SLEEP: A COMPREHENSIVE HANDBOOK

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**INDEX**
A textbook has to meet the needs of various readers, from the specialist who yearns to know “more and more of less and less” to the generalist who is limited by knowing “less and less of more and more.” This need is nowhere more apparent than in the multidisciplinary science of sleep medicine.

Assembled in this preface, as well as in the pages of the textbook, is the collective expertise of the major authorities on contemporary sleep medicine worldwide. The authors have attempted to write a current and comprehensive text that covers the entire spectrum of adult and pediatric sleep medicine, encompassing major disease entities affecting sleep and that are, in turn, affected by sleep itself. Separate sections on sleep among women, in the elderly, and in special patient groups emphasize the unique character of their sleep.

The Science of Sleep Medicine

Normal Human Sleep. Normal human sleep is comprised of two distinct states known as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is subdivided into four stages: stage 1, stage 2, stage 3, and stage 4. REM sleep may be further subdivided into two stages: phasic and tonic. Several models have been proposed to explain the regulation of sleep and wakefulness. One such model proposes that the regulation of the sleep–wake cycle is governed by two processes: a sleep-dependent homeostatic process and a sleep-independent circadian process. (Rama AN et al)

The Neurobiology of Sleep. The basic tenet of the neurobiology of sleep is that sleep is a product of the central nervous system. The neurobiology of sleep and wakefulness can be described as a system distributed along the neuraxis from the medulla oblongata to the neocortex. While mechanisms within the brain produce sleep and wakefulness, brain mechanisms also are the targets of their influence. (Marks GA)

Physiologic Processes During Sleep. Many of the physiologic changes occurring during sleep are associated with changes in the level of activity of the autonomic nervous system. NREM sleep is characterized by a period of relative autonomic stability with sympathetic activity remaining at about the same level as during relaxed wakefulness, and parasympathetic activity increasing through vagus nerve dominance and heightened baroreceptor gain. During tonic REM sleep, a relative increase in parasympathetic activation is noted (mostly as a result of sympathetic input decline). Changes in autonomic function and inherent changes in the control exerted by the central nervous system (CNS) affect most organ systems in the body during sleep. (Rosenthal L)

Biological Rhythms and Sleep. The fundamental behavioral circadian rhythm is the rest–activity cycle. Circadian timing is an inherited adaptation and is genetically determined. The timing of the sleep–wake cycle depends on the interaction of a number of brain systems, in particular the circadian timing system (CTS). The CTS not only coordinates the timing of the sleep–wake cycle by opposing the sleep homeostat but also serves to coordinate the timing of pacemakers and oscillators in other tissues and organs to facilitate adaptation. (Moore RY)

Biology of Dreaming. Correlation of dreaming with a specific, identifiable EEG pattern became the focus
for efforts to describe the physiological processes that are the biological basis for the dreaming process. However, biological dream theories cannot provide us with the content of dreams, the meaning of dreams, the construction of dreams, or the function of dreaming. (Kramer M)

Psychology of Dreaming. The major reason for studying dreaming in the modern context is to understand the functioning of the mind, to understand consciousness. A secondary but important reason for studying dreaming is to see if such a study will unlock the mysteries of psychosis. The dream experience can be influenced by a number of factors and can be usefully quantified. The dream is orderly and organized, signal not noise, as it reflects meaningful psychological differences and responds to and reflects emotionally laden influences. (Kramer M)

The Function of Sleep. Why we sleep remains one of nature’s greatest mysteries. Some tentative conclusions regarding this question can be made. While sleep may have beneficial effects on general health, its primary function concerns the brain and not the body. Sleep, in some general way, facilitates normal neuronal function. It is possible that sleep is a time when overall neuronal function is facilitated either by sleep-dependent increases in gene expression and protein synthesis, or alterations in neuronal activity. (Frank MG)

The Evolution of Sleep: A Phylogenetic Approach. There is extensive variation in both the amount and phasing of sleep across taxonomic groups. In contrast to the wealth of knowledge on mammalian species, there is a relative lack of information on sleep in reptiles, amphibians, fishes, and invertebrates. A phylogenetic evaluation of sleep demonstrates that all mammals, birds, and reptiles engage in sleep, and evidence for sleep in amphibians, fishes, and invertebrates is strong if not certain. (Lesku JA et al)

Neuropharmacology of Sleep and Wakefulness. The two main regions that modulate our sleep–wake cycles are the mesopontine reticular activating system (RAS) and the hypothalamus. In addition, the intralaminar thalamus and the basal forebrain are modulated by the RAS and hypothalamus and participate in the process of arousal and alertness, as well as in the modulation of sleep states. Neuroactive agents that modulate these regions will also modulate the level of arousal. (Garcia-Rill E et al)

Epidemiology of Sleep Disorders. The difficulty in distinguishing between normal and abnormal sleep is reflected in the evolution of the classifications and definitions of symptomatology. This evolution in classifications is also reflected in the epidemiological stu-
dies of sleep disorders. This has rendered comparisons between earlier and more recent surveys problematic. (Ohayon MM, Guilleminault C)

Classification of Sleep Disorders. The American Academy of Sleep Medicine has recently completed the International Classification of Sleep Disorders, Version 2 (ICSD-2). Significant changes have occurred to keep up with the changing field of sleep medicine. As the science of sleep medicine is progressively developing from its early scientific underpinnings, and greater clarity is slowly evolving in many areas of patient diagnosis and treatment, that new data has been applied to the ICSD. (Chesson AL)

Insomnia

Insomnia: Prevalence and Daytime Consequences. Insomnia is a common problem. Most studies assessing the prevalence of insomnia in the general population find that between 30% and 35% of individuals have experienced some difficulty sleeping in the previous year. The disorder is associated with negative consequences including increased use of medical services, absenteeism from work, automobile and industrial accidents, poorer work performance, greater risk for depression, and negative impact on family life. (Brown WD)

Causes of Insomnia. There are many purported causes of insomnia, covering a broad range of medical, psychiatric, and behavioral factors. A model of chronic insomnia has been proposed that assumes a multifactorial etiology and categorizes causal factors according to their role in the formation of insomnia: predisposing, precipitating, or perpetuating. According to this model, all individuals have a certain level of predisposition to insomnia, and insomnia occurs when this predisposition interacts with exposure to a precipitating factor. Common precipitating factors include medical disorders, psychiatric disorders, environmental factors, medication effects, primary sleep disorders, or circadian rhythm changes that negatively affect sleep. Perpetuating factors are behavioral and cognitive changes that occur once an individual has been sleeping poorly for a period of time. (Stepanski EJ)

Medications that Can Cause Insomnia. Medications can cause insomnia, and conversely withdrawal of medications can lead to sleep symptoms, including insomnia. Certain medications are used to treat sleepiness and thereby are designed to have insomnia as a therapeutic effect. Other classes of drugs are associated with insomnia as an unwanted side effect. (Welsh CH, Fugit RV)

Fatal Familial Insomnia. Fatal familial insomnia is a rare but uniformly fatal disease characterized by
sleep disturbances, autonomic dysregulation, and dementia. It is inherited in an autosomal dominant fashion, resulting from a point mutation at codon 178 of the prion gene. It is rapidly progressive once symptoms appear. There is no known specific treatment. (Politsky CA)

**Evaluation of Insomnia.** The evaluation process in the management of an insomnia complaint involves consideration of many potential clinical syndromes. Sleep-focused physical and mental status examinations are important for accurate diagnosis. Sleep diary data recorded before the initial evaluation is useful to assess sleep scheduling across nights more objectively. Data from self-report questionnaires that focus on sleepiness, anxiety, depression, general psychopathology, sleep quality, and insomnia help the clinician to appreciate the clinical issues, identify diagnoses, and select treatments. (Moul DE, Buysse DJ)

**Pharmacologic Therapy of Insomnia.** Hypnotic agents are primarily indicated for the treatment of transient sleep disruption such as those caused by jet lag, shift work, or acute stress, but are also used in selected persons with chronic insomnia (ideally for primary insomnia that failed to respond to behavioral therapy, or secondary insomnia that did not improve with treatment of the underlying condition). The selection of a particular hypnotic medication should be based on the characteristics of the patient, duration and timing of insomnia, and the pharmacological profile of the agent. (Lee-Chiong T, Sateia M)

**Nonpharmacologic Therapy of Insomnia.** Chronic insomnia often is perpetuated by dysfunctional beliefs about sleep, heightened anxiety, and sleep-disruptive compensatory practices. Nonpharmacologic insomnia therapies such as relaxation therapy, stimulus control, sleep restriction therapy, and cognitive–behavioral therapy target behavioral and psychological factors that maintain and exacerbate sleep difficulties. (Means MK, Edinger JD)

**Excessive Sleepiness**

**Sleep Deprivation and Its Effects on Cognitive Performance.** Although sleep deprivation will ultimately lead to the involuntary onset of sleep in an individual, the cognitive performance effects of sleep deprivation can be evident even before sleep occurs uncontrollably in the form of sudden microsleeps or sleep attacks. Sleep deprivation adversely affects basic cognitive processes involving speed and accuracy of attention and memory, as well as higher order cognitive processes involving executive functions. Microsleeps and behavioral lapses increase with sleep loss as a function of wake state instability. (Dorrian J, Dinges DF)

**Narcolepsy.** Narcolepsy is a chronic neurological disorder of excessive daytime sleepiness that characteristically has a childhood onset and is associated with a hypocretin deficiency. The cardinal features of narcolepsy are daytime somnolence, cataplexy, sleep paralysis, and hypnagogic hallucinations. Successful treatment for narcolepsy includes both behavioral and pharmacological treatments. (Pelayo R, Lopes MC)

**Idiopathic Hypersomnia.** The term idiopathic hypersomnia has been used to categorize individuals with prominent daytime sleepiness, but who lack the classic features of narcolepsy or evidence of another disorder known to cause daytime sleepiness, such as sleep apnea. Nocturnal sleep is prolonged and uninterrupted. Naps are usually more than an hour in duration and are nonrefreshing. No amount of sleep ameliorates the daytime sleepiness. Currently, no specific marker is available to confirm the diagnosis. (Brooks SN)

**Post-Traumatic and Recurrent Hypersomnia.** Commonly, patients who have suffered even minor head trauma complain of sleep disturbances, including hypersomnia. Other etiologies of hypersomnia include postinfectious hypersomnia, Kleine–Levin syndrome, idiopathic recurring stupor/endorzepine stupor, and menstrual-related hypersomnia. (D’Ambrosio CM, Baron J)

**Sleeping Sickness, Human African Trypanosomiasis.** Sleeping sickness is an endemic parasitic disease that is exclusively located in intertropical Africa. After a bite by the tsetse fly, the illness evolves in two stages, the hemolymphatic stage I followed by the meningoencephalitic stage II, ending with demyelinization, altered consciousness, cachexia, and death if untreated. Excessive daytime sleepiness is one of the most reported signs during stage II of the illness. (Buguet A et al)

**Medications that induce Sleepiness.** Drug-induced sedation is one of the most common effects and side effects of central nervous system (CNS) active drugs. Drugs known to induce daytime sleepiness are associated with declines in daytime performance and increased rates of automobile accidents. Benzodiazepines, antidepressants, and other agents may be utilized for their sedative side effects in anxious and insomniac patients. (Pagel JF)

**Evaluation of Excessive Sleepiness.** The identification of pathological sleepiness begins the process of establishing a proper diagnosis and allows initiation of treatment and follow-up of the individual’s response. The diagnostic process begins with and is based primarily on a thorough sleep and general medical history. Nocturnal polysomnography is indicated in the evaluation...
PREFACE

Therapy for Excessive Sleepiness. Sleepiness can be affectively managed when the condition is due to a medical, neurological, or psychiatric disorder. When sleepiness results from a primary sleep disorder affecting a presumed underlying sleep–wake mechanism, such as narcolepsy, psychostimulants and/or awake-promoting substances are generally used palliatively to manage the condition. (Hirshkowitz M)

Napping. Short periods of sleep, or naps, during the daytime or at night can be used to actively cope with the physiological need of sleepiness. A nap may also be capable of maintaining waking performance and alertness under prior sleep restrictions. (Takahashi M, Kaida K)

Sleep Loss, Sleepiness, Performance, and Safety. Sleep loss and sleepiness degrade performance efficiency and increase the likelihood of operational errors that may contribute to traumatic or catastrophic incidents. A substantial number of people regularly confront sleep loss and sleepiness because of work, other situational demands, or medical conditions. Still, we are far from a precise estimate of the magnitude of risk from excessive sleepiness or its contribution to societal loss. (Rosa RR)

Sleep Disordered Breathing Syndromes

Physiology of Sleep Disordered Breathing. Upper airway competence involves complex interactions between anatomy and physiology. Airway size is determined by both dilating and collapsing forces. Dilating forces include upper airway muscle tone, mechanical force of the airway wall structure, and positive intraluminal airway pressure. Collapsing forces include tissue mass, surface adhesive forces, and negative intraluminal pressures. The resulting difference in these forces is the distending force, which acts on the wall of the upper airway. When the distending force increases, the airway size increases; when it decreases, the airway size decreases. (Woodson BT)

Snoring. Snoring is a repetitive sound caused by vibration of upper airway structures during sleep. Snoring results from pharyngeal vibration and is triggered by conditions that increase upper airway resistance and/or compliance, such as obesity, male gender, and nasal congestion. As the ramifications of obstructive sleep apnea are becoming clearer, the perception of snoring has changed from a sometimes noxious but otherwise benign marker of slumber, to an indicator of a potentially serious breathing disorder. (Olson EJ, Park JG)

Overview of Obstructive Sleep Apnea in Adults. Obstructive apnea is defined, by convention, as cessation of nasal/oral airflow for at least 10 seconds, despite persistent ventilatory efforts. One definition of obstructive hypopnea consists of reduction of airflow by at least 30% from baseline, of at least 10 seconds in duration and accompanied by oxyhemoglobin desaturation of 4% or more. Obstructive sleep apnea–hypopnea is prevalent in the community. Acquiring objective data supporting its diagnosis, traditionally employing nocturnal polysomnography, is a prerequisite to developing a treatment strategy. (Sanders MH, Givelber RJ)

Upper Airway Resistance Syndrome. Critical upper airway narrowing can also occur during sleep, leading to recurrent arousals and sleep fragmentation, even in the absence of discrete apneas, hypopneas, hypoxemia, or clear airflow reduction. This has been widely termed the upper airway resistance syndrome. This syndrome appears to cause daytime fatigue and sleepiness and may trigger both nocturnal and diurnal hypertension in a fashion similar to discrete obstructive sleep apnea. (Ballard RD)

Central Sleep Apnea. Central apnea is due to temporary failure in breathing rhythm generation resulting in the loss of ventilatory effort, lasting at least 10 seconds. Central apneas occur in many pathophysiological conditions. Depending on the cause or mechanism, central apneas may not be clinically significant. In contrast, in some disorders, central apneas result in pathophysiological consequences. (Javaheri S)

Obesity Hypoventilation Syndrome. Obesity hypoventilation syndrome (OHS) is broadly defined as hypercapnia during wakefulness in obese persons. The exact pathophysiologic mechanisms of OHS have yet to be fully elucidated, but at least four different factors may influence its development, including morbid obesity, mechanical limitation to increase minute ventilation, blunted central chemoreceptor response to...
Cardiovascular Complications of Obstructive Sleep Apnea. Patients with obstructive sleep apnea have an increased risk of hypertension, ischemic heart disease, stroke, and heart failure. Obstructive sleep apnea causes acute changes in cardiovascular regulation during sleep, disrupting the normal state of cardiovascular relaxation. Recent studies intimate an important role for sympathetic activation, inflammation and endothelial dysfunction, disordered coagulation, metabolic dysregulation, and possibly oxidative stress in the development of cardiovascular disease. (Hahn PY et al)

Pulmonary Hypertension and Sleep Disordered Breathing. Sleep disordered breathing (SDB) is associated with a variety of chronic cardiovascular sequelae, including effects on the right heart and pulmonary vasculature. The coexistence of underlying lung disease with SDB raises the risk of pulmonary hypertension, due apparently to lower baseline oxygen tensions. SDB, in the absence of concurrent lung disease, might also be associated with the development of pulmonary hypertension (PH), although the degree of PH identified in this group of patients has been in the mild range and its clinical significance is unclear. (Judd BG)

Neurocognitive and Functional Impairment in Obstructive Sleep Apnea. Persons with obstructive sleep apnea experience greater difficulty in performing everyday activities such as bathing and grocery shopping, role limitations at home and at work, more bodily pain, reduced energy levels, and perception of poorer overall health. Daytime fatigue can result in increased accidents and diminished work performance resulting in fewer promotions or loss of work. The stress of living with a chronic illness can result in increased anxiety and diminished quality of life. (Brown WD)

Sleep Apnea and Cerebrovascular Disease. Sleep apnea has been found at alarmingly high rates in patients with acute stroke and after full neurologic recovery. There are several hematologic and hemodynamic changes in sleep apnea that can play significant roles in the pathogenesis of stroke. Sleep apnea represents a modifiable risk factor, but whether treatment of sleep apnea in the acute stroke setting, the rehabilitation setting, or as primary/secondary prevention is of benefit awaits further treatment studies. (Mohsenin V, Yaggi H)

Radiographic and Endoscopic Evaluation of the Upper Airway. Imaging modalities (magnetic resonance imaging, computed tomography, nasopharyngoscopy, cephalometry, and fluoroscopy) have objectively quantified upper airway structures and identified specific craniofacial and oropharyngeal soft tissue structural risk factors for obstructive sleep apnea. Imaging studies should be considered in sleep apneic patients being evaluated for upper airway surgery or oral appliances. (Schwab RJ, Kline NS)

Evaluation of Sleep Disordered Breathing: Polysomnography. Attended full-channel polysomnography (PSG) is considered the standard assessment and evaluation for sleep disordered breathing (SDB). PSG is also recommended for positive pressure titration in order to determine the optimal therapeutic pressure. A preoperative clinical evaluation including PSG is routinely indicated to evaluate for the presence of SDB prior to upper airway surgery. Follow-up PSG is recommended after good response to oral appliance treatment in patients with moderate to severe SDB to ensure therapeutic benefit, after surgical treatment in patients with moderate to severe SDB to ensure satisfactory response, after surgical treatment of patients with SDB whose symptoms return despite initial success of treatment, after substantial weight loss or gain, and when clinical response is insufficient. (Mehra R, Strohl KP)

Evaluation of Sleep Disordered Breathing: Portable Sleep Monitoring. The number of potential patients usually exceeds the number of sleep laboratory facilities capable of performing the test. To increase access to diagnosis and potentially reduce cost, there has been an effort to produce systems that incorporate part or all of polysomnography but make it portable and ideally usable without an attendant technician. (Littner M)

Indications for Treatment of Obstructive Sleep Apnea in Adults. The primary treatment modality for obstructive sleep apnea is positive pressure therapy. In patients who do not accept positive pressure therapy despite careful attempts to optimize the treatment, second line therapy should be explored. While palatal surgery can effectively treat snoring, the effect on the apnea–hypopnea indices and daytime sleepiness is less robust. Oral appliances may help some patients. (Davé NB, Strollo PJ)

Medical Treatment of Obstructive Sleep Apnea: Lifestyle Changes, Weight Reduction, and Postural Therapy. Several alternative interventions have the potential for success in those patients who fail or refuse treatment trials using continuous positive airway pressure (CPAP) therapy, dental devices, or upper airway surgery. Obesity is a risk factor and probably is a cause or a precipitant of obstructive sleep apnea. Physicians
should advise patients to eliminate evening alcoholic beverages and to reduce overall amounts of alcohol. Many patients could benefit from a trial of supine avoidance treatment including obese and nonobese subjects with or without simultaneous use of CPAP or dental devices. (Kapen S)

Pharmacological Treatment of Sleep Disordered Breathing. Aminophylline, theophylline, acetazolamide, thyroid supplement, tricyclic or serotonin reuptake inhibitor antidepressants, and sedative-hypnotics all have minimal use in the treatment of obstructive sleep apnea. Estrogen replacement appears helpful in postmenopausal females. Oxygen and carbon dioxide are helpful in some patients with obstructive or central sleep apnea by stabilizing ventilatory control. (Hudgell DW)

Positive Airway Pressure Therapy for Obstructive Sleep Apnea. Positive airway pressure is generally the preferred treatment for individuals with moderate or severe obstructive sleep apnea (OSA). The most common type provides a constant pressure and is called continuous positive airway pressure (CPAP). A second type, called bilevel positive airway pressure (BPAP), provides two pressure levels, one during inhalation and a lower one during exhalation. The third type of device is called autotitrating positive airway pressure (APAP) and uses variable flow controlled by computer algorithms in an attempt to determine optimal pressure. Finally, a fourth type of positive pressure device called noninvasive positive pressure ventilation (NIPPV) places two different pressures at a set rate to entrain breathing and provide ventilatory assistance. CPAP improves airway patency during sleep, which in turn improves sleep quality, sleep continuity, daytime alertness, and overall quality of life in symptomatic patients with moderate or severe OSA. (Hirshkowitz M, Lee-Chiong T)

Upper Airway Surgery for Obstructive Sleep Apnea. Upper airway surgery for obstructive sleep apnea (OSA) modifies dysfunctional pharyngeal anatomy (e.g., ablating pharyngeal soft tissue or altering the facial skeleton from which the soft tissues are suspended) or bypasses the pharynx. (Sher AE)

Oral Devices Therapy for Obstructive Sleep Apnea. Oral devices improve airway and tongue space by repositioning the mandible both downward and forward. Indications for the use of these devices include patients who have mild to moderate sleep apnea, patients who only snore and have been diagnosed with apnea or where apnea has been ruled out, and patients who are intolerant to continuous positive airway pressure (CPAP) or might have had surgery that was deemed unsuccessful. (Bailey DR)

Circadian Rhythm Sleep Disorders

Advanced, Delayed, Irregular, and Free-Running Sleep–Wake Disorders. The delicate interplay of endogenous and exogenous factors, required to maintain normal sleep–wake rhythm, can become recurrently or chronically impaired in some individuals, leading to a group of disorders called circadian rhythm sleep disorders. They are characterized by an alteration of the circadian timing system or a misalignment between the timing of the individual’s sleep–wake rhythm and the 24 hour social and physical environment. (Dagan Y et al)

Jet Lag. Jet lag refers to the lag between the time frame of the biological clock and that of the destination time zone. Because the biological clock is slow to adjust, there will be several days after arrival in the new time zone before the biological clock “catches up” with the new routine. (Monk TH)

Shift Work Sleep Disorder. Shift work is generally defined as any schedule that requires work outside a broadly defined “day shift,” usually 6 a.m. to 6 p.m. Shift work is associated with both increased difficulty sleeping and with increased sleepiness during waking hours. (Richardson GS)

Neurological and Medical Disorders Associated with Circadian Rhythm Disturbances. Circadian rhythmicity may play an important role in the expression of some common neurological and medical disorders. Diurnal changes in physiology, behavior, and endocrine function may also influence the already disrupted sleep that is commonly seen in patients with neurological and medical illnesses, further exacerbating the disease process. (Gourineni R, Zee PC)

Psychiatric Disorders Associated with Circadian Rhythm Disturbances. Although there is currently no direct evidence that circadian abnormalities are causally related to any given psychiatric condition, alterations in the amplitude or phase of several circadian output variables, as well as mounting evidence that certain circadian rhythm manipulations prove therapeutically effective, suggest a potential pathophysiological role for the circadian pacemaker in major depressive disorder, bipolar disorder, and seasonal affective disorder or winter depression. (Jones S, Benca RM)

Therapy of Circadian Sleep Disorders. There are two general treatment strategies for circadian rhythm sleep disorders: (1) resetting the clock or (2) overriding the clock. With clock resetting, the phase (timing) of the circadian pacemaker is shifted (reset) so that the output signals for sleep and wake are more congruous with a person’s desired sleep/wake schedule. Light exposure and/or melatonin, administered at the optimal circadian phase, are currently the most practical...
phase-resetting agents available for clinical use. In cases where circadian resetting is impractical or undesirable, overriding the circadian signal with a hypnotic or alerting medication may be the preferred strategy. (Sack R, Johnson K)

Parasomnias

Disorders of Arousal and Sleep-Related Movement Disorders. An arousal disorder is characterized by an incomplete awakening from sleep where the individual has voluntary movements but no awareness of their actions. There are three types of arousal disorders including confusional arousals, sleep terrors, and sleepwalking. Nocturnal leg cramps and rhythmic movement disorders are classified as sleep-related movement disorders and consist of relatively simple movements that disturb sleep. (Cavanaugh K, Friedman NR)

Sleepwalking. Sleepwalkers may engage in complex motor behaviors but lack responsiveness to others. Once they are fully awake, they typically have no memory of having been out of bed, or of what they were doing, or why. (Cartwright RD)

REM Sleep Behavior Disorder and REM-Related Parasomnias. Rapid eye movement (REM) sleep behavior disorder is characterized by the loss of physiologic skeletal muscle atonia during REM sleep in association with excessive motor activity while dreaming. Other REM-related parasomnias include nightmares, catathrenia, painful nocturnal erections, sleep paralysis, and REM sleep-related sinus arrest. (Tippmann-Peikert M et al)

Nocturnal Enuresis in Children. Nocturnal enuresis is characterized by the frequent occurrence of normal complete uncontrolled micturition during sleep in children older than 5 years of age. Pathophysiology is still uncertain and management depends cultural factors. (Challamel MJ, Cochat P)

Sleep Bruxism. Sleep bruxism is a stereotyped, sometimes intense, orofacial movement with bilateral activation of the masseter and temporal “jaw closure” muscles. Bruxism is thought to be a major cause of temporomandibular disorder with patients complaining of pain and/or dyskinesia in the temporomandibular region. (Bader G)

Sleep-Related Eating Disorders. Sleeping and eating comprise two of the basic elements that drive human behavior. When the two are simultaneously affected, a fascinating spectrum of disease states may result. The differential diagnosis of sleep-related eating disorders include nocturnal eating syndrome and sleep-related eating disorder. (Auger RR, Morgenthaler TI)

Other Parasomnias. Sleep paralysis is one of the cardinal symptoms of narcolepsy; it can also occur on its own, in which case it exists in two forms, either familial or isolated. Sudden unexplained nocturnal death syndrome (SUNDS) is defined as sudden death in healthy young adults during sleep, in particular among young Asian males. An impaired sleep related-penile erection is the inability to sustain a penile erection during sleep that would be sufficiently large or rigid enough to engage in sexual intercourse. The cause is usually organic if the reduction occurs in the presence of normal sleep architecture. Sleep-related painful erections are defined as painful erections typically during REM sleep but not during the awake state. Sleep-related abnormal swallowing syndrome is characterized by inadequate swallowing of saliva, which results in aspiration with coughing, choking, and brief arousals or awakenings from sleep. (Qureshi A)

Movement Disorders

Restless Legs Syndrome. Restless legs syndrome (RLS) is characterized by four core symptoms: an urge or sensation to move the limbs, the urge worsens when at rest, movement improves the urge at least temporarily, and symptoms worsen in the evening or at night. RLS impacts up to 10% of adults in North America and Western Europe and is the most common neurologic disorder that causes chronic insomnia. (Becker PM)

Periodic Limb Movement Disorder. Periodic limb movement disorder (PLMD) is characterized by periodic episodes of highly stereotyped and repetitive involuntary rhythmic movements that usually affect the lower extremities during sleep. PLMD is strongly associated with restless legs syndrome. (Khassawneh B)

Sleep in Infants and Children

Ontogeny of EEG Sleep from Neonatal Through Infancy Periods. Maturation of infant behavior requires careful evaluation of both waking and sleep behaviors. Serial neonatal and infant electroencephalographic (EEG)/polysomnographic studies document the ontogeny of cerebral and noncerebral physiologic behaviors. EEG patterns and other physiologic relationships serve as templates for normal brain maturation and help distinguish intrauterine from extraterine development. (Scher MS)

