceptibility to narcolepsy (e.g., HLA-DQB1\*0602).
  - The relationship between health-related quality of life (HRQOL) and SDB has been examined in elderly African Americans screened for snoring and daytime sleepiness who completed a sleep recording, a comprehensive sleep questionnaire (Quality of Well-Being Scale, QWB), and the Medical Outcomes Study Core Measures of HRQOL. Those with moderate to severe SDB had significantly lower Physical Component outcomes summary scores than those with no SDB. Mild but not more severe SDB is independently



related to both general physical functioning and general mental health functioning. The QWB scores of this SDB sample were similar to those found in patients with depression and chronic obstructive pulmonary disease, suggesting that sleep disturbances may impact daily living and health as much as other medical conditions.

- African Americans appear to have fewer chronic sleep complaints than Caucasians. The largest differences are in waking during the night, with African Americans having a prevalence of wakefulness during sleep of only about 60 percent that in Caucasians. The prevalence of insomnia for African Americans is also lower (19.8 percent versus 23.6 percent). African American women have a higher incidence of insomnia than African American men, perhaps related in part to higher risk for chronic persisting symptoms. Caucasian males and females do not differ in incidence. Depressed mood is associated with insomnia in both racial groups. Continued presence of fair or poor health and physical mobility difficulties are associated with incident insomnia in Caucasians, but not among African Americans. The latter, however, show an association between incident insomnia and incident development of perceived fair or poor health. African Americans aged 75 years or more are less likely than Caucasian or Hispanic Americans to attribute sleep problems, as well as heart disease and arthritis, to being part of the normal aging process (about 32 percent versus 46 percent and 43 percent, respectively).
- Interviews and polysomnography (PSG) have been conducted on Hmong people to collect data on sleep disorders and especially SDB in this ethnic group at high risk for Sudden Unexpected Nocturnal Death Syndrome. Hmong subjects appear to have a high prevalence of SDB.

## RESEARCH RECOMMENDATIONS

- *Conduct studies to identify the neurophysiological, neuroanatomical, genetic, and gene-environmental interactions contributing to racial and ethnic disparities in prevalence and severity of individual sleep disorders.*
- *Develop strategies to reach underrepresented minorities in public health education programs designed to maintain health and prevent development and progression of sleep-related conditions.*
- Determine the extent to which higher prevalence of SDB, and lower rates of diagnosis and treatment, contributes to the higher prevalence of learning problems and academic underachievement in African American children.
- Determine the best public health approaches among underserved, underrepresented populations for increasing access to and knowledge of sleep medicine resources.
- Determine the bidirectional link between parameters of sleep, sympathetic nervous system activity, and cellular immunity in African Americans with alcohol dependence.
- Determine the extent to which racial and ethnic disparities in health outcomes related to sleep disorders may contribute to differential responses to treatment or to differences in adherence to treatment recommendations.
- Determine whether ethnic differences in alcohol-induced sleep disturbances contribute to the sympathetic nervous system and immunological effects of alcohol.
- Develop effective strategies to include racial and ethnic minorities in overall efforts to recruit increased numbers of biomedical investigators to sleep-related research, and in sleep-related curriculum development for health care professionals.



# SLEEP AND AGING

## BACKGROUND

Aging is associated with changes in sleep amount, sleep quality, and specific sleep pathologies and disorders. For instance, increased age is associated with increased prevalence of insomnia complaints, daytime sleepiness, Sleep-Disordered Breathing (SDB), Restless Legs Syndrome (RLS), and Periodic Limb Movement Disorder (PLMD) (see Section V). Insomnia alone affects about one third of the older population in the United States. Nocturnal sleep difficulties can result in excessive daytime sleepiness, attention and memory problems, depressed mood, and lowered quality of life. Evidence also suggests that SDB has been associated with dementia and cognitive deficits in the elderly.

Other factors associated with aging, including medical and psychiatric disorders, changes in environment, and psychosocial stressors, such as bereavement, can also be independent contributors to sleep problems. Sleep disturbances can also lead to changes in physiological systems, especially production of appropriate hormone levels and proper metabolic functioning. In addition, the circadian regulation of sleep-wake rhythms is altered with age, such that older adults sleep at an earlier phase of their circadian cycle (see Section I). These changes are seen in the sleep of the healthy elderly, unrelated to complaints about disturbed sleep, but are magnified in those with medical and neuropsychiatric disorders (see Section V). Disrupted sleep-wake patterns are also a major source of stress among caregivers of patients with

dementia, whether in the home or in institutions. Treatments for sleep problems in the elderly can also be associated with morbidity including, for example, the association between hypnotic use and falls or hip fractures.

Recent neuroscience findings regarding sleep regulation have largely focused on young, healthy organisms, and have not explored how age modifies these regulatory mechanisms, or whether such age-related changes can be modified. In humans, there is little consensus regarding which sleep changes are normative developmental changes, and which changes are pathological. This has direct implications for identifying when an intervention is advisable. Given the potential for greater risk of adverse effects in the elderly, there is also a need to develop a broader range of efficacious, safe treatments for all sleep disorders. This issue is particularly salient for individuals with significant medical or neuropsychiatric comorbidity.

## PROGRESS IN THE LAST 5 YEARS

- Epidemiologic studies have identified consistent risk factors for late-life insomnia, and have examined the course of this disorder (see Section V). In addition, the epidemiology of SDB in older adults has been well described (see Section V). SDB has also been identified as a risk factor for adverse cardiovascular outcomes in the elderly, including hypertension and coronary heart disease.

- Excessive daytime sleepiness, a possible marker for SDB, has been found to be associated with diagnosis of incident dementia and incident cognitive decline 3 years later, after adjusting for age and other factors. In contrast, insomnia is not associated with either incident cognitive decline or dementia.
- The period of endogenous circadian rhythms in healthy older persons does not differ from that of healthy young adults. However, older individuals have greater difficulty sleeping at specific circadian phases, which may account for some of the increased sleep complaints seen in aging.
- Behavioral and psychological interventions have been found to be efficacious and durable treatments for older adults with insomnia. On the other hand, behavioral and environmental interventions have shown limited efficacy among institutionalized individuals with dementia.
- Evidence supporting the efficacy of melatonin for treating insomnia in the elderly is equivocal. Low doses of melatonin that raise blood levels to the normal young adult nighttime range significantly improve sleep quality in individuals suffering from age-related insomnia in some studies, but not in others.
- Studies have shown the important sleep regulatory functions of a hypothalamic circuit involving the ventrolateral preoptic nucleus (VLPO). No differences in numbers of VLPO neurons are noted with increasing age, nor are there any differences in levels of adenosine A1 receptor mRNA. Age, however, may affect adenosine receptor function rather than number. While the suprachiasmatic nucleus (SCN) appears to function normally with aging, aging may impair the function of both entrainment (afferent) systems and target (efferent) systems downstream from the SCN.

## RESEARCH RECOMMENDATIONS

- *Investigate the neurobiological mechanisms of age effects on sleep, particularly those related to homeostatic and circadian mechanisms. Circadian studies should investigate the neurobiological causes and consequences of age-related changes in circadian rhythm parameters other than period (e.g., amplitude, waveform), which may be directly related to changes in SCN output or efferent pathways and downstream effector systems. Both basic science and human studies are needed. Genetic, neuroanatomic, neurophysiologic, and neurochemical approaches may be useful in such studies. Conversely, studies investigating the potential effects of sleep, circadian regulation, and sleep disorders on the aging process and the diseases associated with late age are also a high priority.*
- *Test the efficacy and effectiveness of sleep disorder treatments among individuals with a broader range of medical comorbidities, e.g., individuals with “usual” aging. These studies should include conditions such as insomnia and SDB, and populations such as nursing home residents.*
- *Develop a range of novel, safe, and efficacious treatments for sleep disorders in the elderly. These may include the development of new behavioral, pharmacologic, hormonal, behavioral, and physical/environmental (e.g., light) treatments for conditions such as insomnia, sleep-wake disruptions in dementia, and SDB. Long-term trials investigating the efficacy and adverse effects of pharmacologic and behavioral/psychological treatments for insomnia are needed in older patients with both primary and secondary forms of insomnia. The use of techniques such as pharmacogenomics*

should be employed to identify which treatments are likely to be most efficacious in specific patients or populations (see Section I).

- Better define the boundaries of normal and abnormal age-related sleep changes, as well as guidelines for intervention. Examples include defining normative age-related changes in sleep, and thresholds for when SDB or periodic limb movements during sleep require intervention.
- Better define the prevalence of specific sleep disorders in aging. Such studies should employ clinical diagnostic criteria for sleep disorders as well as polysomnographic monitoring. The relationships between sleep disorders and cognitive decline in aging also need investigation.
- Investigate the relationship between daytime and nighttime care procedures and sleep quality and circadian function in the institutionalized elderly. These studies should also investigate modifications of care procedures designed to minimize adverse effects on sleep.



# SLEEP AND SAFETY

## BACKGROUND

Demands on human wakefulness and alertness through increased requirements for shift work, oncall and prolonged work hours, and increased use of time for waking activities, have resulted in more people being awake more of the time. Paralleling these increased demands has been a growing appreciation of the risks posed by fatigue. In this context, fatigue is defined as a reduced capacity for cognitive performance due to time-on-task, inadequate sleep, adverse circadian timing, or the interaction of these factors. Fatigue can adversely affect public health and safety, due, for example, to oil spills, truck, bus and automobile crashes, railroad and commuter train disasters, aviation accidents, power plant mishaps, and medical errors.

The National Highway Traffic Safety Administration (NHTSA) estimates that 100,000 to 150,000 motor vehicle crashes each year and 4 percent of all fatal crashes are caused by drowsy driving. Drowsy driving crashes have a fatality rate and injury severity level similar to alcohol-related crashes. Risk factors for drowsy driving crashes include: late night/early morning driving, people with untreated excessive sleepiness, people who sleep 6 or fewer hours per day, young adult males (ages 16 to 24), commercial truck drivers, and night shift workers.

Recent reports from the National Academy of Sciences, Institute of Medicine, concluded that as many as 100,000 patient deaths per

year may be due to medical errors. Based on surveys of medical residents and other information, it is widely believed that substantial numbers of these adverse events result from fatigue due to prolonged work hours and inadequate sleep among doctors and nurses.

These problems of sleepiness and fatigue, and the contributions of inadequate sleep and night work, to human error and accidents have high costs in both lives lost and economic impact. Options, therefore, for mitigating sleepiness and fatigue need to be explored. The Department of Transportation (DOT) is investing significant resources to better understand and manage fatigue in transportation systems. For example, recent research supported by the Federal Motor Carrier Safety Administration suggests that both work schedules and sleep disorders are primary contributors to fatigue and sleepiness among truck drivers. Long and irregular work schedules that require operators to juggle work demands with family and social demands lead to reduced or disrupted sleep and, therefore, to fatigue.

Excessive fatigue and its risks are largely preventable when the causes are identified and mitigated. For example, establishing cost-effective techniques for identifying and treating transportation workers (such as commercial truck drivers) who have Sleep-Disordered Breathing (SDB) could lessen the likelihood of fatigue-related accidents. Preventing cumulative sleep debt by providing adequate recovery sleep opportunities

for workers could reduce the risks of fatigue-related performance failures and catastrophic outcomes in many industries. Moving school start times to a later hour for adolescents could reduce the likelihood of drowsy-driving automobile crashes and injuries in school activities in this at-risk group. Finding ways to prevent fatigue-related medical errors by physicians and nurses could save thousands of patient lives each year, and improve the learning and safety of the doctors and nurses.

Although ensuring public and personal safety through adequate sleep is a broad issue of interest to many Federal, State, and private entities, the National Institutes of Health have a unique role in ensuring that scientifically sound evidence is acquired on the basic biomedical and health-related factors mediating sleep need, behavioral alertness, and risk.

#### PROGRESS IN THE LAST 5 YEARS

- Scientific evidence increasingly demonstrates that fatigue is a significant causal and contributing factor to adverse events including motor vehicle and other fatigue-related accidents. However, there is no general consensus that these data are definitive and compelling.
- Field and simulator studies in safety-sensitive occupations (e.g., medical and surgical residents, truck drivers, airline pilots) have demonstrated that performance in real-world tasks degrades under conditions of partial sleep loss and night work. Such studies highlight that the biology of neurobehavioral deficits from sleep loss and fatigue is not dependent on one's profession, motivation, or compensation.
- Experiments have demonstrated that chronic reductions in sleep duration by healthy adults result in cumulative deficits

in basic neurobehavioral functions, including vigilance performance, cognitive speed and accuracy, short-term memory, and executive functions. Such data are vital to establishing reliable, evidence-based recommendations for sleep need.

- Research has identified some technologies that can detect fatigue and drowsiness before they result in a serious performance error. Some of these technologies include biobehavioral and physiological assessments, but few have undergone rigorous double-blind validation in controlled experiments.
- Mathematical models of the regulation of sleep have been extended to predict waking performance capability based on sleep history, circadian phase estimates, and additional behavioral and biological variables. There is considerable belief that such models can be used to precisely identify schedules that minimize fatigue.
- Recognition that fatigue-related errors and accidents are inherent in 24/7 operations has led to fatigue management using countermeasures that are preventive (e.g., education about the biological basis of fatigue) and operational (e.g., naps in the workplace). These fatigue management interventions have only recently been developed, however, and have not yet been widely studied to determine the extent to which they will be effective.
- Work-related sleep loss and fatigue in medical professionals, particularly during training, has until recently received little attention. There have been relatively few controlled studies that have examined the impact of sleep loss and fatigue in the medical setting, and many published studies are methodologically flawed. The consequences related to sleep loss and shift work among physicians and nurses include effects on performance of professional duties, learning and memory,



personal health and family consequences, and safety and liability. While the issue of work hours for physicians and nurses is currently being debated nationally, there remains a need for research to elucidate the effects of education and training of physicians and nurses in sleep and fatigue management.

## RESEARCH RECOMMENDATIONS

- *Identify the effects of varying amounts of time for sleep, rest, and recovery (e.g., days off) on biological and behavioral resilience to fatigue-inducing work schedules. One of the most contentious but least well-understood features of fatigue and its consequences for safety concerns the role of recovery days off work. There are very limited data on the chronic (over weeks and months) effects of inadequate recovery opportunities outside the circadian cycle. There is a need to establish time-constants for fatigue buildup as a function of different recovery opportunities. Another need is to identify ways to scientifically design and evaluate work schedules that prevent the accumulation of excessive fatigue by allowing restorative sleep at reasonable intervals.*
- *Establish the validity and reliability of innovative biobehavioral technologies and monitoring techniques that can detect drowsiness, fatigue and sleep propensity in medical and other workplaces. As devices predicated on detecting changes in the biology of wakefulness, these technologies have great potential. To be used effectively as either diagnostic devices or safety devices, however, they should meet rigorous standards for determining whether what is being measured is related to the neurobehavioral deficits induced by sleepiness and fatigue.*
- Establish the biological benefits for brain function, performance, and safety of nap sleep interventions (number of naps, their durations and circadian timing) as a sleep loss countermeasure and fatigue management strategy. Increasingly, 24/7 industries permit opportunities for naps in the workplace (e.g., sleeper berths on trucks, bunks on airplanes, sleeping areas on trains, on-call rooms for residents). There is a need for laboratory, simulator and field experiments on nap sleep physiology and waking neurobehavioral functions to establish the effectiveness of naps used repeatedly as countermeasures. There are many experiments on naps in response to acute sleep loss, but few that determine whether chronic use of naps or split sleep opportunities can effectively maintain waking neurobehavioral functions. If optimal napping strategies can be found to manage sleepiness and its neurobehavioral effects, this can form a basis for evaluating evidenced-based model fatigue management to determine the extent to which fatigue-related neurobehavioral deficits and risks can be reduced.
- Assess the impact of sleep loss and fatigue in the context of medical training, including quality of patient care and patient safety/medical errors, learning and memory in medical education, and the health and well-being of resident physicians (motor vehicle crashes, mental health, etc.). Evaluate the effectiveness of fatigue management educational programs in improving the health and well being of medical trainees, including evaluation of the effectiveness of controlled countermeasures (napping, caffeine, etc.) and evaluation of the impact of "systemic" interventions (work hour restrictions, "night float" etc.) on sleep loss, performance, and medical errors.



