Medical Education Systems, Inc.

Course 703 II

SLEEP DISORDERS

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SLEEP DISORDERS

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Learning Objectives

Upon successful completion of this course, you should be able to:

- Identify and discuss the key elements of basic sleep science, including circadian biology and Sleep Neurobiology Pharmacology and Pharmacogenetics of Sleep and Waking

- Identify and discuss the key elements of restricted sleep, including the neurobehavioral and physiological effects

- Discuss what is referred to as "enabling technology" in regard to analysis of sleep-wake states, and postmortem brain analysis in sleep disorder patients

- Describe the impact of sleep on health, including sex differences, racial and ethnic disparities, aging, safety, and medical conditions

- Identify and explain sleep disorders, including sleep-disordered breathing, insomnia, narcolepsy, restless legs syndrome and parasomnias

Introduction

Sleep-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.

***Sleep Neurobiology*:** The discovery in 1998-99 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 REM, non REM, 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 and has saved thousands of lives. Recent research regarding the physiological, 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 physiological 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 at most medical schools and residency training programs.

A Sleep Academic Award Program was established in 1996 to address these educational gaps. 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 have substantial potential impact on knowledge and public health behaviors.

• *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 Sleep-Disordered breathing abnormalities. These include both rare syndromes and more frequent conditions such as ADHD.

SECTION I – BASIC SLEEP SCIENCE

CIRCADIAN BIOLOGY
SLEEP NEUROBIOLOGY
PHARMACOLOGY AND PHARMACOGENETICS OF SLEEP AND WAKING

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.

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, in rare and extreme cases, 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 active (REM) sleep have different functions than quiet (nonREM) sleep?

Functional significance of the marked differences in amount of sleep within the animal kingdom is unknown. Similarly, the considerable variation in the duration of the sleep cycle (WakenonREM-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.

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 (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 knowledge 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.

SECTION II – RESTRICTED SLEEP: NEUROBEHAVIORAL AND PHYSIOLOGICAL EFFECTS

SLEEP DEPRIVATION IN ADULTS
SLEEP DEPRIVATION IN CHILDREN AND ADOLESCENTS

SLEEP DEPRIVATION IN ADULTS

Background

Studies on the effects of sleep loss on neurobehavioral functions, especially neurocognitive performance, have two primary emphases: (a) specification of the properties of tasks (e.g., cognitive versus physical; long versus short duration) that make them sensitive to sleep loss; and (b) specification of the aspects of performance (e.g., cognitive processing speed versus accuracy, declarative versus implicit memory processes) that are impacted by sleep loss.

Underlying this research 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 has not been resolved due to lack of a basic 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 have been explored have utilized the more efficient total sleep deprivation procedures, and very few studies have examined the effects of chronic sleep restriction. Further, 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:

(a) What are the physiological processes mediating neurobehavioral performance deficits resulting from sleep loss?

(b) What accounts for the wide individual differences that emerge in the ability to maintain performance during sleep loss?

(c) Do the physiological and neurobehavioral responses to chronic partial sleep loss differ from those resulting from total sleep loss?

(d) Relative to the adverse neurocognitive and physiological effects of sleep loss, is there habituation/adaptation or potentiation/sensitization to repeated exposure to sleep loss?

(e) 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)?

(f) Are the neurobehavioral and physiological effects of chronic partial sleep loss different at different circadian phases?

(g) 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?

(h) How much recovery sleep is required following chronic partial sleep loss vs. total sleep deprivation?

(i.) 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?

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 impacts upon 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 and 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 inter-individual 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.

SECTION III – ENABLING TECHNOLOGY

ANALYSIS OF SLEEP-WAKE STATES

Background

The monitoring of sleep states is accomplished using several electroencephalographic (EEG) leads in combination with electro-oculographic (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 – 4 sleep and rapid eye movement (REM) sleep.

Although this system has been useful, it also has weaknesses. The principal weakness is inability to easily detect and quantify microarousals or subtle disruptions of sleep. Thus, the full impact of many disorders of sleep 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.

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.

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 continue 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), magnetoelectroencephalography (MEG), and nearinfrared 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.

POSTMORTEM BRAIN ANALYSIS IN SLEEP DISORDER PATIENTS

Background

The postmortem study of brains of patients suffering from 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 potential 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 postmortem 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.

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

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 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 one or two 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 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 being 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.