Sleep in Infants and Children. Sleep occupies a major portion of the lives of newborns, infants, and children. Three distinct sleep states can be identified in the term newborn: active sleep (REM), quiet sleep (NREM),
and indeterminate sleep. Sleep becomes consolidated into a long nocturnal period of approximately 10 hours in children between 2 and 5 years of age. Generally, sleep patterns of children during middle childhood resemble those of older individuals, but there is considerable individual variability. (Sheldon SH)

Sleep and Breathing During Early Postnatal Life. Instability of the breathing pattern is an inherent characteristic of the normal healthy infant during sleep. Dramatic and profound changes in respiration during sleep occur with maturation of the neurophysiological, metabolic, and mechanical components of the respiratory system. The effect of REM sleep on the various mechanisms involved in respiratory control are of particular importance during infancy. (Goldbart AD et al)

Congenital Syndromes Affecting Respiratory Control During Sleep. The spectrum of disorders of respiratory control can include abnormal integration of responses to respiratory stimuli such as in central congenital hypoventilation syndrome, or abnormal regulation of autonomic function such as familial dysautonomia of which respiratory control is one aspect; or can involve abnormal development of brainstem structures in respiratory control such as myelomeningocele. Therapeutic management of central hypoventilation syndromes usually requires mechanical assisted ventilation or close monitoring for evidence of sleep disordered breathing causing cardiopulmonary compromise. (Witmans MB et al)

Sudden Infant Deaths. Sudden infant death syndrome (SIDS) is defined as sudden death of an infant under 1 year of age that remains unexplained after a complete postmortem examination, death scene investigation, and case conference. In most industrialized countries, SIDS is the leading cause of death in infants between the ages of 1 and 12 months. Little is known on the mechanisms responsible for the deaths of these infants. (Kahn A et al)

Obstructive Sleep Apnea in Children. Obstructive sleep apnea syndrome is common in children. It is commonest among preschoolers due to adenotonsillar hypertrophy. The vast majority of children with obstructive sleep apnea syndrome have both symptomatic and polysomnographic resolution following a tonsillectomy and adenoidectomy. (Bandla P, Marcus CL)

The Sleepless Child. Common causes of sleeplessness in children include sleep-onset association disorder, night wakings, early awakening, nighttime eating/drinking disorder, separation anxiety, parental limit setting, and night fears. Although sleeplessness may be primarily caused by a medical factor, there may also be a comorbid behavioral cause, or a behavioral cause may develop from a medical one and perpetuate the sleeplessness. (Moorcroft WH)

The Sleepy Child. Childhood is a time of growth, learning, and development. In order for these processes to occur the child must be awake, alert, and able to interact with and learn from the environment. Daytime sleepiness impairs the child’s ability to do this. A sleepy child falls asleep at inappropriate times. The problems that lead to excessive sleepiness in children can generally be elucidated by a careful history and eliminated by appropriate treatment. (Rosen G)

Craniofacial Syndromes and Sleep Disorders. Children and adults with craniofacial syndromes represent a population at increased risk for sleep disordered breathing, due to anatomic and, in some cases, neuromuscular differences in the upper airway. All patients with craniofacial anomalies or upper airway compromise should be screened for sleep-related symptoms in order to initiate proper evaluation and treatment. In addition, these individuals may report behavioral sleep complaints, such as sleep-onset or sleep maintenance insomnia. (Wills LM et al)

Medical Disorders. Medical disorders that impact sleep in pediatric patients include asthma, gastroesophageal reflux, and otitis media. Adequate treatment of these conditions may improve the quality of sleep for the child. (Palmer JM, Brooks LJ)

Sleep in Children with Neurological Disorders. Fragmented sleep is common in children with neurological disorders. Alterations in sleep–wake function vary, depending on the anatomic location of the neurological lesion. The severity of alterations in sleep–wake function also depends on the extent of the lesion and whether it is static or progressive. Medications used to treat neurological disease may also impact sleep architecture. (Kotagal S)

Sleep in Children with Neuromuscular Disease. Much of the morbidity and mortality in children with neuromuscular disease occurs because of respiratory muscle weakness, which impairs both ventilation and secretion clearance. Respiratory abnormalities are often first noted during sleep. Once respiratory compromise has progressed to the point of causing sleep-related daytime symptoms, respiratory failure may be imminent. (Givan DC)

Sleep in Children with Behavioral and Psychiatric Disorders. Primary behavioral and psychiatric disorders in children are frequently associated with and/or complicated by sleep disturbances, which may be related to such factors as the psychopathology of the underlying disorder, comorbid conditions, or pharmacologic treatment. Even modest improvements in sleep quality and
duration may have a significant impact on neurobehavioral functioning. (Owens JA, Davis KF)

Circadian Rhythm Disorders in Infants, Children, and Adolescents. Children are in flux with regard to sleep and its timing. The major feature of circadian rhythm sleep disorders is a misalignment between the child’s sleep pattern and the sleep pattern that is required by parents, day care, and school. (Herman JH)

Sleep in the Elderly

Normal Sleep in Aging. With aging, sleep, as with other physiological processes, undergoes increasingly noticeable changes. Many of the changes accompanying aging are part of a gradual process rather than an abrupt change and reflect changes in both homeostatic and circadian processes that occur throughout the life span. Chronological age by itself seems to explain very little of the observed prevalence of sleep complaints. Medical diseases and chronic illness may account for most of the changes in sleep observed in old age. (Ayallon L, Ancoli-Israel S)

Sleep Disordered Breathing in Older Adults. Sleep disordered breathing (SDB) is highly prevalent in older adults, with sleep apnea alone affecting nearly 20% of the elderly. However, sleep apnea syndrome, defined as the presence of an elevated apnea-hypopnea index (AHI) and clinical symptoms, is far less common. It is possible that SDB in the elderly is a different pathophysiologic process than SDB in younger subjects. Those with cardiovascular co-morbidities or other clinical symptoms such as excessive daytime sleepiness can suffer significant morbidity and mortality from SDB. (Gooneratne N)

Insomnia and Aging. Insomnia is a prevalent and persistent problem associated with aging. A large number of physical health conditions such as pain syndromes, primary pulmonary problems, neurologic disturbances, and dementias such as Alzheimer’s disease contribute to the increase in sleep problems associated with aging. Medications used to manage chronic conditions may also contribute to insomnia in the elderly. (Friedman L)

Sleep in Institutionalized Older Adults. Nighttime sleep disruption is characteristic of nursing home residents, and is typically accompanied by daytime sleepiness. Many factors contribute to these sleep problems, including medical and psychiatric illness, medications, circadian rhythm abnormalities, sleep disordered breathing, environmental factors and lifestyle habits. There is some suggestion that these factors are amenable to treatment, particularly improving daytime activity patterns, increasing light exposure and reducing sleep-disruptive care giving practices at night. (Martin JL, Alessi C)

Sleep Among Women

Patterns of Sleep in Women: An Overview. A woman’s changing hormone profile influences her sleep. In general, more disruption can be anticipated with abrupt changes and withdrawal of female hormones. Some sleep disorders, such as sleep disordered breathing and restless legs syndrome, may also be influenced by the reproductive stage. (Driver HS)

Sleep During Pregnancy and Postpartum. Hormonal changes during early pregnancy, continuous enlargement of the fetus throughout pregnancy, and a newborn with random cycles of sleeping and feeding contribute to a woman’s sleep loss. Problems with sleep are experienced as early as the tenth week of pregnancy. The major concern for postpartum women is sleep loss and resulting physical fatigue, negative mood states, and cognitive impairment. (Lee KA)

Menstrual-Related Sleep Disorders. Despite considerable hormonal fluctuations over the course of the menstrual cycle, sleep architecture and circadian rhythm appear to remain relatively stable in normal women. Women with dysmenorrhea may experience sleep disturbance, especially during the menses. Complaints of poor sleep and fatigue are common among women with both premenstrual syndrome and premenstrual dysphoric disorder. Menstrual-associated insomnia and hypersomnia are rare disorders of sleep with manifestations that occur primarily during the late luteal phase. (Pien GW, Beothy EA)

Sleep Disordered Breathing in Women. Sleep disordered breathing is a relatively common disorder in women. Many women with sleep disordered breathing may remain undiagnosed. Although men are more likely to develop sleep disordered breathing, the difference should not lead to missing the diagnosis in women. (Badr MS)

Sleep During the Perimenopausal Period. Perimenopause is a transitional period occurring prior to menopause, or cessation of menses. Changing hormone levels and other physiological alterations may underlie some of the increased sleep disturbances. Other factors such as significant life events, increased weight gain, and incidence of sleep apnea, primary insomnia, and depression may also contribute to the increased incidence of sleep disturbance and dissatisfaction with sleep observed in perimenopausal women. (Rogers NL, Grunstein RR)

Sleep During Postmenopause. Though health-care practitioners and older women have a tendency to attribute
the appearance of sleep disturbance to the onset of menopause or “hormone problems,” the sleep complaints and changes experienced by older women are likely to be attributable to chronic physical or mental illness and related factors such as stress and caregiving. The sleep of older women may be affected by some unique factors such as chronic hot flashes. (Moe KE)

Sleep in the Respiratory Disorders

Respiratory Control During Sleep. Sleep is a regulated state in which the regulation of different elements of the respiratory system is heterogeneous. Wakefulness is associated with an ill-defined, but important excitatory stimulus, which has been called the ‘wakefulness stimulus.’ Removal of the wakefulness stimulus reduces the drive to breathe, but sleep modifies the processing of the chemical and mechanical signals that contribute to stable values of carbon dioxide, oxygen and pH. Those areas of the brainstem involved in the control of sleep state also seem to play an important role in responses to a variety of respiratory stimuli, such as hypercapnia, hypoxia and a variety of upper airway reflexes. (Krimsky WR, Leiter JC)

Asthma. Circadian rhythms clearly play an important role in asthma. The proposed mechanisms of nocturnal worsening of asthma include sleep-related changes in lung volume, bronchial hyperresponsiveness, cortisol and beta-adrenergic receptor responsiveness, parasympathetic tone, and airway inflammation. Perhaps the most intriguing hypothesis is that nocturnal asthma is primarily an inflammatory disorder, with a mechanism that is distinct from nonnocturnal asthma and a pathophysiology that centers on a worsening of both central and peripheral lung inflammation at night. (Beuther DA et al)

Chronic Obstructive Pulmonary Disease and Sleep. - Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterized by chronic airflow obstruction that is incompletely reversible. Increased sleep disruption is common in COPD as evidenced by increased frequency of arousals, increased frequency of sleep stage changes, and decreased total sleep time. Sleep-associated desaturation is often an expression of worsening respiratory failure during sleep. Patients with COPD who have concomitant obstructive sleep apnea may be particularly vulnerable to developing respiratory failure and secondary hemodynamic complications. (Iber C)

Sleep and Breathing in Cystic Fibrosis. In patients with cystic fibrosis, marked gas exchange abnormalities can first appear during sleep, preceding the appearance of daytime respiratory failure. Patients with cystic fibrosis and moderate to severe lung disease may exhibit marked nocturnal desaturation, especially in REM sleep. The main mechanisms responsible for this appear to be reduced respiratory drive and loss of postural muscle tone. (Piper AJ et al)

Restrictive Thoracic and Neuromuscular Disorders. Sleep disordered breathing is common in restrictive thoracic and neuromuscular diseases. Hypoxemia and hypoventilation are common during sleep, related to reductions in functional residual capacity (FRC) and blunting of central drive (either primary or secondary to progressive bicarbonate retention). These gas exchange abnormalities lead to arousals, fragmenting sleep and producing symptoms such as morning headache and daytime hypersomnolence. (Perrin C et al)

Noninvasive Ventilation and Sleep. Noninvasive ventilation has a beneficial effect on ventilation during sleep. Noninvasive ventilation appears capable of improving sleep quality and quantity as well, in patients with restrictive or obstructive ventilatory defects. Although sleep appears improved, it is rarely normalized. (Liistro G, Rodenstein D)

Sleep in the Cardiac Disorders

Hypertension and Cardiovascular Disease. Obstructive sleep apnea has adverse effects on blood pressure, cardiovascular status, and probably cardiovascular mortality. There is also evidence that effective therapy with CPAP can improve blood pressure and cardiac function in adult obstructive sleep apnea patients. (Ballard RD)

Congestive Heart Failure. Both obstructive sleep apnea and central sleep apnea with Cheyne–Stokes respiration can exist separately or together and interact in the same patient with congestive heart failure. Obstructive sleep apnea may impair cardiac function and contribute to increased morbidity and mortality in patients with concomitant heart failure. Central sleep apnea with Cheyne–Stokes respiration may be a marker for poor cardiac function and may indicate a worse prognosis in these patients. (Mazza E, Gurubhagavatula I)

Cardiac Arrhythmias and Sudden Death During Sleep. Autonomic nervous system activity and disturbed respiration during sleep are capable of provoking both atrial and ventricular arrhythmias in patients with cardiovascular disease. A significant number of atrial arrhythmias, in particular atrial fibrillation, in patients under 60 years of age and lethal ventricular arrhythmias have their onset at nighttime. (Verrier RL, Josephson ME)
Sleep in the Other Medical Disorders

Sleep and the Gastrointestinal Tract. The interaction of gastrointestinal functioning and sleep may lead to sleep complaints as well as the pathogenesis of some gastrointestinal disorders. Sleep-related gastroesophageal reflux (GER) is an important factor in the development of esophagitis and respiratory complications of GER. Patients with functional bowel disorders have an increase in sleep complaints. (Orr WC)

Renal Disease. Sleep complaints and primary sleep disorders are very prevalent in end-stage renal disease (ESRD) patients and appear to have important adverse effects on their overall health and well-being. Primary sleep disorders such as sleep apnea (SA), restless legs syndrome (RLS), and periodic limb movement disorder (PLMD) are very common. (Parker KP)

Endocrine and Metabolic Disorders and Sleep. Obesity is frequently associated with sleep disorders, including obstructive sleep apnea (OSA), sleep disruption, and daytime sleepiness and fatigue. The proinflammatory cytokines, TNF-α and IL-6, may play a role in mediating sleepiness in patients with sleep apnea and obesity. Although knowledge on the association between diabetes mellitus and sleep disturbances is limited, it is plausible that there is an association between insulin resistance and sleep apnea. Administration of testosterone worsens SA, whereas female sex hormones appear to be protective of OSA. Disturbances of sleep are not uncommon in patients with acromegaly and disorders of the adrenal and thyroid glands. (Vgontzas AN et al)

Sleep in Fibromyalgia and Chronic Pain. Patients with fibromyalgia often report sleep fragmentation, early morning awakenings, unrefreshing sleep, fatigue, and insomnia. Primary sleep disorders, especially sleep apnea and restless legs syndrome with periodic limb movements of sleep, may also be found in fibromyalgia patients. There is a complex relationship between chronic pain and sleep. Pain can disrupt sleep and poor sleep can increase pain intensity. (Harding SM, Lee-Chiong T)

Sleep and the Immune Response. Sleepiness is frequently experienced during acute infections and other inflammatory diseases. These changes in sleep are part of the microbe-induced acute phase response and are mediated by cytokines. In addition, changes in the immune response are associated with sleepiness and sleep loss. (Kruerger JM, Majde JA)

Sleep in the Neurologic Disorders

Alzheimer’s Dementia. Alzheimer’s disease is a progressive neurodegenerative disorder that accounts for approximately two-thirds of all dementias worldwide. Sleep disturbance adds an additional burden to the compromised function and quality of life directly attributable to dementia. Accurate assessment of sleep disturbances in demented patients can only be done in the context of appreciating the potential contributing associated medical disorders, current drug treatments, psychopathologies, primary sleep disorders, and behavioral and environmental conditions that may exist. (Vitiello MV)

Neurodegenerative Disorders. There are several progressive neurodegenerative dementias and all of them are characterized by a progressive cognitive and functional decline with increasing neuropathology over the course of the illness. Although the sleep disturbances associated with them may appear superficially similar, there are likely to be vast differences in their expression. The impact of homeostatic versus circadian disruption, environmental versus neurodegenerative etiologies, and the role played by aging across the continuum of age-associated sleep and circadian changes all need to be accounted for to ultimately understand the etiology of sleep disturbance associated with a particular neurodegenerative illness. (Harper DG)

Parkinson’s Disease. Problems initiating or maintaining sleep in Parkinson’s disease (PD) may be due to uncontrolled motor symptoms, the effects of medications, restless legs syndrome, depression, or circadian sleep–wake reversal in patients with superimposed dementia. Multiple factors interact to cause sleepiness in PD patients, including somnolence intrinsic to the disorder itself, the effects of medication, and sleep disorder-related breathing. REM sleep behavior disorder (RBD) is present in 15–33% of PD patients assessed in PD clinics. Hallucinations and behavioral problems at night can also occur. (Silber MH)

Seizures. Sleep states have a potent effect on the expression or suppression of epileptic seizure manifestations. NREM sleep, awakening from sleep, and other transitional arousal states are conducive to electrographic and clinically evident seizures, whereas REM sleep is not. Sleep disturbances often parallel the severity of seizure disorders. Antiepileptic drugs can ameliorate seizure-related sleep disturbances, but improvement in sleep architecture is not a critical factor in seizure control. (Shouse MN)

Headaches and Sleep. Sleep may play a role in headache genesis. Certain headache types may be associated with or evolve from certain sleep stages. Various sleep pathologies or disorders may also lead to the development of headaches arising from sleep. (Greenough GP)
Cerebrovascular Disorders. The usual sleep hours between midnight and 6 a.m. have the lowest stroke risk, as well as having the lowest blood pressure and lowest catecholamine and corticosteroid levels. The stroke risk rises with elevations in these three parameters after awakening. Specific sleep–wake cycle anomalies resulting from stroke injury to specific brain regions have been well documented. Obstructive sleep apnea (OSA) and snoring are associated with an increased risk for stroke. (Labib B, Nazarian SM)

Brain and Spinal Cord Injury. There is a complex relationship between disorders of sleep and traumatic brain injury, with evidence supporting the development of a number of sleep disorders as a result of traumatic brain injury, including insomnia, circadian rhythm disorders, periodic limb movement disorder, obstructive sleep apnea, narcolepsy, and post-traumatic hypersomnia. (Castriotta RJ)

The Blind Patient. Blind persons may have defective retinal processing or an impaired retinohypothalamic tract (that conducts photic information from the retina to the biological clock located in the suprachiasmatic nucleus of the hypothalamus) and therefore may be unable to exhibit a 24 hour pattern. There are a higher percentage of insomnia and free-running circadian patterns in blind persons compared to sighted adults. (Leger D, Metlaine A)

Sleep in the Psychiatric Disorders

Schizophrenia. Sleep disruption is a common and very debilitating comorbid symptom of schizophrenia. Sleep disruption can aggravate psychosis; conversely, increased susceptibility to external stimuli imposed by schizophrenia means that the psychopathology would increase sleep disruption. For the most part, medications used to treat schizophrenia improve problematic sleep. However, their discontinuation can, if only temporarily, worsen sleep symptoms. (Norwood RJ, Lee-Chiong T)

Mood Disorders. Sleep complaints are pervasive in those diagnosed with major depressive disorder, including difficulty falling asleep, intermittent awakenings, and early morning awakenings. Most antidepressant medications suppress REM sleep; these agents may also produce alterations in sleep consolidation and sleep architecture. (Armitage R)

Anxiety Disorders and Sleep. The cognitive and physiologic changes associated with excessive anxiety alter sleep and are made worse by the lack of sleep. The sleeplessness that anxiety can cause turns back on itself and magnifies anxiety, thus setting up a vicious cycle. (Weissberg M)

Trauma and Post-traumatic Stress Disorder. Sleep disturbances are common in post-traumatic stress disorder (PTSD). Anxiety dreams, increased REM phasic activity, increased arousals from REM sleep, increased startle response, low dream recall, and possibly elevated awakening thresholds from sleep may characterize PTSD. (Pillar G et al)

Alcohol, Alcoholism, and Sleep. Ethanol has been found to have far-reaching effects on sleep and sleep disorders. The sleep of healthy normals appears to be disturbed with acute high ethanol doses. Individuals with alcoholism commonly have sleep problems, which may occur during active drinking, acute ethanol discontinuation, and prolonged abstinence. (Hyde M et al)

Drugs of Abuse and Sleep. Nearly all drugs of abuse have considerable effects on sleep and wakefulness and on particular stages of sleep. The sleep stage most typically affected by these drugs is REM sleep. It has been hypothesized that sleep and wake changes, although not the primary reinforcing mechanisms, function as contributing factors in maintaining the compulsive and excessive drug use, and in increasing the risk for relapse. (Hyde M et al)

Sleep in Special Patient Groups

Sleep and the Caregiver. Many internal and situational factors can influence the caregiver’s ability to obtain quality sleep. In fact, not getting enough sleep is a major cause of illness and stress in caregivers. Caregivers are “on call” 24 hours per day, 7 days per week. Caregiver anxiety, worry, grief, or bereavement can lead to sleep disturbances. (Carter PA)

Sleep in Patients with HIV Disease. Sleep disturbance (primarily insomnia) and fatigue are very common and often disabling symptoms for this population of individuals. Although it may begin at any point along the spectrum of human immunodeficiency virus (HIV) disease, sleep disturbance often appears very early in the course of infection and seems to contribute to a decrease in quality of life during the course of illness. (Jaffe SE)

The Patient with Cancer. Sleep disturbances are a common complaint in cancer patients. The etiologic factors contributing to the sleep problems are multiplicative and include side effects of treatment, pain, maladaptive sleep behaviors, medications, the diagnosis itself, and the specific treatment of surgery, chemotherapy, radiation, or hormonal therapies. Fatigue, mood disturbance, and a compromised immune system are possible consequences of sleep disturbance. (Engstrom CA)
Sleep in the Intensive Care Unit. Patients in the intensive care unit (ICU) are more susceptible to significant sleep deprivation. The cause appears to be multifactorial and includes the type and severity of the patient’s underlying illness, medications received, use of hemodynamic and respiratory monitoring devices, use of mechanical ventilation, and the ICU environment itself. Sleep deprivation can affect cognitive behavior, as well as cellular immune function and tissue repair. (Krachman SL, Chatila W)

Sleep and the Cardiac Surgery Patient. Sleep deprivation, including decreased quantity, increased fragmentation, and decreased quality of sleep, is prevalent in adults who have undergone cardiac surgery, and it has been shown to be associated with decrements in postoperative physical function and emotional well-being. During the early postoperative period, management of environmental stimuli, including reductions in noise, lighting, and the frequency of intrusive patient care interactions, may facilitate sleep. Adequate medication for pain is also an important consideration. (Redeker NS, Hedges C)

Sleep Disturbances After Noncardiac Surgery. There are profound sleep disturbances in the postoperative period with initial slow-wave sleep and REM sleep suppression and subsequent REM rebound. It seems that the surgical trauma-induced inflammatory stress response, metabolic–endocrine stress response, circadian disturbances, and postoperative opioid use are the most important factors influencing sleep after surgery. Sleep disturbances might play a significant role in the development of cardiopulmonary instability, postoperative cognitive disturbances, and fatigue. (Gögenur I, Rosenberg J)

Relevance of Anesthesiology for Sleep Medicine. Sleep and anesthesia are altered arousal states actively generated by the central nervous system. There are no contemporary data that systematically characterize the effect of volatile anesthetics on the sleep of patients without the confounding factors of surgical insult, polypharmacy, trauma, or coexisting disease. (Lydic R, Baghdoyan HA)

Sleep at High Altitudes. Poor sleep is a prominent manifestation of rapid ascent to high altitude and is in part related to acute changes in ventilatory stimuli. Sleep at high altitude is characterized by frequent arousals and poor quality. It is worsened by the development of high altitude illnesses such as acute mountain sickness and high altitude pulmonary edema. Sleep improves with acclimatization. (Chatila W, Krachman S)

Sleep and Aviation. Modern pilots and aircrews must cope with a variety of nonstandard work schedules in order to effectively meet customer/mission demands. Aviation personnel are likely to be faced with unpredictable work hours, long duty periods, and circadian disruptions, which all lead to difficulties obtaining adequate sleep. Progress toward the widespread development and implementation of scientifically valid sleep/rest- and performance-optimization strategies is already contributing to operational safety throughout the system. (Caldwell JA)

Sleep, Exercise, and Sports. A clear relationship between exercise and sleep remains undetermined; nonetheless, some studies suggest the intriguing possibility of utilizing exercise to improve sleep. The existence of a circadian advantage or jet lag effect on sports performance also remains inconsistently supported. (Enderlin CA, Richards KC)

Sleep, Sleep, Loss and Circadian Influences on Performance and Professionalism of Health Care Workers. Acute care nurses, physicians, interns, residents, medical students, and staff are faced with challenges of prolonged wakefulness time, chronic insufficient sleep, and the need to work at times of low circadian wakefulness stimuli and thus will likely experience times of impaired cognitive performance. The significance of the impaired performance spans lack of sensitivity and reduced compassion to medical error. (Veasey SC)

The Student with Sleep Complaints. In the first two decades of life, when one is most likely to be a student, there are profound changes taking place in physiologic sleep patterns. In addition to these biologic processes, there are profound psychosocial changes that occur especially in early student life. Sleep problems are common and underrecognized in the student group. Poor sleep quality has been linked to increased tension, irritability, depression, more frequent use of alcohol and illicit drugs, accidents, and lower academic performance. (Bijwadia J, Dexter D)

Sleep Assessment Methods

The Sleep Interview and Sleep Questionnaires. A comprehensive sleep interview with the use of appropriate questionnaires should allow clinicians to have a good idea of what sleep disorder or disorders a patient may have. There are some commonly used validated questionnaires that can help with the assessment of daytime sleepiness and fatigue: the Epworth Sleepiness Scale, the Stanford Sleepiness Scale, and the Fatigue Severity Scale. (Bae CJ, Golish JA)

Polysomnography. Polysomnography is the monitoring of physiologic signals from various organs and transduction of those signals to a recording device. Polysomnography is the standard for the diagnoses of
many sleep disorders including, but not limited to, obstructive sleep apnea. Although most sleep laboratories utilize similar montages, equipment and scoring standards may vary. (Collop NA)

**Pediatric Polysomnography.** The polysomnographer faces multiple challenges posed by the evolution of pediatric electroencephalography and sleep staging, changes in respiratory rates and patterns with age, differing presentations and etiologies of disorders such as obstructive sleep disordered breathing in children versus adults, and even the issues of dealing with small children and their families. The complexity of pediatric polysomnography is increased by limited normative data for interpretation of its various parameters. (Griebel ML, Moyer LK)

**Introduction to Sleep Encephalography.** The main limitation with routine electroencephalography (EEG) with a brief 20–30 minute recording is its poor sensitivity for epilepsy. EEG-video monitoring is the highest level of epilepsy monitoring and is the gold standard. (Benbadis SR)

**Monitoring Respiration During Sleep.** Monitoring of respiration during sleep allows the assessment of physiological variables that are required to characterize sleep-related breathing disorders. During an obstructive respiratory event, pharyngeal collapse occurs with an increasing inspiratory effort; measuring changes in intrathoracic pressure and activity of inspiratory muscles is important for defining these events. Although the only direct method for measuring airflow is pneumotachography, indirect measurements of flow are widely used because of better patient tolerance. Measurement of thoracic volume in sleep studies is mainly performed to infer flow. Noninvasive assessments of blood gases are generally employed during sleep studies. (Magalang UJ et al)

**Recording and Monitoring Limb Movements During Sleep.** Proper electrode placement is essential for recording limb movements. Limb movements can be seen and recorded in the legs as well as the arms. The preferred placement to record leg movements is on the belly of the anterior tibialis muscle group. When monitoring the arms, the extensor digitorium is the best site for recording. (Scott CE)

**Actigraphy.** Actigraphy refers to a methodology for recording and analyzing movement from small, computerized devices worn on the body. Actigraphy can be very useful in investigations of group differences, sleep pattern variations over time, and the effects of behavioral or treatment interventions. (Acebo C)

**pH Monitoring and Other Esophageal Tests.** When nocturnal gastroesophageal reflux occurs, physiologic changes associated with sleep may influence the clearance of esophageal acid, upper airway protection, and other defense mechanisms sufficiently to promote an increase in the severity of both esophageal and extraesophageal complications of gastroesophageal reflux disease (GERD). Nocturnal heartburn associated with GERD can result in sleeping difficulties and impaired daytime function. Finally, GERD may result in extraesophageal manifestations that can be disruptive of sleep. Esophageal pH monitoring has become the most common technique used to investigate the potential role of GERD in producing symptoms. (Cott G)

**Psychological Assessment of the Sleep Patient.** The goals of a general psychological assessment of the sleep patient include evaluating psychological factors contributing to sleep problems, diagnosing or ruling out psychiatric disorders, and providing treatment recommendations. An enormous number of instruments have been developed in order to objectively describe, measure, and quantify different aspects of psychological functioning. A more specialized neuropsychological assessment may be performed when neuropsychological abilities such as attention, concentration, memory, and organization are in question. (Ikelheimer ABR, Hoyt B)

**Operating and Managing a Sleep Disorders Center.** Sleep centers began in academic environments. Recognition of the huge numbers of patients with sleep disorders forced expansion beyond the academic sleep center. Standards for the professional staff, facilities, equipment, personnel, and operation of the sleep center were developed, and the American Academy of Sleep Medicine (AASM) now offers accreditation to centers that meet these standards and Standards of Practice documents to guide the practice of sleep medicine. (Rosenberg RS)

**Accrediting a Sleep Program.** American Academy of Sleep Medicine accreditation is considered the “gold standard” for sleep programs and it provides many advantages. It helps assure quality in delivering sleep medicine services for physicians and patients and it can also be useful in distinguishing a program from others in a competitive marketplace. (Arand D)

Painstaking research had been undertaken to assure the accuracy and timeliness of the data in this book. Nonetheless, the disciplines of sleep and dreaming are constantly evolving. Each day, new discoveries prompt us to redefine old concepts and formulate new ones—these will be incorporated in future editions of this book. Readers are encouraged to share their opinions and recommendations regarding this textbook.