- Develop cost-effective methods to screen populations working in safety-sensitive occupations to identify those who are most likely to have sleep disorders that produce excessive sleepiness and performance-impairing risks. A major impediment to removing the risks posed by sleepiness due to unrecognized sleep disorders in the workplace is the lack of valid, simple, cost-effective tools for identifying who is most likely to benefit from a full evaluation. Such tools are needed, however, to enable physicians to certify that people in specific safety-sensitive occupations are fit to perform their jobs safely.
- Develop novel techniques to facilitate worker acclimation to therapeutic interventions and effective use of therapies for sleep disorders (e.g., CPAP adherence). It is not sufficient to diagnose and to treat workers without a treatment compliance program in place.
- Perform studies on the effects of chronic pharmacological enhancement of wakefulness in healthy persons on biology, behavior, and safety. This should extend from unregulated stimulants (e.g., caffeine), to regulated stimulants (e.g., amphetamines), and novel wake-promoting substances. These studies should include identification of long-term effectiveness, side effects, and complications of use and abuse.
- Assess the extent to which educational programs on the biological basis of fatigue, and mitigation of the performance deficits produced by it, are: (1) effective in facilitating improved sleep, alertness, and the use of fatigue countermeasures, and (2) result in reduced risks of adverse events due to sleep loss and circadian biology.
- Determine the extent to which mathematical models of waking performance capability (relative to dynamic interactions of sleep and circadian biology) can be used to precisely identify and develop work-rest schedules that minimize fatigue. Although efforts have been underway to identify the strengths and weaknesses of such computational models, more research is needed to ensure they accurately reflect the underlying biology of circadian rhythms and homeostatic sleep need as they pertain to work-rest schedules.

# SLEEP IN MEDICAL CONDITIONS

## BACKGROUND

Individuals with a variety of common medical illnesses—including adult and juvenile arthritis, asthma, cancer, cardiopulmonary diseases, chronic fatigue syndrome (CFS), diabetes, end-stage renal disease (ESRD), fibromyalgia (FM), human immunodeficiency virus (HIV), irritable bowel syndrome (IBS), obesity, and temporomandibular joint disorders (TMJD)—frequently experience sleep disturbances. It is recognized that medical illnesses can adversely affect sleep quality, and that pain, infection, and inflammation can induce symptoms of excessive daytime sleepiness and fatigue. It is less clear, however, how sleep quality affects disease progression and morbidity. In addition, patients with these medical illnesses may also have a primary sleep disorder (see Section V) that further contributes to significant morbidity. The role of sleep disturbances and sleep disorders in the morbidity of most chronic conditions is understudied in children and adults and, as a result, is poorly understood. Similarly, how sleep disturbances affect responses and adherence to medical therapy for the primary illness and the best ways to manage disturbed sleep in most chronic conditions is understudied. The relationship between sleep processes and the development, progression, and management of chronic diseases, therefore, requires further study.

Insomnia associated with abnormal sleep architecture is most evident in disorders characterized by known structural pathology,

e.g., arthritis, cancer, heart failure, and ESRD. In chronic pain-related conditions without known structural pathology (e.g., FM, CFS, IBS), the most striking observation in these “unexplained disorders,” is a self-report of poor and nonrestorative sleep that is often out of proportion to modest changes in objective measures of sleep. This discrepancy between subjective and objective sleep indicators has been studied extensively in FM and is most evident when patients are selected on the basis of appropriate case definition, compared to women of similar age, and screened for psychiatric disorders, particularly depression. Insomnia in these chronic conditions is known to exacerbate symptoms of pain, fatigue, and daytime sleepiness, negatively impact work performance, social and family relationships, quality of life, and increase use of health care services. Controversy still exists, however, regarding the clinical significance and diagnostic value of abnormal sleep physiology in these unexplained disorders.

Sleep is considered restorative and important for illness recovery. It remains unknown, however, whether sleep actually facilitates recovery processes. Clinicians advise patients to “get plenty of sleep” during an acute febrile illness or following surgery or trauma, but sleep is often fragmented and disrupted. These sleep disturbances are considered “incident” or “transient” forms of insomnia that are treated readily with hypnotic medications and often resolve with recovery. However, mutually exacerbating effects of

disturbed sleep and primary illness may be a significant barrier to full recovery. The role of acute illness-related insomnia in the development and pathogenesis of chronic conditions both in children and adults is understudied and perhaps underestimated. In addition, the impact of acute care environments in exacerbating sleep disruption and further limiting successful implementation of medical or behavioral regimens is understudied.

### PROGRESS IN THE LAST 5 YEARS

- Asthma and other pulmonary diseases commonly exacerbate during sleep, but the mechanisms involved are poorly understood.
- There is an association between daytime sleepiness and cardiovascular disease-related morbidity and mortality (e.g., hypertension, myocardial infarction, and congestive heart failure).
- Severity of diabetes is directly associated with severity of disturbed sleep, and partial sleep deprivation of healthy adults increases insulin resistance.
- Patients with ESRD have disrupted nocturnal sleep with excessive daytime sleepiness and the timing of dialysis treatment affects mortality. ESRD patients on dialysis have among the highest incidence of both SDB and periodic leg movements (PLMs) in sleep, and PLMs are a significant predictor of survival and mortality in this population.
- Sleep disturbance and fatigue are highly prevalent and disabling symptoms in a majority of individuals infected with HIV. Recent findings suggest that symptoms of sleep disturbance and fatigue are independently associated with survival among

people with HIV infection. However, sleep disturbances in children and adults with HIV remains understudied, underdiagnosed, and, therefore, undertreated.

- “Unexplained disorders” are more prevalent in females than in males, but the biologic basis of this sex difference is poorly understood. Failure to identify a structural basis for these disorders has led some researchers and clinicians to embrace sociocultural explanations that can bias research and care.
- Altered timing and reduced nocturnal concentrations of sleep-dependent hormones (e.g., growth hormone, prolactin, melatonin) have been described in a number of chronic conditions and are possibly linked with altered sleep physiology and reduced sleep continuity.
- Lack of altered circadian rhythms observed in FM patients coupled with lower concentrations of sleep-dependent hormones (growth hormone and prolactin) in other studies, underscores the possibility of dysfunctional homeostatic sleep regulation as a basis for symptoms of poor sleep and fatigue.
- Pain is a major factor associated with disrupted sleep in many chronic conditions. Experimental studies in healthy young men and in animals show reduced responsiveness to noxious stimuli during sleep, but the mechanisms involved in sleep-related pain modulation are unknown.
- Neuroimaging studies have identified areas of the thalamus and basal ganglia that may be hypofunctional in women with FM and hence may contribute to abnormal sleep physiology.



## RESEARCH RECOMMENDATIONS

- *As the United States' population ages, the number of people living with chronic medical illnesses will increase dramatically in the next two decades. It will be important to identify chronically ill populations at highest risk for sleep disturbances, determine the factors most associated with disturbed sleep, and the best ways to improve such sleep disturbances. There is also a need to understand how sleep disturbances affect adherence to treatments for chronic disease and ways that improving sleep may improve treatment outcomes.*
- *Study the bidirectional relationship between sleep processes and disease development, progression, and morbidity. Determine identifiable, measurable characteristics of sleep quality that could serve as potential indicators of primary disease diagnosis, progression, and severity. Such markers might indicate how sleep regulation and timing are reciprocally coupled to disease pathophysiology.*
- *Epidemiological and clinical research is needed in children and adults to elucidate the benefits of sleep, the risks associated with insufficient sleep during an acute illness, and the extent of unresolved acute illness-related insomnia. The beneficial outcomes associated with improved sleep during illness using behavioral, pharmacological, and environmental approaches need to be explored.*
- Conduct interdisciplinary basic science studies of the effects of pain and inflammation on sleep physiology both in animals and in humans.
- Conduct experimental challenge studies using sleep delay or partial sleep deprivation to assess the extent of homeostatic sleep regulation dysfunction in chronic illnesses.
- Study sleep, neuroendocrine and autonomic functioning in newly diagnosed patients with FM compared to patients with CFS and with primary insomnia. Studies of children, adolescents, and young women should be particularly informative.
- In patients with chronic illness, determine the effectiveness of self-management strategies (e.g., cognitive-behavioral and sleep hygiene) designed for treating primary insomnia, in relieving symptoms and improving clinical outcomes.

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## SECTION V SLEEP DISORDERS

- Immunomodulation, Neuroendocrinology, and Sleep
- Sleep-Disordered Breathing
- Insomnia
- Narcolepsy and Other Hypersomnias
- Restless Legs Syndrome/Periodic Limb Movement Disorder
- Sleep in Other Neurological Disorders
- Parasomnias
- Sleep in Psychiatric, Alcohol, and Substance Use Disorders

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# IMMUNOMODULATION, NEUROENDOCRINOLOGY, AND SLEEP

## BACKGROUND

Both the neuroendocrine output arm and the immune stimulus arm of brain-immune communications affect sleep. Relevant immune factors include the broad family of immune molecules termed cytokines that include interleukins (IL), chemokines, and other immune products that allow immune cells to communicate. Cytokines are pleiotropic, both affecting and originating from many other cells and organs than simply those of the immune system, and are key communicator molecules that affect many aspects of nervous system and neuroendocrine system function. Resultant sleep alterations induced by cytokines probably affect the course of and susceptibility to a variety of diseases including infectious, inflammatory/autoimmune, and endocrine. Reciprocal interactions between neuroendocrine and immune factors and sleep include the following:

- Immune molecules alter sleep architecture.
- Sleep deprivation alters neuroendocrine and immune responses.
- Immune system activation and neuroendocrine responses alter sleep.
- Sleep quality probably affects the course of and susceptibility to infectious disease.

During infection, patterns of cytokines produced depend on a combination of host responses and specific pathogens to which

the host is exposed. Many cytokines affect sleep, each in different ways (e.g., IL-1, -2, -15, -18, tumor necrosis factor (TNF), interferon). Different combinations of cytokines expressed during infection may have different overall effects on sleep.

Genetic factors that determine sleep patterns interact with environmental factors to contribute to final effects on disease outcome. Genetic host factors, in interaction with environmental factors, influence the set point of neuroendocrine stress response and cytokine production patterns that interact with cytokine patterns produced in response to different pathogens/antigens.

Control of complex phenotypes such as sleep is likely to have the same characteristics as other complex phenotypes, including behavior or complex illnesses such as inflammation/arthritis. Thus, it is likely that many genes, each with small effect (polygenic/multigenic), regulate different aspects of sleep. Inheritance of sleep phenotypes could therefore be additive, as in other complex phenotypes, and hence depend not on single genes but on inherited regions of DNA. Finally, such complex phenotypes often exhibit large environmental variance. Therefore, an important area of study will be to address and dissect gene-environment interactions and to systematically assess the effect of environmental factors on genetic factors in sleep phenotypes and disease outcome. Potential environmental variables that could be examined in the context of defined

genetic backgrounds impacting on sleep include: (1) relative effects of different neuroendocrine and neural stress response pathways; (2) effects, pathways and mechanisms of different pathogen and cytokine exposures; and (3) early developmental factors (maternal-infant interactions).

### PROGRESS IN THE LAST 5 YEARS

- Progress has been made in identifying individual and interfacing effects of different cytokines on sleep architecture and identifying interactions between the individual components of the hormonal stress response system (including CRH and cortisol) and the neuronal stress response system (including sympathetic nervous system responses).
- Progress has included genetic linkage and segregation analysis of linkage regions to identify molecules that affect infectious, cytokine, and sleep interactions. In addition, knock-out animal models and inbred strains have been used to elucidate the role of individual immune and endocrine molecules in sleep.
- Short-term sleep deprivation is associated with complex altered immune responses, but the influence on disease outcome is unclear. There is some evidence that sleep loss and chronic sleep restriction may be associated, in addition to cytokines, with other inflammatory markers (e.g., C-reactive protein) that could impact the development and severity of cardiovascular disease as well as daytime sleepiness and fatigue in sleep disorders.

### RESEARCH RECOMMENDATIONS

- *Identify the effects of interactions between the neuroendocrine and immune systems on sleep phenotype and disease outcome in defined genetic models. These studies should identify the molecular and cellular mechanisms and neuroanatomical pathways of these interactions and their effects on sleep architecture, sleep responses to cytokines, and infectious disease outcome.*
- *Further define the role of sleep, sleep deprivation, and chronic sleep restriction on host defense. Human studies are needed to determine the extent to which sleep disturbance and sleep deprivation are related to markers of nonspecific inflammatory responses (e.g., leukocytes, cytokines, C-reactive protein). Studies are needed in transgenic or knock-out animals, including linkage and segregation studies, to identify the functional significance to infection resistance and susceptibility of candidate genes in linkage regions or of newly discovered cytokines, candidate neurohormones, or other molecules.*
- *Study the biology of the relationships among cytokines, neuroendocrine function, and sleep, including studies of the relationships of the neuroendocrine stress response and cytokine induction of sleep in animal models and human studies. Analysis of gene-environment interactions and of sleep responses to infectious agents in genetically manipulated animal models is relevant to the question of how sleep alters disease susceptibility and outcome. Specific pharmacological agents (e.g., specific cytokine or neuroendocrine antagonists/agonists) will be useful to assess the effects of specific neurotransmitters/neurohormones/interleukins/cytokines on sleep phenotypes.*



- Conduct genetic studies to identify neuroendocrine and immune genes relevant to sleep phenotypes. Approaches to identify potential candidate genes of interest could include animal studies utilizing candidate gene knock-out and transgenic animals, expression microarrays, and linkage and segregation studies including congenics studies. Studies in humans and animals could include sequencing of candidate genes and phenotype characterization of subjects with candidate gene mutations or of transgenic or knock-out animal models.
- Conduct animal and human studies to integrate circadian biology and homeostatic sleep regulation with cytokine biology. This approach could include both *in vitro* and *in vivo* studies.

# SLEEP-DISORDERED BREATHING

## **Adult**

### **BACKGROUND**

Sleep-Disordered Breathing (SDB) describes a group of disorders characterized by abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep. Obstructive sleep apnea (OSA), the most common such disorder, is characterized by the repetitive collapse or partial collapse of the pharyngeal airway during sleep and the need to arouse to resume ventilation. Sleep is thus disrupted, yielding waking somnolence and diminished neurocognitive performance. The recurrent sleep arousal in association with intermittent hypoxia and hypercapnia has been implicated in the occurrence of adverse cardiovascular outcomes. In addition, there is evolving evidence that SDB may contribute to insulin resistance and other components of the metabolic syndrome. Despite considerable progress, most patients remain undiagnosed, and the principal therapeutic approach—continuous positive airway pressure (CPAP)—remains somewhat cumbersome and therefore is not associated with optimal compliance rates.

SDB is exacerbated by alcohol intake. In addition, current understanding of the neurobiologic mechanisms responsible for the sleep-induced changes in upper airway motor control that lead to pharyngeal

collapse is incomplete. The reversibility, with therapy, of apnea-induced hypertension and other presumed adverse cardiovascular outcomes is largely untested. The explanations for reduced prevalence of SDB in women compared to men, and why women present for therapy even less often than the prevalence numbers would suggest, remain unclear. It is unclear to what extent SDB in the elderly represents the same disorder as is encountered in younger populations and thus deserves similar therapy.

Cheyne-Stokes respiration, another type of SDB, is characterized by a crescendo—decrescendo pattern of respiration and is commonly seen during sleep in patients with congestive heart failure. The presence of this respiratory pattern appears to be an important risk factor for the progression of heart failure. More data are needed, however, to clarify the mechanisms leading to Cheyne-Stokes respiration, the impact of this abnormal ventilatory pattern on cardiac function, and the effect of treatment on survival.

### **PROGRESS IN THE LAST 5 YEARS**

- Reversibility with CPAP therapy of many of the neurocognitive and quality of life detriments associated with SDB is suggested by relatively small, short-term trials.
- The strength of the association between SDB and systemic hypertension in animal

models and large, prospective epidemiologic studies is becoming more evident. Cross-sectional data also suggest an important association between SDB and stroke, myocardial infarction, and congestive heart failure.