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% of adults 30 to 64 years old, and 44% of young adults 18 to 29 years old 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 eight to nine hours of sleep at night with few interruptions. A majority of adolescents and adults, however, report habitual sleep durations of fewer than seven hours per night during the week and fewer than eight 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 one to four 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 four hours each night for six 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 eight 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 six hours sleep per night) or long sleep duration (more than nine hours sleep per night) is associated with increased mortality. A recent epidemiological report found that self-reported sleep duration averaging either less or more than seven 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 eight 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 is associated with higher mortality by a large comprehensive study of the effects of sleep on health and risk for disease.

SLEEP, SEX DIFFERENCES, AND WOMEN'S HEALTH

Background

Women from adolescence to post-menopause are underrepresented in studies of sleep and its disorders. Although sleep complaints are twice as prevalent in women, 75% of sleep research has been conducted in men. More sleep studies in the past five 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 gonadatropin 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 female sex 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 non-ovulating 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. 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 post-partum 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 post-partum 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, post-menopause) complain of sleep disturbances that are attributed to vasomotor symptoms (e.g., hot flushes and night sweats) rather than to menopausal status. Estimates of self-reported menopausal-related Insomnia range from 33 to 51%, 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 hyper aroused (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 hormone replacement therapy for the treatment of menopausal symptoms, fewer women in the future may receive HRT and 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% 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 impact 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 posttraumatic 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.

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) may contribute to the increased prevalence and severity of heart disease, and may also contribute to these disparities through other mechanisms not yet clarified.

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) (Section V). Insomnia alone affects about a 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 (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 (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.

SLEEP AND SAFETY

Background

Demands on human wakefulness and alertness through increased requirements for shift work, on-call 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 100,000–150,000 motor vehicle crashes each year and 4% of all fatal crashes are due to 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 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. We thus need to explore options for mitigating sleepiness and fatigue. 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 in 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 hence to fatigue.

Excessive fatigue and its risks are largely preventable when 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.

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 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 (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 hence 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 thus 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 non-restorative 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.

SECTION V – SLEEP DISORDERS

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 they 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 individually in different ways (e.g. IL-1, -2, -15, -18, 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. Thus 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).

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 hence not associated with optimal compliance rates.

SDB is exacerbated by alcohol intake. We continue to have a very incomplete understanding of the neurobiologic mechanisms responsible for the sleep-induced changes in upper airway motor control that lead to pharyngeal collapse. The reversibility with therapy of apnea-induced hypertension and other presumed adverse cardiovascular outcomes is largely untested. The explanation 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 unresolved. 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.

PEDIATRIC

Background

Snoring, a symptom of increased upper airway resistance during sleep, is extremely frequent in children, and affects 18-20% of infants, 7-13% of 2-8 year-old children, and 3-5% of older children. The pathos-physiology of SDB in children is still poorly understood. Indeed, while Aden tonsillar hypertrophy is certainly a major contributor to SDB, other factors such as obesity, cranio-facial 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.

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 30-40% 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%. Evidence suggests that insomnia has significant consequences on quality of life, healthcare 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, in identification of adverse outcomes, and in identifying effective treatments.

However, there is still much we do not know 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 advances in the neurobiology of sleep and circadian rhythms (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.

PEDIATRIC

B**ackground**

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 -25% 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. Thus, 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%, and to be 50% in children with less severe cognitive impairment. The prevalence of sleep problems in autism is estimated to be 50 to 70%.

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, 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, and social development and behavior in these already at-risk children is potentially profound.

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

NARCOLEPSY AND OTHER HYPERSOMNIAS

Background

Narcolepsy is a disabling neurological disorder characterized by sleepiness and symptoms of abnormal 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 a short mean sleep latency indicative of daytime sleepiness and more than 2 REM episodes in the MSLT.

Narcolepsy-cataplexy affects 1 in 2,000 people and is the 4th most common condition treated in sleep disorder clinics. The exact prevalence of essential hypersomnia and of 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 20-40 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 neuroanatomical 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 (6 month of age) 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.

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%, 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 among women than men, and 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 is quite common in end-stage-renal disease and during pregnancy.

About 85-90% 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. Similar to 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, like RLS, is higher in the elderly. Without better understanding of the etiology, pathogenesis, and neurophysiology of these disorders, treatment strategies are limited, and can be unsatisfactory. Both disorders have profound negative impact on 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 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 micro-structure of the EEG sleep pattern.

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 Parkinson's disease. 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 Parkinson's disease 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.

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, NREM sleep, or REM sleep and are often divided into two groups. Primary parasomnias are disorders of sleep states per se, and secondary parasomnias are 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 are often unrecognized, misdiagnosed, or ignored in clinical practice. The pathophysiology, morbidity, and functional consequences of secondary parasomnias are unknown.

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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 there is a genetic predisposition 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.