Sleep is as ancient as life itself. It is a universal phenomenon that occupies nearly a third of human existence. Yet
until as recently as a century ago, sleep has remained almost exclusively in the realm of fables, poetry, and theology. Advances in our understanding of the complex biology and physiology of sleep and of the various sleep disorders have radically transformed the role of sleep in our lives. Nonetheless, many fundamental questions on the nature of sleep remain unanswered. Why do we sleep? What is the function of sleep across the span of ages in one’s lifetime, and in the diversity of species? How does sleep alter biologic processes?

This textbook is not meant to be the culmination of our knowledge of the science of sleep. Rather, consider it but a pause as we reflect on our place in the rapidly altering landscape of sleep medicine.

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SLEEP: A COMPREHENSIVE HANDBOOK
PART I

THE SCIENCE OF SLEEP MEDICINE
Normal human sleep is comprised of two distinct states known as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is subdivided into four stages (stage 1, stage 2, stage 3, and stage 4). Stages 3 and 4 are collectively referred to as slow-wave sleep. REM sleep may be further subdivided into two stages: phasic and tonic. The purpose of this chapter is to provide the reader with an overview of normal human sleep.

SLEEP ARCHITECTURE

NREM Sleep

NREM sleep accounts for 75–80% of sleep time. Stage 1 NREM sleep comprises 3–8% of sleep time. Stage 1 (Figure 1.1 and Figure 1.2) sleep occurs most frequently in the transition from wakefulness to the other sleep stages or following arousals during sleep. In stage 1 NREM sleep, alpha activity (8–13 Hz), which is characteristic of wakefulness, diminishes and a low-voltage, mixed-frequency pattern emerges. The highest amplitude electroencephalography (EEG) activity is generally in the theta range (4–8 Hz). Electromyography (EMG) activity decreases and electro-oculography (EOG) demonstrates slow rolling eye movements. Vertex sharp waves (50–200 ms) are noted toward the end of stage 1 NREM sleep.

Stage 2 NREM (Figure 1.3) sleep begins after approximately 10–12 min of stage 1 NREM sleep and comprises 45–55% of total sleep time. The characteristic EEG findings of stage 2 NREM sleep include sleep spindles and K-complexes. A sleep spindle is described as a 12–14 Hz waveform lasting at least 0.5 s and having a “spindle”-shaped appearance. A K-complex is a waveform with two components: a negative wave followed by a positive wave, both lasting more than 0.5 s. Delta waves (0.5–4 Hz) in the EEG may first appear in stage 2 NREM sleep but are present in small amounts. The EMG activity is diminished compared to wakefulness.

Stage 3 and stage 4 (Figure 1.4 and Figure 1.5) NREM sleep occupy 15–20% of total sleep time and constitute slow-wave sleep. Stage 3 sleep is characterized by moderate amounts of high-amplitude, slow-wave activity; whereas stage 4 sleep is characterized by large amounts (e.g., >50% of a 30 s period) of high-amplitude, slow-wave activity. EOG does not register eye movements in stages 2–4 of NREM sleep. Muscle tone is decreased compared to wakefulness or stage 1 sleep [1].

REM Sleep

REM sleep (Figure 1.6) accounts for 20–25% of sleep time. The first REM sleep episode occurs 60–90 min after the onset of NREM sleep. EEG tracings during REM sleep are characterized by a low-voltage, mixed-frequency activity with slow alpha (defined as 1–2 Hz slower than wake alpha) and theta waves.

Based on EEG, EMG, and EOG characteristics, REM sleep can be divided into two stages—tonic and phasic. Characteristics of the tonic stage include a desynchronized EEG, atonia of skeletal muscle groups, and suppression of monosynaptic and polysynaptic reflexes. Phasic REM sleep is characterized by rapid eye movements in all directions as

---

well as by transient swings in blood pressure, heart rate changes, irregular respiration, tongue movements, and myoclonic twitching of chin and limb muscles [2–5]. Sawtooth waves, which have a frequency in the theta range and have the appearance of the teeth on the cutting edge of a sawblade, often occur in segments of equal size (e.g., epoch length of 300 mm and a duration of 30 sec [10 mm/sec]). A single stage score is assigned to each epoch. In Stage Wakefulness (W), the EEG typically demonstrates alpha activity and/or a low voltage, mixed frequency activity. Rapid eye movements and eye blinks can be evident in the EOG. There is usually a relatively high tonic EMG.

Figure 1.1 Wakefulness
Sleep is polygraphically defined by Non-Rapid Eye Movement (NREM) Stages 1, 2, 3, 4, and Rapid Eye Movement (REM) based on electroencephalographic (EEG), electrooculographic (EOG) and electromyographic (EMG) changes. The polygraph record is divided into segments of equal size (e.g., epoch length of 300 mm and a duration of 30 sec [10 mm/sec]). A single stage score is assigned to each epoch. In Stage Wakefulness (W), the EEG typically demonstrates alpha activity and/or a low voltage, mixed frequency activity. Rapid eye movements and eye blinks can be evident in the EOG. There is usually a relatively high tonic EMG.

NREM–REM Cycle
The NREM–REM sleep cycle occurs about every 90 min and approximately four to six cycles occur per major sleep episode. The ratio of NREM sleep to REM sleep in each cycle varies during the course of the night. The early cycles are dominated by slow-wave sleep and the later cycles are dominated by REM sleep. The first episode of REM sleep may last only a few minutes and subsequent REM episodes progressively lengthen in duration during the course of the major sleep period. In summary, slow-wave sleep is prominent in the first third of the night and REM sleep is prominent in the last third of the night. The temporal arrangement of sleep type is described graphically by a hypnogram (Figure 1.7).

SLEEP AND AGING
Sleep patterns change throughout life. Newborns may spend more than 16 h of the day asleep but intermittently sleep and awaken throughout the 24 h period. At the age of three months, infants should be able to sleep through the course of the night and take two or more daytime naps. As the child first enters school, he or she should be able to solidify a major nocturnal sleep period with perhaps a single daytime nap. As the child ages and during adulthood, the major nocturnal sleep is typically not accompanied by a daytime nap. Age-associated deterioration of
the sleep pattern results in fragmented sleep in the elderly, where more time is spent in bed but less time asleep.

Slow-wave sleep and REM sleep patterns also change throughout life. Slow-wave sleep declines after adolescence and continues to decline as a function of age. REM sleep decreases from more than 50% at birth to 20–25% during adolescence and middle age.

SLEEP NEUROPHYSIOLOGY

NREM Sleep

The transition from wakefulness to NREM sleep is associated with altered neurotransmission at the level of the thalamus, whereby incoming messages are inhibited and the cerebral cortex is deprived of signals from the outside world. NREM sleep is characterized by three major oscillations (Figure 1.8). Spindles (7–14 Hz) are generated within thalamic reticular neurons that impose rhythmic inhibitory sequences onto thalamocortical neurons. However, the widespread synchronization of this rhythm is governed by corticothalamic projections. There are two types of delta activity [6, 7]. The first type is clock-like waves (1–4 Hz) generated in thalamocortical neurons and the second type is cortical waves (1–4 Hz) that persist despite extensive thalamectomy. However, the hallmark of NREM sleep is the slow oscillations (<1 Hz), which are generated intracortically and have the ability to group the thalamically generated spindles as well as thalamically and cortically generated delta oscillations, leading to a coalescence of the different rhythms [8, 9].

REM Sleep

Transection studies demonstrate that the pontomesencephalic region is critical for REM sleep generation [10]. When the mesopontine region is connected to rostral structures,
Figure 1.3  Stage 2 Sleep  In Stage 2 sleep, a relatively low voltage, mixed frequency pattern, also characterizes the EEG. Sleep spindles and/or K complexes occur intermittently. A sleep spindle is defined by activity between 12 and 14 cycles per second (cps) of at least 0.5 sec duration, whereas K complexes are negative sharp wave immediately followed by a positive component with a total duration of over 0.5 sec. There is no sufficient high amplitude, slow activity that defines Stages 3 and 4 of sleep.

Figure 1.4  Stage 3 Sleep  In Stage 3 sleep, \( \geq 20\% \) but \( < 50\% \) of the epoch consists 2 cps or slower waves having amplitudes \( > 75 \mu V \) from peak to peak are present in the EEG.
Figure 1.5  Stage 4 Sleep  In Stage 4 sleep, >50% of the epoch consists 2 cps or slower waves having amplitudes >75 μV peak to peak are present in the EEG.

Figure 1.6  Stage REM  In Stage REM Sleep, the EEG is relatively low voltage with mixed frequency, resembling Stage 1 Sleep EEG. Episodic REMs can be appreciated in the EOG. The EMG is low in amplitude; tonic mental-submental EMG tracing almost always reaches its lowest levels.
REM sleep phenomena such as a desynchronized EEG and pontogeniculo-occipital (PGO) spikes are seen in the forebrain. When the mesopontine region is continuous with the medulla and spinal cord, REM sleep phenomena such as skeletal muscle atonia can be seen.

The pontomesencephalic area contains the so-called cholinergic “REM-on” nuclei, specifically the laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei. The LDT and PPT nuclei project through the thalamus to the cortex, which produces the desynchronization of REM sleep. PGO spikes are a precursor to the rapid eye movements seen in REM sleep and are formed in the cholinergic mesopontine nuclei and propagate rostrally through the lateral geniculate and other thalamic nuclei to the occipital cortex [11]. The LDT and PPT nuclei project caudally via the ventral medulla to alpha motor neurons in the spinal cord, where skeletal muscle tone is inhibited during REM sleep by the release of glycine [12]. In addition, as NREM sleep transitions to REM sleep, tonic inhibition of REM-generating cholinergic pontomesencephalic nuclei by brainstem serotonergic and adrenergic nuclei decreases, thereby allowing the development of PGO spikes and muscle atonia [13]. Thus the cholinergic REM-on nuclei of the PPT and LDT slowly activate the monoaminergic “REM-off” nuclei of the dorsal raphe and locus caeruleus that inhibit REM-on nuclei (Figure 1.9).

Hypocretin has an important role in the modulation of wakefulness and REM sleep. Hypocretin neurons are located in the lateral hypothalamus and widely project to brainstem and forebrain areas, densely innervating monoaminergic and cholinergic cells. Hypocretin neurons promote wakefulness and inhibit REM sleep [14]. Elevated levels of hypocretin during active waking and in REM sleep compared to quiet waking and slow-wave sleep suggest a role for hypocretin in the central programming of motor activity [15]. Hypocretin projections to the nucleus pontis oralis may play a role in the generation of active (REM) sleep and muscle atonia [16].

**AUTONOMIC NERVOUS SYSTEM**

The autonomic nervous system (ANS) regulates the vital functions of internal homeostasis. The ANS is comprised of the sympathetic nervous system and parasympathetic nervous system. The essential autonomic feature of NREM sleep is increased parasympathetic activity and decreased sympathetic activity. The essential autonomic feature of REM sleep is an additional increase in parasympathetic activity and an additional decrease in sympathetic activity, with intermittent increases in sympathetic activity occurring during phasic REM (Table 1.1). For example, pupilloconstriction is seen during NREM sleep and is maintained during REM sleep with phasic dilatations noted during phasic REM sleep.

<table>
<thead>
<tr>
<th>Sleep Period</th>
<th>Parasympathetic Nervous System</th>
<th>Sympathetic Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>NREM sleep</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>REM sleep</td>
<td>Tonic Increases further</td>
<td>Decreases further</td>
</tr>
<tr>
<td>Phasic</td>
<td>Intermittent increases</td>
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**TABLE 1.1 Autonomic Nervous System Fluctuations During Normal Human Sleep**
MODEL OF SLEEP REGULATION

Several models have been proposed to explain the regulation of sleep and wakefulness. One such model proposes that the regulation of the sleep–wake cycle is governed by two processes: a sleep-dependent homeostatic process (Process S) and a sleep-independent circadian process (Process C) [17].

Process S is a homeostatic process that is dependent on the duration of prior sleep and waking. This process shows an exponential rise during waking and a decline during sleep. In other words, the longer a person stays awake, the sleepier he or she becomes; conversely, the longer a person sleeps, the lower the pressure to remain asleep.

Process C is a circadian process that is independent of duration of prior sleep and waking. This process is under the control of an independent circadian oscillator, which determines the rhythmic propensity to sleep and awaken. In other words, each person has an endogenous drive to fall asleep and awaken at a certain time regardless of the duration of prior sleep or wake.

The two-process model posits that the timing of sleep and waking is determined by the interaction between Process S and Process C. Sleep onset is thought to occur when both the homeostatic and circadian drive to sleep intersect.

Other models have also been proposed, such as the opponent-process model and the three-process model of alertness regulation; however, further work is necessary to determine the biological substrates of the elements of these models and the pathways by which they interact.

CONCLUSION

Considerable research has been directed toward elucidating the basic mechanisms of normal human sleep. A firm understanding of the principles of normal human sleep is critical to understanding abnormal sleep and the disorders associated with sleep.

REFERENCES


ADDITIONAL READING

THE NEUROBIOLOGY OF SLEEP

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INTRODUCTION
Progress in the understanding of the neurobiology of sleep, as with basic science in general, is greatly dependent on two circumstances. One is advance in technology and the other is discovery. Rational questions on the nature of sleep behavior have a long published history and, with little doubt, extend to prehistory. It is not surprising that much attention would be paid to a prominent human endeavor such as sleep. Yet the current condition of our knowledge of how, and for what purpose, we sleep is far from complete. The paucity of technology through most of the past to observe the operation of the central nervous system has resulted in a relatively short history of efforts to identify neural mechanisms underlying the generation and maintenance of sleep and wakefulness. A limitation of time as it impacts the capriciousness of the process of discovery is one factor. Another critical factor, which has become apparent with the accumulation of knowledge, is the complexity of the problem.

A large body of knowledge has accumulated on sleep/wake behavior including natural observation, pathological alterations, and experimental manipulation. The conclusion that constitutes the basic tenet of the neurobiology of sleep is that sleep is a product of the central nervous system. To understand how the brain produces sleep is to identify those neural mechanisms necessary and sufficient to produce it. Early investigations employing the emerging technology of modern neuroscience conceived of a brain made up of centers of localized function. Thus destruction of the "sleep center" would result in the elimination of sleep and serve to identify the structure and its function. In as much as the use of this approach has yet to yield a consensus as to what structure constitutes the "sleep center," a concept of interacting, distributed systems has emerged as a more plausible mechanism of this process.

While mechanisms within the brain produce sleep and wakefulness, brain mechanisms also are the targets of their influence, and these various mechanisms need not be mutually exclusive. Alterations in brain activity accompanying changes in state of arousal are so widespread and global in nature that they can be viewed as constituting reorganization in whole brain. In every region of brain, neurons alter their rate or pattern of firing with changes in state [1]. The specific roles played by such mechanisms are being elucidated as technological tools for study become available.

Despite the level of complexity, a great deal is known of the neural mechanisms subserving sleep. This knowledge is sufficient to impact the development of rational therapies for many sleep disorders. General concepts on the neuroscience of sleep are emerging and serious candidates for critical neural mechanisms have been identified. Through further advances in technology and discovery a full understanding will be achieved. The following is an overview of the current perspectives in the field of sleep.

PROBLEM OF DEFINITION
Defining sleep/wake behavior is not a trivial matter nor is a single definition appropriate for all cases. Definitions based on overt, gross behavior suffer from an inability to distinguish several conditions generally not recognized as sleep. The problem of definition is most acute when applied...
THE NEUROBIOLOGY OF SLEEP

across species. Circadian patterns of rest and activity are observed across phyla including single-celled organisms and plants [2]. Conservation through evolution may provide a clue to the adaptive value of temporally regulating activity and may also indicate that the mechanisms subserving this behavior probably vary with the complexity of the organism expressing them. From the viewpoint of neurobiology, definitions of sleep are couched in subservience to a nervous system. This requires that the subject not only possess a nervous system but also that the behavior be dependent on its operation.

Neurobiological investigations of sleep/wake mechanisms have been conducted almost exclusively with mammalian species. This has generated a definition of sleep based on a confluence of several electrophysiological correlates of brain activity. It should be pointed out that these indicators of state are defining properties and not chosen because of any relationship to fundamental saliency or functional significance; nor is the definition invariant. For example, a specific pattern in the electroencephalogram (EEG) is used to define sleep, yet other measures of neural activity clearly indicate the presence of sleep in a cat with its neocortex removed [3]. This flexibility in defining sleep can result in a high degree of ambiguity in interpreting effects of experimental manipulations and pathological conditions. There is no absolute agreement on how many indicators are required to identify sleep. Problems also arise when neurobiological definitions of sleep are applied to species other than mammalian and avian. Current investigations are revealing many similarities between the inactive states of the fruit fly and mammalian sleep [4]. Electrophysiological correlates of neural activity may be uncovered, but brain mechanisms implicated in the control of sleep/wake behavior in the mammalian brain do not exist in the fly. If the fly sleeps, then it will have to be defined differently than mammalian sleep. Inasmuch as the functions of sleep are currently unknown, it remains to be determined whether the sleep states of mammals and flies are even analogous and, if so, on what basis.

Among mammalian species, there appears to be a high degree of similarity in both expression and mechanism [5]. Differences exist in daily amounts and temporal distribution of sleep. Certain species’ specializations exist, such as the unihemispheric sleep of some cetaceans and the single, consolidated, sleep period of some primates, including humans. Consensus among workers in the field is that the basic neural mechanisms identified in work on cats and rats likely apply to humans and other mammals.

DEFINING CHARACTERISTICS OF SLEEP AND WAKEFULNESS

In the third decade of the twentieth century, the application of the newly discovered EEG [6] began to yield insights into the altered brain activity associated with the sleep/wake cycle. Initial findings recognized clear distinctions in the EEG during wake and sleep. The low-amplitude, high-frequency activity characteristic of wakefulness increases in amplitude and decreases in frequency during sleep. At first, degrees of slowing and increased amplitude within sleep were viewed along a single dimension, depth, with the lightest sleep being most similar to wake [7]. With hindsight, many subsequent observations on sleeping subjects report data indicating multidimensional aspects to sleep. It was not, however, until the mid-twentieth century that Aserinsky and Kleitman reported the cyclic appearance of a distinct stage of sleep associated with dreaming and characterized by a wake-like EEG in the presence of rapid eye movements [8].

The pioneering work of Jouvet and colleagues utilizing cats [9] identified the presence of rapid eye movement (REM) sleep, which they called paradoxical sleep for the wake-like brain activity present. Several defining characteristics differentiated this state from that of the rest of sleep or what is now referred to as non-REM (NREM) sleep. In addition to the low-voltage, fast EEG, and rapid eye movements absent from NREM sleep, there appears an inhibition of muscle activity between paroxysmal muscle movements, wake-like activity in the hippocampus, and a unique spindling activity in the pons, now recognized as PGO waves. Based on threshold to arousal by the presentation of sensory stimuli, REM sleep is a deep sleep: thus the association of EEG amplitude and frequency with sleep depth had to be revised. Work on animals permitted neurophysiological investigations that initially took the form of gross brain lesions. Results of these studies confirmed the individual identities of the two stages of sleep by indicating reliance on different neural mechanisms for their generation [3].

In adult therian mammals studied, the general organization of sleep and wakefulness assumes a similar form [5]. In addition to a cyclic alternation of sleep and wake states, there is a more rapid alternation within sleep between NREM and REM. The occurrence of REM sleep is always preceded by NREM. The distribution of sleep/wake episodes repeats daily, thus expressing a circadian rhythm shared by many physiological functions under a common temporal influence [10]. The faster ultradian rhythm of the sleep cycle also may be served by mechanisms independent of sleep. Many observations support a basic, rest/activity cycle, with relatively fixed period, underlying several physiological functions [2]. Sleep stage amounts, temporal, daily distributions, and the period of the ultradian sleep cycle are species-specific traits. The period of the sleep cycle is highly correlated to the size of the species and, inversely, to its basal metabolic rate [5].

In addition to temporal factors controlling sleep/wake behavior, total sleep time and time in the individual stages
also express homoeostatic types of regulation [11]. That is, when sleep, or a specific stage, is not permitted to be expressed, the amount lost tends to be recovered, as if a quota were being maintained. Time lost, however, is usually greater than time recovered, giving rise to the concept that sleep intensity increases, permitting recovered sleep to be more efficient. The amplitude of slow-wave activity in the EEG is an indicator of intensity of NREM sleep [12] and density of phasic activity, such as eye movements or PGO waves, has been used to reflect REM sleep intensity [13]. The rates of incurring a sleep debt and of recovery appear not only to be species specific but also characteristic of strains within a species, indicating a high degree of heritability [14]. The inverse dependence of sleep, or stage amounts, on prior expression creates another factor contributing to the oscillation among states of arousal making up the cyclic nature of sleep/wake behavior.

NATURE OF SLEEP/WAKE MECHANISMS

Two of the major characteristics of sleep are its reversibility and sensitivity to modulation by a variety of influences. In addition to inducing arousal from sleep by stimuli in any sensory modality of sufficient magnitude, amounts of sleep are affected by many factors such as ambient temperature, lighting conditions, and level of oxygen in the air, as well as by a host of wake experiences, including stress and learning. These would indicate that neural mechanisms whose primary function are not the generation of sleep and wake can control sleep and wake behavior. This raises a question as to how a sleep mechanism can be identified. Does the observation that loud sounds inhibit sleep make the auditory system a sleep mechanism? On some levels the answer is yes. Yet we know that the auditory system is not necessary for the production of sleep and wakefulness. Is necessity then the criteria for judging primacy? In a system of distributed, interactive mechanisms, it may be that no one mechanism is necessary.

Historically, it was thought that the withdrawal of sensory input produced sleep by removing excitation to the neural systems of the brain that give rise to wakefulness [15]. Studies utilizing brain transections and lesions were not successful at proving this hypothesis. They did, however, provide the antecedents to the discovery by Moruzzi and Magoun that the reticular core of the brain, when stimulated electrically, was sufficient to induce arousal. This led to the concept of the ascending reticular activating system as a primary mechanism of conscious wakefulness [16]. Additional work utilizing lesion techniques found that destruction of certain regions resulted in decreased sleep (reviewed in [3]). The conclusion was that there existed mechanisms within the brain opposed to the arousal induced by the activating system. The sleep process, then and now, was no longer viewed as a passive result of disfacilitation, but rather as an active process subserved by active mechanisms. The discovery of the neurally active REM sleep stage firmly entrenched this view as doctrine in sleep research.

Differences in neural activity as well as in behavior among wake, NREM sleep, and REM sleep are so great that they appear to constitute discrete states of arousal. If each state is actively produced, then there may exist mechanisms exclusively subserving each state. Evidence supports such a division and most of the putatively identified brain mechanisms are categorized as such. The individual states, however, are not completely independent of each other. As mentioned previously, there is a dependence of REM sleep on prior NREM sleep. And with only three states, an increase or decrease in one will by necessity tend to have a reciprocal effect on time spent in the other states. A decrease in the efficacy of a wake-inducing mechanism, for example, may reduce wakefulness, but also will result in more sleep. There are circumstances under experimental and pathological conditions in which other than the three normal states can occur, such as coma or dissociated states, that do not conform to the definitions of any one state. However, the common and most often repeated finding with experimental destruction or pharmacological intervention of brain function is the tenacity with which only the three states appear, though possibly at altered levels, as well as the trend toward complete recovery of preintervention amounts.

Although the action potential of a single neuron can be considered an all-or-none event, neural interactions within networks are graded phenomena. The fact that neural networks produce the discrete states of arousal with rare instances of dissociation is an important clue to their organization. Saper and colleagues [17] have likened this to a switch that is only stable within one of the configurations of the confluen of processes attendant to one of the three states of arousal. Historically, this function was performed by “executive mechanisms” centralizing decision making by integrating input from multiple sources. A more egalitarian alternative consists of relatively equipotent mechanisms interacting through reciprocal connectivity. The process suggested for the “switch” is mutual inhibition. This type of interaction favors stable configurations in which only one mutually inhibitory influence dominates at one time. Inasmuch as the executive mechanisms of sleep and wakefulness have not been found and evidence is accumulating for the reciprocal connectivity of sleep and arousal centers, a view of interacting, distributed mechanisms is currently in favor. Such a system is also consistent with the difficulty with which selective destruction of individual components of the system fail to chronically eliminate any state of arousal. Putative sleep/wake mechanisms are segmentally distributed through the brain. Determination
of the specific roles played by each mechanism will be
needed to understand the whole.

MECHANISMS OF WAKEFULNESS

Since the original proposal of the ascending reticular acti-
vating system [16] to account for wakefulness, several sys-
tems have been implicated in contributing to this function.
With the introduction of sophisticated immunological and histochemical techniques, certain aminergic systems in
the brainstem were differentiated from the diffuse reticular
core of the brain [18, 19]. These systems share several
properties that include widespread projections and utiliza-
tion of neurotransmitters associated with neuromodulation,
making these systems appealing candidates for control over
the global alterations accompanying state changes. The nor-
adrenergic system of the locus coeruleus and the serotoner-
gic midline, raphe system have been speculated to play
various roles [20], but the current consensus is that these
wake-active neurons are involved in setting a general prepar-
ateness for wake activity associated with alertness and sensory–motor function [21, 22]. These monoaminergic
systems are virtually silent in REM sleep. The brainstem also
contains a population of cholinergic neurons in the lateral
dorsal tegmental nucleus and the pedunculopontine teg-
mental nucleus in which the majority are most active during
wake and REM sleep [23, 24]. This system is thought to
contribute to the activation associated with both these
states. While sharing many targets with the adrenergic
and serotonergic systems, cholinergic brainstem neurons
differ in that they do not project directly to the neocortex
[23]. Their influence on cortical activation is relayed
through the thalamus and extrathalamic pathways of the
hypothalamus and basal forebrain. The brainstem cholin-
ergic and monoaminergic systems also innervate the reticular
formation [19, 23].

