

## CHRONOBIOLOGY AND SLEEP DISORDERS

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In this section on chronobiology and sleep disorders, the seven chapters describe considerable advances in this field since the *Fourth Generation of Progress* was published. This group of chapters seeks to integrate our basic and clinical knowledge and to convey the high level of current excitement in sleep and biological rhythm research. All these chapters present certain cross-cutting themes providing a basic and clinical integration of both primary sleep disorders and those disorders in which sleep alterations represent important aspects of serious neuropsychiatric disorders.

In Chapter 128, on basic mechanisms, Pace-Schott and Hobson add a wealth of new detail to our knowledge of the brain structures involved in the control of sleep and waking, as well as the cellular level mechanisms that orchestrate the sleep cycle by neuromodulation. This chapter focuses on the brainstem neuromodulatory systems and the more specific organization of those systems in controlling the alternation of wake, non-rapid eye movement (NREM) sleep, and REM sleep. Interactions of diverse neuromodulatory systems operate in widespread subcortical areas to amplify or suppress REM sleep generation, as well as to facilitate onset and offset of the control of behavioral state by the pontine REM-NREM oscillator. This existence of an executive aminergic-cholinergic reciprocal interaction system controlling REM-NREM alternation in the pontine brainstem has been strongly confirmed by recent findings.

In Chapter 129, Lewy discusses circadian phase sleep and mood disorders and covers the following areas: circadian anatomy and physiology; the shifting of circadian phase using bright light; an update on seasonal affective disorders; discussion of other circadian phase disorders such as shift work and jet lag; and, finally, a section on melatonin and

circadian phase disorders. In this review, the author discusses phase typing sleep and mood disorders, including both advanced and delayed types, phase shifts with both bright light and melatonin administration, and whets our appetite on the considerable activity on melatonin research. Optimal dosing of melatonin will depend on minimizing its soporific side effect while maximizing its phase-shifting effects. This may entail using a low-dose sustained-release formulation to smooth out any sharp spikes in melatonin levels that appear to cause sleepiness in some people. Another useful product that we may look forward to is a delayed-release sustained-release formulation that can be taken at bedtime to produce increases in melatonin conveniently throughout the night.

Chapter 130, by Kloss, Szuba, and Dinges, covers sleep loss and sleepiness and reviews the four major types of sleep disorder: pathophysiology of difficulty initiating or maintaining sleep; pathophysiology of disorders of excessive somnolence; neurobehavioral and physiologic effects of sleep loss; and treatment for sleep loss and sleepiness. This chapter discusses the causes, consequences, and mechanisms of sleep disruption and concomitant daytime sequelae, namely, sleepiness and neurobehavioral performance decrements. Several advances in the psychopharmacologic and behavioral treatments of the causes and consequences of sleep loss have evolved. Technologies are rapidly developing and show promise for effective evaluation of these highly prevalent problems. The authors also present recent advances in assessment and prevention technology and go well beyond Multiple Sleep Latency Test (MSLT) and pupillometer evaluations. As examples, they also discuss the sleep switch and other operator-centered fatigue monitoring technologies.

Mignot and Nishino's Chapter 131, on the pathophysiologic and pharmacologic aspects of narcolepsy, provides an

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exciting set of insights to the advances in this particular area. Narcolepsy is frequently both overdiagnosed and underdiagnosed. However, the condition is not rare and has a population prevalence similar to that of multiple sclerosis. With the availability of validated animal models and as the only known disorder with a complete disorganization of sleep and REM sleep, narcolepsy is also a unique disease model for basic sleep researchers. Our understanding of the pathophysiology of the disorder is rapidly emerging as a result of the discovery that narcolepsy or cataplexy is associated with a deficiency in the hypocretin (orexin) neuropeptide system. The discovery that a deficit in hypocretin neurotransmission, as revealed by cerebrospinal fluid hypocretin studies, frequently causes human narcolepsy opens the door to new diagnostic and therapeutic strategies. Measuring hypocretin levels in the cerebrospinal fluid or other biological fluids may soon be used as a diagnostic test for narcolepsy. The finding that human narcolepsy is HLA associated also suggests a possible autoimmune mediation in many cases.