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, increasing evidence 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 an impairment in the homeostatic recovery of sleep following sleep deprivation. Moreover, insomnia and certain types of EEG sleep patterns, such as reduced 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 on 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.

Given the 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 follow-up studies have not yet been done to determine whether intervention can reduce these risks and the progression of these disorders.

SECTION VI – PEDIATRICS

SLEEP AND EARLY BRAIN DEVELOPMENT AND PLASTICITY
ADOLESCENT SLEEP
SLEEP IN MEDICAL DISORDERS
NEUROPSYCHIATRIC DISORDERS IN CHILDHOOD AND SLEEP

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% of their day in active (REM) sleep and the remainder in quiet (non-REM) sleep and wakefulness. By 5-6 months of age, human infants spend only 20-30% of their time in REM sleep, with the remainder of time equally spent in non-REM 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 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.

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. Finally, 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.

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). Very few sleep studies have been performed, however, in children with craniofacial malformations, chromosomal/genetic abnormalities, and 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 requiring 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 due to an abnormal rib cage, small foramen magnum, and SDB. Disorders with a protuberant tongue include the mucopolysaccharidoses, (ex. 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, 15-20% of children with Duchenne Muscular Dystrophy will develop sleep disturbances, and this prevalence is even greater among patients with spinal muscular atrophy and myelomeningocele. There are currently no well defined clinical or biological criteria that allow for prediction of which affected children will have a sleep disturbance, and hence there is widespread under-

recognition of these problems. The morbidity and impact on quality of life due to sleep disturbances in this population are 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 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 that have secondary effects on sleep, particularly disturbed nocturnal sleep and sleep apnea. It is thus often difficult 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.

NEUROPSYCHIATRIC DISORDERS IN CHILDHOOD AND SLEEP

Background

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood, affecting some 5 to 10% of children. The etiology of sleep disturbances observed in association with ADHD is likely to be multi-factorial and to vary among patients. In addition to medication-related sleep effects and the influence on sleep behavior of such common co-morbid conditions as oppositional defiant disorder, depression, and anxiety disorders, the primary sleep disorders such as 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. There is considerable evidence to suggest that 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.

SECTION VII – EDUCATION AND TRAINING

SCIENTIFIC TRAINING
CLINICAL EDUCATION AND TRAINING
PUBLIC AND PATIENT EDUCATION
100

SCIENTIFIC TRAINING

Background

A critical mass of appropriately trained scientists across multiple disciplines is necessary in order 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 the recommendations in this Plan, for example, will necessitate 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, post-graduate, fellowship, and early career levels is an especially 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, seeding the future with the needed numbers of sleep researchers in many scientific areas.

PUBLIC AND PATIENT EDUCATION

Background

Support and promotion of health education is a necessary step 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 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. In order 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, define and prioritize the educational messages, and identify potential opportunities and barriers related to behavioral health-related 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. Sleep disorders that are prevalent, serious, and/or frequently under recognized are another key component, including SDB, insomnia, narcolepsy, and Restless Legs Syndrome/Periodic Limb Movement Disorder (RLS/PLMD). Target audiences may be defined by high risk for sleep disorders and/or sleep deprivation by virtue of age (elderly, adolescents), demographics (minority, medically underserved), gender (pregnant and menopausal women, young adult males), other health risks (obesity), and work schedules (shift workers, commercial drivers).

Educational campaigns directed towards 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 need to include groups that can facilitate behavioral change but may 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 impact.

ABBREVIATIONS

ASPS Advanced Sleep Phase Syndrome
AD Alzheimer's disease
ADHD Attention Deficit Hyperactivity Disorder
ANS Autonomic Nervous System
CNS Central Nervous System
CFS Chronic Fatigue Syndrome

CCHS Congenital Central Hypoventilation Syndrome
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
MRS Magnetic Resonance Spectroscopy
MEG Magnetoelectroencephalography
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
PLMD Periodic Limb Movement Disorder
PSG Polysomnography
PET Positron Emission Tomography
REM Rapid Eye Movement Sleep
RBD REM Sleep Behavior Disorder
RLS Restless Legs Syndrome
SPECT Single Photon Emission Computed Tomography
SDB Sleep-Disordered Breathing
SIDS Sudden Infant Death Syndrome
SCN Suprachiasmatic Nucleus
TMJD Temporomandibular Joint Disorder

POST TEST

Select the ***best*** answer to each of the following items. Mark your responses on the Answer form.