Although much has been discovered, it is ironic that the
least progress has been made in specifically identifying
mechanisms of the reticular formation itself [25, 26].
Extending from the medulla oblongata to the midbrain,
the complex structure has been resistant to revealing its
secrets. Early stimulation and lesion experiments impli-
cated the more rostral aspects of the reticular formation
[3] and it was shown later that neurons residing in this
region of the midbrain, projecting to the midline thalamus,
discharge at their highest rates during the states of cortical
activation, wake and REM sleep [1]. In that the majority
of reticular neurons utilize the excitatory transmitter glut-
amate, as do the thalamic neurons that relay to the neocortex,
this mechanism provides another path for cortical activa-
tion. Reticular influences also can be relayed through the
extrathalamic pathways. Most sensory and motor systems
collaterally innervate the reticular formation. Excitation
of the reticular formation by sensory, or electrical, stimula-
tion probably is responsible for the rapid arousal from sleep
following their presentation. The reticular formation is not
a homogeneous mass with respect to its innervation, projec-
tions, or local circuitry; however, one property characteris-
tic of its structure is the high degree of intraconnectivity.
As one moves more caudal, fewer and fewer long, ascending
projections of reticular neurons reach the thalamus, but
rather end in more rostral regions of the reticular formation.
There also is a high degree of local interconnectivity. The
structure of the reticular formation is well suited for the
propagation of ascending as well as descending influences.
This is consistent with the findings of focal electrical stimu-
lation and local microinjection of drugs into the reticular
formation inducing global changes in arousal. The specific
role played by the reticular formation in behavior during
wakefulness is not clear at this time. Its intraconnectivity
may aid in the integration of multiple systems [25].

Characteristic of the distributed nature of structures con-
trolling states of arousal, wake mechanisms are located ro-
stral to the brainstem—in the diencephalon, thalamus and
hypothalamus, and the telencephalon, basal forebrain and
neocortex [27, 28]. A population of neurons in the posterior
lateral hypothalamus, tuberomammillary nucleus, utilizes
histamine as a neurotransmitter [29]. Shared with the ami-
ergic cell groups of the brainstem, these neurons have
widespread projections and activity patterns selective to
wakefulness. Antagonism of this arousal system produces
the hypnotic effects of antihistamines. Also found in the
posterior hypothalamus are neurons that synthesize a
newly discovered peptide transmitter, orexin [30]. Sharing
with the adrenergic and monoaminergic systems, the reticular
formation inducing global changes in arousal. The specific
role played by the reticular formation in behavior during
wakefulness is not clear at this time. Its intraconnectivity
may aid in the integration of multiple systems [25].

The medial nuclei of the thalamus link, though not
exclusively, brainstem activation to widespread areas of
the neocortex [28]. This region has been considered a ro-
stral extension of the reticular formation. It is at least a
major target of it. The entire thalamus, as well as the ne-
ocortex, undergo profound alterations in activity with
changes in state. The specific alterations are dependent on
mutual interactions between these structures and provide
many of the defining characteristics of each state [28].
Excitation of the thalamus is critical to the accurate relay
of sensory information to the cortex during wakefulness.

Cortically projecting cholinergic neurons are distributed
within several nuclei of the basal forebrain and include the
nucleus of the diagonal band of Broca, the substantia inno-
mimata, and the magnocellular preoptic nucleus. This
appears to be a major activation system of the neocortex
achieved through the release of acetylcholine [32].
More caudal arousal systems project to this region; the
cholinergic neurons discharge at their highest rates during states of cortical activation, and antagonism of cholinergic transmission in the cortex is sufficient to block spontaneous activation. The role of the basal forebrain is not solely to relay excitation to the cortex. Stimulation, lesion, and drug manipulation can have great effects on the time spent in individual states. This is probably accomplished through the reciprocal connections that basal forebrain neurons make with many other arousal-related systems [27].

**MECHANISMS OF NREM SLEEP**

Despite the original premise that inhibition of reticular activation is the basis for the presence of active sleep mechanisms, identification of specific neural circuitry in the inhibition of the reticular formation has not been forthcoming. By some estimates, 20–25% of reticular neurons utilize the inhibitory transmitter gamma-aminobutyric acid (GABA) [26]. One possibility is that excitatory inputs to inhibitory neurons are at work; however, injection of GABA receptor agonists into the pontine reticular formation induces wakefulness [33]. If direct inhibition of the reticular formation is a mechanism of NREM sleep, identification will require an increased understanding of the reticular formation itself. Evidence in support of other active NREM sleep mechanisms is compelling.

Several sources of evidence implicate the presence of a sleep-generating mechanism in the anterior hypothalamus–basal forebrain region [34, 35]. The finding of neurons selectively active during sleep has identified several mechanisms. One of these mechanisms is comprised of a collection of neurons in the ventrolateral preoptic (VLPO) nucleus, in which the vast majority contain GABA and the inhibitory peptide transmitter galanin (reviewed in [17] and [34]). Small excitotoxic lesions of these neurons cause a reduction in sleep correlated to the amount of cell loss. Reciprocal connections have been observed between the VLPO nucleus and several wake-related structures, including the histaminergic and orexinergic neurons, locus coeruleus, dorsal raphe, and cholinergic regions of the brainstem and basal forebrain. It has been hypothesized that reciprocal inhibitory connections between wake-active centers and the sleep-active VLPO nucleus constitutes the sleep switch preventing the expression of mixed or disassociated states of arousal [17]. Additional sleep-active neurons are found throughout the hypothalamic preoptic area with a more dense aggregation in the median preoptic nucleus. These neurons share many of the properties of the VLPO nucleus in connectivity and utilization of GABA [34]. An additional property is that they are warm-sensitive and are posited to mediate the relationships between sleep and temperature.

Just anterior to the preoptic area lies the basal forebrain, which was discussed as a wake mechanism but also serves NREM sleep [32, 35]. Distributed among the cholinergic neurons of these nuclei are a large population of GABA-containing cells. NREM sleep-active neurons are found in this region and evidence indicates that at least some are GABAergic. Some of these GABAergic neurons are projection neurons with one target being the neocortex. Thus sleep-active GABAergic neurons of the basal forebrain may serve to inhibit the wake-active cholinergic neurons and directly inhibit cortical activity in the production of NREM sleep. The GABAergic nature of sleep-promoting neurons is probably responsible for the hypnotic effects of systemically administered agents that potentiate GABA transmission such as the benzodiazepines. A role for the basal forebrain in sleep production has been supported further by the action of adenosine in this region to increase sleep [36]. Adenosine is a product of cellular energy utilization. Levels of adenosine increase with the sustained increase in activity accompanying prolonged wakefulness. The basal forebrain may be one site of this action. Sleep-active neurons of the preoptic area also are excited by adenosine. Both these regions may mediate the wake-promoting effects of caffeine, an adenosine receptor antagonist.

**MECHANISMS OF REM SLEEP**

The results of brain transections that isolate the medulla oblongata and pons from the rest of the brain clearly indicate that structures sufficient to produce REM sleep lie within these regions of the brainstem [37]. Additional evidence indicates that communication between these two regions is necessary for the appearance of REM sleep [37]. Many mechanisms have been identified in the pons, but medullary mechanisms remain relatively obscure.

The many physiological phenomena occurring during REM sleep are separated into two categories. They are the phasic events occurring discontinuously and sporadically and the tonic events occurring rather continuously throughout a REM sleep episode (discussed in [38]). The phasic events include autonomic irregularities, muscle twitches, rapid eye movements, and field potentials recorded at various places along the neuraxis called PGO waves. The widespread distribution of REM sleep phasic activity, in a variety of systems, depends on propagation. With the use of discrete lesions and histochemical tracing methods, some of these pathways have been identified [39]. Phasic events tend to occur at the same time within REM periods, which has raised speculation of a phasic event system with a single or a few central generators. An area in the caudal pontine reticular formation, in the subcoeruleus (below the locus coeruleus), has been putatively identified as a generator of PGO wave activity [39].

The major tonic events of REM sleep are the muscle atonia and the widespread neural activation, which includes a
wake-like EEG. During NREM sleep there is a diminution of muscle activity; however, during REM sleep, there is an increase in activity in the motor centers of the brain while an active inhibition is exerted on motor neurons. The result is paralysis and atonia in the majority of the skeletal musculature. This phenomenon appears to be dependent on the activation of a population of neurons in the caudal pontine reticular formation projecting to and facilitating activity in the medial medullary reticular formation that provides the inhibition to the motor neurons [40]. Bilateral lesions in the subcoeruleus area of the pons can result in REM sleep without muscle atonia, whereby animals express a variety of integrated behaviors during this sleep state [41].

The wake-like activation of REM sleep recruits many of the mechanisms involved in wakefulness. Neurons of the reticular formation, brainstem and forebrain cholinergic neurons, thalamus, and neocortex all exhibit firing rates and levels of excitability equal to or greater in REM sleep as compared to wake [1, 24, 27, 28]. One notable exception are the aminergic systems for their almost complete silence. It is tempting to conclude that the absence of the widespread neuromodulatory influences of norepinephrine, serotonin, and histamine are the basis for all the differences between REM sleep and wake, but few demonstrations of this have been produced at the cellular level. It is hard to conceive that the turning-off of these major systems does not make a major contribution to the nature of the REM sleep state.

With the early indication from transection data of where the critical REM sleep mechanisms reside, numerous brainstem systems have been investigated but no complete picture has yet to emerge. The most enduring concept stems from the initial discovery of the brainstem cholinergic system by Shute and Lewis in 1963 [42]. Based on neuronal projections, they suggested that this was the substrate of the ascending reticular activating system. It was subsequently found in the cat that when agents potentiating cholinergic transmission were microinjected into the pontine reticular formation, they induced a dramatic, rapid onset of long-lasting, REM sleep episodes [43]. The state-related activity of cholinergic neurons is still open to question, since while some neurons in the area fire selectively in REM sleep, most discharge at their highest rates in REM sleep and wake [24, 44]. It has been suggested that a reciprocal inhibition between cholinergic REM-on cells and aminergic REM-off cells provides the mechanism for reciprocal activities and state oscillations [45]. This model differs from the switch discussed earlier in that what would have been an unstable condition now becomes the NREM sleep that intervenes between REM and wake. It has been found that acetylcholine levels are highest in the reticular formation during REM sleep [46]. This may be due to reticular formation projections from cholinergic REM-on cells or a mechanism that inhibits cholinergic release during wake. Evidence supports such a role for the REM-off (or wake-on) noradrenergic neurons through projections to presynaptic, cholinergic terminals in the reticular formation [47]. Wake-on/REM-on cholinergic neurons provide ascending activation in REM sleep as in wakefulness, and levels of acetylcholine are high in the thalamus during both states.

It would appear that the release of acetylcholine in the pontine reticular formation is a condition sufficient to induce REM sleep. Directly or indirectly, brainstem cholinergic neurons may excite the reticular formation initiating ascending activation, excite the pontine neurons responsible for muscle inhibition, inhibit serotonin release responsible for the appearance of PGO waves [38], and provide additional ascending activation via thalamic and extrathalamic relays to the cortex. Much of this description of the role of brainstem cholinergic neurons may be shown to be true. But acetylcholine in the pontine reticular formation is not sufficient to induce REM sleep. Pontine microinjections fail to do so after ponto medullary transections [48]. There is still some undisclosed mechanism in the medulla required for REM sleep. It is not clear that the integrity of brainstem cholinergic neurons is necessary for REM sleep [49]. Excitotoxic lesions of the region produce a long-lasting decrease in REM sleep amounts correlated to the number of cholinergic cells lost. However, this effect also is correlated to the size of the lesion: the latter being consistent with a distributed system of multiple mechanisms in the region including the rostral pontine reticular formation.

While evidence supports the brainstem as sufficient in the generation of REM sleep, additional structures are implicated in its control. In the preoptic area of the hypothalamus, known as the extended VLPO nucleus, there is a population of GABAergic neurons projecting to brainstem aminergic nuclei that appear to selectively fire in REM sleep, possibly contributing to the inhibition of aminergic neurons [17, 50]. Pharmacological manipulations of the basal forebrain can effect all states. One telling finding is that microinjection of cholinergic agonists in the basal forebrain blocks the REM sleep induction by injections in the pontine reticular formation [51]. Similar to the mechanisms of NREM sleep and wake, mechanisms of REM sleep also appear to be distributed and interactive.

### CONCLUSION

The view expressed in this chapter describes the neurobiology of sleep and wakefulness as a system distributed along the neuraxis from the medulla oblongata to the neocortex. The high degree of interaction among components of the system gives rise to the unique and interdependent expression of the states of arousal. Some of the concepts may not survive the final analysis, as has been the fate of several
compelling notions of the past, and novel mechanisms await to be found. Sleep/wake mechanisms appear so highly integrated in the brain that a complete understanding of them will require advances in technology and the chance of discovery that only time can offer.

REFERENCES


Sleep is a highly organized, complex behavior characterized by a relative disengagement from the outer world and variable but specific brain activity. Under normal conditions, sleep is associated with little muscular activity, a stereotypic posture, and reduced response to environmental stimuli. Sleep may be delayed but is indispensable for the survival of the species. As such, it is endogenously generated, homeostatically regulated, and reversible.

Sleep is typically evaluated using polysomnographic techniques, which enable the simultaneous characterization of the electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG). Since 1968, standardized criteria have been followed to record and score human sleep.

THE NREM–REM CYCLE

Sleep is organized into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, which are easily characterized using polysomnographic techniques. In humans, NREM sleep appears as wakefulness-maintaining mechanisms wane. NREM sleep is divided into four stages based on the pattern of the brainwaves. Stage 1 NREM sleep is a transitional phase between full wakefulness and sleep. It can also emerge briefly during transitions from sleep to wake or after brief body movements. The EEG is characterized by relatively low-voltage slow activity in the theta range (4–7 Hz). Slow eye movements may be present and the EMG usually reveals a decline in the tonic activity relative to the waking state. Stage 2 NREM sleep is marked by the appearance of EEG spindles (fast activity in the 7–14 Hz range lasting at least 0.5 s) and K-complexes, which consist of high-voltage waves with a negative sharp component followed by a positive component. Stage 2 NREM sleep is the first bona fide sleep stage; adults spend 50–60% of sleep time in this particular stage of sleep. Stage 3 and stage 4 NREM sleep are frequently combined and called delta sleep, deep sleep, or slow-wave sleep. The EEG during this period is characterized by high-amplitude waves of 0.5–2 Hz.

REM sleep represents an active form of sleep and is characterized by low-voltage, intermixed cerebral activity associated with striated muscle atonia and rapid eye movements. Most dreams are thought to occur during this phase of sleep. REM sleep can be separated into tonic and phasic components. Tonic REM sleep is associated with near paralysis of most muscular groups. Only the diaphragm, the cardiac muscle, and some sphincters at the top and the bottom of the gastrointestinal tract remain active during REM sleep. In fact, the reduction of muscle tone is actively induced by the release of glycine onto the motoneurons. Phasic REM sleep is characterized by occasional bursts of EMG activity (myoclonias), rapid eye movements, and activity of the middle ear ossicles.

Human adults typically begin sleep by progressing from stage 1 NREM sleep through stage 4 NREM sleep. The progression of sleep stages might be intermittently interrupted by changes in body posture or partial arousals. After 70–80 min of NREM sleep, the first REM phase might be initiated, which typically lasts 5–10 min. The length of the NREM–REM cycle (from the start of NREM sleep to the end of the first REM period) is about 90–110 min. The NREM–REM cycle is usually repeated four to six times during a typical
Table 3.1 Physiologic Characteristics of Adult Human Sleep

- NREM–REM cycle (90 min long)
- NREM sleep
  - Stage 1 NREM: diminution of alpha waves by theta waves, rolling eye movements
  - Stage 2 NREM: spindles, K-complexes
  - Stage 3/4 NREM: delta waves
- REM sleep
  - Tonic: desynchronized EEG (low-voltage fast pattern mixed with small amount of theta rhythm and, often, with “sawtooth” waves), muscular atonia, depression of monosynaptic and polysynaptic reflexes
  - Phasic: bursts of rapid eye movements, myoclonic twitchings, irregular heart beat and respiration (with variable blood pressure), spontaneous activity of the middle ear muscles
- Endogenously generated
- Regulated by homeostatic and circadian factors
- Modulated by environmental factors
- Sleep rebound follows sleep loss
- Functional impairment produced by sleep loss/deprivation

night of sleep. While stage 3 and stage 4 NREM sleep are more prevalent at the beginning of the night (usually during the first NREM–REM cycles), REM sleep is usually of short duration during the initial NREM–REM cycles and lengthens in subsequent cycles of the night (Table 3.1).

In young adults, stage 1 NREM sleep constitutes about 5–10% of the night; stage 3 and stage 4 NREM sleep about 10–20%; REM sleep 20–25%; and the largest amount of sleep time, 50–60% is spent in stage 2 NREM sleep. The most significant factor affecting total sleep time and sleep stages is age. Newborn infants, during the first months of life, sleep 17–18 h a day and spend 50% of sleep time in REM sleep. The cyclical alternation of NREM–REM sleep is also shorter in the newborn, at about 50–60 min. Also, slow-wave sleep is maximal in young children and decreases markedly with age. In the elderly, sleep requirements decrease and nighttime awakenings increase.

Circadian and Homeostatic Determinants of Sleep

Sleep, as other physiological variables, is regulated by the circadian timing system. The suprachiasmatic nucleus in the hypothalamus serves as the central neural pacemaker of the circadian timing system. The dominant synchronizing input to the human circadian pacemaker is environmental light. The retinohypothalamic tract links the retina to the suprachiasmatic nucleus, conveying photic information that enables synchronization to the light–dark cycle. Humans are usually synchronized to the 24 h day, with most adult humans sleeping at night. It is in fact the temporal interplay of the circadian pacemaker and the sleep homeostatic drive that determines alertness, neurobehavioral performance, and sleep.

The propensity to fall asleep follows a biphasic pattern during the 24 h day. Two peaks of sleepiness have been characterized—one during nocturnal hours (2–6 a.m.) and another during daytime hours (2–4 p.m.). The sleepiness rhythm parallels the circadian variation in body temperature, with shortened latencies occurring in conjunction with temperature reductions. Likewise, more difficulty falling and staying asleep is associated with the rising phase of the temperature curve.

Sleep per se is considered a basic physiologic need state. It has been likened to hunger, which is critical to the survival of the organism. The homeostatic drive for sleep increases during wakefulness and decreases during sleep. Acute sleep deprivation is followed by an increase in the propensity to fall asleep and a parallel response in the propensity to stay asleep. The homeostatic drive to sleep is impacted by the oscillations of the circadian rhythm, which, for example, enhance alertness in the early evening, even after a sleepless night.

Regulation of NREM Sleep

NREM sleep expresses the unified activity of many neuronal networks. Neurons found in the solitary tract nucleus of the medulla, raphe nuclei of the brainstem, reticular thalamic nuclei, anterior hypothalamus, preoptic area, basal forebrain, and orbital cortex are involved in the generation of NREM sleep.

The anterior hypothalamus and the adjacent basal forebrain have the most significant sleep-promoting effects in the brain. Gamma-aminobutyric acid-ergic neurons are involved in the inhibition of activating systems. The reticular nucleus of the thalamus is the synchronizing pacemaker of EEG spindle oscillations. It is in fact the thalamus, the first relay station, where afferent information is blocked at sleep onset, thus enabling the preservation of sleep. Serotonin-containing neurons of the raphe nuclei provide diffuse innervation to the brain and might be important in dampening certain sensory input and attenuating cortical activation in the initiation of slow-wave sleep. Adenosine, CSF-borne factors, and opiates may also have an effect on sensory modulation and are likely to play a role in the initiation and maintenance of sleep. However, no single neurotransmitter or neuromodulator has been found to be critical or sufficient for the initiation and/or maintenance of sleep.

Regulation of REM Sleep

The nucleus reticularis pontis oralis in the caudal midbrain and rostral pons is critical to the generation of REM sleep.
NORMAL AUTONOMIC CHANGES IN SLEEP

Many of the physiologic changes occurring during sleep are associated with changes in the level of activity of the autonomic nervous system. NREM sleep is characterized by a period of relative autonomic stability with sympathetic activity remaining at about the same level as during relaxed wakefulness, and parasympathetic activity increasing through vagus nerve dominance and heightened baroreceptor gain. During tonic REM sleep, a relative increase in parasympathetic activation is noted (mostly as a result of sympathetic input decline). Phasic REM sleep is characterized by an increase of both sympathetic and parasympathetic activity. The status of autonomic activity during sleep can be summarized as reflecting prevalent parasympathetic influence during NREM sleep (associated with quiescence of sympathetic activity), and great variability in sympathetic activity (associated with phasic changes in tonic parasympathetic discharge) during REM sleep. Changes in autonomic function and inherent changes in the control exerted by the central nervous system (CNS) affect most organ systems in the body during sleep. A brief review of some of the relevant changes affecting the cardiovascular system, respiration, cerebral blood flow, thermal control, and endocrine and genital function follows.

Cardiac Physiology

NREM sleep is usually characterized by brief heart rate acceleration during normal inspiration to accommodate venous return. During expiration, there is a progressive decrease in heart rate. This variability in cardiac rhythm is considered a marker of cardiac health. During REM sleep, heart rate becomes variable with episodes of tachycardia and bradycardia. Phasic REM sleep might be associated with significant increases in heart rate as a result of bursts of sympathetic activity and might lead to significant arrhythmias, in particular, when associated with ventilatory instability. Likewise, striking changes in coronary blood flow occur during REM sleep and sleep-state transitions. Individuals with heart disease may experience life-threatening arrhythmias and myocardial ischemia (and/or infarction) during REM sleep as a result of sympathetic nerve activity, which is concentrated in short, irregular bursts. These bursts trigger momentary and intermittent increases in heart rate and arterial blood pressure to levels similar to wakefulness.

Respiratory Physiology

Sleep not only modifies the neural control of ventilation but also impacts its mechanical and chemical control. NREM sleep is characterized by regularity of both respiratory frequency and amplitude. There is a decrease in alveolar ventilation with a concomitant decrease in arterial Po2 and increase in Pco2. During REM sleep, there is a further decline in tidal volume and minute ventilation drops to its lowest level. Central apneas and periodic breathing are more frequent during REM sleep and these are mostly associated with phasic REM sleep. Hypoxic ventilatory response is lower during NREM sleep when compared to wakefulness, although some studies have described gender differences in this response. Both men and women experience a similar decline in the hypoxic ventilatory response during REM sleep. Increases in end-tidal Pco2 during sleep results in an increase in ventilation. However, this response is variable. Likewise, hypocapnia has an important inhibitory effect on respiration during sleep. It should also be noted that sleep results in a general decrease in muscle tone. This is particularly relevant to the muscles of the upper airway, which in turn have an impact on ventilation. The genioglossal muscle activity pulls the tongue down and forward enabling the airway to remain open. NREM sleep results in decreased discharge activity with further reductions noted during REM sleep. The potential result of this physiological change is the obstruction of the upper airway, which might result in a pathological condition (obstructive sleep apnea).

Cerebral Blood Flow

Cerebral blood flow (CBF) mostly decreases during NREM sleep when compared to wakefulness. During REM sleep there are significant regional changes in CBF. In general, a significant increase in CBF is associated with REM sleep. Certain areas of the brain have been described as experiencing significant increases in CBF—among these,
the pontine tegmentum, the dorsal mesencephalon, thalamic nuclei, the amygdala, and the anterior cingulated and the entorhinal cortex. Interestingly, a decrease of CBF in cortical and limbic structures during post-sleep wakefulness has been described (when compared to pre-sleep wakefulness). It has been speculated that such a change might be a reflection of a resetting process by which the circulatory and metabolic activity of the brain is set at a lower level of activity. Some researchers have interpreted these findings as evidence of the “restorative” function of sleep.

Temperature Regulation

Core body temperature (T_b) shows a circadian variation. The T_b cycle is a sinusoidal-like function with a maximum in the early evening and a minimum in the early morning. The amplitude of temperature variation is about 1 °C. It should be noted that the circadian T_b variation is independent of muscular activity. Under normal conditions, the drop in T_b during nocturnal sleep is accomplished by two separate mechanisms. One is the sleep-related reduction in the body’s thermal set point (the result of increased heat dissipation and decreased heat generation) and the second is the intrinsic circadian temperature variation (which is independent of sleep). The preoptic-anterior hypothalamic area is critical to the regulation of T_b. During NREM sleep T_b is regulated at a lower set point when compared to the wake state. In contrast, T_b is not regulated during REM sleep, which represents a poikilothermic state. As a result, the body temperature during REM sleep drifts toward the environmental temperature.

Endocrine Function

Sleep in humans is associated with prominent changes in the function of virtually every endocrine system in the body. It is through the various hormones secreted in the body that tissue growth is promoted, sexual development and activity are regulated, the absorption of sodium is synchronized, and, perhaps most importantly, the response to stress is modulated to preserve homeostatic balance. The plasma concentrations of many hormones display sleep-related variations. However, such correlations do not necessarily indicate a causal relationship between them. In fact, circadian regulation in many instances synchronizes these events. The endocrine systems that undergo sleep-related changes include the adrenocorticotropic hormone, thyrotropin, growth hormone, gonadotropic hormones, prolactin, and melatonin. New research also suggests that sleep duration per se might have an effect on endocrine function. Specifically, short sleep duration has been found to be associated with decreased leptin levels (which suppresses food intake) and a concurrent increase in ghrelin levels (which stimulates appetite). These findings suggest for the first time that a potential association might exist between poor sleep schedule practices (specifically insufficient sleep) and obesity.

Genital Function

Penile erections are a naturally occurring phenomenon associated with REM sleep. This phenomenon has been demonstrated to be present in all healthy males from infancy to old age. Similar clitoral erections and vaginal engorgement have been documented in women during REM sleep. These physiologic events are the result of increased parasympathetic activity, which results in local vasodilation, decreased venous outflow, and increased bulbocavernous muscular activity. In contrast, few changes in genital function are present during NREM sleep.

THE FUNCTION OF SLEEP

The available research provides strong evidence that sleep is critical to the survival of the species. In fact, chronic sleep deprivation in rats has shown that these animals die after 2–3 weeks. REM-deprived rats survive for longer periods but end up dying as well. Unfortunately, a clear cause for the death of these animals has not been identified. While no widespread agreement exists on why sleep is important, it is clear that sleep deprivation (or chronic insufficient sleep) results in increased sleepiness and decreased functioning. In addition, several hypotheses about the function of sleep have been advanced. Perhaps a critical function of sleep is the one related to thermoregulation. The studies in sleep-deprived rats showed them to experience an inability to retain heat as their body temperature dropped during the experiment despite experiencing an increase in metabolic rate. Other theories have suggested that sleep might have a role in the conservation of metabolic energy and cognition. The ontogenetic changes documented in REM sleep across the process of maturation and a series of elegant experiments using REM deprivation during critical phases of development have enabled researchers to study the effects of these manipulations on neural maturation. In addition, REM sleep seems to have an important role in memory consolidation.

CONCLUSION

The description of REM sleep in the 1950s was instrumental in enabling the systematic study of sleep. Since that time, research in this area has progressed from a nascent research discipline to a clinical medical specialty. Critical to both research and the clinical aspects of the discipline are the characterization of the physiological manifestations
of sleep and the understanding of the implications of these processes. The available evidence has established that sleep serves an important function, as evidenced by the rebound of sleep following sleep loss and the developmental, functional, and metabolic impairments produced by sleep deprivation. While no unitary theory of sleep function has explained the wealth of data on available sleep phenomena, the evidence suggests that the function of sleep is likely multidimensional and differential depending on the organism’s stage of development.