- Studies addressing control of the pharyngeal musculature, both awake and asleep, have demonstrated the ability of these muscles to respond to local stimuli awake, thereby compensating for deficient anatomy/collapsibility and maintaining airway patency. The loss of these reflex mechanisms during sleep is an important factor in the pathogenesis of SDB.
- Increasing evidence suggests a familial/genetic influence on predisposition to SDB, independent of obesity. This genetic influence may be mediated differently in different racial and ethnic groups (see Section IV).
- The efficacy of oral appliances (primarily mandibular advancing devices) in patients with mild to moderate SDB and of upper airway surgical procedures over a range of apnea severity has been evaluated. However, more information is needed before the respective roles of these approaches can be clearly delineated.
- Data suggest that positive airway pressure therapy can, over several weeks, eliminate Cheyne-Stokes respiration in heart failure patients and lead to improved transplant-free survival.

## RESEARCH RECOMMENDATIONS

- *Investigate and advance understanding of the genetic, neurobiologic, and physiologic mechanisms that are pathophysiologically important in the development, potentiation, and maintenance of SDB. Studies are also needed to assess the interaction between cardiac dysfunction and the ventilatory control system in the pathogenesis of Cheyne-Stokes respiration.*
- *Conduct adequately powered clinical trials, particularly in high-risk populations, to assess the impact of therapy of SDB on functional status, psychiatric disorders, neurocognitive function, and other disease processes (hypertension, cardiovascular disease, metabolic syndromes, etc.). Studies assessing the impact of successful therapy of Cheyne-Stokes respiration on cardiac dysfunction, quality of life and survival are also needed.*
- Design new and improved modalities for the treatment of SDB, including pharmacologic, surgical, oral appliance, behavioral, muscle stimulation, positive airway pressure (including CPAP compliance), and other novel approaches. Methods to individualize these therapies to the different SDB phenotypes are also needed, for example, improved upper airway imaging approaches to define site of collapse.
- Develop novel noninvasive screening/diagnostic methodologies that are less expensive and more widely applicable than standard full polysomnography. This might include biomarkers as indicators of the presence of SDB, its severity, or its consequences.



## Pediatric

### BACKGROUND

Snoring, a symptom of increased upper airway resistance during sleep, is extremely frequent in children, and affects 18 to 20 percent of infants, 7 to 13 percent of children ages 2 to 8, and 3 to 5 percent of older children. The pathophysiology of SDB in children is still poorly understood. Indeed, while adenotonsillar hypertrophy is certainly a major contributor to SDB, other factors, such as obesity, craniofacial genetics, and neural control mechanisms of upper airway patency, also appear to be important. It is clear that the spectrum of disease and morbidity associated with SDB in children is expanding. As such, degrees of severity that might have once been considered clinically irrelevant are now recognized as having substantial neurobehavioral and cardiovascular consequences.

### PROGRESS IN THE LAST 5 YEARS

- In recent years, it has become apparent that SDB and snoring are not as innocuous as previously thought. Indeed, epidemiological and pre-post treatment analyses have identified substantial morbidities that primarily affect cardiovascular and neurobehavioral systems. These morbidities include pulmonary hypertension, arterial hypertension, nocturnal enuresis, reduced somatic growth, learning and cognitive deficits, and behavioral problems that resemble attention deficit-hyperactivity disorder.
- Failure to diagnose and treat in a timely manner may prevent some of these morbid complications from being completely reversible, leading to long-lasting residual consequences. However, the point of transition between what constitutes pathology and what is normal remains to be defined.

- Improved phenotypic characterization of SDB and its manifestations are facilitating extrapolation of basic science concepts to the pediatric population. Extended population studies are needed that incorporate gene databases and also include multi-organ multifunctional categorization of SDB-related morbidity and response to therapy. Such studies would allow for development of databases permitting correlation analyses of large datasets and exploration of multiple hypotheses generated from basic research findings.
- As part of such phenotype delineation, development of more sensitive and accurate tools for definition of disease and morbidity is needed. Currently available tools are insensitive to morbidity and do not provide accurate determinations of the degree of homeostatic disturbance that occurs during sleep and during daytime.

### RESEARCH RECOMMENDATIONS

- *Develop longitudinal normative data on sleep and cardiorespiratory patterning in children.*
- *Identify genes and gene products that may contribute to the pathophysiology of SDB. Conducting these studies in pediatric populations may have distinct advantages, because they are less likely to be "contaminated" by age-associated comorbidities present in adult populations. Some of the "at-risk genes" may be operative only during infancy and childhood, e.g., genes responsible for immune modulation and lymphatic tissue growth, while other genes, such as those underlying obesity or craniofacial phenotype, appear applicable to both children and adults. In addition, environmental factors or gene-gene interactions during childhood may modify the phenotypic expression of the disease during adulthood.*

- There is considerable variation in the magnitude of SDB associated morbidities in both children and adults, and this heterogeneity in end-organ injury could be due to differences in gene and protein responses to the various components of SDB. Identification of such genes/proteins, their functions and interactions, and their posttranslational modifications, using currently available genomic and proteomic approaches, may provide opportunities for development of promising targets for intervention and for reducing morbidity.
- Longitudinal studies are needed to assess the long-term impact of SDB during childhood and into adulthood. Attention to outcomes among obese children is particularly important considering the increasing prevalence of obesity in children.
- One of the major limitations in diagnosing SDB is the need for relatively complex, burdensome, and costly procedures, such as overnight polysomnography. Research efforts need to focus on development of reliable screening methods that are applicable to children and to provide accurate indicators of either the presence/absence of the disease or the occurrence of end-organ morbidity. Such developments include, for example, application of new biomedical sensor technologies, multi-modality imaging strategies, development of disease-related artificial intelligence networks, and systematic exploration of gene and protein markers in biological fluids.
- First-line treatment of pediatric SDB routinely relies on surgical removal of the tonsils and adenoids. However, since this treatment does have measurable morbidity, mortality, and financial cost, novel interventional approaches need to be developed.

# INSOMNIA

## **Adult**

### **BACKGROUND**

Insomnia is defined as difficulty falling asleep, difficulty staying asleep, or short sleep duration, despite having an adequate opportunity for sleep. It is the most common sleep complaint, affecting approximately 30 to 40 percent of the adult population. Even when more stringent criteria are required, such as daytime impairment or marked distress, insomnia disorders have a prevalence of approximately 10 percent. Evidence suggests that insomnia has significant consequences on quality of life, health care utilization, and subsequent psychiatric disorders. Efficacious short-term behavioral and pharmacologic treatments for insomnia are available, and progress has been made in epidemiology and risk-factor identification, identification of adverse outcomes, and in identifying effective treatments.

However, much remains unknown regarding the causes, characterization, consequences, and optimal management of insomnia disorders. For instance, we do not have a consistent phenotype(s) for insomnia disorders that could be applied to human and animal studies. Despite major research advances in the neurobiology of sleep and circadian rhythms (see Section I), the implications of these findings for insomnia have not been carefully investigated. Instead, the pathophysiology of insomnia has been examined from a number of clinically derived theoretical frameworks, with little replication of the findings reported in individual studies.

Effective treatments for insomnia have been developed, but important issues still remain. For instance, the exportability of behavioral treatments to usual care settings and the effectiveness (as opposed to efficacy) of insomnia treatments have yet to be determined. Finally, there is a need to develop novel pharmacologic treatments based on new findings in sleep neurobiology.

### **PROGRESS IN THE LAST 5 YEARS**

- The efficacy and durability of standardized behavioral treatments for insomnia have been demonstrated in a number of well-controlled clinical trials.
- The epidemiology of insomnia in adults has been well described. Consistent risk factors, such as psychological symptoms, medical illness, and female sex, have been identified.
- Independent studies have demonstrated that insomnia is a risk factor for subsequent development of psychiatric disorders and for worse outcomes among individuals with concurrent psychiatric disorders.
- A small but growing body of evidence has demonstrated "hyperarousal" among patients with insomnia, including increased central nervous system activation (indexed by increased high-frequency EEG activity), sympathetic nervous system activation, and hypothalamic-pituitary-adrenal (HPA) axis activation.



## RESEARCH RECOMMENDATIONS

- *Basic and preclinical studies are needed that focus on the neurobiology of insomnia. These should include: (1) the development of animal models of insomnia with specific insomnia phenotypes; (2) the application of neurophysiological, neurochemical, neuroanatomic, and functional neuroimaging approaches to human studies; and (3) genetic, genomic, and proteomic studies.*
- *Pharmacological treatment studies are needed to define the efficacy, safety, abuse liability and role of long-term hypnotic treatment. Priority should be given to studies defining the optimal duration and pattern of administration of traditional hypnotic medications, including investigations of their use in populations with high rates of utilization, such as with psychiatric disorders. Studies are also needed on widely used but poorly documented treatments, such as sedating antidepressants, and on the development and testing of novel pharmacologic agents based on neuroscience findings (e.g., drugs affecting corticotropin release, adenosine, or hypocretin systems).*
- *Insomnia phenotypes need to be characterized and include: (1) development and validation of clinical phenotypes (e.g., define diagnostic criteria), (2) physiological characterization and biomarkers (which may include measures of EEG, HPA axis, sympathetic nervous system, and functional neuroanatomy using neuroimaging techniques), and (3) indices of discriminant validity versus mood and anxiety disorders. Definition of insomnia phenotypes should also address subjective-objective discrepancies in sleep measures, as well as the relationship between insomnia and co-existing sleep, psychiatric, and physical disorders.*
- Further studies of behavioral/psychological treatments are needed. These studies should include: (1) the use of behavioral/psychological treatments in routine care settings (e.g., primary care offices), (2) the development of alternative delivery methods (e.g., simplified treatment regimens, computer or Internet administration), (3) studies in patients with medical or psychiatric comorbidity, and (4) large-scale effectiveness studies. Priority should also be placed on investigating the specific efficacious components of these behavioral treatments.
- More precisely define the potential physical health risks, morbidity, and functional consequences of insomnia, distinct from the morbidity and consequences of associated medical and psychiatric conditions.
- Examine the extent of use, efficacy, and adverse effects associated with alternative treatment approaches, including nutritional supplements, herbal remedies, and non-pharmacological treatments.

## **Pediatric**

### BACKGROUND

Difficulties in initiating and maintaining sleep are extremely common in children. The overall prevalence of sleep onset delay/bedtime resistance has been reported to be in the range of 15 to 25 percent in healthy school-aged children and even higher in adolescents. However, because behaviorally-based sleep problems in children are often defined by caregivers, the range of sleep behaviors that may be considered "normal" or "pathologic" is wide and the definitions highly variable. In addition, population-based normative data on sleep patterns across childhood are lacking, creating further challenges in defining "abnormal" sleep in infants, children, and

adolescents. Therefore, a common nosology for defining sleep disorders in children needs to be developed and evaluated.

### *Insomnia in Special Populations*

Sleep disturbances in pediatric special needs populations are extremely common, and often a source of considerable stress for families. Prevalence of sleep problems in children with severe mental retardation has been estimated to be as high as 80 percent, and to be 50 percent in children with less severe cognitive impairment. The prevalence of sleep problems in children with autism is estimated to be 50 to 70 percent.

Significant problems with initiation and maintenance of sleep, shortened sleep duration, irregular sleeping patterns, and early morning waking have been reported in many neurodevelopmental disorders, including autism and pervasive developmental disorder, Asperger's syndrome, Smith-Magenis syndrome, Angelman's syndrome, tuberous sclerosis, San Filippo syndrome, Rett syndrome, and William syndrome. Other studies have suggested that similar rates of sleep problems also occur in both younger and older blind children, with the most common concerns being difficulty falling asleep, night wakings, and restless sleep.

The types of sleep disorders in these children are not unique to this population, but are more frequent and more severe than in the general population and often reflect the child's developmental level rather than chronological age. Multiple sleep disorders are also likely to occur simultaneously. The incremental impact of disrupted and/or inadequate sleep on cognitive, emotional, social development, and behavior in these already at risk children is potentially profound.

Little is understood, on either a pathophysiologic or behavioral level, about the interaction between sleep disorders and acute and chronic health conditions such as asthma, diabetes, and juvenile rheumatoid arthritis. In chronic pain conditions, these interactions are likely to significantly impact morbidity and quality of life.

### PROGRESS IN THE LAST 5 YEARS

- In addition to risk factors such as social and communication developmental abnormalities and cognitive impairment, a primary arousal dysfunction in children with neurodevelopmental disorders may contribute to sleep problems.
- There may also be a primary disturbance of melatonin production and synchronization in autistic children, and some autistic children seem to respond to treatment with exogenous melatonin. Studies have documented improvements in sleep onset delay, night wakings, early morning waking and total hours of sleep using a small dose (0.3 to 0.5 to 2.5 to 5 mg) of melatonin approximately 1 hour before desired bedtime in up to 80 percent of children with disorders such as cortical blindness, Rett syndrome, autism, tuberous sclerosis, and Asperger's syndrome. However, melatonin is not effective in all developmentally delayed children with sleep problems, and little is known overall about long-term side effects.
- Some studies have examined the role of sleep disturbances in chronic medical conditions of childhood, such as sickle cell disease and asthma, disorders particularly common in high-risk and minority populations. The interaction between sleep and physical and emotional dysfunction in acute and chronic pain conditions such as burns and juvenile rheumatoid arthritis,



has also begun to be explored. Additional factors, such as the impact of hospitalization, family dynamics, underlying disease processes, and concurrent medications are also important in assessing the bidirectional relationship of insomnia and chronic illness in children.

- Clinical psychology and pediatric studies have examined the efficacy of empirical behavioral treatment for sleep problems in small samples. Most of these studies have relied on parental assessment of treatment success. Additional outcomes research to systematically assess efficacy of various treatment modalities for sleep disorders, including behavioral management protocols, is needed to generate recommendations for “best practices.”
- Pharmacologic intervention in conjunction with behavioral techniques has been shown to be effective in some cases. However, little is known overall about the safety and efficacy of pharmacologic interventions for sleep disturbances in children, alone or in combination with behavioral therapy. Medications used to treat insomnia in children include diphenhydramine, chloral hydrate, trazadone, clonidine, and benzodiazepines. Hypnotic medications, however, can result in unpredictable side effects, development of tolerance necessitating increasingly higher doses, paradoxical effects (agitation instead of sedation), and withdrawal effects. Rebound sleep onset delay on discontinuation and morning “hangover” can be significant problems as well. Little is known about the scope and patterns of use of pharmacologic interventions in pediatric sleep disorders, about possible indications, and about potential target populations for short-term use of hypnotics in conjunction with behavioral interventions.

## RESEARCH RECOMMENDATIONS

- *Develop a common definition and document the prevalence and functional impact of pediatric insomnia across the age spectrum in the general population and in high-risk populations, such as special needs children (e.g., neurodevelopmental disorders, sensory deficits) and children with chronic medical conditions (e.g., diabetes, asthma). Normative data should be collected regarding sleep practices and patterns in order to define “abnormal” sleep. Studies should also examine the developmental aspects of insomnia in children—including the role of early sleep patterns and behaviors, parenting practices, temperament, and genetics—as well as risks and protective factors for the persistence of insomnia into adolescence and adulthood.*
- *Develop and evaluate optimal evidence-based treatment strategies and management protocols for pediatric insomnia:*
  - *In otherwise healthy children, using standardized measures for such outcome variables as sleep quality and quantity, sleepiness/alertness, mood, behavior, academic functioning and parental stress.*
  - *In children with special needs, including evidence-based behavioral and pharmacologic treatments for insomnia and circadian rhythm disturbances, and including outcome measure, such as neurocognitive performance measures and assessment of impact on quality of life for children and caregivers.*
- *Examine the interrelationships between insomnia and chronic medical conditions in children, including effects on disease processes, pain management, quality of life, and caregiver well-being.*



# NARCOLEPSY AND OTHER HYPERSOMNIAS

## BACKGROUND

Narcolepsy is a disabling neurological disorder characterized by sleepiness and symptoms of abnormal rapid eye movement (REM) sleep such as sleep paralysis, hypnagogic hallucination, cataplexy and, frequently, disturbed nocturnal sleep. Narcolepsy is most commonly diagnosed using nocturnal polysomnography and the Multiple Sleep Latency Test (MSLT). In this test, sleep latencies and the occurrence of REM sleep are evaluated during 4 to 5 naps, scheduled every 2 hours during the daytime. Narcoleptic patients typically display short mean sleep latency, indicative of daytime sleepiness and more than two REM episodes in the MSLT.