1. Sleep-related problems affect _____ Americans of all ages.

a. 5 to 10 million
b. 15 to 25 million
c. 50 to 70 million
d. 74 to 80 million

2. The main categories of sleep disorders include _____.

a. Primary Sleep Disorders
b. Secondary Sleep Disorders
c. Sleep Neurobiology
d All of the above

3. 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 _____ nuclear tissues have genes and can demonstrate circadian rhythms.

a. suprachiasmatic
b. non-suprachiasmatic
c. circadian controlled
d. none of the above

4. _____ has been identified as a risk factor for the onset of subsequent depression, anxiety, and substance use disorders.

a. Narcolepsy
b. Insomnia
c. Sleep deficit syndrome
d. None of the above

5. 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 _____, the "Star Sleeper" as the "spokescat" for healthy sleep.

a. "El Gato"
b. Felix
c. Garfield
d. None of the above

6. 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 _____ in which the drive or need for sleep depends upon the prior amount of wakefulness and sleep.

a. sleep-wake homeostatic process
b. synapses
c. hypothalamic activity
d. REM

7. Sleep disorders may arise from dysfunction at several levels within these two timing systems. Alterations in the circadian _____ 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. clock
b. rhythm
c. pacemaker
d. none of the above

8. Discovery that chronic partial sleep loss for _____ 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:

a. as little as one day
b. as little as one week
c. more than three weeks
d. more than two months

9. Sleep time is defended by an accumulation of _____, 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, in rare and extreme cases, 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.

a. “mental cob webs”
b. “slow wave” sleep time

c. “sleep debt”
d. none of the above

10. Research has delineated the molecular basis of Narcolepsy and circadian rhythm disorders (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_____.

a. inconsistent
b. chronic
c. short term
d. none of the above

11. _____ 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, the physiological effects of acute and chronic sleep loss in vital organ systems other than the brain have only just begun to be explored.

a. Work
b. Eating
c. Napping strategies
d. all the above

12. 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 _____ between sleep disturbance and behavioral problems.

a. no connection
b. some slight connection
c. a strong link
d. none of the above

13. 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 _____. 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, with the discovery of other human mutations and polymorphisms affecting circadian regulation.

a. sleep phenotypes
b. rhythm patterns
c. REM sleep
d. synapses

14. Functional neuroimaging techniques (primarily_____) reveal that 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). 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.

a. MRI
b. PET
c. 3-D Ultrasound
d. Neural Radiographs

15. _____ 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.

a. MRI
b. PET

c. 3-D Ultrasound
d. Neural Radiographs

16. Scans taken at 5 vs. _____ minutes after awakening suggest that re-emergence 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.

a. 10
b. 15
c. 20
d. 30

17. Excessive daytime sleepiness is a major public health problem associated with interference with daily activities including _____. Optimum daytime performance with minimal sleepiness in adolescents and young adults appears to require at least eight to nine hours of sleep at night with few interruptions. A majority of adolescents and adults, however, report habitual sleep durations of fewer than seven hours per night during the week and fewer than eight hours of sleep each night on weekends.

a. cognitive problems
b. motor vehicle crashes
c. reduced productivity
d. all the above

18. The relationship between sleep (quantity and quality) and estimates of morbidity and mortality _____. Data from epidemiological studies suggest that a habitual short sleep duration (less than six hours sleep per night) or long sleep duration (more than nine hours sleep per night) is associated with increased mortality. A recent epidemiological report found that self-reported sleep duration averaging either less or more than seven 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.

a. has been well established
b. seems to be quite remote
c. remains controversial
d. none of the above

19. Sleep architecture is unaffected by menstrual cycle phase. But 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_____.

a. REM period
b. circadian body temperature rhythm
c. slow wave patterned sleep
d. none of the above

20. Women _____ 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.

a. who are having their period
b. under 30-years-of-age
c. on oral contraceptives
d. none of the above

21. Many medical disorders can impair sleep quality and can, in turn, be adversely affected by poor sleep. Common examples include

a. diabetes
b. congestive heart failure, pain, and obstructive lung disease
c. glaucoma
d. hypothyroidism

22. Sleep is a powerful _____ 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.

a. modulator
b. curative
c. preventor
d. none of the above

23. 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 _____ 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.

a. repetitive
b. long waveform
c. diurnal
d. bipolar

24. Narcolepsy is a disabling neurological disorder characterized by sleepiness and symptoms of abnormal REM sleep. It is most commonly diagnosed with the following tests:

a. an ECG
b. Polysomnogram and Multiple sleep latency test
c. MRI
d. a blood test

25. Risk factors for drowsy driving crashes include:

a. all the factors below
b. late night/early morning driving,
c. people who sleep 6 or fewer hours per day
d. commercial truck drivers and night shift workers.

END