**ADDITIONAL READING**


INTRODUCTION

There are many biological rhythms. A rhythm is a repetitive biological event with three features—period, phase, and amplitude. Period is the length of the rhythm. Phase is the timing of the rhythm in relation to a stimulus, and amplitude is a measure of the amount of the rhythmic event. In this review, I will focus on circadian rhythms—rhythms with a period of approximately 24 hours. The solar cycle of light and dark is the most important recurring stimulus in our environment. Not surprisingly, living organisms have evolved adaptive mechanisms that utilize the solar cycle to promote survival and reproduction. These mechanisms, termed “circadian rhythms” (from circa, about, and diem, a day) are now known to depend on genetically controlled rhythmic molecular events that control a wide array of rhythms in cellular, system, and behavioral functions. Circadian rhythms are expressed in essentially all living organisms from prokaryotic through eukaryotic species to the human and are critical to survival. An example of a typical circadian rhythm is shown in Figure 4.1.

The fundamental behavioral circadian rhythm is the rest–activity cycle. This rhythm first appeared in animals with the evolution of the nervous system. In mammals it is expressed as a sleep–wake rhythm presenting in one of two patterns. Some mammals, particularly rodents and carnivores, are nocturnal—awake at night and asleep during the day. Nocturnal animals depend on olfaction and audition as the primary senses to perceive their environment and have evolved very elaborate peripheral sensory receptors and brain mechanisms to support these sensory modalities. Diurnal mammals, primates are the best example, sleep at night and are awake during the day, and use vision as their primary sensory modality.

The circadian rhythm in sleep–wake behavior in humans is a fundamental component of behavioral adaptation. Placing wake behavior during the solar day ensures maximal use of vision to guide behavior. Sleeping during the night provides an optimal time for this critical restorative behavior. The functional effect of circadian regulation is to provide a temporal organization of wake and sleep to permit maximally effective adaptive waking behavior.

The following are briefly reviewed: (1) molecular mechanisms of circadian timing, (2) circadian pacemakers, (3) the circadian timing system, (4) the waking system, and (5) the interaction of circadian and homeostatic control of sleep and waking.

MOLECULAR MECHANISMS OF CIRCADIAN TIMING

Circadian timing is an inherited adaptation and, as such, is genetically determined. Over the last 15 years extensive research on the molecular basis of circadian timing has been performed, and we now have a detailed body of information. Two important generalizations have emerged: (1) the fundamental basis of circadian timing is interacting positive and negative transcriptional feedback loops [1], and (2) in mammals and other complex organisms, many tissues contain circadian clocks and pacemakers [2]. There are two important sets of genes involved in these feedback loops in the mammalian circadian pacemaker:
period (per) genes and cryptochrome (cry) genes are part of the negative loop, while clock and Bmal1 are components of the positive loop. The general organization of the molecular pathways is shown in Figure 4.2. Rhythmic transcriptional enhancement by the transcription factors, Clock and Bmal1, is essential for clock function and provides a basic drive to the molecular clock. These proteins form heterodimers in the cytoplasm that enter the nucleus to activate per and cry transcription by binding to E box enhancers.

The resultant Per and Cry proteins also form heterodimers and translocate to the nucleus to act as negative regulators through inhibition of the Clock–Bmal1 activation of transcription. The positive component of the process involves rhythmic regulation of Bmal1. In order to generate a positive feedback loop, Clock–Bmal1 heterodimers both activate per and cry transcription and transcription of the orphan nuclear receptor gene, Rev-Erbα. The Rev-Erbα protein acts on specific response elements in the Bmal1 promoter to repress Bmal1 transcription. The Cry protein also inhibits transcription of the Rev-Erbα gene, allowing increased transcription of Bmal1. This indicates that the positive and negative loops are both regulated by Clock–Bmal1 heterodimers [1]. This appears to be the basic organization of the molecular clock but much remains to be learned. The significance of this is emphasized by recent findings that a familial form of advanced sleep phase syndrome is the result of a mutation in one of the per genes, per2 [3].

CIRCADIAN PACEMAKERS

Circadian pacemakers are clocks that regulate the temporal organization of function in other circadian clocks or in other brain systems or tissues. The first mammalian circadian pacemaker to be identified was the suprachiasmatic nucleus (SCN) of the hypothalamus [4–6]. The SCN is comprised of neuronal oscillators that are coupled though connections to form a pacemaker [7]. Each oscillator contains the molecular machinery noted above and clock function is accomplished by coupling the molecular feedback loops to the control of neuronal membrane potential [7]. The SCN is comprised of multiple component oscillators that can dissociate and function independently [8]. In part, these are identifiable anatomically [5] (Figure 4.3). The SCN has two principal subdivisions. The core is the central part of the nucleus and contains neurons that produce GABA and a peptide, either vasoactive intestinal polypeptide (VIP) or gastrin releasing peptide (GRP). The major afferent input to the core is from visual centers, primarily the retina. Retinal afferents use the excitatory transmitter
glutamate (GLU) and one of two peptides, melanopsin (melan) or pituitary adenylate cyclase activating peptide (PACAP). The other SCN division, the shell, surrounds the core and contains neurons that produce GABA and arginine vasopressin (AVP). The shell receives input from the limbic cortex, thalamus, hypothalamus, and brainstem. There are extensive intrinsic connections within the SCN. Each subdivision projects densely upon itself and the homologous contralateral SCN. The core projects on the shell but the shell has only minimal projections on the core. Thus the flow of information is from visual receptive areas and raphe to the core and from multiple forebrain and brainstem areas, and the core, to the shell. As will be described later, both subdivisions project to effector systems under circadian control in an overlapping but not identical pattern. The organization of the SCN is similar in all mammals including primates and virtually identical with respect to core and shell organization.

THE CIRCADIAN TIMING SYSTEM

The SCN is part of a set of brain structures whose function is circadian regulation and, hence, are designated the circadian timing system (CTS). The principal features of circadian rhythms determine the basic organization of the system. This is clearly presented by the sleep–wake rhythm (Figure 4.4). Under normal conditions of a light–dark cycle, the period of the rhythm is 24 h and the onset of sleep and onset of waking occur at about the same time each day. This is an entrained rhythm and the entrainment process requires input through the eyes. With removal of time cues, as in temporal isolation where subjects do not have access to time information or a regular light–dark cycle, sleep–wake cycles remain quite regular but with a period that exceeds 24 h. This is referred to as a free-running rhythm. Entrainment requires visual photoreceptors and a visual pathway from the photoreceptors to the circadian pacemaker. The free-running rhythm is established by the intrinsic period of the pacemaker—the SCN—and is slightly longer than 24 h in humans. These two features of circadian rhythm establish the necessary components of the CTS (Figure 4.4).

The entrainment pathway is initiated with specific photoreceptors. Over the last few years, it became apparent that these were not conventional photoreceptors. For example, in transgenic mice, a knockout of the genes for both rods and cones did not affect entrainment and the process was mediated by a set of ganglion cells that contain photopigments, particularly melanopsin [9]. These ganglion cells project to the SCN core through the retinohypothalamic tract. There is an important secondary visual pathway that also projects to the SCN core from the intergeniculate leaflet, a ventral thalamic component of the lateral geniculate complex. This pathway, the geniculohypothalamic tract, contains GABA colocalized with the peptide neuropeptide Y [5] and appears to modulate the effect of retinal input on the SCN. As noted earlier, there are numerous other inputs to the SCN, particularly to the shell, that probably modulate output from that subdivision. The output of the SCN is predominantly through the hypothalamus with differing sets of projections mediating control over differing functional systems [10, 11]. These include rostral projections to autonomic centers and the neuroendocrine systems and caudal projections to the posterior hypothalamic arousal systems (Figure 4.5). With the recent rapid application of molecular methods to circadian research, it has become evident that there is a hierarchy of pacemakers and oscillators that extend from the SCN pacemaker to other brain pacemakers and oscillators to a large series of clock elements in many tissues and organs [2].

**Figure 4.4** Suprachiasmatic nucleus pacemaker organization in mammals. See text for description.

**WAKE PATHWAYS**

As described earlier, behavior occurs in one of two distinctive states, wake and sleep. Wake is a state in which the cerebral cortex is activated with awareness of the sensory and internal environment and a continual elaboration of adaptive behavior. The maintenance of the waking state is an active process requiring the integrity of a well-defined set of brain pathways. The first evidence for wake pathways came from a clinical pathological analysis of an unusual encephalitis that occurred in association with the influenza pandemic of 1918–1926. The encephalitis, studied by von Economo, was characterized by impaired responsiveness, extending into prolonged coma in many sufferers, and had a restricted pathology involving the upper brainstem and posterior hypothalamus which von Economo viewed
as critical components of waking. Although this was confirmed by animal studies with discrete lesions, research over the next 20 years on waking function was focused on the brainstem and resulted in identification of the pontine and mesencephalic reticular formation as an “ascending reticular activating system.” The hypothalamus became neglected, and it was assumed that the principal waking pathways involved either direct projections from the brainstem to cerebral cortex, as with the monoamine neuron systems, or a relay through the nonspecific nuclei of the midline-intralaminar thalamus (Figure 4.6).

Recent data have emphasized the importance of hypothalamic projections in maintenance of waking. The hypothalamus has extensive neocortical projections and many of these arise from the posterior hypothalamus. The function of these projections, particularly those producing hypocretin [12] or histamine [13], is clearly to promote wake. Input through the cholinergic systems is also an important component of the waking systems [14]. Hypothalamic input to the cortex is critical to maintaining the waking state but inputs from a number of other areas are important for both arousal and modulation of specific thalamic input and cortical processing. The circuitry involved in sleep regulation has been reviewed recently [15].

**HOMEOSTATIC AND CIRCADIAN CONTROL OF THE SLEEP–WAKE CYCLE**

It is evident to nearly everyone that the propensity to sleep increases with the time since the last sleep episode and this fits with the general concept that sleep has a restorative function. The obvious questions are why sleep–wake cycles are so regular and why the timing of waking behavior, and sleep, is so precise. The propensity to sleep as a function of time awake is referred to as homeostatic sleep drive, and we now recognize that the precise regulation of sleep–wake behavior occurs through an interaction of the CTS with homeostatic drive for sleep. The basis for homeostatic sleep drive is not fully established and is probably quite complex. There are two hypotheses that have substantial support. The first is that sleep permits restoration of energy resources in the brain [16]. The second is that homeostatic drive is a function of accumulation of a sleep-promoting substance. This is an old idea but a large body of recent evidence supports the view that increasing adenosine content, perhaps in local areas, is a critical component of the homeostat [17]. It is likely that other factors contribute.

How do circadian function and homeostatic drive interact in sleep–wake regulation? An early formulation of this was proposed by Daan and Borbely [18] and is shown in Figure 4.7. Homeostatic sleep drive is maximal at the time of sleep onset and is dissipated gradually through the sleeping period.

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**Figure 4.5** Organization of the circadian timing system. See text for description.

**Figure 4.6** Waking pathways. Waking is maintained by pathways originating in the brainstem, hypothalamus, thalamus, and basal forebrain. See text for description. Abbreviations: ACH, acetylcholine; DA, dopamine; GLU, glutamate; HCT, hypocretin; HST, histamine; NE, norepinephrine; 5HT, serotonin.

**Figure 4.7** Interaction of circadian and homeostatic factors in sleep–wake regulation. See text for description.
At the time of waking, little or no homeostatic drive remains but it begins to accumulate with time awake and gradually increases over the waking period. During the waking day, increasing homeostatic drive is opposed by a circadian drive for arousal until shortly before sleep, when circadian influences gradually decrease. Although there was relatively little evidence for the Daan–Borbely model at the time it was first proposed, more recent data have supported it. This includes behavioral and electrophysiological data and studies of the circadian timing system. The current evidence indicates that the output of the SCN pacemaker is an important component of the circadian promotion of arousal. Ablation of the SCN in primates abolishes the circadian rhythm in sleep–wake behavior and increases total sleep time [19]. SCN control of the rest–activity rhythm can be mediated by a diffusible factor. The nature of this signal and the SCN signal mediating arousal effects are unknown but a recent study implicates a peptide—prokineticin [20].

**SUMMARY**

The timing of the sleep–wake cycle depends on the interaction of a number of brain systems, in particular, sleep–wake systems and the CTS. The CTS not only coordinates the timing of the sleep–wake cycle by opposing the sleep homeostat but also serves to coordinate the timing of pacemakers and oscillators in other tissues and organs to facilitate adaptation.

**REFERENCES**

BIOLOGICAL THEORIES OF DREAMING

Observations by Aserinsky and Kleitman [1, 2] identified that there were episodic bursts of rapid eye movements during sleep associated with dreaming, and Dement and Kleitman [3] showed that there was a particular electroencephalographic (EEG) pattern associated with these periods of rapid eye movements, which recurred regularly during the night. This combination of bursts of conjugate rapid eye movements and a relatively low-voltage mixed-frequency EEG with muscle atonia [4] has been designated rapid eye movement (REM) sleep. It is this correlation of dreaming with a specific, identifiable EEG pattern that became the focus for the efforts to describe the physiological processes that are the biological basis for the dreaming process. Furthermore, interest in the biological basis of mental function in psychoanalysis reflects Freud’s conviction [5] that psychology will have a physiological basis. This leads to the idea that the current neuroscience approach may provide a way to bridge the mind/brain divide.

There are currently only two competing theories, from a neuroscience point of view, of the functional anatomy of dreaming. The activation-synthesis theory of Hobson and collaborators [6] has been extended into their activation information modulation (AIM) space state model, which is still a bottom-up, subcortical brainstem view of the origin and content of dreaming. The source for the initiation of dreaming is in the pons, which sends random signals to the cortex. The cortex responds passively to the pontine signals in that its response is determined by these random signals. The cortex elaborates the dream experience, making the best of a bad job. The content of the dream experience is shaped by affect in the dream [7]. The model for dreaming is the verbal output seen in the productions of demented patients.

The competing view of a brain-based theory of dreaming has been that articulated by Solms [8]. This theory is based on a clinicoanatomical approach, brain lesions, using neuropsychological techniques. It is allegedly a top-down, cortically based theory. Any stimulus that activates the brain can initiate the dreaming process. It requires engaging the ventral tegmental area of Tsai, whose fibers pass through the ventromedial prefrontal area adjacent to the anterior horns of the ventricles.

In order to appreciate the value and, more importantly, the limitations of the neuroscience approach to dreaming, it is worthwhile to review the two theories [6–8]. They have major points of difference.

The orientation in the activation-synthesis (A-S) AIM (activation information modulation) space state model [6] toward dreaming is:

1. that dreaming is coextensive with REM sleep;
2. that the model for the experience of dreaming is dementia;
3. that the stimulus for cortical activation is random discharges from the pons in what has been described as pontogeniculo-occipital (PGO) waves;
4. that the cortical response to the PGO waves is a relatively passive one; and
5. the content of the dream is shaped by the affect in the dream.
Dreaming is defined in the A-S theory [6] as “mental activity occurring in sleep which is characterized by vivid sensorimotor imagery, that is experienced as waking reality, despite such distinctly cognitive features as impossibility or improbability of time, place, person, and actions; emotions, especially fear, elation, and anger predominate over sadness, shame, and guilt and sometimes reach sufficient strength to cause awakening, memory for even vivid dreams is evanescent and tends to fade quickly unless special steps are taken to retain it.” This definition captures, Hobson believes, what people mean by dreaming and serves both psychological and cognitive neuroscience.

In the A-S theory [6], differences among REM, non-REM, and wake mentation will be explained by the distinctive physiology of REM sleep. REM sleep is related to dreaming because:

“Dream reports are more likely to be reported from a REM awakening than a non-REM awakening (80% versus 40%);

Dream recall decreases quickly after the REM period ends;
The word count of the dream report correlates positively with REM time and external stimuli are appropriately incorporated into the time sequence of the dreaming narrative;
Judges can tell REM reports from non-REM reports; and
Qualitatively there are REM/non-REM report differences. REM reports are generally longer, more vivid, with more movement and emotion and are less related to waking life. Non-REM is more thought like.”

The aspects of REM dreaming that are rare in non-REM according to A-S theory [6] include:

“The hallucinatory nature of the experience;
That the images change rapidly and are often bizarre;
The delusional nature of the experience;
The decreased self-reflection;
The creation of a confabulatory narrative;
The effect of instinctual programs such as fight/flight that organize the cognition; and
The attenuated volitional control.”

These features of dreaming, A-S theory [6] holds, will be explained by the distinctive biology of REM sleep. The A-S theory postulates an isomorphism between the biology and psychology of dreaming, which reflects either a similarity (biological meaning of isomorphism) or an identity (mathematical meaning) between the two. It is a highly reductionistic theory that explains the experience of dreaming by its biology.

The control of REM dreaming [6] is described anatomically, physiologically, cellurally, and chemically. The anatomic control is in the pons; therefore it is subcortical, that is, in the brainstem. Physiologically, it is represented by PGO waves from the pons to the lateral geniculate body to the occipital cortex. At the cellular level in the pons, the REM-on cells are in the mesopontine tegmentum. The REM-off cells are in the nucleus locus caeruleus and dorsal raphe nucleus. The chemical control of dreaming is a consequence of REM-on cells secreting acetylcholine, while the REM-off cells secrete norepinephrine and serotonin.

The AIM space state model of the A-S hypothesis [6] shows in a three-dimensional model the change in activation during dreaming sleep from low to high; while the information source shifts from external to internal; and the modulation shifts from high norepinephrine and serotonin to high acetylcholine.

The activation of various brain areas in A-S theory [6] is somewhat in this order:

1. “There is stimulus from the pontine and the midbrain reticular activating circuits and nuclei. This leads to an ascending arousal of multiple forebrain structures. The contribution to the dream experience is consciousness, eye movements, and motor pattern information via the PGO system.”
2. “Diencephalic structures (e.g., hypothalamus and basal forebrain) are activated involving autonomic and instinctual (fight/flight) functions, and cortical arousal. The contribution to dreaming is to further support consciousness and provide instinctual elements.”
3. “Anterior limbic structures are active including the amygdala, anterior cingulate, parahippocampal cortex, hippocampus, and medial frontal areas. This contributes emotional labeling of stimuli, goal directed behavior, and movements. This activation contributes to the dream’s emotionality, affective salience, and movement.”
4. “The dorsolateral prefrontal cortex is inactive during dreaming. This area is involved with executive functions, logic, and planning. This would explain in the dream the absence of volition, logic, orientation, and working memory.”
5. “The basal ganglia become active. They are involved in the initiation of motor actions. In the dream, they may account for the initiation of fictive movement.”
6. “The thalamic nuclei become active, for example, the lateral geniculate nucleus that would be involved in the relay of sensory and pseudosensory information to the cortex. For the dream experience, it transmits PGO information to the cortex.”
7. “Primary motor and sensory cortices are blocked. Therefore, sensory percepts and motor commands do not occur.”
8. “The inferior parietal cortex is stimulated. This area is involved in the spatial integration of processed heteromodal input. It provides the spatial organization for the dream.”
9. “The visual associational cortex becomes active and involves the higher order integration of visual percepts and images.”
10. “The cerebellum is activated and is involved in fine tuning of movement and in vestibular function and contributes fictive movement to the dream.”

In the A-S theory, dreaming is generated by the random output of the brainstem and passively synthesized by the forebrain. The cortex, it is said, makes the best of a bad job. Dementia is the model for the dream.

The forebrain or cortical theory of Solms [8] is based on a clinicoanatomical approach in patients with localized brain lesions, utilizing neuropsychological techniques to specify the functional deficiency and CT scanning to confirm the lesion site. Dreaming is explained as a top-down process despite the nuclei of Tsai being subcortical. Solms observed that “there was a reported loss of the experience of dreaming in patients who had either (1) a bilateral mediobasal frontal cortex lesion involving fibers from the ventral tegmental area of Tsai, an appetitive center which is the source of seeking, wishing/desiring behavior; or (2) a lesion of the inferior parietal area of either side of the brain which on the right involves spatial orientation and on the left involves symbolic activity. Those individuals who reported they had lost the experience of dreaming were those who also reported poorer sleep. In those patients with a lesion in the parieto-temporo-occipital association region, the visual elements in dreaming are lost as well as the ability to create visual images from memory while awake.”

Dreaming is not assumed to be REM sleep dependent in the cortical theory [6, 8]. “Dreaming is thought to be initiated by an arousing stimulus; such as REM sleep, seizures, or noise. This activation stimulates circuits that arise from cell groups in the ventral tegmental area of Tsai. It is a dopaminergic system. It is connected to frontal and limbic structures. The ventral tegmental area of Tsai circuits instigate goal-seeking behavior. It is the wanting, wishing command system. Anterior limbic structures block transmission, which interrupts goal directed behavior (e.g., voluntary motor activity) and facilitates ‘back projection’ processes. The dorso-lateral cortex (the voluntary executive center) and primary visual cortices (the site for perception) are inhibited. The inferior parietal cortices become active and provide the spatial (right side) and symbolic (left side) aspects of dreaming. Lastly, the occipital association areas provide memories of perceptions from which the imagery of dreaming is constructed.”

For Solms [8] dreaming does not isomorphically reflect simple activation of perceptual and motor areas, as these are not activated during dreaming. The imagery of dreaming is not just reproduced, it is constructed each time from memory. Dreaming is not REM bound.

What particularly are the limitations in the A-S hypothesis [6]? Is the A-S theorists’ particular definition of the dream representative of the dreaming process? Dreaming is defined in the A-S theory as “vivid, sensorimotor imagery, experienced as waking reality, despite it being improbable or impossible at times, and emotions are seen as prominent.” This is a highly selective and arbitrary definition of dreaming. Nielsen [9] points out that there is a continuum of cognitive experiences during sleep from so-called apex dreaming, to regular dreaming, to cognitive activity (often called sleep mentation), to cognitive processes. There is no generally accepted or standardized definition. The position put forth by the A-S theorists, that their definition captures what people mean by dreaming and that it serves both psychology and cognitive neuroscience, is questionable. Taub and colleagues [10] have shown that what people say they think a nightmare is like and what they report as a personal nightmare experience are clearly differentiable. The concept of nightmare (e.g., what people think nightmares are like) is more intense, better constructed, and reported in fewer words than their own nightmare experience. A definition of dreaming needs to be made on an empirical basis rather than out of opinions about what it is or is not. Utilizing idealized versions of experience may be suitable for literary undertakings but not for scientific ones either in psychology or in the neurosciences.

The assumptions by the A-S hypothesis theorists [6] that dreaming is coextensive with REM sleep has been widely challenged. Solms [11] has pointed out that dreaming and REM sleep are doubly dissociated; not all REM sleep yields a dream report, and dream reports can be recovered from non-REM sleep. Furthermore dreaming may not even be sleep bound as both Foulkes and Fleisher [12] and Kripke and Sonnenschein [13] have collected dream reports from subjects who were awake.

The position that dreaming is the result of the activity of the pontine generator for REM sleep is challenged by the clinicoanatomical studies of Solms [8]. He reports that patients with core brainstem lesions, which would have prevented the PGO wave from reaching the cortex and who are hypoaroused while awake, continued to report dreaming.

The idea that the model for the dream experience is the output of the demented brain is related to the description of the physiologic process that A-S theorists assume underlies
dreaming. In this view, random discharges from the pons, so-called PGO waves, stimulate cortical structures that do the best they can to organize these chaotic stimuli and the results are hallucinations and narratives that are poorly organized, confabulated, and easily forgotten, allegedly like the experiences of the demented awake. The cortex makes the best of a bad job. However, Snyder [14] has pointed out, based on his large series of laboratory-collected dreams, that it is the dreams mundane nature that best characterizes them, rather than their being impossible or improbable. Heynick [15], in a systematic analysis of speech reported as part of the content of the dream experience, observes how well constructed the speech in dreams is from a grammatical and syntactical point of view. Apparently our linguistic capacity during dreaming operates with surprising efficiency and is capable of generating well-formed, often syntactically complex sentences. Kramer [16] has shown that dream content is highly ordered and where we know there are psychological differences there are dream content differences. This is true at the group level as demographic variables such as gender, age, race, marital status, and social class show dream content differences as do psychiatric illnesses. The dreams of schizophrenics are different from those of the depressed.

Dream content is highly ordered at the individual level as well, [16] and dream content varies across the REM period, and from REM period to REM period throughout the night. The dreams of one individual are different from those of another. Within an individual, dreams are different night to night, but there is a content correlation from night to night such that across 20 nights of laboratory-collected dreams, night 19 correlates 0.8 with night 20. Dreams are more predictive night to night than the physiology of sleep [17]. Dreaming is ordered, not chaotic, and certainly not random.

The assumption that the cortical response to PGO stimulation is a relatively passive one underpins the conviction that the form of the dream will be determined by the physiological stimulus and the dream will be isomorphic with the determining physiology—PGO waves. Pivik [18] has concluded from a review of the psychophysiological studies of dreaming that there is a “general absence of robust psychophysiological relationships between tonic levels of physiological activity and sleep mentation”; and that “studies... were unable to demonstrate a consistent correlation of phasic activity with the qualitative aspects of sleep mentation.” Pivik’s conclusions contradict any suggestion of isomorphism, a central tenant of the A-S hypothesis. Furthermore, as the sensorimotor cortices are not activated during dreaming and the association areas are activated, the images experienced during dreaming are constructed each time and are not the result of perception—thus decreasing the likelihood of an isomorphic relationship between the physiological and psychological aspects of dreaming.

Reiser [19] along with Hobson [7] are of the opinion “that emotion is a prominent part of the dream experience and that it plays a role in generating and shaping both the process and the content of dreaming.” Dream content studies [20–22] have not found emotions to be an inevitable part of the dream experience. Hall and Van de Castle [20] found emotions in at most 56% of spontaneously reported dreams of men and 84% of the dreams of women. Strauch and Meier [21] noted that emotion was present in about half of laboratory-reported dream experiences. Kramer and Brik [22] found emotions reported in at most 37% of the laboratory-collected dreams of men. Kramer, in his selective affective theory of dream function [23], suggests that it is the change in emotion from pre-sleep to post-sleep that is related to dream content.

In summary, the specific critiques of the A-S hypothesis of dreaming [6] include: the recognition of the limited and arbitrary nature of the definition of dreaming; doubt cast on the idea that dementia is an appropriate model for dreaming; the evidence that REM sleep and the dreaming experience are not coextensive; the work showing that dreaming is not isomorphic with REM sleep; the observations that emotion in the dream may not be the shaper of dream experience; and that the narrative nature of the dream is not explained.

The anatomical cortical theory of Solms [8] is offered as a top-down theory. It, too, is not able to predict the content of the dream from the pattern of neuronal activation. It may be helpful to review aspects of the theory to see how it compares to the A-S hypothesis and in what way it may lend anatomic support to Freudian dream theory [5]. Reiser [19], however, has advised that we not look to the neurosciences to confirm or refute Freud. In his clinicoanatomical approach, Solms [8]:

1. Places the initiation of the dreaming process in a subcortical area related to goal-seeking behavior of an appetitive sort and not in the pons as in A-S theory (this suggests the Freudian wish fulfilling motive force).
2. Calls attention to the blocking of access to the sensorimotor cortex by anterior limbic structures leading to a backward (regressive) movement in dream formation (suggesting both the Freudian censor in the block and topographical regression).
3. Points out that it is the visual association areas that are activated during dreaming, not the primary visual cortex, and therefore images are constructed from memory and are not perceptions, making the isomorphism postulated by A-S theory less likely.
4. Recognizes that both spatial and symbolic activities are involved in dreaming, while A-S theory incorporates but does not address this issue.
5. Notes the loss of dreaming occurring in those who complain of sleep problems (suggesting the possible sleep protective function of dreaming).
6. Observes that dreaming is actively constructed and not passively elaborated (suggesting the Freudian dream work).

Hobson, Pace-Schott, and Stickgold [6] provide a telling and detailed critique of the anatomical cortical theory [8]. “They point out the limitations of lesion studies, for example, the recovery across time of the lost function raises questions about the role of the damaged brain area as essential to the transiently lost function. They wonder if REM awakenings studies are the basis for the claim of lost dreaming (which they are not), as spontaneous memory of dreaming would be an inadequate test. They question the support Solms seeks from the leucotomy literature for the role of the medio-basal prefrontal area in dream initiation. Not all leucotomy patients, for example, reported the loss of dreaming. The surgery could well have interfered with the recovery of intrapsychic experiences. The surgery could well have destroyed connections to subcortical limbic structures as well as those from [the] ventral tegmental area. They see the role of dopamine in dreaming as problematic. They point out that dopamine has been reported as both inhibiting dreaming and enhancing it.”