Narcolepsy-cataplexy affects 1 in 2,000 people and is the fourth most common condition treated in sleep disorder clinics. The exact prevalence of essential hypersomnia and narcolepsy without cataplexy, two related disorders characterized by sleepiness and abnormal MSLT results, is unknown. These two disabling disorders are at least of similar frequency as narcolepsy with cataplexy, but few research data are available.

In humans, narcolepsy-cataplexy is genetically complex, human leukocyte antigen (HLA) associated, and environmentally influenced. Fine mapping studies in the HLA class II region indicate a primary role for HLA-DQ. Multiplex families are rare, but relative risk

in first-degree relatives is 20 to 40-fold higher than in the general population for narcolepsy-cataplexy. HLA susceptibility genes play a minor role in overall genetic susceptibility. Human narcolepsy is currently treated symptomatically with dopaminergic amphetamine-like stimulants, gammahydroxybutyrate, and monoaminergic antidepressant therapy. Behavioral and social interventions are also helpful.

The study of narcolepsy is facilitated by the existence of two animal models: canine and murine narcolepsy. A 10-year positional cloning study identified canarc-1 as the hypocretin (orexin) receptor-2 gene (*Hcrtr2*). This was followed by the discovery that preprohypocretin knockout mice also have narcolepsy and by the discovery that human narcolepsy is associated with decreased hypocretin transmission. Hypocretin-1 and 2 (orexin-1 and 2) are excitatory neuropeptides encoded by a single gene selectively expressed in a small subset of lateral hypothalamic neurons. Hypocretin neurons project widely in the central nervous system and have especially dense monoaminergic cell group projections. Two hypocretin receptors (*Hcrtr1* and *Hcrtr2*) with differential neuro-anatomical distribution are currently known.

In humans, narcolepsy cases are not associated with hypocretin ligand or receptor mutations but, rather, with undetectable cerebral spinal fluid (CSF) hypocretin-1 levels.

Only a single hypocretin gene mutation in an unusual patient with a very early onset (age 6 months) disorder and severe symptomatology has been reported to date. In sporadic cases, neuropathological studies indicate a dramatic loss of both hypocretin-1 and hypocretin-2 in the brain and a disappearance of hypocretin-containing cells in the hypothalamus. Together with the observation that hypocretin-1 is potently wake-promoting in vivo, these results demonstrate that narcolepsy-cataplexy is due to a hypocretin deficiency. HLA association in humans suggests the possibility of an autoimmune disorder directed against hypocretin-containing cells in the lateral hypothalamus.

The cause(s) of narcolepsy without cataplexy and of other hypersomnias of central origin (e.g., idiopathic hypersomnia) are currently unknown.

### PROGRESS IN THE LAST 5 YEARS

- Our understanding of narcolepsy-cataplexy has been revolutionized in the last 5 years. The discovery in 1999 that hypocretin gene alterations produce narcolepsy in canines and mice rapidly led to the finding that human narcolepsy is associated with decreased hypocretin transmission.
- Novel pharmaceutical treatments have been developed including modafinil, a wake-promoting compound, and gammahydroxybutyric acid (GHB), a sedative used for treating disturbed nocturnal sleep and cataplexy. These are useful therapeutic treatments but only symptomatically treat the condition.

### RESEARCH RECOMMENDATIONS

- *Conduct basic research on hypocretins in animal models. Even though recent findings have stimulated some basic research studies on hypocretins, the exact role of this system in the regulation of normal sleep and other behaviors is still unknown.*
- *Study the epidemiology and pathophysiology of narcolepsy without cataplexy, essential hypersomnia, and periodic hypersomnia. Our understanding of narcolepsy has been largely limited to cases with cataplexy, and little information is available on these other conditions. With the increased availability of wake-promoting medications, such as modafinil, there is an urgent need to evaluate the prevalence, treatment strategies, and etiologies of these related conditions.*
- The field is ready for direct clinical applications. Measuring CSF hypocretin-1 has been shown to be a reliable diagnostic procedure for narcolepsy-cataplexy in limited case series, and efforts should be made to further validate and distribute this new diagnostic procedure. Furthermore, efforts should be made to design alternate diagnostic procedures based on the knowledge that narcolepsy is caused by hypocretin abnormalities. These may involve (but should not be limited to) measuring hypocretin levels in blood or imaging studies of the hypothalamus.
- Study the effectiveness of replacing hypocretins or hypocretin-producing cells. Since animal models are available to test this hypothesis and design new treatments, studies should be conducted in both animals and humans. Hypocretin peptide supplementation, the development of hypocretin receptor agonists, cell transplantation, and gene therapy are all possible treatments.

- Studies designed to identify the causes of destruction of hypocretin-containing cells in human narcolepsy are needed. Studies are also needed to define the immune connection in narcolepsy and/or to discover why narcolepsy is HLA-associated. In this regard, the study of cases of recent onset (most likely still at the stage of active destruction) may be critical.
- Studies to find other narcolepsy genes, and identify rare cases of narcolepsy without known hypocretin abnormalities, are needed to better understand these pathologies.
- Studies of new medications such as modafinil and gammahydroxybutyric acid (GHB) are needed to determine their mode of action. Efforts to study the mode of action of current narcolepsy treatments could lead to improving current treatments. Additionally, there is a need for studies on the effect of drugs used in other areas of neurology and psychiatry as novel indications in narcolepsy (e.g., stimulants for daytime sleepiness, antidepressants for cataplexy, sedative agents for disturbed nocturnal sleep).
- Since narcolepsy typically starts in childhood or early adolescence, management of these patients is particularly challenging and clinical protocols need to be developed. Studying narcolepsy as closely as possible to its onset, generally during childhood, may also provide unique clues to the cause of the disorder.
- Commonly used therapies in narcolepsy include napping and other behavioral treatments, but data establishing efficacy are sparse. More research in this area is needed.
- Studies in twins indicate that not only genetic background but also environmental factors are involved in the pathophysiology of narcolepsy. Studies are needed to characterize these factors and determine the potential effectiveness of prevention strategies.



# RESTLESS LEGS SYNDROME/PERIODIC LIMB MOVEMENT DISORDER

## BACKGROUND

Restless Legs Syndrome (RLS) is a sensorimotor disorder characterized by periodic irresistible urges to move the legs, usually associated with unpleasant and uncomfortable sensations in the legs. These symptoms occur during wakefulness, but are exacerbated or engendered by rest/inactivity and partially relieved by movement. The diurnal pattern of symptoms likely reflects modulation by the circadian system. RLS is reported to profoundly disturb sleep, yet the extent of nocturnal sleep disturbance and of daytime sleepiness has not been established. Estimates of RLS in various populations range from 2 to 15 percent, but incidence and prevalence have not been precisely defined, particularly as a function of gender and ethnicity. Several reports indicate a higher prevalence of RLS in women than in men, and also in individuals of Northern European ancestry. The etiology and pathogenesis of RLS are thought to involve alterations in efficiency of central dopamine neurotransmission, based largely on the clinical observation that dopaminergic drugs relieve symptoms. The inheritance pattern of RLS suggests an autosomal dominant mode of transmittance, but the genes accounting for this observation are not known. RLS is also associated with iron deficiency, and it is quite common in end-stage renal disease (ESRD) and during pregnancy.

About 85 to 90 percent of patients with RLS also exhibit periodic limb movements (PLMs) during sleep. Unlike RLS, which is diagnosed

on the basis of history and symptoms, periodic limb movement disorder (PLMD) relies upon quantification of repetitive stereotypic leg movements associated with a brief arousal during sleep monitoring. Patients manifesting PLMD have complaints of daytime fatigue and sleepiness or insomnia. As in RLS, PLMD may involve altered central dopamine mechanisms since dopaminergic agents or other drugs that interact with dopamine mechanisms, (e.g., opiates) are equally effective treatments for most patients. The incidence of PLMD, as with RLS, is higher in the elderly. Without better understanding of the etiology, pathogenesis, and neurophysiology of these disorders, treatment strategies are limited and can therefore be unsatisfactory. Both disorders can have profound negative impacts on the quality of life including daytime functioning, work performance, and social and family life.

Controversy exists about the clinical significance of PLMs during sleep in the absence of sensory complaints consistent with RLS. PLMs can occur without associated electroencephalographic (EEG) micro-arousals and in the absence of sleep complaints or of daytime symptoms. If associated with micro-arousals, the frequency of PLMs does not correlate with objective measures of daytime sleepiness or with indices of disrupted sleep. This lack of a correlation may reflect insensitivity in the methods used for scoring EEG micro-arousals and sleep fragmentation. Abnormal limb movements during sleep have been associated with physiological correlates of arousal in autonomic or cortical functioning, suggesting

that PLMs are part of an underlying arousal disorder. It is possible that abnormal limb movements during sleep may be associated with an unidentified neurophysiological alteration in microstructure of the EEG sleep pattern.

#### PROGRESS IN THE LAST 5 YEARS

- Several potential animal models of RLS and PLMD have been developed based upon interruption of normal dopaminergic responsivity.
- Imaging studies suggest reduced central dopamine receptor binding with age, but only small and inconsistent decreases in dopaminergic transmission have been reported in traditional nigrostriatal dopaminergic pathways in patients with RLS. This finding suggests that alterations might exist in extrastriatal dopaminergic pathways.
- RLS and PLMD are more common in children with attention deficit hyperactivity disorder (ADHD) providing an opportunity to address developmental aspects of these disorders and responsivity to dopaminergic interventions.
- Neurophysiological studies in humans suggest that RLS is associated with inefficiencies of spinal cord inhibition that may be brainstem mediated and state dependent.
- RLS shows high familial aggregation. A recent study of genes involved in central dopaminergic transmission and metabolism showed no evidence of involvement in RLS. However, other recent studies have identified a susceptibility locus for RLS on chromosome 12q in a large French-Canadian family, and a polymorphism in a gene involved in catecholamine (monoamine oxidase A) metabolism in women with RLS.

- Central nervous system (CNS) imaging studies have shown reduced iron concentrations in some brain regions. These reductions correlate with RLS severity and low cerebral spinal fluid (CSF) ferritin combined with high serum and CSF transferrin levels.
- The RLS case definition was updated and revised in 2002, thereby providing a basis for the development of specific questionnaires to advance clinical recognition, and to clarify RLS prevalence.
- EEG patterns of cortical activation precede PLMs and indices of autonomic arousal, suggesting that PLMs are associated with an underlying arousal disorder.

#### RESEARCH RECOMMENDATIONS

- *Determine the role of altered central dopaminergic mechanisms, iron metabolism, and other possible mediators in the pathogenesis of RLS and PLMD through animal and human studies. The development, refinement, and validation of animal models for RLS and PLMD are needed. Modern techniques of neuropathology in the evaluation of brains and spinal cords from patients with RLS and PLMD should be used to identify potential abnormalities underlying these disorders.*
- *Identify and further characterize genes involved in RLS and PLMD.*
- Determine the extent of nocturnal sleep disturbance and daytime sleepiness in children and adults with RLS and PLMs.
- Develop and validate questionnaires based on the new RLS case definition, and determine the population-based incidence, prevalence, and morbidity, particularly in children and as a function of gender, race, and ethnic distribution.

- Establish the developmental changes in adults explaining the higher incidence of RLS and PLMD in the elderly.
- Pregnancy and uremia provide reversible models to study the development and remission of RLS and the role of altered iron metabolism. Conduct clinical trials of iron supplementation in RLS patients with low ferritin levels.
- Improve available treatment strategies for RLS and PLMD. Dopamine agonists, opioids, and anticonvulsants are used most frequently, and are effective in reducing RLS symptoms and PLMs, but the necessary large multicenter trials and long term studies have not been conducted. These studies should include assessment of quality of life and assess the sensitivity of existing questionnaires to treatment changes.



# SLEEP IN OTHER NEUROLOGICAL DISORDERS

## BACKGROUND

Sleep disturbances and sleep disorders are commonly associated with neurological diseases, and neurological impairments of sleep reveal much about the brain circuitry involved in sleep regulation. Many neurological disorders are now recognized to cause disruptions of sleep. For example, pathological sleepiness is associated with neurological and neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and progressive supranuclear palsy. Pathological sleepiness is also associated with neuromuscular disorders such as myotonic dystrophy, inflammatory conditions such as encephalitis or multiple sclerosis, and with traumatic or ischemic injury to the brain. In addition, conditions such as REM Sleep Behavior Disorder (RBD) are recognized as precursors of PD. Conversely, Fatal Familial Insomnia (FFI), a prion disorder related to Creutzfeldt-Jakob disease, causes prolonged wakefulness.

Sleep is a powerful modulator of epilepsy, with some epilepsy syndromes occurring exclusively or predominantly during sleep. These include benign childhood epilepsy with centrotemporal spikes, autosomal dominant nocturnal frontal lobe epilepsy, and continuous spike-wave activity during sleep. Sleep deprivation has also been described as a risk factor for epileptic seizures, although alcohol use and work-related stress are confounding factors.

Treatment of sleep disorders that fragment sleep, such as Sleep-Disordered Breathing (SDB), has improved seizure control in case series.

Sleep disorders can also occur as a consequence of treating neurological disorders. For example, pathological sleepiness may occur during treatment of PD and other movement disorders with dopamine-related drugs. In addition, many drugs used to treat neurological disorders can cause excessive sleepiness or wakefulness.

Sleep disorders also interact in complex ways with neurological disorders and are frequent after head trauma, stroke, encephalitis, or in association with neuromuscular disorders. For example, stroke has been shown to be associated with SDB, and SDB likely decreases potential for recovery in stroke patients. Stroke may also produce SDB by interacting with the central regulation of breathing. Similarly, the intermittent hypoxia that accompanies SDB may hasten the neurodegenerative cascade in disorders such as PD and AD.

Neurological disorders provide models for understanding sleep circuitry in the brain. In addition, understanding sleep mechanisms and disorders will be integral to treating these neurological diseases.

## PROGRESS IN THE LAST 5 YEARS

- Studies of patients with Parkinson's disease reveal a range of sleep disorders, including PLMS, RBD, and daytime sleepiness. These disorders are part of the disease spectrum, occur commonly, and suggest an important role for dopaminergic pathways in sleep/wake regulation. Dopamine-like drugs are useful in treating these disorders, and it is recognized that when these drugs stimulate dopamine D2/D3 receptors they can cause "attacks" of excessive sleepiness, potentially resulting in automobile and other accidents.
- An important advance has been the empirical application of wake-promoting drugs to treat sleep disorders in various neurological conditions. The use of wake-promoting compounds in treating fatigue and sleepiness in various neurological disorders such as PD, head trauma, and multiple sclerosis is increasing, but these treatments deserve controlled study.
- Vagus nerve stimulation (VNS), an approved treatment for medically refractory epilepsy, has been shown to cause apneas and shallow breaths (hypopneas) during sleep, but these effects are ameliorated by reducing VNS stimulus frequency. In addition, VNS has been shown to reduce daytime sleepiness in epilepsy patients. These findings emphasize the interconnections of the vagus nerve with brainstem networks that regulate respiration and alertness.
- Advances in all of these disorders depend upon understanding the brain circuitry involved in sleep regulation. Elucidation of important components of the wake and sleep promoting circuitry in the hypothalamus and the brainstem has occurred over the last 5 years. Drug development is currently under way to take advantage of this new information in order to treat pathological wakefulness or sleepiness and to cause sedation, when necessary, with fewer side effects.

## RESEARCH RECOMMENDATIONS

- *Evaluate the prevalence and impact of sleep disorders and disturbances in neurological conditions, such as neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease), movement disorders, post head trauma, encephalitis, stroke, and epilepsy. These studies should evaluate whether sleep disorders predispose to specific neurological conditions, whether neurological conditions can produce sleep disorders, and whether sleep disorders impair recovery from selected neurological disorders. Studies of sleep in animal models of neurological disorders should also be conducted.*
- *Study natural models of locally disrupting sleep circuits (tumors, trauma, multiple sclerosis plaques, infarcts, neurodegenerative conditions, paraneoplastic syndrome, etc.). Studies should be performed that combine imaging techniques or neuropathology with sleep/sleep disorders analyses.*
- Study the impact of pharmacological and nonpharmacological neurological treatments on sleepiness and sleep (for example, in epilepsy, multiple sclerosis, PD).
- Study sleep and sleepiness in inflammatory states (encephalitis, infarcts, multiple sclerosis, autoimmune disorders, etc.).
- Determine if sleep disruption due to sleep disorders or sleep deprivation lowers the threshold for epileptic seizures, and explore the mechanisms responsible for this effect.
- Perform controlled studies to determine if treatment of sleep disorders improves seizure control.