In Chapter 132, Mendelson discusses certain basic mechanisms on how hypnotics act. Thus, we are beginning to have some insight into an early issue in sleep research: how administration of sedative-hypnotic compounds from such diverse pharmacologic classes can result in sleep induction. It appears that most or all of them produce their pharmacologic effects by altering the function of various moieties of the γ-aminobutyric acid<sub>A</sub> (GABA<sub>A</sub>)-benzodiazepine receptor complex. One possibility that has received little attention has been that classic hypnotics such as benzodiazepines or barbiturates may alter the ascending histaminergic arousal system, which is presumably the mechanism by which antihistamines produce sedating effects. Certainly, one area of interest would be the tuberomamillary nucleus (TMN), which lies adjacent to the mamillary bodies, just above the ventral surface of the hypothalamus. Another focus for dysregulation in insomnia may involve the ventrolateral preoptic area (VLPO) and its interactions with the TMN in the posterior hypothalamus. The GABAergic VLPO has been identified as one of the few "sleep-active" areas of the brain; dysregulation in this nucleus and its efferent projections to histaminergic, cholinergic, and noradrenergic nuclei could conceivably shift the sleep-wake balance in the direction of wakefulness. In principle, benzodiazepine or other hypnotic compounds may act by enhancing GABAergic inhibition of the TMN and thereby decreasing its arousing effects.

In Chapter 133, Buysse and Dorsey provide a superb review on experimental therapeutics of insomnia. Although considerable progress has been made with regard to the epidemiology of insomnia, further work needs to be done regarding its consequences for health and role functioning. Persons

with insomnia complain not only of sleep disturbance, but of daytime consequences as well. In addition, investigations into the neurobiology of insomnia are clearly needed. This will help to define the underlying pathophysiology of insomnia in the general sense, but it will also help to define the boundaries of specific insomnia disorders. Several issues also remain with regard to treatment aspects of insomnia. First, the relative benefits and risks of treatment in terms of symptomatic relief, health-related quality of life, and morbidity remain to be defined. These issues are of considerable importance, given the potential for some insomnia treatments to cause significant adverse effects, such as cognitive impairment and injurious falls. The optimal duration of treatment and the conceptualization of potential "maintenance" treatments for insomnia are also areas open for further investigation. With regard to behavioral treatments, one of the major challenges is designing well-manualized and "exportable" treatments that can be applied more readily in a variety of treatment settings, including primary care settings. Data from several studies examining the optimal combination of behavioral and medication treatment approaches suggest better durability of treatment effects with behavioral treatment alone. However, sequential treatments and concurrent treatments need to be investigated. In addition, treatment strategies for nonresponders to either behavioral or pharmacologic interventions must be developed.

The final chapter in this section, Chapter 134, reviews our current understanding of sleep disturbances associated with neuropsychiatric disease. Nofzinger and Keshavan provide a brief review of the advances relating basic research on sleep with clinical sleep findings in major neuropsychiatric diseases such as depression, schizophrenia, Alzheimer disease, and other disorders across the life span. As one of the earlier tools available to psychiatric research for discovering the biological basis of mental disorders, EEG sleep recordings have been used extensively to characterize alterations in brain function across diverse mental disorders. Newer tools available include refinements in electrophysiologic recordings using automated EEG and the concurrent use of electrical recordings of cognitive processes such as evoked responses to characterize changes in information processing during sleep in relation to mental disorders. Advances in functional neuroimaging could provide us with dynamic images of brain function as it makes transitions throughout the sleep-wake cycle. In this manner, the functional neuroanatomic basis of the electrophysiologic abnormalities could be determined, and interventions could be designed targeting not only specific neurotransmitter systems but also systems that are specific to a discrete brain region responsible for the sleep-wake disturbance.