The cortical theory is a reductive theory that also poses biology as explaining the psychological experiences of dreaming, but less so than A-S theory. It does not address, anymore than the A-S theory did, the narrative aspects of dreaming.

What we want to know about dreaming begins with our desire to know the content of the dream experience. Dream content is the base for our search for what the dream experience means, what it is made of, how it is constructed, and what it accomplishes. The functional anatomical explanations or the descriptions of the secretions from various cells of neurotransmitters or neuromodulators contribute little, if anything, to answer our questions about the content, meaning, construction, or function of the dream experience.

As McGuinn [24] has so elegantly pointed out, there are no transduction rules to go from the discharge of neurons in the central nervous system or from the secretions of neurons to the concomitant mental states. He is so pessimistic as to doubt that we have the intellectual tools to develop such a system. The biological dream theories cannot provide us with the content of dreams, the meaning of dreams, the construction of dreams, or the function of dreaming. They cannot address the differences in the content of the dream experience among individuals or within an individual night to night. These theories do not address the semantics or pragmatics of dreaming; they limit themselves, at best, to the syntax of dreaming.

CONCLUDING REMARKS

The mind/brain problem has not been resolved by the biological approaches to dreaming. It is not that biology is uninteresting, it simply does not answer the questions that are asked. Biology does not address the meaning of behavior or the goal-directed nature of behavior, nor does it explain the nature of experience (Qualia). The problem of consciousness is not illuminated. The explanatory gap between biology (body) and consciousness (mind) remains.

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ADDITIONAL READING


INTRODUCTION

The traditional interest in the dream experience had been to foretell the future. It was believed that the will of God was revealed to prophets in dreams. Some 5% of people in a scientific population survey reported that they have the conviction that dreams predict the future. The most popular dream books for many years were those that linked images that appeared in dreams to various numerical values and these values were used by people to select what number to pick in “playing the numbers,” the illegal forerunner to the modern-day lottery. Psychotherapists, influenced by Freud, have used the reports of the dream experience to help them understand the dreamer, their patient. Unfortunately, there had been very little scientific basis to support the conviction that therapists had about the revelatory potential in dream analysis.

The major reason for studying dreaming in the modern context is to understand the functioning of the mind, to understand consciousness. The dream may be seen as the mind in pure culture. Dreaming may present us with a consciousness that is the least influenced by external events [1, 2]. A secondary but important reason for studying dreaming is to see if such a study will unlock the mysteries of psychosis as had been suggested by Jung, Freud [3], and Hughlings Jackson. Mental illness has been and remains a major public health problem.

There has been great reluctance to studying the dream experience in a scientific manner. Neuroscientists have been interested in the study of the functions of the brain and have seen the dream experience as epiphenomenal. The dream has been and continues to be seen by some as a degradation or waste product. It is for them the foam on the beer of sleep. The dream experience is a first-person experience and until quite recently only third-person experiences were considered as amenable to scientific study. First-person or subjective experiences depend on the introspective ability of the subject as well as the willingness of the subject to be an honest reporter. It was thought that the difficulty in collecting reasonable size dream samples coupled with the great variability assumed possible in dreaming made scientific studies of dreaming impossible. The view that dreams could not be studied scientifically was enhanced by the belief that the reliability of dream measurement had been unexplored and that the validity of dream measurement was open to serious question. The discovery in 1953 of a physiological correlate of dreaming, rapid eye movement (REM) sleep, which occurred several times a night, made possible the collection of large dream samples and experimental paradigms became feasible. Dream reports, it was shown, could be reliably scored and dreams were found to be more predictive night to night than sleep stage scoring.

The dream as a psychological experience, reflected in the dream report, should not be confused with REM sleep, a physiological experience. The reductive algorithm to move from dreaming consciousness to brain physiology does not currently exist and may never exist. With apologies to Emerson, a foolish biological “reductionism” may be the hobgoblin of little minds. Dreaming to be the object of scientific scrutiny must be regular, that is, orderly and not random, signal not noise. The remainder of this discussion will explore studies directed at establishing the regularity of dreaming.
DO DREAMS EXIST?

The question has been raised whether the dream experience exists as an event in time or as a confabulation either of the awakening process or of waking consciousness [1, 4]. Freud mentioned the work of Goblot who argued that the dream was elaborated during the waking process. Malcolm, an English philosopher of mind, argued, in his seminal book *Dreaming*, that on logical grounds dreaming could not be a concomitant of the sleeping state and that it is probably an event related to the waking process. In an unpublished essay entitled “The Goblot Phenomenon,” the great empiricist of dream studies, the late Calvin Hall, also suggested that dreaming was an experience concomitant with the waking process.

There are experimental studies that directly and indirectly address the issue of whether the dream is an experience extended in time during sleep. Incorporation of tactile and aural stimuli presented early or late during a REM period appears appropriately in the subsequent dream reports from these awakenings. Familiar and unfamiliar names presented during a REM period are differentially incorporated into the subsequent dream report. The familiar names are more likely to be incorporated. The content of the dream report (e.g., intensity) shows a developmental course across a REM period. The direction of eye movements during a REM period has been shown in some but not all studies to be appropriate to the action described in the dream report from that REM period. Subjects awakened from a REM period are more likely to tell a “dream-like” story in response to a stimulus than when awakened from non-rapid eye movement (NREM) sleep. Subjects asked to make up a nightmare, to report a nightmare they have experienced, and to tell a dream they have had report three different experiences, with the made up nightmare being the most intense, shortest, and best organized of the three. Dreams are experiences that are concomitant with sleep and are not constructed during the awakening process.

COLLECTION AND MEASUREMENT OF DREAM REPORTS

Dream recall is a highly variable process, and to be able to study dreaming, an awareness of those factors that may influence the ability to recall the dream experience is necessary [1, 5, 6]. The place where the dream is experienced and reported (e.g., at home or in a laboratory) may well influence the nature of the dream experience and whether the experience is recalled to be reported. The method of awakening will influence the recall of the dream. The faster the awakening, the more likely a dream will be recalled. The interpersonal situation between the dreamer and the dream collector will influence how much and what will be reported. The gender similarity or difference of the pair and the status relationship of the collector and dreamer will influence recall and content. The style of collection will influence recall and content. For example, asking whether emotion occurred in the dream will increase the number of reports of emotion obtained. The stage of sleep from which the subject awakens will affect dream recall, with greater recall if the awakening is from REM sleep. The method of recording the dream experience will affect the recall of dreams. The dreamer writing out the dream gives shorter and better organized dream reports than telling them into a recorder. The type of subject who is reporting the dream experience will affect the frequency and nature of what is recalled. The subject who recalls dreams, who is more attuned to inner processes, and who is more verbal will provide more dream reports with greater detail than a less introspective, less verbal subject.

There are characteristics of the dream experience itself which are determining of which of the several dreams of the night are most likely to be remembered the next day. There is a recency effect so that it is the last dream that is most likely to be remembered. There is a primacy effect as well so that the first dream experience is more likely to be recalled than the second dream of the night. The longer the dream experience, a length effect, the more likely the recall. And, the more dramatic the dream experience, the more likely it will be recalled. These characteristics have been described as the saliency theory of dream recall.

There are other factors such as gender and age that are known to influence dream recall. Women recall more dreams than men and the older one gets the less dream recall is reported. Brain damage independent of age decreases dream recall. Psychological variables such as ego strength, anxiety, repression, and field independence in most people do not co-vary with dream recall. The meaning of the dream in the context of the interpersonal collection procedure can influence the dreamer’s ability to recall and his/her willingness to report the dream experience.

Serious question has been raised by those interested in the spiritual and creative aspects of dreaming that measuring the dream destroys its very essence. Examining the contribution that the scientific study of dreaming has made to our knowledge of dreaming belies such a negative assessment. There are a number of problems associated with efforts to measure the dream experience as reflected in the dream report. First, we are trying to capture an event experienced in one state, sleep, reported in another state, wakefulness. Our earlier discussion offering evidence that dreams exist and are not products of the awakening process supports the idea that the dream report is an adequate representation of the dream experience. Second, the dream experience is presented as a verbal report. The verbal abilities of the subject may account for dream differences between subjects and a waking verbal control should be.
considered. Third, what in the dream report is to be counted as the scoreable report? A set of rules to deal with asides and redundancies is necessary, as would be the case in dealing with any effort to quantify verbal behavior. Fourth, the question of word length and how to deal with dream reports of differing lengths arises. A word length correction may be appropriate, but it has been suggested that some things may require more words to describe them than others. Fifth, there are scoring systems available for the quantification of dream reports. The reliability and validity of these systems have been established. Clinical concepts of interest can be found or created by combining aspects of an extant system, analogous to using Nissl staining for cell bodies and Golgi staining for dendrites in studying the nervous system. A series of dream reports were scored for hostility with a number of different systems. There was considerable overlap among the various systems, but some 75% of the variance was unexplained. The systems apparently had different conceptualizations of hostility and perhaps some of the prized ineffability of dreaming was in the unexplained variance.

The content of dream reports is reliable as shown by comparing home dream reports to laboratory-collected reports both scored with the same content system by two different investigators. Dream content reports are remarkably stable across time comparing home-reported dreams of college students some three decades apart and from two different institutions. Yet, dream reports of the same person are variable enough from night to night such that the dreams of one night can be distinguished from those of another night.

NORMATIVE, UNIVERSAL, REPETITIVE DREAMS AND NIGHTMARES

The quantitative work with dreams [1, 6–10] has provided a picture of the normative dream. The average dream has 2.6 characters, 4.8 activities, 1.4 social interactions, and 1.3 settings per dream. Other features of dreams which occur in some but not all dreams include negatives 0.77, emotions 0.70, misfortunes 0.41, failure 0.13, success 0.12, and good fortune 0.06 per dream. Aspects of dreams which do not occur in all dreams are less likely to be central to the dream experience.

The major demographic organizer of dreams is the gender of the dreamer, with age, race, marital status, and social class relatively less important. Males have fewer characters in their dreams than women, but they are mostly men and are less likely to be known to the dreamer. Women have more people in their dreams who are equally likely to be men or women and are more likely to be known to the dreamer. Men have more physical activity and aggressive social interactions than women. Women have more friendly social interactions than men but fewer sexual interactions. Men have more outdoor settings in their dream reports and women more indoor settings.

There are typical or universal dreams that occur to most people and in which the content is essentially the same across dreamers. Freud listed some 23 different typical dreams such as feeling embarrassed being naked, the death of a loved one, swimming, or being in a fire. He attributed an identical meaning to some (e.g., being naked and loss of a loved one) and a dreamer-specific meaning to others (e.g., swimming and being in a fire). Harris [9] has pointed out that universal dreams such as falling reflect feelings of insecurity, while dreams of being pursued reflect a feeling of being attacked and may have a differential gender frequency. Ward and co-workers [7] related universal dreams to different aspects of development. It has been observed that the frequency of the various universal dreams is quite similar across cultures.

The repetitive dream has been the object of some interest. It has generally been seen as the response to a similar set of troubling emotional circumstances, usually starting in childhood, involving only the dreamer, and generally having a negative tone. Domhoff [8] has suggested that dreams are a metaphorical attempt at problem resolving and that repetitive dreams may be an attempt to deal with unresolved emotional concerns of the dreamer.

There has long been a fascination with the nightmare experience. Nightmares are a universal experience as almost everyone has been awakened from a disturbing dream feeling anxious with some sense of difficulty in breathing. Bad dreams, which have a negative emotional tone but do not awaken the dreamer, are even more common. The actual nightmare experience is not nearly as intense as what people imagine a nightmare to be but is clearly distinguishable from an ordinary dream. Nightmares cannot be defined based on their content or explained by chronic nightmare sufferers being better dream recallers. There is the suggestion that the discomfort experienced by those experiencing nightmares is a reaction to the experience rather than a concomitant of the nightmare. Not all people who experience nightmares are troubled by them. Those individuals who are troubled by their nightmares and who describe their nightmares as reactive to daytime distress are more likely to seek help for their nightmares. Techniques that encourage rescripting of the nightmare experience have been shown to be helpful.

DREAMS AND PSYCHOLOGICAL DIFFERENCES

Dreams, to be ordered (i.e., nonrandom and meaningful), should reflect psychological differences in circumstances where we know such differences exist, and indeed that is what has been found. It has been shown at the group
level that there are demonstrable dream content differences associated with demographic variables (e.g., gender, age, race, marital status, and social class) [1, 11, 12]. The major psychiatric illnesses show clear psychological differences from normals as the dreams of people with schizophrenia and depression have different dream content from each other and from normals. The schizophrenic has strangers as its common character type while the depressed have family members and normals have friends.

Psychological differences among people at the group level is also found at the individual level, and these differences are also found in their dreams. The dreams of individuals can be distinguished one from another. People are to some degree different from day to day and the dreams of one night can be distinguished from those of another night from the same person. The regularity in dreaming is suggested by dreams becoming increasingly predictive from night to night such that in a series of 20 consecutive nights of dream collection, the 19th night’s dreams predict the 20th night’s dreams at a level of 0.8.

Two patterns of dream relationships across the multiple dreams of a night have been described. One pattern is of a progressive-sequential (P-S) nature, in which metaphorically a problem is posed, worked on, and to some degree resolved. An illustration of a P-S dream series of a young single woman is one in which she first dreams she is a child clinging to stay in the hospital, then of being rejected by a colleague’s wife; in the third dream she has a partner and they are victorious in a game; in the next dream she decides she doesn’t need the doctor despite evidence to the contrary, and in the last dream she turns on the doctor. The other pattern is of a traumatic-repetitive (T-R) nature, in which a concern or problem is expressed metaphorically with different imagery in each dream of the night. An illustration of a T-R dream series from the same young woman is one in which in the first dream someone is lost and trying to call home; in the second dream she is at an orphanage and because there was no room in the car she had to go home with someone else; and in the last dream she is being left by her mother in a laboratory where there might not be enough room. The dream reports across a night’s dreaming support the possibility of content change in as simple a form as the number of words in each dream report. In a series of dreams it was found that the first dream was shorter than the second and the third was shorter than the fourth, but there was no length difference between the second and the third. There were content differences as well across the night with the word content held constant. There were three content differences between the first and second dream of the night and five between the second and the third dream but none between the third and the fourth.

There is a pattern of development or organization even within a dream. The content of the dream shows an increase in intensity for the first 10 min and then shows a plateau for 10–20 min and resumes again. A timing pattern similar to the ebb and flow of the eye movements across a REM period is shown by the content change across the dream.

Content differences in dreams are found where we expect to find psychological differences between people. Demographic variables and psychiatric illnesses show dream content differences. Dreams of individuals are different one from the other as are dreams of different nights of the same individual. There are different patterns of dreams across the night and there is a developmental pattern of dream content within the dream itself. The dream appears to be a highly ordered experience in reflecting psychological differences.

INFLUENCES ON DREAM CONTENT

The dream experience has been described as responsive to a number of manipulations [1, 13, 14]. Tart has summarized some of these manipulations as including direct suggestion, stimuli introduced during the dream experience, hypnosis, conditioning, and REM deprivation and rebound.

The more intensely emotional experiences of the previous day are more likely to be represented in the dreams of the following night. The beginning and ending of an experience, such as sleeping for 20 consecutive nights in a sleep laboratory for dream collection, can be correctly identified in dreams while the middle of the experience cannot. References to sleeping in the unusual situation of a sleep laboratory continue to be represented at the same frequency (i.e., without adaptation) across a 20 night series. The vagaries of the interpersonal situation between the dreamer and the dream collector are reflected in the reported dreams. Dreams critical of the morning dream collector, a psychiatrist, are reported at night to the technician but not in the morning. And a very macho man does not report scary dreams with homosexual implications to the psychiatrist in the morning but does report dreams that capture his sexual relationship to women and his fighting with men. Male volunteers in the sleep laboratory reported dreams suggestive of their fears of being exploited by the male experimenters while female subjects had dreams that suggested a fear of being raped. A female subject, a nurse, dreamed about problems with an intravenous (IV) infusion that had continuing trouble when there was a female dream collector, but on nights when a male physician was the dream collector the IV ran without a problem. Patients had dreams about their therapists while sleeping in the laboratory, while their therapists who slept in another laboratory on the same night dreamed about the conference the next day where their work with the patient was to be discussed. The conference leaders dreamed about the
research group and the research group probably about the research funding agency. We dream about what concerns us. Depressed patients who were given medications that alter their depressed mood had concomitant changes in their dreams showing increased motility, intimacy, and sexuality as the depression lifted. Playing the names of familiar people and unfamiliar people during the dream experience leads to a greater incorporation of the familiar person into the dream. Emotionally significant experiences from the waking state are what become represented in dreams.

DREAMS AND WAKING THOUGHT

Dreams are organized not random events as they reflect psychological differences among people and are influenced by significant emotional events [1, 11, 15]. The next question to ask is about the relationship between dreaming and waking thought.

The themes of pre- and post-sleep verbalizations have been shown to be more closely related to each other than the multiple REM dream reports of a night are to each other. Waking thought is more thematically constrained than the more fluid dreaming thought.

The themes of pre-sleep thought are more closely related to the themes of subsequent dream reports than the dream reports are to the themes of post-sleep verbalizations. Dreams appear to be more reactive to prior wakeful thought than proactive to subsequent wakeful thought.

Dreamers show both a trait and state relationship between dream reports and waking fantasy. Subjects had their REM dream reports and Thematic Apperception Test (TAT) stories scored with ten of the need press variables described by Murray. The rank order intensity scores of the ten variables were significantly related. In another study, spontaneous verbal samples were collected immediately before and after REM dream collection in the sleep laboratory. The contents of the verbal samples and dream reports were found to be significantly related. The TAT study demonstrates a trait and the verbal sample study a state relationship between dreams and waking thought.

The changes in feeling states (mood) across the night are related to the content of the intervening dreams. Mood adjective checklists done before and after REM dream collection show a relationship between who and what was dreamed about and the change in aspects of mood from night to morning. The strongest relationship is between the characters in dream reports and the change in the unhappy aspect of mood. The change in sleepiness across the night is related to the amount of NREM sleep one obtains.

Some aspects of pre-sleep mood correlate with some dream report contents and some dream report contents correlate with some aspects of post-sleep mood. However, the same aspect of pre- and post-sleep mood does not correlate with the intervening dream content. The changes in mood across the night are not a simple pass through the night’s dreams.

Inferences drawn about patients from waking observations and dream reports are similar. Patients had their histories written down by their therapists and had a psychological test report prepared based on their TAT and Rorschach Tests. The patients also had five REM dreams collected. Independent judges read the history, the dream reports, and the test results and based on each data source did a 100 item Q sort describing the patient. The therapist did a Q sort as well. These Q sorts were significantly correlated among the judges. The dream led to similar inferences about the patient as one would obtain from the history and psychological testing. Yet as the amount of overlap—explained variance—was low, there are areas where different inferences could be drawn from the dream than from the other data sources.

Successful from unsuccessful treatment in long-term psychodynamic psychotherapy or psychoanalysis has been distinguished by comparing the change from the first to the last dream report in therapy. The therapist’s ranking of the degree of improvement among a series of similar long-term psychotherapy treatments has been significantly correlated to a judge’s ranking based on comparing the degree of change between the first and the last dream report in therapy. The degree to which patients change in the dynamic psychotherapies is reflected in changes in their dream reports.

Waking and sleeping fantasy are related. However, waking thought is more thematically constrained than the more fluid dreaming thought. Dream themes appear to be more related to pre-sleep thought than to post-sleep thought. Dreamers show both a trait and state relationship between dream reports and waking fantasy. The changes in feeling states (mood) across the night are related to the content of the intervening dreams. But the changes in mood across the night are not a simple pass through the night’s dreams. Inferences drawn about patients from waking observations and dream reports are similar but not identical. Changes in dream content parallel the differential outcomes reported in the dynamic psychotherapies.

DREAM MEANING

Does dreaming have the necessary structure to make a search for the meaning of a dream reasonable? If the content of dreaming is random, more like noise than a signal, then a search for the meaning of a dream would be futile.
However, the evidence does indicate that the dream has the necessary order to support meaning [1, 3, 16–18]. Dreaming has to be related to the ongoing and changing waking concerns of the dreamer if it is to have meaning.

Dreams have order, as they are organized within a REM period, showing an increase in the intensity of content and across the REM periods of the night, and as there are differences in content between REM periods. The dreams of one night can be distinguished from those of another night of the same dreamer, but the dream reports of a dreamer are also related across nights. The dream reports of one dreamer can be distinguished from those of another dreamer. There are dream content differences related to demographic variables such as gender, age, race, marital status, education, and social class. Gender is the major demographic organizer of dream content with age and race a distant second. The dreams of schizophrenics are different from those of the depressed and both are different from normals.

Dreams have been shown to have a connection to the waking emotional concerns of the dreamer. Similar clinical inferences can be drawn from dreams as from the clinical history and psychological test reports of patients. Dream contents have both a trait and state connection to the dreamer as shown by TAT stories and verbal sample analysis. Mood change across the night is related to who and what is dreamed about and mood change in depressives treated with antidepressants has concomitant dream content change. There is a thematic connection from pre-sleep mentation to dream content to post-sleep mentation, with the dream content appearing to be more reactive than proactive. Dream content changes reflect the changes in long-term psychotherapy.

The dream to be understood needs to be approached as a figurative rather than literal statement. A psychological meaning system needs to be applied to a dream to establish its meaning. There are a number of such systems of psychological meaning such as provided by Freud, Jung, Adler, Gendlin, Delaney, Hall, Kramer, the Existentialists, and the Gestaltists.

Kramer [16] has suggested that the dream be parsed into phrases and that one begins at the beginning to use one’s associations to each phrase, keeping in mind that the dream is to be understood figuratively, that meaning is contextual, and that the dream is its own context. The associations to each succeeding phrase serve to select from and narrow down the possible meanings. In the end, the understanding that requires the fewest assumptions and accounts for most of the content is accepted as the most likely meaning, recognizing that other meanings are possible.

Dreams have the essential structure, orderliness and connection to waking fantasy so that a search for meaning appears justified. Approaches to establish meaning have been suggested by many both with and without the co-operation of the dreamer.

THE FUNCTIONS OF DREAMING

An interest in the psychological function of dreaming remains to the present day [1, 3, 19, 20]. Freud saw dreaming as the disguised attempted fulfillment of an infantile wish in the service of maintaining the continuity of sleep. He recognized that a theory of dreaming did not require that it attribute a function to dreaming, but given his teleological predilections he preferred functional theories. The function of dreaming can refer either to how the dream is constructed or to what dreaming achieves, to the consequences of the dream experience. The consequence of dreaming is often related to how it is constructed. Theories of dreaming generally are either assimilative or accommodative. The assimilative theories are more likely to account for the totality of dreaming and function outside conscious awareness (i.e., without recall and secondary reworking). These theories generally have the dream achieve some corrective or reductive goal. An accommodative theory has the dreamer recalling the dream experience either alone or in therapy and, following some exploration, an understanding develops that serves to alter the dreamer. Dream theories may encompass both an assimilative and an accommodative function.

Many functions have been suggested for dreaming. Freud saw the dream as the protector of sleep; Jung saw it as a compensation for conscious exaggeration; Adler as an affective generator to support the life style; French as solving emotional problems; Giora saw the dream as a form of emotional thinking; Breger saw it as an information processing process; and Kramer as a selective affective modulator.

SUMMARY

The dream [1] is a legitimate object for scientific study. It exists as an experience in time, which is adequately captured as a verbal report. The dream experience can be influenced by a number of factors and can be usefully quantified. The dream is orderly and organized, signal not noise, as it reflects meaningful psychological differences and responds to and reflects emotionally laden influences.

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**ADDITIONAL READING**


THE FUNCTION OF SLEEP

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INTRODUCTION

In the last fifty years scientists have made extraordinary progress characterizing the neurobiology, regulation, and genetic underpinnings of mammalian sleep. Mechanisms generating rapid eye movement (REM) and non-rapid eye movement (NREM) sleep have been identified, genes important in the timing and intensity of sleep have been isolated, and much is known about the detrimental effects of abnormal sleep on human performance [1]. It is thus a bit ironic and even distressing that the most fundamental question about sleep is still unanswered. Why we sleep remains one of nature’s greatest mysteries. Several representative theories about sleep function are discussed in this chapter. As will become evident, no one theory holds preeminence; rather, each theory has its merits and faults. An emphasis is therefore placed on theoretical considerations that may improve experimental approaches to understanding sleep function.

FRAMING THE PROBLEM OF SLEEP FUNCTION:
LITTLE THEORIES VERSUS BIG THEORIES

Even the casual reader will be impressed by the abundance of competing theories regarding sleep function. Sleep has been proposed to be important for somatic anabolic processes, brain cooling, restoration of brain molecules, removal of neurotoxins, and higher-order functions such as brain maturation, species-specific “programming,” and memory [2, 3]. These theories are “little” because they explain only a portion of sleep behavior. But are these little theories of sleep function merely incomplete descriptions of a deeper, more basic process? Could there still be a “big,” unifying theory of sleep function that has greater explanatory power than a collection of little theories? Before reviewing some representative ideas about sleep function, it is useful to consider what would constitute a unifying theory of sleep function. We can start by listing several points that should be addressed by such a theory.

1. Phylogeny. A unifying theory of sleep function should explain the presence (or absence) of sleep across the animal kingdom. Animals as diverse as flies to field mice all exhibit sleep-like states that are regulated by homeostatic and circadian mechanisms [1]. In particular, molecular studies have revealed several genes common to drosophila and mammals whose expression is tied to the sleep–wake cycle [4]. This raises the intriguing possibility that the function of sleep is quite ancient. Therefore a unifying theory of sleep function should explain the presence of sleep in all species in which it has been identified. In addition, such a theory should explain how and why sleep evolved in the first place by identifying those aspects of sleep that proved adaptive during the course of evolution.

2. Ontogeny. A unifying theory of sleep function should account for the dramatic changes in sleep during development. REM sleep amounts are greatly elevated in the first weeks of life in most mammals and rapidly decline concurrent with postnatal development. NREM sleep amounts are initially low, then rapidly rise to adult values during the same time [5]. In rodents, REM sleep does not “rebound” following total or selective REM sleep deprivation until the third to fourth postnatal week. NREM sleep, however, shows rebounds in amounts and later in EEG slow-wave
activity quite early in development [5]. A unifying theory of sleep function should account for these dramatic changes in sleep expression and should address whether the presumed function is different in developing animals, or preserved in some fashion across the life span.

3. Regulation. A unifying theory of sleep function should relate the homeostatic regulation of sleep to the proposed function. A sleep homeostat determines the amount and intensity of sleep based on prior sleep–wake history [1]. As discussed by Benington, the homeostatic regulation of sleep should be closely associated with its function [6]. According to this argument, for any sleep-dependent process there should be a feedback mechanism that communicates the state of progress of that process to the homeostat if that process is central to sleep expression. A unifying theory of sleep function must therefore indicate how that function communicates with the sleep homeostat.

4. The Primacy of Sleep. A unifying theory of sleep function should explain why this function only (or preferentially) occurs during sleep. The first requirement of any theory of sleep function is that it explain why sleep, and no other state (e.g., quiet wakefulness) or change in other systems (e.g., increased enzymatic activity), is required for that function. In particular, such a theory should explain why the specific somatic or nervous system changes unique to sleep, such as loss of consciousness, are required or conducive for that function.