# PARASOMNIAS

## **Adult**

### **BACKGROUND**

Parasomnias are undesirable behavioral, autonomic nervous system, or experiential phenomena during sleep, usually characterized by increased motor and/or autonomic activity, sleep-wake state dissociation, altered responsiveness to the environment, and retrograde amnesia. Specific parasomnias arise during sleep-wake transitions, non rapid eye movement (NREM) sleep, or rapid eye movement (REM) sleep, and are often classified as either primary parasomnias—disorders of sleep states per se—or secondary parasomnias—disorders of other organ systems that arise during sleep. Virtually all primary parasomnias represent an admixture or simultaneous occurrence of elements of both wakefulness and sleep.

The most common primary parasomnias are disorders of arousal and REM sleep disorders. Disorders of arousal include confusional arousals, sleepwalking, and sleep terrors, all characterized by partial arousals from NREM sleep. REM sleep parasomnias include nightmares, characterized by frightening dreams and autonomic arousal, and REM behavior disorder (RBD), characterized by absence of the muscle atonia normally present during REM sleep. The behaviors associated with primary parasomnias may lead to injury of the patient or bed partner and may have forensic implications.

Numerous secondary parasomnias, such as sleep-related expiratory groaning or esophageal spasm, have been reported. Typically, descriptions have been provided for single cases or very small case series, making scientific evaluation difficult. These phenomena are likely to be quite common, but they are often unrecognized, misdiagnosed, or ignored in clinical practice. The pathophysiology, morbidity, and functional consequences of secondary parasomnias are unknown.

### **PROGRESS IN THE LAST 5 YEARS**

- Epidemiological studies have shown that disorders of arousal occur in about 10 percent of adults, and are usually not associated with significant underlying psychiatric or psychological disorders. These disorders are very common in children but may begin during adulthood or persist into adulthood. There is growing evidence for genetic determinants of these disorders of arousal.
- Exogenous triggers, including sleep deprivation, alcohol ingestion, and medications have been identified for disorders of arousal in predisposed individuals.
- The basic sleep architecture and sleep macrostructure is normal in patients with disorders of arousal. "Hypersynchronous delta" activity has not been substantiated as an EEG marker for disorders of arousal.



However, quantitative EEG analyses in patients with disorders of arousal indicate instability of slow-wave sleep, particularly during the first slow-wave sleep period of the night. This instability may be related to cyclic alternating patterns.

- RBD, which may have a prevalence rate as high as 0.5 percent, has two striking demographic features: 90 percent of affected individuals are male, and most cases begin after 50 years of age. Clonazepam is efficacious in 90 percent of cases.
- At least 50 percent of RBD cases are related to recognized neurologic conditions, particularly narcolepsy and the synucleinopathies (Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies). RBD may precede the appearance of other features of the underlying disease by as many as 10 years. RBD may also be iatrogenic, due primarily to medications such as selective serotonin reuptake inhibitors (SSRIs).
- Functional neuroimaging studies have documented reduced dopamine transporters and decreased dopaminergic innervation of the basal ganglia in patients with RBD.
- Other conditions characterized by sleep-wake state dissociations have been identified, and may be related to RBD. These include parasomnia overlap syndrome, agrypnia excitata, and status dissociatus.

## RESEARCH RECOMMENDATIONS

- *Better define the pathophysiology and neuroanatomic substrates of primary parasomnias in human and animal studies. In humans, specific methods could include functional neuroimaging and quantitative*

*EEG studies (e.g., investigations of cyclic alternating pattern in disorders of arousal). Psychophysiological and neurophysiological studies could help to identify factors that trigger and maintain chronic parasomnias. A brain bank for RBD and other parasomnias would be particularly useful to study their structural and genetic origins. The identification of genetic and environmental factors involved in the etiology and pathogenesis of primary parasomnias may be facilitated by the presence of distinctive phenotypes for these disorders. Animal models for parasomnias could involve techniques such as genetic manipulations, brain lesions and brain stimulation, sleep deprivation, and other behavioral provocation techniques, and pharmacologic manipulations. In particular, animal studies investigating motor control and sleep could help to further elucidate the pathophysiology of parasomnias.*

- *Investigate pharmacologic and behavioral treatments for primary and secondary parasomnias in clinical trials. Intervention studies could help to identify both common and distinctive mechanisms of action for different treatments in different disorders.*
- *Further define the relationships between the different parasomnias, and between parasomnias and other neurological disorders. For instance, the relationship between disorders of arousal and nocturnal seizures, particularly nocturnal frontal lobe epilepsy, should be further investigated. Relationships between RBD, neuropsychiatric disorders, and specific medications need to be better defined.*
- *Obtain clinical and physiological information regarding secondary parasomnias as a first step toward identifying the prevalence, etiology, and efficacious treatment of these disorders.*

## **Pediatric**

### **BACKGROUND**

Although parasomnias are among the most common clinical sleep disturbances experienced in childhood, little is known about the underlying neurophysiologic mechanisms and neurotransmitter systems responsible for their development and relative importance.

Although a genetic predisposition exists for many parasomnias, the specific genes involved have yet to be identified, and little is known about the interaction between genetic phenotype, other aspects of sleep physiology, such as arousal threshold, and sleep inertia and environmental factors. Treatment strategies involving pharmacologic and behavioral interventions have been developed, but most outcome studies have included very small sample sizes and short-term follow up.

### **PROGRESS IN THE LAST 5 YEARS**

- Several studies have reported an association between partial arousal parasomnias and both migraine headaches and Tourette's syndrome in children, thus raising the possibility that serotonergic pathways may be involved. Case reports of novel treatment strategies for partial arousal parasomnias have suggested that behavioral interventions, such as scheduled awakenings and hypnotherapy, may be effective nonpharmacologic treatment options, but little is known about the underlying mechanism responsible for the clinical response.

### **RESEARCH RECOMMENDATIONS**

- *Examine interactions between the developing central nervous system, genetics, other aspects of sleep physiology, and environmental factors in determining phenotypic expression of partial arousal parasomnias in childhood.*
- *Examine the role of various neurotransmitter systems in the neurophysiology of partial arousal parasomnias.*
- Evaluate the efficacy of, and underlying mechanisms for, pharmacologic and nonpharmacologic treatment strategies for partial arousal parasomnias and rhythmic movement disorders in childhood.

# SLEEP IN PSYCHIATRIC, ALCOHOL, AND SUBSTANCE USE DISORDERS

## BACKGROUND

Virtually all psychiatric and substance use disorders are associated with sleep disruption. Epidemiological and clinical studies indicate that psychiatric disorders are the most common cause of chronic insomnia. Alcohol dependence leads to complaints of insomnia and sleep disruption that can persist for months into abstinence and recovery. Psychiatric disorders can also be associated with daytime sleepiness, fatigue, abnormal circadian sleep patterns, disturbing dreams, and nightmares. Conversely, evidence increasingly suggests that primary insomnia (without concurrent psychiatric disorder) is a risk factor for later developing psychiatric disorders, particularly depression, anxiety, and substance use disorders

Preliminary studies suggest that sleep disorders such as Sleep-Disordered Breathing (SDB), Restless Legs Syndrome (RLS), and sleep-related movement disorders may be unrecognized or under recognized in children and adults presenting with psychiatric symptoms and psychiatric disorders, and occur with increased prevalence in alcohol-dependent persons. The relationship between sleep and psychiatric disorders is further supported by the observation that sleep deprivation can ameliorate depressive symptoms and exacerbate manic symptoms, and that alcohol-dependent persons show impairment in the homeostatic recovery of sleep following sleep deprivation. Moreover, insomnia and certain types of electroencephalographic (EEG) sleep patterns, such

as reduced rapid eye movement (REM) latency or increased REM sleep, have been associated with poor treatment outcomes in psychiatric disorders, including relapse or recurrence of depression and alcoholism.

Increasing attention has been paid to sleep abnormalities in post traumatic stress disorder (PTSD) and nightmares, both in terms of descriptive studies (e.g., findings regarding REM and NREM dream disturbances, movement disorders), and therapeutic studies (e.g., dream rehearsal therapies). Polysomnographic markers for adult depression, such as decreased latency to REM sleep onset, have not been consistently found in depressed children and adolescents, but other EEG measures (such as inter- and intrahemispheric coherence) have been identified as potential correlates of mood disorders in children. African Americans are particularly vulnerable to the effects of alcohol dependence, and polysomnographic and spectral analytic studies show a striking loss of delta sleep and delta power in this population. Furthermore, studies using structural and functional neuroimaging paradigms have begun to elucidate possible mechanisms linking sleep disturbance and psychiatric illness.

Psychoactive substances have acute and chronic effects on sleep architecture. Several aspects of sleep are compromised in individuals taking these drugs, depending on the drug. Difficulty in initiating and maintaining sleep as well as poor sleep quality are common in patients who take opiates.



In fact, heroin addicts seeking treatment often report sleep disturbances, notably insomnia, as precipitating causes of relapse. A similar dysregulation in the normal cycles of sleep may contribute to severe dependence observed with gammahydroxybutyrate (GHB) where regular users report constant waking and must take more to reinstate sleep. Even patients stabilized on methadone may have SDB, daytime sleepiness, and poorer sleep efficiency. Infants born to substance-abusing mothers have a several times greater risk of Sudden Infant Death Syndrome (SIDS). Chronic cocaine users also have lower sleep efficiency and significant sleep onset delay. By contrast, abstinence from cocaine as well as amphetamines produces hypersomnia. Since some investigators have observed sleep disruption despite long abstinence in chronic cocaine users, the mechanisms underlying sleep architecture and homeostasis and the mechanisms underlying effects of psychoactive drugs may have much in common. Further understanding of these relationships will advance both fields.

Most of the recent research progress has been related to improved understandings of the associations between psychiatric disorders and various sleep symptoms (e.g., insomnia and nightmares), sleep EEG patterns (e.g., delta EEG activity), and sleep disorders (e.g., SDB and movement disorders). Less progress has been made in identifying fundamental pathophysiological mechanisms linking psychiatric disorders and sleep. Despite some promising early leads, for example, sensitive and specific sleep biomarkers of psychiatric disorders have not been validated. Similarly, endogenous circadian rhythm disturbances have not been identified in most patients with depression or other psychiatric disorders.

Based on basic observations that cytokines regulate sleep in animals, increasing attention has focused on the role of cytokines in the regulation of sleep in humans and the contribution of abnormal regulation

of the complex cytokine network to sleep disturbance in alcohol-dependent persons. Despite initial progress in the study of sleep disturbances among children with depression, little is known about the characteristics or consequences of sleep disturbances in most childhood psychiatric disorders. After focusing almost exclusively on the relationships between sleep and depression, psychiatric sleep research has only recently begun to focus attention on other disorders, such as PTSD. The application of sleep and circadian rhythm therapies to psychiatric disorders has also been limited, and their efficacy not consistently demonstrated. Clinical neuroscience studies are only beginning to move beyond the examination of EEG sleep correlates of psychiatric disorders to the investigation of common mechanisms and the consequences of disordered sleep in psychiatric and substance dependent populations. Abnormalities of immune system functioning are coupled, for example, with disordered sleep in alcohol-dependent populations. Finally, insomnia and sleep disturbances are known to be risk factors for psychiatric disorders including alcohol dependence, but long-term followup studies have not yet been done to determine whether intervention can reduce these risks and the progression of these disorders.

## PROGRESS IN THE LAST 5 YEARS

- Insomnia has been identified as a risk factor for the subsequent development of psychiatric disorders, including mood, anxiety, and substance use disorders.
- Insomnia has also been correlated with poor outcomes in depression, schizophrenia, and alcohol dependence.
- Structural and functional neuroimaging studies have begun to identify neuroanatomic correlates of sleep disturbance in depression and schizophrenia, and of therapeutic sleep deprivation in depression. For instance,

slow-wave sleep deficits in schizophrenia are associated with negative symptoms and frontal cortical volume loss. Patients with depression have higher absolute cerebral glucose metabolic rate than healthy subjects, and blunted activation of limbic structures (amygdala, anterior cingulate) during REM sleep compared to wakefulness. Improvement of depression following 1 night of sleep deprivation is associated with decreased relative metabolism in the anterior cingulate cortex.

- Reduced latency to REM sleep has been identified as a familial sleep biomarker for increased risk of developing depression.
- Differences in sleep responses to cholinergic and serotonergic drugs have been identified in patients with depression compared to healthy controls.
- Individuals with PTSD have a high incidence of SDB, motor dyscontrol, and dream disturbances during both NREM and REM sleep.
- The efficacy of dream imagery rehearsal for traumatic nightmares has been demonstrated in early clinical trials.
- Abnormalities of sleep quantity and sleep depth persist for months into recovery from alcohol dependence, and are more profound in African American alcoholics compared to Euro-American alcoholics. The decay of delta sleep in alcoholics is coupled with impairment in the regulation or plasticity of slow-wave sleep.
- Dysregulation of cytokine expression is a biomarker of abnormal sleep in recovering alcohol-dependent persons.
- Sleep disturbances are apparent in individuals taking psychoactive drugs and have been found to persist long after withdrawing from these drugs. For some, sleep disturbance can be so severe as to reverse treatment success and precipitate a relapse to addiction or dependence.

- Drugs can damage brain areas and neural systems involved in sleep maintenance. For example, studies primarily in animals have shown that MDMA (“ecstasy”) causes reduction in serotonin in axons and axon terminals. Cocaine causes severe depletion of dopaminergic neural systems.

## RESEARCH RECOMMENDATIONS

- *Evaluate whether insomnia and hypersomnia are modifiable risk factors for poor outcomes in mood, anxiety, and psychotic disorders, alcoholism, and substance abuse disorders. Three types of studies are needed: (1) Studies to investigate whether insomnia and hypersomnia are modifiable risk factors for the development of new-onset psychiatric disorders; (2) Studies to investigate whether insomnia or specific EEG sleep characteristics are modifiable risk factors for poor outcomes among individuals with existing psychiatric disorders; and (3) Prospective, long-term longitudinal studies to follow the concurrent course of sleep and psychiatric disorders from childhood into adulthood and to elucidate possible mechanisms for the relationship between sleep disturbance and psychiatric disorders. These studies will be aided by the identification of sensitive, specific, and objective markers of insomnia and hypersomnia.*
- *Further evaluate the relationships between stress and sleep in clinical disorders such as PTSD and other forms of acute and chronic stress. Studies are specifically needed to: (1) further characterize the nature of stress-related sleep disturbances (e.g., insomnia, nightmares and other dream disturbances, movement disorders during sleep); (2) examine causal relationships between stress and sleep disturbances; and (3) investigate the efficacy of behavioral and pharmacological interventions for treating stress-related sleep disturbances.*



- Evaluate the neurobiological characteristics and mechanisms of sleep disturbances in primary insomnia, depressive disorders, and anxiety disorders to better define the inter-relationships. Such studies should include approaches such as functional neuroimaging studies and neurochemical studies in living human subjects and in brain tissue.
- Identify relationships between neurobiological mechanisms involved in the development of regulatory aspects of arousal, affect, and sleep in childhood and adolescence, including the role of various neurotransmitter systems. Examine the relationship between critical periods of brain development and sleep-wake cycle regulation, and the impact of sleep disturbances and insufficient sleep in early childhood in modifying the normal evolution of these various regulatory systems. These studies should also assess: (1) potential links between entrainment of circadian rhythms in the first year of life and circadian irregularity during childhood and subsequent vulnerability to psychiatric illness, (2) potential effects of stressful or traumatic events on hyper and hypo arousal mechanisms in children, and (3) development of sleep patterns and maladaptive coping mechanisms.
- Determine the role of cytokines in the homeostatic regulation of sleep in humans and whether abnormalities in the cytokine network lead to disturbances of sleep in psychiatric populations also at risk for infectious or inflammatory disorders. Studies are also needed to determine whether proinflammatory cytokine antagonists can ameliorate sleep disturbance in alcohol populations who show evidence of immune activation.
- Evaluate the efficacy and safety of behavioral and pharmacologic treatments for sleep disturbances in both adults and children with psychiatric disorders. The influence of such treatments on outcome of the coexisting psychiatric disorder should also be examined. Examples include the concurrent treatment of insomnia in individuals with major depression, and the use of dream-imagery rehearsal in individuals with PTSD.
- Assess the efficacy of behavioral and pharmacological interventions targeting sleep in improving the clinical course of alcoholism and risk of relapse.
- Further investigate the neurobiological basis for the beneficial effects of sleep deprivation in mood disorders. Such studies should also be useful generally to address fundamental questions regarding the mechanism of antidepressant treatments. Functional imaging methodologies, including receptor ligand studies, may be particularly relevant.
- Investigate the prevalence and impact of primary sleep disorders (e.g., SDB and sleep-related movement disorders) on psychiatric disorders.
- Investigate sleep effects of medications commonly used to treat psychiatric disturbances in adults, children, and adolescents. Studies should include short and long-term investigations examining beneficial and adverse effects of these medications on subjective measures, sleep architecture, respiration during sleep, and motor control during sleep.
- Investigate the brain mechanisms underlying sleep architecture that are also affected by psychoactive drugs, including temporary acute effects and long-term effects related to chronic drug taking. Knowledge of the neural changes brought on by drug effects should help to better understand which of these neural mechanisms are associated with sleep cycles. Conversely, an improved knowledge base of neural systems involved in sleep can aid in the understanding of the process of drug reward, addiction, and dependence.





## SECTION VI PEDIATRICS

- Sleep and Early Brain Development and Plasticity
- Adolescent Sleep
- Sleep in Medical Disorders
- Neuropsychiatric Disorders in Childhood and Sleep

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# SLEEP AND EARLY BRAIN DEVELOPMENT AND PLASTICITY

## BACKGROUND

Sleep may have important roles in adult brain plasticity related to learning and memory consolidation. Unlike adults, the human fetus and neonate spend a remarkable proportion of their time sleeping, with approximately 80 percent of their day in rapid eye movement (REM) sleep and the remainder in non rapid eye movement (NREM) sleep and wakefulness. By 5 to 6 months of age, human infants spend only 20 to 30 percent of their time in REM sleep, with the remainder of time equally spent in NREM sleep and wakefulness. Reasons for such increased requirements for sleep, particularly REM sleep, in early life are not well understood, but improved understanding of these developmental requirements may provide insight into the functions of sleep throughout life.

The high percentage of time spent in REM sleep during the critical period in human brain growth and maturation in late fetal and early postnatal life may indicate that the neural activity controlled by REM state mechanisms may be developmentally functional and contribute directly to physiological and structural brain maturation. REM sleep may be important in providing early stimulation and activity requirements of the growing brain. Subsequent recognition of activity-dependent development of neural connections *in utero* provides a specific mechanism by which endogenously controlled, correlated, spontaneous neural activity

mediates brain maturation. The resulting hypothesis is that one function of REM sleep is to generate specific patterns of intrinsic activity in neuronal populations whose development is dependent upon activity. The classic example of activity-dependent maturation is the visual system, in which spontaneous neural activity in each retina in the fetus (before visual experience) is necessary for the anatomic segregation of eye-specific synaptic connections in the lateral geniculate nucleus. Research studies in experimental models support the idea that activity-dependent maturation occurs during sleep.

Understanding the roles of sleep in brain maturation and plasticity is of critical importance since perturbations during fetal life or early postnatal life can have major impact on developmental processes and thus on adult phenotype. Suppression of neonatal REM sleep in rats, for example, alters ventilatory pattern, metabolism, and regional brain concentrations of neurotransmitters and their receptors at maturity, suggesting adverse adult consequences on brain rewiring due to disruptions in sleep in early life. Furthermore, early hyperoxic exposures as may occur in mechanically ventilated premature infants, or sleep-associated episodic hypoxemia such as occurring in apnea of prematurity, may result in permanent impairments in cardiovascular and respiratory control. Thus, despite the existence of redundant protective mechanisms and increased



system plasticity at these early stages of development, the fetus and newborn are likely to be extremely susceptible to disruption of the normal homeostatic processes for normal tissue and organ growth and function. Furthermore, although the interactions between sleep processes and early life perturbations are unknown, it is reasonable to assume that these early disruptive events may alter the hierarchical organization of functional gene clusters and lead to both early and late increases in vulnerability to specific disease states.

Those at greatest risk for early disruptions in sleep and sleep-related brain maturation are premature infants in intensive care nurseries. Sleep deprivation in this setting is a major problem, due largely to the absence of a diurnal rhythm of light/dark cycles, and sleep interruption by constant medical and nursing procedures. The functional short-term and long-term implications associated with disruption of the normal sleep cycles at such early stages of development are just beginning to be understood. Premature infants exposed to bright/dim light cycles in the nursery are more likely to sleep longer, begin to feed earlier, and grow better than those under constant bright lights. There has been extensive progress in understanding the functional properties and cellular and molecular mechanisms regulating sleep-wake periodicities and the circadian clock, but little is known about the maturation of such systems, especially considering the huge alterations in sleep-wake schedules that accompany fetal and early postnatal development.

## PROGRESS IN THE LAST 5 YEARS

- Sleep has been shown to enhance the effects of a preceding period of monocular deprivation on visual cortical responses during the peak critical period of the maturation of the visual cortex. These findings demonstrate that sleep and sleep loss modify experience-driven cortical plasticity *in vivo*, and support a crucial role for sleep in early life upon brain development.
- Sleep and sleep loss have been shown to modify the expression of several genes and gene products that appear to be important for synaptic plasticity.
- Studies in neonatal animals indicate that suppression of REM sleep can lead to behavioral, anatomic, and biochemical deficiencies, including respiratory problems, that extend into adulthood. Neonatal active sleep may be a critical factor in the normal development and expression of respiration.
- The functional properties of the supra-chiasmatic nucleus are developing and become functional from mid-to-late gestation in experimental animals, allowing for sleep-wake rhythm entrainment before and at birth.
- National guidelines for the regulation of light intensity in neonatal intensive care units have been established.

## RESEARCH RECOMMENDATIONS

- *Establish the ontogeny of fundamental biological mechanisms mediating the regulation of sleep and waking needs to better understand the normal and abnormal consequences of the development of such systems.*
- *Conduct studies to elucidate the underlying mechanisms of changes in circadian rhythmicity during early postnatal life in full-term and premature animal models and in humans.*
- Conduct studies to assess the effects of prematurity per se and of treatment conditions (e.g., light-darkness cycles) in intensive care nurseries on cognitive function and brain development, and on the physiological maturation of circadian regulation.
- Increase basic understanding of the specific effects of sleep state on neural plasticity and synaptic connectivity in developing mammals.
- Investigate the neurochemical, cellular, and molecular aspects of human sleep ontogeny, including the use of mapping techniques in post mortem human fetal and infant brains.
- Study the short- and long-term consequences of medical conditions associated with disruption of normal pregnancy and/or early postnatal life, (e.g., maternal cigarette smoking, cocaine or opiate addiction, materno-fetal insufficiency, prematurity). These results may yield a better understanding of altered sleep and cardiorespiratory control in early life and may provide insight into regulatory mechanisms ultimately responsible for the occurrence of disorders such as apnea of prematurity, sudden infant death syndrome (SIDS), congenital central hypoventilation syndrome, and developmental neurobehavioral deficits.

# ADOLESCENT SLEEP

## BACKGROUND

Sleep and the unique features of physical, cognitive, and social-emotional development that take place in adolescence must be considered separately and in relationship to sleep in children and in adults. Not only do the biological changes associated with puberty profoundly affect sleep and wakefulness, but many environmental and social factors are also implicated. Several sleep disorders are particularly prevalent (delayed sleep phase syndrome) or emergent (narcolepsy) in adolescence. Furthermore, the public health consequences of inadequate sleep (academic failure, drowsy driving) and the potential for primary and secondary prevention in this age group are important.

## PROGRESS IN THE LAST 5 YEARS

- Studies of normal sleep and sleep patterns in adolescents have identified important issues regarding the basic developmental physiology of sleep and circadian rhythms in adolescence. The role of pubertal/hormonal influences on circadian sleep-wake cycles and melatonin secretion has been recognized, and the effects include development of a relative phase delay (later sleep onset and wake times) in early puberty and the development of a physiologically based decrease in daytime alertness levels in mid-to-late puberty. The genotypic expression in adolescence of delayed circadian phase

preference has also been explored as an important factor determining the timing of sleep/wake cycles.

- Studies of homeostatic regulation of sleep and wakefulness have demonstrated that sleep needs in adolescence do not decline significantly, and optimal sleep amounts remain about 9 hours into late adolescence. However, epidemiological research on "normal" sleep patterns and amounts suggests that adolescents only average 7 to 7.5 hours of sleep per night, resulting in the accumulation of a considerable sleep debt over time. These data suggest that chronic partial sleep deprivation is a serious problem in this age group and that particular subgroups may be at relatively higher risk.
- Environmental and social factors also impact significantly upon delayed sleep onset in adolescents, including. For example, many adolescents have highly irregular sleep/wake patterns from week-day to weekend. Another important factor potentially contributing to insufficient sleep is the early start time of many middle and high schools in the United States.
- Chronic sleep restriction in adolescents leads to significant neurobehavioral consequences related to decline in alertness levels, including negative impact on mood, vigilance, reaction time, attention, memory, behavioral control, and motivation. These



impairments may, in turn, be associated with significant declines in school and work/occupational performance, increased risk-taking behaviors (use of alcohol, illicit drugs, nicotine, caffeine, stimulants), and injuries. Adolescent males, for example, are one of the highest risk groups for motor vehicle crashes associated with falling asleep.

## RESEARCH RECOMMENDATIONS

- *Ascertain the impact of chronic partial sleep deprivation on health outcomes, including susceptibility to infection, metabolic consequences, immune function, and use of potentially harmful alertness-promoting agents, such as caffeine and stimulant medications. Delineate the effects of chronic partial sleep deprivation and sleepiness in adolescents on higher level cognitive or “executive” functions, such as verbal creativity and working memory, on motivation, and on affect regulation. The assessment of health outcomes should also include occupational and sports injuries, and motor vehicle crashes, and should determine scope of the problem, high-risk groups, and interactions with other high-risk behaviors and substances (alcohol, marijuana, etc.).*
- *Define the specific neurophysiologic mechanisms involved in the relationship between sleep and circadian timing and puberty.*
- *Determine the extent, patterns, and psychosocial factors responsible for chronic sleep restriction in adolescence. These studies should include cross-cultural analyses and should also include special and high-risk populations such as adolescents with comorbid psychiatric conditions, mood disorders, attention deficit hyperactivity disorder (ADHD), and chronic illness.*
- *Determine the impact of interventions to address chronic sleep restriction in adolescents, including later school start times and high school education programs about sleep.*
- *Determine the biopsychosocial and genetic factors that result in delayed sleep phase syndrome in adolescents, and assess the safety and efficacy of various treatment modalities, including administration of exogenous melatonin, chronotherapy, and bright light therapy.*

# SLEEP IN MEDICAL DISORDERS

## ***Genetic Diseases and Syndromes Affecting Sleep and Breathing***

### BACKGROUND

A large number of unique genetic disorders have primary or secondary sleep abnormalities. Understanding the pathophysiology of the autonomic nervous system (ANS) dysregulation that occurs in many of these pediatric disorders could improve our understanding of the maturation of the ANS and the abnormalities that occur in common sleep disorders such as Sleep-Disordered Breathing (SDB). Investigating anatomical mechanisms for the upper airway obstruction found in children with craniofacial malformation could shed light on mechanisms for upper airway obstruction in SDB. Understanding how other disorders produce primary insomnia or daytime hypersomnolence may also shed light on novel sleep-regulatory mechanisms.

Studies have demonstrated SDB and symptoms compatible with ANS dysregulation in children with Idiopathic Congenital Central Hypoventilation Syndrome (CCHS), Rett Syndrome (Xq28, MECP2), and Familial Dysautonomia (9q31, IKBKAP). Few sleep studies have been performed, however, in children with craniofacial malformations, chromosomal/genetic abnormalities, or in children with neuromuscular diseases.

Genetic and familial craniofacial syndromes are often subdivided into those with micrognathia, midfacial hypoplasia, and protuberant

tongue disorders. The micrognathia syndromes include Treacher Collins Syndrome, an autosomal dominant syndrome (5q32-33.1, TCOF1), and Pierre Robin Sequence. Infants with these syndromes can experience profound SDB that requires aggressive intervention to prevent physiologic compromise. The midfacial hypoplasia syndromes include Apert Syndrome (10q26, FGFR2), Crouzon Syndrome (10q26, FGFR2), and Pfeiffer Syndrome (8p11.2-p11.1 or 10q26, FGFR1 or 2). These are all autosomal dominant and typically represent a fresh mutation. Children with midfacial hypoplasia often have increasingly severe SDB with advancing age due to maldevelopment and surgical intervention. Another example of midfacial hypoplasia is achondroplasia, an autosomal dominant skeletal dysplasia (4p16.3, FGFR3) in which respiratory compromise is caused by an abnormal rib cage, small foramen magnum, and SDB. Disorders with a protuberant tongue include the mucopolysaccharidoses, (e.g., Hunter Syndrome and Hurler Syndrome) and Down Syndrome (Trisomy 21), all with identified genetic mutations and often with severe SDB requiring early intervention.

Disorders of the neuromuscular system impose a substantial burden at the multi-system level. Many of these children exhibit dysfunction of the respiratory and upper airway musculature that contributes to the development of SDB. For example, 15 to 20 percent of children with Duchenne Muscular Dystrophy will develop sleep disturbances, and this prevalence is even greater among patients with spinal muscular atrophy and

myelomeningocele. Since no well-defined clinical or biological criteria currently exist that enable prediction of which affected children will have a sleep disturbance, there is significant under recognition of these problems. The morbidity and impact on quality of life due to sleep disturbances in this population are, therefore, currently unknown.

SDB is frequently observed in the above-described syndromes as a result of anatomic malformation, neuromuscular weakness, or morbid obesity. In addition, however, central factors also appear to be involved in addition to or independently of symptoms related to SDB. This may be the case for Prader Willi Syndrome (15q12, SNRPN) and Angelman Syndrome (15q11-q13, UBE3A), in which daytime sleepiness and low hypocretin levels have been reported independently of SDB, suggesting hypothalamic dysregulation of sleep regulation. These disorders also frequently produce complex behavioral and medical problems with secondary effects on sleep, particularly disturbed nocturnal sleep and sleep apnea. It is often difficult, therefore, to identify disease-specific sleep phenotypes.

Other unique genetic syndromes without overt SDB may also have associated primary central nervous system (CNS) sleep disorders. Fragile X Syndrome (Xq28, FRAXF; Xq28, L1CAM) children experience sleep disturbances and low melatonin levels, while subjects with Norrie disease (genetic alterations in a region encompassing the monoamine oxidase genes at Xp11.4, NDP; Xp11.2, BMP15) or Niemann Pick Type C (18q-q12, NCPC1; 18q12.1-q12.2, DSG2) may experience cataplexy and sleep disturbances. Subjects with myotonic dystrophy (DM1, 19q13) often have abnormal breathing during sleep and possibly centrally mediated hypersomnolence. Smith-Magenis syndrome (SMS), including multiple congenital anomalies and mental retardation (17p11.2, SMCR; 17q, PSORS2), is also associated with severe sleep disturbances.

## PROGRESS IN THE LAST 5 YEARS

- The phenomenon of generalized ANS dysfunction has become clearer among children with CCHS and Rett syndrome. Patients with Rett syndrome exhibit unique respiratory disturbances that are state-dependent.
- Patients with Prader Willi syndrome present with universal reductions in their hypoxic ventilatory responses and with frequent alterations in their breathing patterns during sleep. Animal models for some of these genetic conditions have become available, thereby opening important opportunities for the study of respiratory control and sleep interactions.
- The study of control of breathing patterns in wakefulness and sleep in inbred mice strains has allowed for identification of putative chromosomal locations for several of the respiratory control components.
- Despite extensive progress in understanding the molecular and genetic mechanisms underlying many of the neuromuscular diseases, the progress achieved in understanding and defining when patients with these disorders will manifest sleep disturbances has been extremely limited.