In addition, when considering a theory of sleep function it is useful to ask:

1. **Is the theory mutually exclusive?** That is, does the theory exclude other theories if true, or does it subsume or is it subsumed by competing theories?
2. **Is the theory supported by mutually reinforcing lines of evidence?** That is, is there a convergence of evidence in support of the theory, and are these lines internally consistent with each other?
3. **Is the proposed function central to sleep expression?** Sleep has numerous effects on physical processes, but not all of these processes are necessarily linked to sleep function.
4. **Does the theory deal with REM and NREM sleep?** A unifying theory should account for both sleep states, and in cases where REM sleep does not exist (e.g., in invertebrates and possibly reptiles) it should explain why.

EVALUATING THEORIES OF SLEEP FUNCTION

No one theory of sleep function has adequately addressed all the points listed in the preceding section. However, we can organize “little” theories in a manner that may reveal larger, unifying principles. We can begin by first addressing whether sleep is primarily for the brain or for the body (somatic versus neural theories). Somatic theories of sleep function propose that sleep facilitates anabolic processes or restores some bodily function worn down by wakefulness. Neural theories, on the other hand, propose that sleep is primarily for the brain and are further subdivided into metabolic and cognitive categories. Metabolic or “housekeeping” theories propose that sleep detoxifies substances that accumulate during wake (e.g., from increased oxidative metabolism or glutamate release) [7], or restores and repairs neural substrates degraded by wakefulness. Cognitive theories propose that sleep serves higher-order functions such as neural development or memory, presumably by promoting synaptic plasticity.

**Somatic Theories of Sleep Function**

Sleep appears to have beneficial effects on the body and general health. Sleep amounts may influence mortality and morbidity and there are important interactions between sleep and the endocrine and immune systems [8]. Prolonged sleep deprivation (SD) in rodents, drosophila, and possibly humans is fatal—which would support a general “life-sustaining” function for sleep [3, 4, 9]. Such a function would satisfy phylogenetic considerations since the adaptive value is obvious, and evolution might favor the periodic release of anabolic substances during periods of quiescence when energy output is low. Developing infants might also have a greater need for heightened activity in endocrine and immune systems and thus a greater need for sleep. Nevertheless, it is unclear if the primary function of sleep is to facilitate bodily functions. The prolonged SD studies are intriguing, yet death may be caused by abnormalities in hypothalamic regulatory mechanisms that are secondary to a general loss of neural function. Interestingly, shorter periods of SD (24–72 h) have negligible effects on autonomic output and only modestly affect organ function, athletic performance, and recovery from exercise [10, 11].

A serious obstacle to a pure somatic theory of sleep function is that it does not explain the extensive neural changes accompanying sleep. It is difficult to imagine why facilitation of anabolic processes or endocrine or immune function would require the loss of consciousness and other peculiarities of NREM and REM sleep. These events could just as easily occur during periods of quiet wake when the animal is less subject to predation.

**Neural Metabolic Theories: Detoxification and Regeneration**

Metabolic theories are appealing because they relate sleep function to brain processes and the function they propose is intuitively sensible. Who hasn’t felt more mentally alert
after a good night of sleep? Metabolic theories, however, have little experimental support. There is no convincing evidence that sleep removes a toxic by-product of wakefulness. Nor does there appear to be any gross brain damage in sleep-deprived animals, even in cases where the animals are sleep-deprived to death [3, 12, 13]. Detoxification theories also fail to address the respective roles of NREM and REM sleep. Indeed, it is difficult to imagine how REM sleep could counteract the ill effects of heightened brain metabolism since it is a state characterized by intense cortical activation. Phylogenetic considerations pose an additional problem because contrary to predictions of the neurotoxin theories, metabolic rate (when corrected for body mass) is negatively correlated with sleep time [3]. Considering that the brain is an organ of unusually high metabolism, one would have instead predicted that animals with faster overall metabolism would sleep more not less.

There is slightly stronger evidence in support of neurorestorative theories, but it is still not clear what (if anything) sleep restores in the brain. There is no convincing evidence that REM sleep promotes the synthesis of molecules important for neuronal function or structure. NREM sleep is associated with cerebral protein synthesis and sleep in general may upregulate several genes important for neuronal membranes and other structural components [2, 14]. However, the functional consequences of these sleep-related changes in protein and genes are unknown. A recent hypothesis that sleep restores cerebral energy stores is not convincingly supported by the evidence [15–17]. A critical problem with neurorestorative theories is that they do not explain the abundance of sleep during infancy. Even though waking amounts are very low during infancy, neonates sleep much more than adults. This is especially true in precocial species such as the lamb that have fully developed REM and NREM sleep in utero with little or no wake [5]. Nor is neonatal sleep a passive response to the environment because it is regulated at very early ages [5]. Simply stated, if the primary function of sleep is to restore something depleted in wake, then infants should sleep less not more than adults.

Cognitive Theories of Sleep Function: Learning and Brain Development

The prevailing view among the general public is that sleep is good for learning and memory but among sleep scientists this idea has been bitterly contested for decades [2]. In contrast to metabolic theories that have foundered for lack of evidence, cognitive theories suffer from an abundance of evidence of very mixed quality. The situation has improved over the last decade and there appears to be a convergence of findings supporting a role for sleep in adult learning and plasticity and brain development [2]. Several issues need to be resolved; for example, there is little agreement over which sleep state is important for learning (REM versus NREM), nor is it clear what kind of learning is most affected by sleep (episodic versus procedural) [2]. There are three additional obstacles for a purely cognitive theory of sleep function. To begin with, it is not clear why sleep should be needed for learning in the first place. Animals certainly learn while awake, and many forms of synaptic plasticity are induced during wake (and perhaps only in wake) [2]. A common reply is that sleep is important for the consolidation of synaptic changes, which occurs after the initial induction of plasticity [18]. This may be true, but the underlying mechanisms responsible for sleep-dependent consolidation have not been identified. Until they are, the role of sleep in this process will continue to be debated. A second unresolved issue is that there is no obvious communication between learning or plasticity mechanisms and sleep homeostasis. A final point is that the main supports for a cognitive theory of sleep function, namely, the effects of sleep on brain development and the effects of sleep on adult mnemonic processes, have not been integrated in a manner that explains how sleep influences brain morphology and plasticity across the life span. It is possible that sleep function is different in developing and adult brains, but a parsimonious theory should propose mechanisms common to both.

CONCLUSIONS

For all their achievements, sleep scientists remain in the ticklish position of not knowing why we sleep. An analogous situation in the sciences is hard to find. For example, eating, like sleep, is a complex, regulated behavior governed by specific brain regions and hormones. Eating, like sleep, is ubiquitous in the animal kingdom and undergoes important transformations during ontogeny. The function of eating, however, is not disputed. In this chapter representative theories of sleep function have been reviewed in the hopes of revealing a deeper, more unifying understanding of sleep function. The evidence is equivocal, but some tentative conclusions can be made. First, it appears that while sleep may have beneficial effects on general health, its primary function concerns the brain and not the body. Second, sleep has profound effects on mental performance, which suggests that sleep in some general way facilitates normal neuronal function. Strong evidence for this are findings showing that sleep affects learning and synaptic plasticity—which are experimentally accessible manifestations of normal neuronal activity. It is therefore possible that sleep is a time when overall neuronal function is facilitated either by sleep-dependent increases in gene expression and protein synthesis or alterations in neuronal activity. Why this process primarily occurs in sleep and not in wake is but one of many unanswered questions that must await future investigation.
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THE EVOLUTION OF SLEEP: A PHYLOGENETIC APPROACH

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INTRODUCTION

Although scientists and physicians have been pursuing the meaning of sleep for decades, the functions of sleep remain elusive [1]. There is strong consensus that the comparative method is a powerful, yet underutilized, approach for illuminating sleep function [2–5]. Under the comparative paradigm, sleep is compared across the animal kingdom with the aim of revealing the evolutionary history of sleep. Studies utilizing this approach have demonstrated extensive variation in both the amount and phasing (e.g., monophasic—diurnal or nocturnal; or polyphasic—crepuscular or arrhythmic) of sleep across taxonomic groups [2]. Although most, if not all, vertebrates sleep, the study of sleep in these organisms is not likely to yield the fundamental function(s) for which sleep evolved. Additional adaptations likely became associated with sleep after its initial evolution. Sleep in mammals may therefore perform a tapestry of functions, making the dissection of sleep’s original evolutionary function that much more difficult to understand or recognize.

The usefulness of the comparative method is clear, it is impeded by a lack of information on sleep in nonmammalian vertebrates and sleep-like behavior in invertebrates. Consequently, the electrophysiological hallmarks of mammalian sleep are often used as the “gold standard” for sleep in nonmammals, while sleep in other vertebrate classes has largely been neglected. Although the relative lack of information on sleep in reptiles, amphibians, and fishes has been the main obstacle to wide-ranging comparative work, the relative wealth of knowledge on mammalian species has allowed for detailed comparisons among mammalian taxa [6].

Sleep is foremost a behavioral state. At the organismal level, sleep is readily identifiable by (1) behavioral quiescence, (2) increased arousal threshold, (3) rapid reversibility to wakefulness [7], (4) a species-specific sleep site and posture [8], (5) circadian organization, and (6) homeostatic regulation [9]. Both circadian rhythm and homeostatic regulation dictate propensity to sleep [5]. The circadian rhythm aligns sleep with a period(s) of the 24-hour day, whereas homeostatic regulation is a function of prior time awake. Sleep deprivation results in a “debt that is repaid” during successive sleep periods. In essence, sleep loss is compensated for by an increase in sleep time and intensity during recovery sleep. Intensity of sleep is measured via slow-wave activity (i.e., mean electroencephalogram power density between 0.75 and 4.0 Hz) [5] and is correlated with an increased arousal threshold following sleep deprivation.
This review aims to provide insight into variation in sleep architecture among the vertebrate classes as well as an overview of the limited, yet increasing information on sleep-like behavior in invertebrates. We focus on the evolution of sleep as measured by electrophysiological attributes using extant organisms as models for ancestral forms.

MAMMALS

Marsupials and Terrestrial Placentals

All mammals studied to date show some form of sleep [6]. Although total sleep time and the relative proportions of the sleep stages vary greatly among taxa, all exhibit an alternating cycle of slow-wave sleep (SWS; also called quiet sleep or non-rapid eye movement (NREM) sleep), punctuated by episodes of rapid eye movement (REM) sleep (also called active sleep or paradoxical sleep). SWS is characterized by an electroencephalogram (EEG) of high-amplitude, low-frequency waves, which are the result of synchronous neuronal firing between adjacent neurons in the neocortex and thalamocortical interactions. In humans, SWS refers only to stages 3 and 4 of NREM; whereas in the animal literature, SWS usually refers to all stages of sleep other than REM sleep. During SWS, heart and respiratory rate remain steady, and thermoregulation remains functional. Eye movements (measured by the electro-oculogram (EOG)) are absent, while muscle tone (measured by the electromyogram (EMG)) persists.

REM sleep is distinguished from SWS by a low-amplitude, mixed-frequency or activated EEG. Heart and respiratory rate are irregular and thermoregulation is suspended; therefore an endotherm is essentially poikilothermic during REM sleep. Rapid eye movements are present and, unlike in wakefulness, there is EMG atonia. The mammalian sleep cycle consists of an alternation between SWS and REM sleep. Normally, the sleep cycle is entered through SWS and terminates after an episode of REM sleep with a brief awakening.

Insectivores, carnivores, and ungulates engage in drowsiness, a stage intermediate between wakefulness and sleep. Although it is probable that all terrestrial mammals exhibit drowsiness to varying degrees, it is most notable in the aforementioned groups. The EEG of a drowsy animal usually shows sleep spindles or slow waves superimposed on a background of waking EEG activity. Arousal thresholds remain low and eye states are intermediate between open and closed. The function of drowsiness is unknown, drowsiness may permit vigilance during sleep in perilous environments [6].

Monotremes

Monotremes are the earliest offshoot of the mammalian evolutionary line [10]. There are only three living representatives of monotremes: the short-beaked echidna (Tachyglossus aculeatus), the long-beaked echidna (Zaglossus bruijni), and the duck-billed platypus (Ornithorhynchus anatinus). EEG sleep studies have been conducted on the first and third. Understanding sleep in these egg-laying mammals may clarify the earliest sleep state from which all existing sleep states evolved.

The first sleep study on a monotreme (the short-beaked echidna) concluded that although the mammal engaged in SWS, it did not exhibit the EEG correlates and common features of REM sleep [11]. However, a reanalysis of sleep in T. aculeatus revealed concurrent cortical features of SWS and subcortical signs of REM sleep [12]. Specifically, the forebrain generated a high-amplitude, low-frequency EEG typical of SWS, while brainstem neurons fired with an irregular pattern similar to that observed in placental mammals during REM sleep. Thus the echidna exhibited a state composed of markers common to both SWS and REM sleep, suggesting that the two temporally distinct states arose in the placental and marsupial mammalian clade from a single, heterogeneous sleep state. Some controversy persists, however, over the characterization of sleep states in the echidna. In a subsequent study, Nicol et al. [13] reported SWS and REM sleep characterized by an activated EEG, reduced tonic EMG, intermittent EOG activity, and decreased heart rate, typical of REM sleep in placental and marsupial mammals.

The only study on sleep in the platypus identified both SWS and REM sleep [14]. As in the echidna, sleep was characterized by a high-amplitude, low-frequency EEG, typical of SWS. Although brainstem neuronal units were not recorded, the platypus showed bursts of rapid eye movements and twitching of the bill and head, similar to phasic skeletomuscle activity in other mammals during REM sleep. Arousal thresholds were higher in REM sleep than in SWS, again consistent with placental and marsupial mammals. Calculations of REM sleep time, based on the temporal distribution of eye movements and twitches, suggest that the platypus spends more time in REM sleep than any other animal studied.

Aquatic Mammals

There are three extant aquatic mammalian orders: Cetacea, Pinnipedia, and Sirenia. Aquatic mammals are conflicted by the need to simultaneously sleep, surface to breathe, and maintain vigilance. Several species of aquatic mammals appear to have overcome this conflict by engaging in unihemispheric slow-wave sleep (USWS), a unique state during which one cerebral hemisphere shows EEG activity indicative of SWS, while the other hemisphere shows activity indicative of wakefulness (Figure 8.1; reviewed in [15]). Interhemispheric asymmetries in the
EEG are associated with interhemispheric asymmetries in temperature, with the sleeping hemisphere having a lower parietal cortex temperature relative to the awake hemisphere [16]. During USWS, the eye contralateral to the sleeping hemisphere is usually closed, while the eye contralateral to the awake hemisphere is open.

USWS has been identified in five cetacean species: pilot whale (*Globicephala scammoni*), bottlenose dolphin (*Tursiops truncatus*), common porpoise (*Phocoena phocoena*), Amazonian dolphin (*Inia geoffrensis*), and the beluga whale (*Delphinapterus leucas*). In all cetaceans examined, USWS is the predominant form of SWS; only rarely do cetaceans engage in unambiguous bihemispheric slow-wave sleep (BSWS). Interestingly, REM sleep either is absent, is greatly reduced, or occurs in a modified form in cetaceans; therefore the majority of sleep time is USWS. Bottlenose and Amazonian dolphins may swim slowly or hover at the surface of the water during USWS, while periodic fin movements maintain a stable posture. Furthermore, they breathe periodically without arousing to bilateral wakefulness. Interestingly, BSWS induced via pentobarbital administration, inhibit respiration [17], suggesting that USWS in cetaceans is, in part, an adaptation to maintain motor activity to allow surfacing to breathe. However, dolphins may also engage in USWS to monitor their environment. During USWS in a captive bottlenose dolphin, a visual stimulus presented to the open eye elicited a behavioral and electrophysiological response, such that the animal aroused to bilateral wakefulness. Indeed, Goley [18] found that Pacific white-sided dolphins (*Lagenorhynchus obliquidens*) kept their open eye on adjacent dolphins, perhaps to maintain relative position within the pod. Thus USWS may be used during long-distance migrations as it allows both vigilance and motor control concurrent with sleep.

Selective sleep deprivation studies in dolphins have been instrumental in identifying the biological targets benefiting from sleep. USWS allows for one hemisphere to be deprived of sleep while permitting sleep in the other. As deprivation continues, only the deprived hemisphere increases its attempt to fall asleep and when allowed to recover from sleep deprivation, only the deprived hemisphere exhibits a rebound in SWS, indicating that sleep is homeostatically regulated independently within each hemisphere [19] and that sleep benefits primarily the brain and not the body, a finding consistent with the fact that cetaceans may continue to swim while sleeping.

Within the order Pinnipedia there are three families: Odobenidae (walruses), Otariidae (eared seals: fur seals and sea lions), and Phocidae (true seals). Electrophysiological sleep studies have been conducted in eared and true seals, yet no such study has been attempted in walruses. Pinnipeds, unlike cetaceans, partition their time between terrestrial and aquatic environments and may therefore sleep both in and out of the water. In contrast to cetaceans, much of SWS in eared seals is BSWS, rather than USWS. Eared seals engage in USWS both in and out of the water, with the proportion of SWS composed of USWS being greater during sleep in the water. Also unlike cetaceans, eared seals engage in unequivocal REM sleep.
Interestingly, REM sleep as a percent of total sleep time decreases in the water, when compared to sleep on land. Like cetaceans, however, eared seals engage in USWS to allow respiration concurrent with sleep. For example, fur seals assume a stereotypic sleep posture in the water with three flippers in the air while one flipper paddles in order to keep the nares above the water’s surface. Conversely, true seals only display BSWS and REM sleep and must hold their breath while asleep at sea. Periodic, brief awakenings permit motor control and the seal surfaces to breathe. On the other hand, elephant seals floating near the surface simply raise their heads above the water and breathe without arousing to wakefulness.

Manatees (Order: Sirenia) also engage in USWS [20]. A captive Amazonian manatee (Trichechus inunguis) exhibited REM sleep (1% of recording time) and SWS (27% of recording time) with 25% of SWS being unihemispheric. However, during bouts of USWS the manatee remained motionless underwater [20]. USWS in the manatee was not used to allow respiration concurrent with sleep; rather the manatees aroused to bilateral wakefulness for each respiratory act. In this instance, USWS may serve another function, such as predator detection.

Correlates of Sleep Architecture in Mammals

Correlational studies have led to various hypotheses on sleep function and factors influencing sleep architecture. For example, there are two clear energy conservation hypotheses about mammalian sleep [6]. Energy conservationists suggest that sleep limits energy expenditure by reducing metabolic rate below that accomplished by rest alone. Alternatively, sleep may enforce rest, which, in turn, limits energy expenditure. If so, one would predict that mammals with higher mass-specific metabolic rates would sleep more, and although this prediction was initially supported (Table 8.1) [21], the relationship was negative after controlling for body weight via partial correlation (as mammals with higher mass-specific metabolic rates actually sleep less) [22]. Elgar et al. [22] suggest that animals with higher mass-specific metabolic rates need to allocate more time to foraging than those with lower mass-specific metabolic rates. Foraging time may thus limit sleep time.

Potential predation may restrict REM sleep time as REM sleep is negatively correlated with an index of “overall danger” [23]. Under these conditions, prey species should not engage in lengthy bouts of REM sleep and it’s associated high arousal thresholds due to increased predation threat. Elgar et al. [22] did not address the potential role of predation in influencing sleep architecture; however, they did demonstrate that geographic latitude correlated positively with cycle length after controlling for body weight. Presumably, the inhibition of thermoregulatory mechanisms (which occurs during REM sleep) limits the amount of time an animal in a temperate climate can endure long periods of uninterrupted REM sleep. Theoretically, extended bouts of REM sleep would be detrimental to an endothermic animal if the ambient temperature were significantly below that of thermoneutrality. Precocial species, those that are relatively self-sufficient at birth, exhibit less REM sleep as adults than altricial species, those that are relatively helpless upon birth or hatching [22, 23]. However, since precocial animals are generally larger than their altricial counterparts, Elgar et al. [24] reanalyzed a revised version of their 1988 dataset and revealed that although altricial families have significantly more REM sleep than precocial families, this correlation was no longer significant after controlling for body weight.

Mammals with greater mass-specific metabolic rates may sleep longer [21], leading Siegel and co-workers to hypothesize that increased sleep requirements are necessary as a consequence of increased metabolic rate and the associated production of free radicals [25, 26], which are detrimental to protein structure. Finally, since sleep is likely of principal importance to the brain rather than to the body [1], one would expect larger brains to require more sleep; however, brain weight negatively correlated with total sleep time, suggesting that larger brained organisms may be able to handle sustained periods of wakefulness better than smaller brained organisms.

### Table 8.1 Summary of Correlational Studies

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cycle Length (min)</th>
<th>Metabolic Rate (cm$^3$ O$_2$/g/h)</th>
<th>Body Weight (kg)</th>
<th>Brain Weight (g)</th>
<th>Life Span</th>
<th>Overall Danger Index</th>
<th>Geographic Latitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time</td>
<td>−[21]</td>
<td>+[21]/−[22]</td>
<td>−[22]</td>
<td>−[21, 22]</td>
<td>−[21]</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>SWS (h/day)</td>
<td>−[21]</td>
<td>+[21]/−[22]</td>
<td>−[22, 23]</td>
<td>−[21–23]</td>
<td>−[21, 23]</td>
<td>−[23]</td>
<td>?</td>
</tr>
<tr>
<td>REM sleep (h/day)</td>
<td>ns [21]</td>
<td>+[21]/−[22]</td>
<td>−[22, 23]</td>
<td>−[21–23]</td>
<td>−[21, 23]</td>
<td>−[23]</td>
<td>?</td>
</tr>
<tr>
<td>Cycle length (min)</td>
<td>n/a</td>
<td>−[21]+[22]</td>
<td>+[22]</td>
<td>+[21, 22]</td>
<td>+[21]</td>
<td>?</td>
<td>−[22]</td>
</tr>
</tbody>
</table>

*A plus (+) denotes a significant ($p < 0.05$) positive correlation between the two variables, a minus (−) denotes a significant ($p < 0.05$) negative correlation, and ns means that the correlation was not significant. A question mark (?) indicates that the correlation was not calculated. For the correlations of metabolic rate with various sleep characteristics, Elgar et al. [22] calculated a partial correlation between total and SWS times with metabolic rate, after controlling for adult body weight, whereas Zepelin and Rechtschaffen [21] correlated sleep characteristics with mass-specific metabolic rate.*
All of these correlational studies, however, are fraught by a common concern. Zepelin and Rechtschaffen [21] and Allison and Cicchetti [23] used each species as a statistically independent unit, whereas Elgar et al. [22] pooled data at the family level. However, the simple phylogenetic framework used by Elgar et al. [22] is no longer considered valid. Thus all studies experienced pseudoreplication since phylogenetic relationships between taxa were neglected. Data from mouse to elephant, bat to human, and horse to kangaroo were weighted equally against one another. Future work should readdress these datasets under an explicit, phylogenetic context using independent contrasts to control for pseudoreplication where possible.

**BIRDS**

The EEG of a sleeping bird is similar to that of a sleeping mammal; and yet, birds are more closely related to extant reptiles (i.e., crocodilians) than they are to mammals. A sleeping bird meets all of the behavioral criteria listed for mammals (Figure 8.2) and exhibits both SWS and REM sleep. Birds, like mammals, may be classified as nocturnal, diurnal, crepuscular, or arrhythmic with respect to their timing of sleep. A waking bird exhibits bilateral eye opening, complex body movements, an activated, low-amplitude, mixed-frequency EEG, a highly active EOG, highly tonic EMG, variable heart rate, and low arousal threshold. As in mammals, avian SWS is characterized by high-amplitude, low-frequency EEG activity (reviewed in [27]). Interestingly, sleep spindles and K-complexes during SWS are absent. Neck EMG is typically tonic without phasic events. Eye movements are infrequent with the exception of brief, high-frequency oscillations of the eye. Heart, respiratory, and metabolic rate are all stable and reduced relative to waking.

REM sleep is characterized by the highest arousal threshold and a relatively high-frequency, low-amplitude EEG. Birds typically show much less REM sleep than mammals and periods of REM sleep are usually shorter than 10 s. Eye movements are present in clusters. Hippocampal theta waves and PGO spikes have not been recorded during avian REM sleep. Heart rate is either variable or may increase or decrease. Finally, as in mammals, thermoregulation is inhibited during REM sleep in birds.

In mammals, sleep intensity is gauged by slow-wave activity (SWA). Unlike in mammals, sleep deprivation does not appear to result in an increase in SWA in subsequent bouts of sleep in birds. However, sleep duration and amount of REM sleep all increase during recovery after sleep deprivation. Interestingly, migratory songbirds, such as the white-crowned sparrow (*Zonotrichia leucophryns gambelii*), appear to reduce their amount of time sleeping by over 60% during migration [28].

The ontogenesis of avian sleep is similar to that of mammalian sleep patterns. Domestic fowl exhibit EEG components of an adult bird (i.e., SWS and REM sleep) while in the egg, but unlike most natal mammals, birds experience little REM sleep prehatch. SWS is identifiable by day 17 and is of typical form by day 18. REM sleep appears during day 18 or 19, just before hatching on day 20. REM sleep declines rapidly in chickens from 16.5% to 6.4% by the end of posthatch day 3.

Like aquatic mammals, birds engage in USWS [15, 27, 29]. Avian USWS is defined by unilateral eye closure (UEC) and associated interhemispheric asymmetries in SWS-related EEG activity. However, the degree of interhemispheric asymmetry in birds is small compared to aquatic mammals. USWS has been reported in 8 species across 6 avian orders and UEC has been reported in 29 species from 13 orders. Spooner [30] was the first to demonstrate an association between asynchrony eye closure and interhemispheric asymmetries associated with USWS. However, the function of avian USWS remained unclear until Rattenborg et al. [31, 32] showed that USWS allows birds to maintain vigilance for predators while sleeping. Using the “group edge effect” paradigm (birds on the periphery of a group perceive greater danger than those in the center), birds on the outside of the group increased their use of USWS by 150% relative to the birds in the middle and showed a strong preference for directing their open eye.

![Figure 8.2](image-url) Emperor penguins (*Aptenodytes forsteri*) displaying the typical avian head postures associated with wakefulness (right) and sleep (left and middle). (Courtesy of Grass-Telefactor, An Astro-Med, Inc. Product Group.)
away from the other birds and toward potential threats. Not only does this show the adaptive significance of USWS, it also reveals the plasticity of the trait under changing predation regimes. Unihemispheric REM sleep has never been reported in birds (or mammals).

**Correlates of Sleep Architecture in Birds**

Only two comparative studies exist that examine the correlates of sleep architecture in birds [33, 34]. Amlaner and Ball [33] calculated correlations between total sleep time (TST) and environmental (latitude and hours of daylight) and ecological (sleep exposure, social sleep index, and an index of vulnerability or exposure to potential predation) factors thought to affect sleep architecture. However, they did not differentiate between SWS and REM sleep as their dataset was based totally on a behavioral definition of sleep. (At the time, there existed very little information on sleep architecture in wild birds—an ongoing limitation of sleep studies in comparative bird studies even today; see [34].) Like the correlational studies in mammals, there was great interspecies variability of TST. The average TST was 7 h. There was a negative correlation between TST and latitude and for species variability of TST. The average TST was 7 h. There was a negative correlation between TST and latitude and for species experiencing longer relative day length. Birds at arctic latitudes (>68.00°) during the summer, when day length is virtually 24 h, averaged a TST of 3.7 ± 1.3 h (mean ± s.e. n = 12). This may reflect (1) a bird’s need to increase vigilance during the long daylight hours, (2) the need to accomplish more important behaviors at the expense of sleeping (a natural form of sleep deprivation), and/or (3) the direct alerting effects of light. A stepwise multiple regression based on these variables revealed that day length accounted for 49.1% (r = −0.7) of the variance contributing to TST; however, latitude was also a good predictor of TST (r = −0.62).