## RESEARCH RECOMMENDATIONS

- *Conduct extended population studies in children, incorporating gene databases and including multi organ and multifunctional categorization of disease-related morbidity and response to therapy, to improve phenotypic and genotypic characterization of SDB with ANS dysfunction and craniofacial maldevelopment.*
- *Increase our understanding of primary sleep disturbances in genetic disorders of children, with the goal of discovering new sleep-regulating mechanisms.*



- Conduct studies in naturally occurring diseases of ANS dysfunction to better understand the ontogeny of the ANS from infancy through adulthood.
- Conduct studies in naturally occurring diseases with anatomical malformations of the face and upper airway, to better understand SDB, and its pathophysiology and consequences with advancing age.
- Determine how and if SDB in these unique diseases during childhood is linked to other diseases in adulthood.
- Develop novel interventional approaches to treat SDB in these special children, in collaboration with craniofacial and dental colleagues.
- Develop animal models to test hypotheses generated from delineation of phenotype-genotype correlations.
- Establish the clinical correlates of sleep disruption and SDB in children with neuromuscular disease.
- Determine the implications of sleep disturbances on end-organ morbidity and mortality as well as on health related cost and quality of life in children with neuromuscular disease.

### ***Sudden Infant Death Syndrome (SIDS)***

SIDS is the sudden and unexpected death of an infant under 1 year of age that remains unexplained after an autopsy, examination of the death scene, and thorough review of the medical and family history. With the introduction of the Back to Sleep programs over the past decade, a remarkable decline in the incidence of SIDS has occurred worldwide. In the United States alone, the aggressive educational campaign targeting infant sleep position and other modifiable factors known to be related to SIDS has resulted in a decrease from 7,000 babies dying annually to fewer than 3,000. The National Institute of Child Health and Human Development (NICHD) has completed a 5-year SIDS plan divided into four sections: Etiology and Pathogenesis, Prognostics and Diagnostics, Prevention, and Health Disparities. The NICHD plan, in each of these sections, discusses: background, and makes specific recommendations to address gaps in knowledge, intervention activities, and infrastructure needs. For a comprehensive review of SIDS and concomitant research recommendations, readers are directed to the NICHD document, available online at [http://www.nichd.nih.gov/strategicplan/cells/SIDS\\_Syndrome.pdf](http://www.nichd.nih.gov/strategicplan/cells/SIDS_Syndrome.pdf).

# NEUROPSYCHIATRIC DISORDERS IN CHILDHOOD AND SLEEP

## BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood, affecting approximately 5 to 10 percent of children. The etiology of sleep disturbances observed in association with ADHD is likely to be multifactorial and to vary among patients. In addition to medication-related sleep effects, and the influence on sleep behavior of such common comorbid conditions as oppositional defiant disorder, depression, and anxiety disorders, primary sleep disorders, such as Sleep-Disordered Breathing (SDB) and Restless Legs Syndrome/Periodic Limb Movement Disorder (RLS/PLMD) may present with “ADHD-like” symptoms or exacerbate underlying ADHD. Primary abnormalities in central nervous system (CNS) regulation of arousal, behavioral inhibition and self-regulation, and/or vigilance associated with ADHD have also been postulated to result in sleep disturbances, suggesting a more primary or fundamental sleep-wake dysregulation in at least some children. Considerable evidence suggests brain systems regulating sleep and attention/arousal are linked and that abnormalities in similar neurotransmitters, such as the noradrenergic and dopaminergic systems, may be found in ADHD and in sleep disturbances. These relationships are at present still poorly understood.

## PROGRESS IN THE LAST 5 YEARS

- Studies of children with ADHD have examined the relationship between sleep architecture, sleep patterns and behaviors, and sleep disturbances and ADHD. When using primarily parental (or self-report) surveys or polysomnography (PSG), results have been mixed and, at times, contradictory. While most “objective” studies have not found consistent significant differences in sleep architecture and patterns between children with ADHD and controls, most parental report studies have reported sleep problems including difficulty falling asleep, night wakings and restless sleep in children with ADHD. These consistent discrepancies between parental and more objective sleep measures remain an important research and clinical question. In addition, methodological concerns with many of these studies include small sample sizes and selection bias, variability in diagnostic criteria for ADHD, variability in defining the control groups, and failure to consider the effects of potential confounders, such as diagnostic subgroup of ADHD, medication status, the presence of comorbid psychiatric conditions, and age. Virtually no studies have examined sleep disturbance in adolescents and young adults with ADHD.

- Studies have examined the complex relationship between primary sleep disorders, such as SDB and PLMD, and the constellation of neurobehavioral symptoms that comprise the syndrome of ADHD (inattention, hyperactivity, impulsivity, executive function impairment).
- Some small studies have explored the use of medications, such as clonidine for sleep disturbances associated with ADHD, but no systematic studies of behavioral and/or clinical trials of pharmacologic treatment have been conducted.

## RESEARCH RECOMMENDATIONS

- *Examine the neuroanatomical and neurophysiologic relationships between regulation of sleep and of attention and arousal, including the roles of the noradrenergic, dopaminergic, and other neurotransmitter systems. Develop animal models that present phenotypes associated with ADHD.*
- *Describe the scope and magnitude of sleep disturbances in children and adolescents with ADHD, compared to the general population, including the natural history of sleep disturbances as ADHD progresses into adolescence and*

*adulthood. Describe the impact of ADHD on morbidity, including adverse behavioral outcomes such as injuries and motor vehicle crashes, substance abuse, and academic failure. Describe the risks and protective factors for sleep disturbances in children and adolescents with ADHD, and the impact of potential confounders, such as comorbid psychiatric disorders and ADHD medication use.*

- Examine the relationships and clarify directionality between primary sleep disorders, such as SDB and RLS/PLMD, and symptoms of hyperactivity and inattention in children and adolescents. Prevalence studies of primary sleep disorders in children diagnosed with ADHD are also needed.
- Evaluate the efficacy of various treatment modalities for sleep problems in ADHD, including behavioral interventions and pharmacotherapy, and the impact of treatment on the natural history of the disorder into adulthood.
- Examine the long-term effects of psychopharmacologic treatment for ADHD, especially with psychostimulants, on sleep and sleep patterns of children and adults with ADHD.



## SECTION VII EDUCATION AND TRAINING

- Scientific Training
- Clinical Education and Training
- Public and Patient Education

12



# SCIENTIFIC TRAINING

## BACKGROUND

A critical mass of appropriately trained scientists across multiple disciplines is necessary to address fundamental scientific questions regarding mechanisms and functions of sleep, its circadian regulation, and its role in human health, safety, and quality of life. Sleep research is highly multidisciplinary. The Sleep Research Society's current membership, for example, includes more than two dozen academic disciplines.

This diversity notwithstanding, the number of scientists being trained in sleep research remains inadequate for the many basic and patient-oriented research questions needing investigation. Implementation of recommendations in this Plan, for example, will require scientific training opportunities in all relevant areas and at all career levels. Encouragement and mentoring of trainees (Ph.D. and M.D.) at the graduate, postgraduate, fellowship, and early career levels is a particularly urgent need. Scientific trainees learn cutting-edge techniques in stable academic laboratories, which, in turn, requires a critical mass of established investigators in sleep research. Expanded opportunities to become engaged in sleep research would enhance the entry of young investigators into the field, thereby seeding the future with the needed numbers of sleep researchers in many scientific areas.

## PROGRESS IN THE LAST 5 YEARS

- Despite growth in the number of trainees in sleep science at all levels in the past 5 years, this growth has been modest and has not kept pace with the number of basic and clinical science research questions.
- Efforts to determine the barriers to attracting more students to scientific work on sleep have focused on: (1) lack of departmental or graduate program support for the study of sleep, (2) lack of sleep science training opportunities in established laboratories, (3) insufficient numbers of physicians engaged in sleep research, and (4) uncertainty about career opportunities in sleep research. Recent multidisciplinary conferences involving sleep researchers have sought to attract trainees from other scientific areas to the study of sleep.

## SCIENTIFIC TRAINING RECOMMENDATIONS

- *Enhance and sustain entry of new investigators in the basic sciences and patient-oriented research, as well as researchers with multidisciplinary backgrounds into the sleep research field. Expand programs in sleep research training, including the training of investigators in new, basic, and behavioral research areas targeted at sleep research questions (genetics, proteomics, molecular biology, neuroimaging,*



*bioinformatics, etc.) and patient-oriented sleep research areas (clinical trials, epidemiology, preventive medicine). Expand dedicated sleep training programs and provide incentives to existing non sleep training programs to include sleep research tracks where there is a critical mass of investigators. This would build upon existing training infrastructures and also would be cost effective.*

- *Increase the number of investigators in sleep neuroscience. Systems neuroscience, particularly neurophysiological, is a strong component of current sleep research. However, the number of investigators in this field is small in comparison to the number of scientific questions.*
- Encourage training of basic scientists and clinical investigators with interest in sleep research in development, as well as endocrine, metabolic, cardiovascular, and immune functions, given evidence that sleep may have important roles in these areas. Currently there are few opportunities to combine training in these areas with sleep research. Training awards that specifically provide incentives to both trainees and established investigators should help close this gap.
- Encourage innovative collaborative training mechanisms, with interactive training provided by investigators from different disciplines with complementary skills. Training investigators in patient-oriented sleep research will be critical in addressing the clinical and applied research recommendations in this Research Plan. Residency research tracks that include sleep research electives are needed. Medical school research tracks that focus on sleep should also be encouraged.
- Develop research training programs that encourage and support the initiation of small sleep research projects by medical students, nursing and other allied health professionals, and postgraduate trainees in related disciplines.

# CLINICAL EDUCATION AND TRAINING

## BACKGROUND

Education and training are integral to meeting the goals of sleep medicine in improving clinical practice and patient-oriented outcomes. Successful educational interventions require the development, implementation, and dissemination of materials covering a wide range of topics, including the basic neurobiology of sleep and circadian rhythms, clinical sleep disorders and evidenced-based treatment, the consequences of sleep deprivation, and the role of sleep in health and disease. Education and training must be targeted toward all relevant professional and public audiences, and must include evaluation of the impact of such programs on public health.

### *Physician Education and Training*

The practice of sleep medicine is inherently multidisciplinary, drawing physicians from many areas such as geriatrics, neurology, internal medicine and pediatrics (including pulmonology, neonatology, critical care), psychiatry, and surgery. Because of this diversity, the field of sleep medicine continues to evolve standards, practices, and training opportunities. In April 2002, for example, the American Academy of Sleep Medicine submitted an application to the Accreditation Council on Graduate Medical Education requesting the establishment of a Residency Review Committee approval of fellowship training programs in sleep medicine. Despite advances in defining sleep medicine

as a specialty and in formalizing training infrastructure to sustain sufficient growth in the field, empirical data from survey and clinical outcome studies indicate that, in general, physician education regarding the recognition, diagnosis, management, and prevention of clinical sleep disorders in both adults and children is inadequate. Substantial knowledge deficits exist at the medical school level, as well as at the post-graduate training and continuing education levels.

Important public health implications result from the large gaps between scientific knowledge, clinical teaching and practice. For example, it is known that physicians outside sleep medicine significantly under-diagnose or misdiagnose sleep disorders, leading to increased morbidity and decreased quality of life. Furthermore, early intervention efforts to detect and prevent sleep disorders are likely to be significantly compromised by this lack of education and training.

To address these concerns, the need exists to further define a knowledge base in sleep medicine and circadian biology, develop a basic sleep curriculum for medical schools, and create appropriate educational tools as a foundation for enhanced learning at all levels. Current medical education activities are involved with curriculum development, and will require application of rigorous methodological criteria for outcome measures and demonstration of efficacy of teaching methods and tools.

Knowledge, competence, and behavioral change objectives involve different methods of assessment. Specific knowledge acquisition, for example, is usually measured with standard written tests, skills acquisition with performance-based assessment, and behavioral changes with self-report or structured observational methods.

Assessment of impact on clinical practice may depend upon a variety of health outcome measures, including quality of life and disease prevalence data, tracking of health care utilization, and cost-benefit analyses. However, little research in sleep education has yet been directed toward evaluation of these types of outcomes related to professional knowledge, attitudes, and changes in clinical practice behavior. Some evaluation tools do exist, such as knowledge surveys and standardized clinical examinations, but most are not validated, and few are widely available. Although clinical care is likely to be improved by continuing medical education efforts targeted at improving knowledge and skills, and fostering behavioral change in practicing physicians, sleep medicine has not been included in research on effective strategies to change physician behavior. Prospective, multicenter, structured trials are needed to accomplish these goals.

#### *Education and Training of Other Health Professionals*

Dentists, nurses, pharmacists, and psychologists are increasingly involved in identification and treatment of sleep disorders. These disciplines should also be targeted for educational interventions. The educational needs of these various disciplines overlap with those of physicians, but additional educational resources and strategies are needed to address their unique concerns. For example, nurses potentially have a key role in the identification of

sleep disorders in patients being treated by other medical specialties. Psychologists have become increasingly important in the evaluation and behavioral treatment of insomnia. Dentists have become actively involved in the treatment of sleep apnea with mandibular devices. These health care initiatives would benefit from coordination of evaluation research to determine the impact on behavioral change, clinical practice, and ultimately on the quality of patient care in sleep medicine across these disciplines.

#### **PROGRESS IN THE LAST 5 YEARS**

- In a 1978 survey of sleep education in medical schools in the United States, the American Sleep Disorders Association found that less than 10 percent of schools offered adequate training and 46 percent included no sleep medicine at all in the curriculum. In 1990, a medical education survey reported relatively little progress, with 37 percent of medical schools offering no sleep education. In those schools that did, the average time devoted to sleep in the 4-year curriculum was less than 2 hours. Subsequent surveys of post-graduate training programs in adult and pediatric medicine have found similar results, with lack of time in the curriculum and of qualified instructors cited as major barriers. Surveys of practicing physicians conducted in the last 5 years reveal similar gaps in knowledge and clinical practice despite increasing recognition of the importance of sleep in the health and well-being of their patients.
- In 1996, the National Center on Sleep Disorders Research (NCSDR) developed the Sleep Academic Award (SAA) Program to help address these educational gaps. Twenty medical schools in the United States were awarded 5-year



grants to develop model medical school curricula in sleep medicine, to promote interdisciplinary learning environments, and to improve the quality of sleep education and education research at all levels, including the public arena. The SAA Program has raised awareness of sleep education in both the sleep and general medical communities, and has laid the foundation for continued sleep education development by facilitating the creation of screening and evaluation tools such as the ASK-ME Survey of sleep knowledge, regional and national faculty development workshops, and public education programs on sleep. Development of MedSleep, a Web-based repository of over 50 sleep education tools and products developed by the awardees and available to all health professional and educators, was the result of a collaborative effort between the SAA Program and the American Academy of Sleep Medicine (AASM).

- The SAA Program, in collaboration with the AASM and the American Medical Association (AMA), has initiated a collaborative education and research effort to address the issue of sleep and fatigue in medical training. Several research projects, including a multiple site collaborative study, have evolved from this initiative. In 2001, a national conference was held to define specific research goals and objectives regarding consequences of sleep loss in physicians and to develop effective interventions.

## CLINICAL EDUCATION AND TRAINING RECOMMENDATIONS

- *Develop sleep education programs at the medical school, postgraduate, and continuing medical education levels, and develop a coordinated, structured, and scientifically rigorous approach to evaluate the impact of sleep education programs and tools across multiple institutions and clinical settings. Outcome measures should include assessment of changes in:*
  - *Physician knowledge, attitudes, skills, and behavior*
  - *Clinical practice*
  - *Patient health and quality of life*
- *Evaluate the effectiveness of strategies to address these training gaps. This should be based on a needs assessment of educational gaps in sleep training among other health professions including but not restricted to nursing, dentistry, pharmacy, clinical psychology and other mental health disciplines. Outcome measures should include assessment of changes in:*
  - *Professional knowledge, attitudes, skills, and behavior*
  - *Clinical practice*
  - *Patient health and quality of life*

# PUBLIC AND PATIENT EDUCATION

## BACKGROUND

Support and promotion of health education are necessary steps to establish links between basic science and clinical outcomes and to facilitate the translation of research findings to address public health concerns, such as those outlined in the U.S. Department of Health and Human Services "Healthy People 2010" initiative. Health education initiatives support primary prevention and increase recognition of sleep disorders in the general community, as well as broaden the scope of secondary and tertiary prevention efforts in patients with diagnosed sleep disorders. Public education campaigns provide information to increase knowledge, to enable modification of health risks, and also to help foster a supportive social environment for facilitating positive behavioral change. To accomplish these goals, effective teaching tools and strategies need to be developed and mechanisms need to be implemented for evaluation of sleep educational materials for the general public.

It is important to delineate the educational needs of the target audience, to define and prioritize the educational messages, and to identify potential opportunities and barriers related to health-related behavioral change. Specific topics that have been identified as key components in public and patient sleep education programs include those related to basic regulation of sleep and circadian rhythms, sleep deprivation (extent, signs, causes, and consequences), and sleep hygiene. Prevalent, serious, and/or frequently under recognized sleep disorders, including SDB, insomnia, narcolepsy, and Restless Legs Syndrome/Periodic

Limb Movement Disorder (RLS/PLMD) are another key component. Target audiences may be defined as high risk for sleep disorders and/or sleep deprivation by virtue of age (elderly, adolescents), demographics (minority, medically underserved), gender (pregnant or menopausal women, young adult males), other health risks (obesity), and work schedules (shift workers, commercial drivers).

Educational campaigns directed toward high-risk populations (e.g., adolescents) and toward receptive audiences (e.g., elementary school children) may be efficient and cost-effective ways to enhance prevention and early detection of sleep problems. These campaigns also should include groups that can facilitate behavioral change but may be hard to reach, including teachers, coaches, school nurses/health educators, parents, and pediatricians). Specific educational strategies should include culturally sensitive materials appropriate for a range of literacy levels and novel methods of translation and dissemination of information (e.g., Web-based products). Finally, outcome measures to assess the effectiveness of educational interventions include changes in knowledge, attitudes, health-related behaviors, and ultimately in the health of the target audience. Process measures describing the extent to which information is disseminated, programs are utilized, and target audiences are reached may be surrogate measures for evaluating results.

## PROGRESS IN THE LAST 5 YEARS

The National Center on Sleep Disorders Research (NCSDR), part of the National Heart, Lung, and Blood Institute (NHLBI),

coordinates public and patient sleep disorders education in collaboration with the Office of Prevention, Education, and Control (OPEC). These efforts facilitate the translation and dissemination of research and scientific consensus to the general public, patients, and health professionals. Recent sleep education programs include:

- Initiation of a 5-year media-based public awareness campaign on Sleep-Disordered Breathing (SDB).
- Development of fact sheets for the public and patients on sleep disorders including SDB, insomnia, narcolepsy, RLS, and problem sleepiness. Companion booklets for primary care physicians have been developed and published in the journal *American Family Physician*. Partnerships with professional organizations, such as the American Academy of Family Practice, the American Academy of Pediatrics, the American Sleep Apnea Association, the American Academy of Sleep Medicine, and other national organizations involved in sleep research and education, have enabled wider dissemination of these materials than would otherwise have been possible.
- Development of the NCSDR Web site, [www.nhlbi.nih.gov/sleep](http://www.nhlbi.nih.gov/sleep), where educational materials are available and can be viewed and downloaded.
- Development of a "Sleep IQ" quiz to raise public awareness of the signs of sleep deprivation and the symptoms of sleep disorders.
- Development of a drowsy-driving educational campaign targeted at high school students in partnership with the National Highway Traffic and Safety Administration.
- Initiation of Latino education efforts about sleep disorders, including translation of selected materials into Spanish and development of lay health educator programs. School-based interventions were

implemented to encourage awareness of sleep as a health issue and to foster healthy sleep habits in children and adolescents. These interventions include the "Sleep well. Do well. Star Sleeper" campaign for children ages 7 to 11, and a high school supplemental curriculum on the biology of sleep, "Sleep, Sleep Disorders, and Biological Rhythms". The school-aged intervention highlights Garfield as the "spokescat" for healthy sleep and includes classroom activities, national and local media components, and a Web site with content targeted specifically for children, teachers, and pediatricians.

## RESEARCH RECOMMENDATIONS

- *Develop effective and innovative educational approaches based on needs assessments of high risk and target groups that include both quantitative and qualitative research methodologies. These approaches should identify specific educational opportunities and barriers, target sleep health educational interventions, and improve strategies for dissemination of educational materials to patients and the general public.*
- *Evaluate the effectiveness of:*
  - *Public sleep education initiatives on public health outcomes in high risk, minority, and medically underserved populations.*
  - *School-based sleep education programs on knowledge, attitudes, and sleep practices of children and adolescents, parents, and teachers.*
  - *Educational efforts directed to relevant State regulatory agencies (e.g., Departments of Motor Vehicles) and related to adverse consequences of sleep deprivation and sleep disorders on safety including drowsy driving, and to identifying education efforts that have positive impact on public education and safety.*



## ABBREVIATIONS

AD	Alzheimer's disease
ADHD	Attention Deficit Hyperactivity Disorder
ANS	Autonomic Nervous System
ASPS	Advanced Sleep Phase Syndrome
CCHS	Congenital Central Hypoventilation Syndrome
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
DHHS	Department of Health and Human Services
EMG	Electromyogram
EOG	Electrooculogram
ESRD	End Stage Renal Disease
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
IL	Interleukin
MEG	Magnetoencephalography
MRS	Magnetic Resonance Spectroscopy
NCSDR	National Center on Sleep Disorders Research
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIR	Near-Infrared Optical Imaging
NREM	Non-Rapid Eye Movement Sleep
OSA	Obstructive Sleep Apnea
PD	Parkinson's disease
PET	Positron Emission Tomography
PLMD	Periodic Limb Movement Disorder
PSG	Polysomnography
RBD	REM Sleep Behavior Disorder
REM	Rapid Eye Movement Sleep
RLS	Restless Legs Syndrome
SCN	Suprachiasmatic Nucleus
SDB	Sleep-Disordered Breathing
SIDS	Sudden Infant Death Syndrome
SPECT	Single Photon Emission Computed Tomography
TMJD	Temporomandibular Joint Disorder

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## APPENDICES

- *Appendix A:* National Sleep Disorders Research Plan Revision Task Force
- *Appendix B:* National Sleep Disorders Research Advisory Board
- *Appendix C:* NIH Sleep-Related Initiatives, 1996 to 2002

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## **APPENDIX C: 1996 NATIONAL SLEEP DISORDERS RESEARCH PLAN RECOMMENDATIONS AND RESULTING NIH SLEEP-RELATED RESEARCH INITIATIVES (1996 TO 2002)**

The title of each RFA/PA and total funding awarded for each initiative (cumulative through Fiscal Year 2002) are listed in descending chronological order by year of initiative release under the relevant research recommendations from the 1996 National Sleep Disorders Research Plan. In some instances, an individual initiative applies to more than one recommendation and is therefore listed under each relevant recommendation.

## 1996 National Sleep Disorders Research Plan Research Recommendations

### BASIC SCIENCE RESEARCH RECOMMENDATIONS

- ▶ Increase efforts to understand the basic mechanisms responsible for sleep by applying molecular biological approaches in concert with techniques of cellular and systems neurobiology.
- ▶ Conduct basic studies to understand the brain mechanisms responsible for sleepiness.
- ▶ Study basic mechanisms underlying the interaction between the circadian and neurophysiological systems that regulate sleep and wakefulness..
- ▶ Characterize the genetic factors controlling the basic mechanisms of sleep.
- ▶ Increase research efforts to elucidate the fundamental functions of sleep.

<i>Initiative Title</i>	<i>Participating Institutes/Centers</i>	<i>Total Costs Awarded (through FY 2002)</i>
Interrelationships Between Sleep and Heart, Lung, and Blood Diseases: HL01-009*†	NHLBI, NIDA	\$ 1,357,253
Research on Alcohol and Sleep: AA00-005*†	NIAAA	4,512,605
Oxygen Sensing During Intermittent Hypoxia: HL00-004*	NHLBI	10,673,975
Nocturnal Asthma, Chronobiology and Sleep: HL99-011*†	NHLBI	3,530,381
Phenotypic Characterization of Sleep in Mice: HL99-001	NHLBI, NIMH, NIA, NINDS	13,512,185
Bioengineering Research Grants: PAR 99-009	NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIMH, NINDS, NINR, NLM	546,594
Research on Musculoskeletal Fitness and Sports Medicine: PA97-025*	NIAMS, NICHD, NINR	999,146
SCOR in Neurobiology of Sleep and Sleep Apnea: HL96-014*†	NHLBI	18,553,207
Molecular Biology and Genetics of Sleep and Sleep Disorders: HL96-015*	NHLBI, NIMH, NICHD	7,335,059
Basic and Clinical Research on Sleep and Wakefulness: PA95-014*	NIA, NIAAA, NICHD, NIDA, NHLBI, NIMH, NINDS, NINR	28,384,156

\* Also listed under Patient-Oriented Research Recommendations

† Also listed under Applied Research Recommendations



## PATIENT-ORIENTED RESEARCH RECOMMENDATIONS

- ▶ Identify the genetic basis of sleep disorders that have a genetic component.
- ▶ Conduct epidemiological research to assess prevalence, risk factors, and long-term consequences of common sleep disorders and determine the role of ethnicity, age, and gender in their causation.
- ▶ Conduct outcomes research and clinical trials on the management of common sleep disorders.
- ▶ Develop new technological approaches for diagnosis of sleep disorders, screening for sleep disorders among high-risk populations in whom sleepiness presents a particular danger (e.g., transportation workers), monitoring the effectiveness of therapy, and detecting abnormalities of sleep as early biological markers of psychiatric illnesses.
- ▶ Elucidate the pathogenesis/pathophysiology of sleep disorders and their consequences.
- ▶ Provide the research infrastructure needed to carry out patient-oriented research.

<i>Initiative Title</i>	<i>Participating Institutes/Centers</i>	<i>Total Costs Awarded (through FY 2002)</i>
Interrelationships Between Sleep and Heart, Lung, and Blood Diseases: HL01-009*†	NHLBI, NIDA	\$ 1,357,253
Sleep and Sleep Disorders in Children: HL01-006 NINR, NICHD	NHLBI, NIMH,	1,499,621
Restless Legs Syndrome and Periodic Limb Movement Disorder: PA01-086	NINDS, NHLBI, NIA, NIMH	334,178
Research on Alcohol and Sleep: AA00-005*†	NIAAA	4,512,605
Ancillary Studies in Conjunction with SHOW Trial: DK-00-017 NIAMS, NIDCR	NIDDK, NHLBI, NINR,	1,143,165
Oxygen Sensing During Intermittent Hypoxia: HL00-004	NHLBI	10,673,975
Biobehavioral Research for Effective Sleep: PA00-046*†	NINR, NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NCI	1,717,977
Data Coordinating Center for Sleep Heart Health Study: HL99-014	NHLBI	2,913,228
Nocturnal Asthma, Chronobiology and Sleep: HL99-011*†	NHLBI	3,530,381
Occupational Safety and Health Research: PA99-143†	NIOSH, NCI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIDCD, NIEHS	381,250
Obstructive Sleep Apnea in Children: HL98-004†	NHLBI, NIDR, NICHD	10,826,226

(CONTINUED ON PAGE 138)

PATIENT-ORIENTED RESEARCH RECOMMENDATIONS (CONTINUED)

<i>Initiative Title</i>	<i>Participating Institutes/Centers</i>	<i>Total Costs Awarded (through FY 2002)</i>
Sleep Academic Award: HL97-015, HL96-021, HL96-006‡	NHLBI	\$ 4,995,123
Institutional National Research Service Award in Sleep Research: PA97-064†	NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINDS, NINR	737,625
Research on Musculoskeletal Fitness and Sports Medicine: PA97-025*	NIAMS, NICHD, NINR	999,146
Molecular Biology and Genetics of Sleep and Sleep Disorders: HL96-015*	NHLBI, NIMH, NICHD	7,335,059
SCOR in Neurobiology of Sleep and Sleep Apnea: HL96-014*†	NHLBI	18,553,207
Basic and Clinical Research on Sleep and Wakefulness: PA95-014*†	NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINDS, NINR	28,384,156

\* Also listed under Basic Science Research Recommendations

† Also listed under Applied Research Recommendations

‡ Also listed under Research Training Recommendations

## APPLIED RESEARCH RECOMMENDATIONS

- ▶ Conduct epidemiological research to define the prevalence, etiology, risk factors, morbidity, and costs of sleepiness in the general population.
- ▶ Define the decrement and recovery processes associated with chronic partial sleep deprivation.
- ▶ Develop efficient, objective measures of daytime sleepiness.
- ▶ Evaluate the utility of interventions to prevent and manage sleepiness, with the goal of improving productivity and safety.

<i>Initiative Title</i>	<i>Participating Institutes/Centers</i>	<i>Total Costs Awarded (through FY 2002)</i>
Interrelationships Between Sleep and Heart, Lung, and Blood Diseases: HL01-009*†	NHLBI, NIDA	\$ 1,357,253
Research on Alcohol and Sleep: AA00-005*†	NIAAA	4,512,605
Biobehavioral Research for Effective Sleep: PA00-046†	NINR, NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NCI	1,717,977
Nocturnal Asthma, Chronobiology and Sleep: HL99-011*†	NHLBI	3,530,381
Implementation of the National Occupational Research Agenda: OH99-02	NIOSH, NCI, NHLBI, NIA, NIDCD, NIEHS	423,750
Occupational Safety and Health Research: PA99-143†	NIOSH, NCI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIDCD, NIEHS	381,250
Human Brain Project (Neuroinformatics): PAR 99-138	NIMH, NIDA, NSF, NIA, NICHD, NIDCD, NLM, NASA, FIC, DOE, NIAAA, NHLBI, NIDCR, NCI, NINDS	370,125
Obstructive Sleep Apnea in Children: HL98-004†	NHLBI, NIDR, NICHD	10,826,226
Institutional National Research Service Award in Sleep Research: PA97-064†	NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINDS, NINR	737,625
Innovative Approaches to Developing New Technologies: PAR-97-014	NCRR	222,740
SCOR in Neurobiology of Sleep and Sleep Apnea: HL96-014*†	NHLBI	18,553,207
Basic and Clinical Research on Sleep and Wakefulness: PA95-014*†	NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINDS, NINR	28,384,156

\* Also listed under Basic Science Research Recommendations

† Also listed under Patient-Oriented Research Recommendations



## RESEARCH TRAINING RECOMMENDATIONS

- ▶ Enhance the number of trained investigators and trainees in biological and behavioral research related to basic sleep mechanisms and patient-oriented research.

<i>Initiative Title</i>	<i>Participating Institutes/Centers</i>	<i>Total Costs Awarded (through FY 2002)</i>
Sleep Academic Award: HL97-015, HL96-021, HL96-006*	NHLBI	\$4,995,123

\* Also listed under Patient-Oriented Research Recommendations

**GRAND TOTAL** **\$ 114,969,569**

## NIH TOTAL SLEEP DISORDERS RESEARCH FUNDING, 1996 TO 2002\*

<i>Institute/ Center</i>	<i>1996</i>	<i>1997</i>	<i>1998</i>	<i>1999</i>	<i>2000</i>	<i>2001</i>	<i>2002</i>
<i>Dollars in thousands</i>							
NHLBI	16,450	19,219	22,932	31,845	35,128	37,579	45,155
NINDS	9,453	11,598	13,639	15,231	12,495	17,603	22,918
NICHD	7,368	7,217	9,131	7,116	6,797	7,084	7,344
NIA	7,800	9,179	11,818	13,296	13,034	14,533	14,600
NIMH	27,231	28,601	34,027	39,219	40,667	50,742	56,647
NIDA	1,201	1,042	1,586	2,163	2,553	2,517	3,235
NIAAA	551	728	766	736	1,132	1,681	4,342
NINR	2,842	3,565	3,394	3,503	4,635	5,375	8,091
NCRR	3,247	3,570	5,542	6,637	7,117	7,193	11,490
NCCAM †	N/A	N/A	N/A	N/A	N/A	177	900
NIAMS †	N/A	N/A	N/A	N/A	N/A	N/A	300
NHGRI	N/A	N/A	N/A	N/A	N/A	599	0
<b>Total</b>	<b>76,143</b>	<b>84,719</b>	<b>102,835</b>	<b>119,746</b>	<b>123,558</b>	<b>145,083</b>	<b>175,022</b>

\* Detailed listings of NIH Sleep Related Grants for Fiscal Years 1999 through 2002 can be found online at:

<http://www.nhlbisupport.com/sleep/research/research3.htm>

† Became Trans-NIH Sleep Research Coordinating Committee Member Institute in FY 2002

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