Schmidt [34] used an electrophysiological dataset that did differentiate between SWS and REM sleep. Like mammals, SWS time correlated negatively with resting mass-specific metabolic rate. However, the correlation between SWS time and body weight was not significant. SWS time was highly conserved between taxonomic orders, whereas REM sleep time varied significantly between orders. Since altricial mammals have more REM sleep than precocial mammals, one would expect birds to exhibit a large proportion of REM sleep, as birds are extremely altricial at birth. However, although birds have comparable amounts of SWS as mammals, they exhibit half the amount of REM sleep [34]. Interestingly, precocial birds (Order: Sphenisciformes, Anseriformes, and Galliformes) exhibited more REM sleep (but not SWS) than altricial orders (Order: Columbiformes, Psittaciformes, Strigiformes, Passeriformes). Arboreal birds require less REM sleep than either terrestrial or aquatic birds, or mammals. Most passerines appear to have extremely small amounts of REM sleep (3–10 min per 24 h), although 16% of sleep is REM sleep in white crowned sparrows [28]. Amlaner and Ball [27] speculated that passerines engage in less REM sleep because perching, which requires muscle tone, is inhibited during REM sleep. Alternatively, Schmidt [34] suggests that since passerines have larger optic lobes (relative to other avian orders) they require less REM sleep, although details and empirical support for this hypothesis are lacking. Diurnal birds did not differ in amounts of either SWS or REM sleep relative to nocturnal or polyphasic birds.

**REPTILES**

The class Reptilia is composed of four orders: Crocodilia (alligators, caimans, crocodiles, and gharials), Chelonii (tortoises and turtles), Squamata (lizards and snakes), and Rhynchocephalia (tuataras). Sleep has been investigated in all orders with the exception of Rhynchocephalia and all representatives studied exhibited sleep, according to behavioral criteria. However, the electrophysiological correlates of behavioral sleep in reptiles are often inconsistent and contradictory, sometimes within the same species [2, 3, 5, 35]—thus inferring the evolutionary pathway of sleep in birds and mammals from reptilian studies has been impeded and the need for future reptilian work is apparent.

**Order: Crocodilia**

Animals of this order are the closest extant relatives to modern-day birds. One might therefore expect crocodilian sleep architecture to be similar to that of birds (i.e., SWS and REM sleep). Studies in the caiman (Caiman sclerops) have been most telling. High-voltage sharp spikes in the EEG were prominent during periods of behavioral quiescence and were reduced upon arousal [36]. After sleep deprivation, there was an increase in spike activity similar to the rebound in slow-wave activity (SWA) in mammals. Interestingly, some studies have reported SWA (i.e., high-amplitude, low-frequency activity) reminiscent of mammalian SWS [37, 38]. Warner and Huggins [37] attribute the difference between their findings and that of Flanigan et al. [36] to the presence of other caimans in their study, which, presumably, relaxed their animals. REM sleep was not observed in either study. Unilateral eye closure (UEC) has been observed in caimans, but the possibility of unihemispheric sleep was not investigated [37].

**Order: Testudines**

Although turtles and tortoises sleep, their sleep apparently does not resemble mammalian and avian SWS or REM sleep. Box turtles (Terrapene carolina) [39] and the red-
footed tortoise (*Geochelone carbonaria*) [40] both meet the behavioral criteria for sleep: a species-specific sleep posture, behavioral quiescence, increased arousal threshold, rapid reversibility, and homeostatic regulation. Additionally, both had an EEG of high-amplitude spiking activity superimposed over a low-voltage background. EEG spikes disappeared with spontaneous or induced arousal. Spiking activity increased after sleep deprivation and was associated with increased arousal thresholds. Neither classical high-amplitude slow waves nor REM sleep was observed in either species. However, administration of atropine sulfate—a cholinergic blocking agent that increases mammalian slow waves—increased spiking activity in red-footed tortoises [41]. Furthermore, administration of parachlorophenylalanine—a serotonin synthesis inhibitor that suppresses mammalian slow waves—reduced spiking activity in the three tortoises studied, suggesting that these spikes are homologous to mammalian SWS [42]. UEC was reported for both box turtles and the red-footed tortoise [39, 40]. In the margined tortoise (*Testudo marginata*), quiescence was associated with bilateral eye closure, body relaxation, increased arousal threshold, reduced EMG activity, and high-voltage slow waves. Likewise, the EEG of the yellow-footed tortoise (*Testudo denticulata*, now *Geochelone denticulata*) exhibited high-voltage spiking activity during sleep. In contrast, the loggerhead sea turtle (*Caretta caretta*) did not show spiking activity or slow waves during behavioral sleep. One study on the European pond turtle (*Emys orbicularis*) reported both SWS and REM sleep, a result that remains unreplicated.

**Order: Squamata**

Sleep in the desert iguana (*Dipsosaurus dorsalis*) [43] and spiny-tailed iguana (*Ctenosaura pectinata*) [44] consisted of a reduction of EEG amplitude and frequency relative to waking. Upon arousal, EEG amplitude increased in brainstem and forebrain electrodes [44]. Eye movements occurred at 4–25 min intervals, reminiscent of mammalian REM sleep [44]; however, this may be recording artifacts due to brief awakenings or nictitating membrane activity and not reflective of true REM sleep. Following sleep deprivation, the green iguana (*Iguana iguana*) and spiny-tailed iguana exhibited a rebound in sleep as indicated by total sleep time and by the increased frequency of high-voltage spikes. Chameleons (*Chamaeleo jacksoni* and *Chamaeleo meleri*) also exhibited bursts of high-voltage spikes during sleep.

REM sleep in reptiles appears to be ambiguous based on historic reports. Although REM sleep has been reported in the chameleon (*Chamaeleo sp.*) [45], desert iguana [43], and spiny-tailed iguana [44, 46], in the desert iguana, REM sleep was characterized by an increase in EEG amplitude to that of wakefulness with a concurrent atomic EMG [43]. REM sleep was temperature sensitive and appeared with greater incidence at higher temperatures. Conversely, other studies have not observed REM sleep in either the green or spiny-tailed iguana [47] and SWS has never been reported in squamates.

Despite the pervasiveness of UEC in squamates, only one behavioral study has explicitly investigated UEC in reptiles. Mathews et al. [48] demonstrated that the frequency of UEC increased in the western fence lizard (*Sceloporus occidentalis*) following exposure to a predator. Furthermore, lizards preferentially directed their open eye toward the last known position of the predator, suggesting at least a predator-detection function for UEC in reptiles similar to that of birds [31, 32].

Reptiles exhibit unambiguous behavioral sleep that is associated with concurrent changes in brain activity. However, the inconsistencies among and within species and between studies make interpretation difficult from many perspectives. High-voltage spikes are present in most studies, yet absent in others, which may reflect underlying methodological differences between studies, such as laboratory adaptation, electrode placement, and ambient temperature. Interestingly, it has been proposed that high-voltage spikes may occur in a state that is the precursor to mammalian and avian SWS. Sleep in reptiles appears to be homeostatically regulated as deprivation results in a reduction of sleep latency and an increase in sleep time when allowed to proceed. Furthermore, following sleep deprivation there is often an increase in spiking activity, leading some to suggest that spiking may reflect sleep intensity. Along these lines, it has been suggested that the spiking activity of reptiles resembles subcortical spiking during SWS in mammals. The fact that reptiles have a comparatively small cortex has also led some to suggest that reptiles lack the neuroanatomy necessary to generate SWS-related SWA. However, the minimal amount of cortex required to generate SWA remains unclear. Finally, the prevalence of UEC in crocodilians [37], chelonians [39, 40], and squamates (Family: Chamaeleonidae [45], Iguanidae [44, 47], Phrynosomatidae [48]) suggests that reptiles are able to engage in unihemispheric sleep; however, no study to date has examined the EEG correlates of UEC in reptiles.

**AMPHIBIANS AND FISHES**

Evidence for the existence of sleep in both amphibians and fishes is ambiguous [3, 5]. Although some species may show signs of behavioral sleep, others do not. Three species of tree frog (*Hyla cinerea*, *H. septentrionalis*, and *H. squirella*) were monitored in the lab with EEG. Behavioral sleep was associated with decreased amplitude and increased frequency relative to waking (opposite of the typical mammalian/avian pattern). Arousal thresholds were not measured. The EEG of the common frog (*Rana temporaria*) showed
increased low-frequency activity during periods of behavioral quiescence and reduced muscle tone and bradycardia. Alternatively, captive bullfrogs (Rana catesbeiana) may not sleep; a tentative conclusion based on a lack of reduction in responsiveness to electrical stimuli and continuous bilateral eye opening. Furthermore, no EEG changes were noted during quiescence, although bullfrogs exhibited an EEG similar to that of sleeping tree frogs (i.e., decreased EEG activity). Sleep-like behavior in the western toad (Bufo boreas) was accompanied by a slowing of the EEG. However, high-voltage, fast spiking activity has also been reported during sleep-like behavior in the toad.

Behavioral sleep in amphibians may occur in the absence of changes in brain activity. Conversely, electrophysiological changes associated with sleep may be observed in the absence of accompanying behavioral measures of sleep. The few amphibian studies that report EEG correlates of behavioral state also contain significant intersubject differences that impede interpretation. It is also possible that recorded sleep patterns may not be representative of natural patterns. Experimental animals may have been stressed due to novel laboratory conditions and they may require a more prolonged acclimation period. Of course, these criticisms could be said of many laboratory studies that involve wild animals belonging to all taxa.

Electrophysiological data on fishes is scarce. Indeed only two studies have recorded neuronal activity during periods of behavioral quiescence. Sleep-like periods in the catfish (Ictalurus nebulosus) were defined by decreased behavioral motility and, unlike wakefulness, were associated with EEG slow-wave activity and spiking. Spiking disappeared upon arousal. Conversely, a study on the tench (Tinca tinca) did not find an association between behavioral state and variation in EEG activity, but observed decreased muscle tone and respiratory rate during sleep-like behavior. One laboratory reported decreased sleep latency in carp following 96 h of sleep deprivation. Similarly, sleep-deprived perch exhibited rebound in sleep during recovery. Thus, as in amphibians and reptiles, although the electrophysiological correlates of sleep in fishes are ambiguous, fish show behavioral signs of a homeostatically regulated sleep-like state.

INVERTEBRATES

It is now evident from behavioral, pharmacological, and electrophysiological data, mostly on terrestrial arthropods, that invertebrates engage in sleep or a state homologous to sleep [3, 5]. The fruit fly [49] (reviewed in [50]), cockroach, scorpion, honey bee, butterfly, locust, and mosquito all exhibit sleep-like behavior, characterized by increased arousal thresholds and associated postures. The deprivation of sleep-like behavior in cockroaches resulted in a subsequent rebound effect. Scorpions are the oldest extant arthropod group and exhibit three distinct vigilant states: (1) activity, (2) alert immobility, and (3) relaxed immobility. Arousal thresholds, measured by response to mechanical stimulation, were lowest for alert scorpions and highest for relaxed scorpions [51]. Like cockroaches, sleep-like behavior deprivation enhanced sleep-like behavior when allowed to proceed unimpeded. Honey bee (Apis mellifera) sleep-like behavior follows a circadian rhythm. Furthermore, it is monophasic and persists in constant darkness, indicating that it is not a direct response to photoperiod. Optomotor interneurons in the optic lobes of honey bees showed circadian rhythm in response to moving visual stimuli [52]. Sensitivity was higher during the day than during the night and corresponded with an increase and decrease in locomotor activity, respectively. Head position was the lowest and antennal immobility was the greatest during sleep-like behavior [53]. Like mammals and birds, sleep-like behavior decreased with increasing age. EEG recordings have been achieved from the mushroom bodies of sleeping honey bees [54]. Spiking activity increased with behavioral rest, characterized by antennal immobility. Following 12 h sleep deprivation via forced activity, bees showed a decreased latency and increased total time of antennal immobility, suggesting sleep in honey bees is homeostatically regulated [55].

Sleep in Drosophila has been characterized by behavioral quiescence, increased arousal threshold, and homeostatic regulation [49, 56]. Sleep deprivation studies using per01 mutant fruit flies (i.e., flies that lack a circadian rhythm) have revealed Drosophila sleep to be homeostatically regulated (Figure 8.3). Furthermore, stimulants and hypnotics affect Drosophila sleep in a manner similar to mammalian sleep. Young fruit flies exhibit significantly higher total sleep time than older fruit flies, a pattern typical of mammals and birds. Interestingly, chronic sleep deprivation results in fly death after approximately 70 h [57]. Drosophila also exhibit stereotypic correlates of neuronal activity depending on behavioral state. Nitz et al. [58] recorded local field potentials (LFPs) from the medial brain between the mushroom bodies of Drosophila in various behavioral states. Awake, interactive flies exhibited spike-like potentials in their LFPs, which disappeared with behavioral quiescence. Taken in concert, this suggests that behavioral quiescence in Drosophila is homologous to vertebrate sleep.

Many genes are differentially expressed in Drosophila due to changes in behavioral state independent of the circadian clock [59]. Sleep architecture and timing appear to have a strong genetic component [60]. Similar genes are up- and down regulated within sleep/wake states in Drosophila [61] and in the rat [62], further suggesting that sleep in the fruit fly is homologous to mammalian sleep. Specifically, certain “waking” genes in Drosophila are activated
in the first few hours after waking. These genes are functionally homologous to “waking” genes in the rat. One such shared “waking” gene is BiP (Hsc70-3) that codes for an endoplasmic reticulum chaperone protein. Chaperone proteins are thought to promote proper folding and shaping of other proteins. Their expression at the onset of wakefulness and during sleep deprivation may very well hold an important clue to sleep function [57]. Some genes are upregulated after wakefulness and more so after sleep deprivation. Three hours of sleep deprivation results in an increase in the transcription of genes coding for transcription factors and/or genes involved in energy metabolism. After 8 h of deprivation there is an upregulation of growth factors, molecular chaperones, higher mRNA levels of heat shock proteins, neurotransmitters, transporters, and enzymes [62] and the synthesis of cholesterol, myelin structural proteins, and myelin-related receptors [61]. The increase in molecular chaperone protein expression suggests an increase in the mobilization of either newly synthesized proteins or those destined for catabolism. Furthermore, the upregulation of synaptic plasticity genes (e.g., brain-deprived neurotrophic factor (BDNF)) suggests the remodeling of neuronal configurations [62] or memory acquisition [61]. Wakefulness in Drosophila is also characterized by an increase in the levels of mRNA for arylalkylamine N-acetyltransferase (aaNAT1, also called dopamine acetyltransferase (DAT), an enzyme responsible for the catabolism of monoamines. Although rats lack this enzyme, arylsulfotransferase serves a similar function. Interestingly, an increase or decrease in gene expression can occur in

Figure 8.3  (A) The activity record for Drosophila maintained on a 12L:12D (open horizontal bar:dark horizontal bar) light cycle. (B) Sleep−activity cycle of undisturbed flies (circles) and flies sleep deprived via manual stimulation (squares) or by an automated system (triangles). Sleep-deprived flies showed an increase in sleep during the subsequent light period. (C) The amount of sleep during the 12 h recovery period was not correlated with the amount of activity during sleep deprivation. (D) Stimulation of flies during the light period did not result in a compensatory increase in sleep during recovery (diamonds) relative to baseline (circles). (E) Under constant darkness, per1 flies had the same amount of sleep as under a light−dark photoperiod but sleep was evenly distributed across the 24 h (circles). Twelve hours of automated sleep deprivation resulted in an increase in sleep during the first 6 h of recovery (squares) compared to baseline (circles). (Reprinted with permission from Shaw et al. Correlates of sleep and waking in Drosophila melanogaster: Science 287:1834−1837. Copyright © 2000 AAAS.)
brain regions where EEG correlates of sleep are reduced or nonexistent [61].

A recent study reported behavioral sleep accompanied by slow-wave activity in crayfish [63]. Behavioral sleep was associated with specific postures (i.e., floating, lying on one-side) and this “sleep-posture” was associated with the highest arousal threshold to a vibratory stimulus. Sleep deprivation resulted in a compensatory increase in total sleep time during subsequent sleep bouts. Interestingly, the authors presented a waking EEG of high-voltage spikes and a sleeping EEG of continuous slow-wave activity. Slow-wave activity disappeared upon arousal. REM sleep was not observed.

The cephalopod, *Octopus vulgaris*, displays color patterns and associated postures that correlate with rest during the nocturnal phase of the photoperiod. While resting, arms are upturned, skin texture is smooth, and chromatophores are relaxed, resulting in a gray-green color to be expressed only on the dorsal body surface and purple on the ventral arms [64]. Furthermore, specific postures are associated with elevations in arousal threshold [2]. Another study revealed a rest/activity cycle in cuttlefish. Captive cuttlefish would lie still for 10–15 min periods interrupted by flashes of bold color from their chromatophores and twitches of the tentacles resembling mammalian and avian REM sleep.

**CONCLUSION**

A phylogenetic evaluation of sleep demonstrates that all mammals, birds, and reptiles engage in sleep, and evidence for sleep in amphibians, fishes, and invertebrates is strong if not certain. In critically important sleep studies of rats and fruit flies, it has been shown that chronic sleep deprivation is fatal [57, 65], attesting to the necessity for sleep and to its ancient evolutionary age.

Sleep in mammals and birds can be divided into two states: SWS and REM sleep. Although it is necessarily intuitive that sleep evolved from wakefulness, it is unclear which of the two sleep states (if either) evolved first. An understanding of this sequence can have significant consequences for our understanding of the functions of sleep. For example, the SWS–REM sleep cycle may be unique to mammals and birds, suggesting an association with a shared character of the two groups, such as endothermy or an enlarged forebrain. Below we summarize three theories currently circulating on the evolution of the sleep cycle exhibited in mammals and birds (Figure 8.4) [4, 35, 66].

The first hypothesis, henceforth called *SWS-first* (Figure 8.4a) is advanced in direct opposition to the *REM sleep-first* hypothesis [35]. The first sleep study in monotremes concluded that the short-beaked echidna did not exhibit REM sleep [11], supporting the notion that REM sleep evolved after SWS in the evolutionary lineage of mammals and birds. SWS was therefore assumed to be the ancestral sleep state and REM sleep subsequently evolved twice: once in birds (or their dinosaur ancestors) and once in the placental and marsupial mammalian clade, a finding consistent with reptilian studies at the time [36, 47] (see Reptiles section). However, slow waves, which are the hallmark of SWS, originate in the mammalian neocortex. Reptiles, perhaps void of necessary telencephalic structures, may not be able to generate slow-wave activity. Nevertheless, sleep deprivation experiments and pharmacological evidence suggest that the high-voltage spikes often reported in reptilian sleep studies may occur in a state that is the precursor to mammalian and avian SWS.

The second hypothesis, REM sleep-first, states that REM sleep is the ancestral sleep state [66] and that SWS is derived in the mammalian and avian lineages through convergent evolution (Figure 8.4b). This hypothesis is supported by a great deal of correlational data leading to the

![Figure 8.4](image_url) Three hypotheses for the evolutionary origins of SWS and REM sleep seen in endotherms (i.e., birds and mammals; see text for description). Phylogeny adapted from [10].
following four conclusions. (1) Monotremes, the oldest extant group of mammals, exhibit REM sleep (see Monotremes section) and, interestingly, the platypus, the oldest of the monotremes, may engage in more REM sleep than any other mammal. The identification of REM sleep in both the echidna and platypus suggests that REM sleep originated earlier in mammalian evolution than had previously been thought. Furthermore, it suggests that REM sleep, or a REM sleep-like state, was present in the reptilian ancestor to both the mammalian and avian lineage.

(2) During REM sleep, an endotherm’s thermoregulatory mechanisms are either suspended or impaired. Therefore an endothermic animal is essentially poikilothermic during REM sleep. Assuming that REM sleep is indeed the antecedent sleep state exhibited by our reptilian ancestors, such heterothermic animals would not be adversely affected by the inhibition of, albeit, nonexistent metabolic heat production mechanisms. However, with the evolution of endothermy, REM sleep became detrimental to survival.

A second sleep state (i.e., SWS) evolved to permit thermoregulation concurrent with sleep. (3) The ontogenesis of the sleep cycle may also be used as evidence for the REM sleep-first hypothesis. REM sleep is the dominant sleep state of the mammalian fetus. After birth, REM sleep time decreases rapidly until it stabilizes at adult levels. The decrease in REM sleep is marked by a concurrent increase in SWS and wakefulness throughout early maturation. (4) Lastly, whereas the slow waves of mammalian SWS are propagated from the neocortex, REM sleep originates in the rhombencephalon (pons) of the brainstem—the most ancient caudal brain structure. Thus evolution of the SWS/REM sleep cycle may have begun with REM sleep and not SWS as once thought. The obvious drawback of this hypothesis is the absence of unequivocal REM sleep in extant reptiles. However, REM sleep or a REM sleep-like state may be highly temperature sensitive as it is in mammals, and future studies of sleep in reptiles must examine this factor further.

The existence of alternating SWS and REM sleep in the mammalian and avian lineages may be due to convergent evolution and not to inheritance from a common reptilian ancestor (Figure 8.4c), since evidence for unequivocal SWS and REM sleep in reptiles is controversial. Although REM sleep in placental and marsupial mammals is characterized by low-amplitude EEG activity, REM sleep in the platypus was associated with SWS-like cortical activity [14]. REM sleep with an activated EEG may have thus evolved in marsupial and placental mammals after divergence of the monotreme line. Moreover, due to the absence of unambiguous REM sleep and SWS in extant reptiles, SWS and REM sleep with cortical activation may have evolved twice: once in the mammalian and once in the avian clades.

Sleep differs from wakefulness on all levels of organization: behavioral, electrophysiological, cellular, molecular, and genetic. Indeed, sleep and wakefulness favor different cellular processes [61]. Present information suggests that a proximate sleep function is likely focused at the level of the neuron or synapse rather than the organ or tissue. Current criteria for sleep are based largely on changes in neural activity. In instances where such indicators are cryptic or absent (see Reptiles section and Amphibians and Fishes section), new criteria are needed, perhaps at the level of gene expression. This does not discount a functional significance for the EEG correlates of sleep in mammals and birds; it merely acknowledges that since invertebrates also sleep, the physiological criteria for sleep should not be limited to EEG correlates, which are clearly not shared by invertebrates, fishes, amphibians, and reptiles. Such investigations can shed much light on the nature and functions of sleep.

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REFERENCES


THE EVOLUTION OF SLEEP: A PHYLOGENETIC APPROACH


NEUROPHARMACOLOGY OF SLEEP AND WAKEFULNESS

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INTRODUCTION

There are two main regions that modulate our sleep–wake cycles—the mesopontine reticular activating system (RAS) and the hypothalamus. In addition, the intralaminar thalamus and the basal forebrain are modulated by the RAS and hypothalamus and participate in the process of arousal and alertness, as well as in the modulation of sleep states. Neuroactive agents that modulate these regions will also modulate the level of arousal. By the same token, disorders that manifest changes in sleep–wake states and/or affect arousal, alertness, and sleep can be expected, of necessity, to include dysregulation in the above-named regions. Many neurological and psychiatric disorders involve, and may even be presaged by, disruption of sleep–wake control regions. For example, many patients with Parkinson’s disease exhibit sleep dysregulation years before the clinical signs of the disease, and almost half of REM sleep behavior disorder (RBD) patients will develop Parkinson’s disease as many as 13 years after developing the symptoms of RBD [1]. Sleep dysregulation is a hallmark of psychiatric disorders such as schizophrenia, anxiety disorders, and depression [2]. The hallucinations in schizophrenia have been equated with REM sleep intrusion into waking, that is, dreaming while awake [3]. Moreover, because the process of arousal is essential to attention, and attention to learning and memory, disruption of arousal-related systems has profound effects on higher cognitive functions. That is, sleep–wake disorders, or the effects of psychoactive agents on these systems, may be at the root of decrements in cognitive performance.

CONNECTIVITY

The RAS is composed of three main nuclei—the cholinergic pedunculopontine nucleus (PPN) (and its medial partner, the laterodorsal tegmental nucleus), the noradrenergic locus coeruleus (LC), and the serotonergic raphe nucleus (RN). The RN sends inhibitory projections to the PPN and LC, and the LC inhibits the PPN while the PPN activates the LC. The RAS sends the majority of its ascending cholinergic and monoaminergic projections to the thalamus and hypothalamus, while also synapsing on other regions [4]. During waking, all three cell groups are active while, in slow-wave sleep, the cholinergic cells decrease firing while monoaminergic cells remain active. However, in REM sleep, the cholinergic cells are highly active while monoaminergic cells decrease their firing rates markedly [4]. Therefore cholinergic RAS neurons are active during waking and REM sleep, that is, during synchronization of fast cortical rhythms, but slow their firing during synchronization of slow cortical rhythms [5].

The RAS receives input from all afferent sensory systems in parallel to primary afferent sensory projections. That is, the “nonspecific” projection system to the RAS relays “arousal” information through the intralaminar thalamus (ILT) to the cortex. This system functions in parallel to the shuttling of “specific” sensory information through...
the primary sensory thalamic nuclei to the cortex. It is the temporal summation of intralaminar “nonspecific” inputs (the context) with primary “specific” inputs (the content) at the level of the cortex that is thought to participate in “binding,” that is, the conscious perception of a sensory event [6]. Disturbances in RAS driving of the ILT and/or of thalamocortical reverberating activity thus can be expected to lead to disturbances in perception.

The RAS also sends descending projections to postural and locomotion control systems. Such connectivity allows the RAS to act as the “fight-or-flight” control system, simultaneously activating higher centers while priming motor systems to respond appropriately to sudden stimuli. These descending projections modulate the (1) pontine inhibitory area (PIA) that is thought to control the atonia of REM sleep, (2) pontine neurons that generate the startle response, a flexor response that primes the motor system, and (3) reticulospinal systems that drive locomotion [7]. RAS projections to the dorsal subcoeruleus region also modulate the generation of pontogeniculo-occipital (PGO) waves during REM sleep. This region generates high-frequency bursts of activity (like those required for long-term potentiation) that have been proposed to promote consolidation of certain memories during REM sleep via its projections to the hippocampus [8].

The hypothalamic sleep–wake modulatory system is composed mainly of the (1) tuberomammillary nucleus (TMN) with excitatory histaminergic projections, (2) lateral hypothalamus (LH) with excitatory orexinergic projections, and (3) ventrolateral preoptic (VLPO) region with mostly inhibitory GABAergic projections. These hypothalamic sleep–wake modulatory systems are thought to help stabilize sleep–wake states [9]. On the one hand, the excitatory LH orexin projections can be thought of as an “on” switch, promoting waking, especially through their activation of excitatory TMN histaminergic neurons, which are tonically active during waking (and significantly decrease firing during sleep), and of excitatory basal forebrain and RAS, especially cholinergic, neurons. The basal forebrain cholinergic projection system is especially active during waking and serves to raise the excitability of the cortex. Interestingly, acetylcholine release from the basal forebrain is greater during REM sleep than during waking [10]. On the other hand, the inhibitory VLPO GABAergic projections can be thought of as an “off” switch, promoting slow-wave sleep through its inhibition of the RAS, LH, basal forebrain, and cortex.

Figure 9.1 outlines the main ascending and descending projections described. The dorsal ascending cholinergic (labeled PP for PPN) and monoaminergic (LC, RN) projections from the RAS to the ILT serve to activate the cortex via thalamocortical projections. There is also a massive set of ventral projection systems that bypass the thalamus to terminate diffusely throughout the cortex. These originate in the RAS (noradrenergic LC and serotonergic RN) and are joined by ascending projections from the TM (histaminergic TMN), LH (orexinergic), and VP (GABAergic VLPO), as well as from the basal forebrain (acetylcholine, not shown). In turn, the TMN, LH, and VLPO send descending projections to the RAS that may act reciprocally to stabilize sleep–wake states.

In addition to these transmitters, adenosine (A, diffusely localized) is a ubiquitous homeostatic factor thought to be involved in sleep–wake regulation [11]. Conditions of high metabolic activity or prolonged wakefulness lead to a buildup of adenosine, which decreases subsequent to sleep. Therefore adenosine also may modulate sleep–wake states via its inhibitory actions on most cells, but particularly on excitatory cholinergic RAS and basal forebrain neurons. Adenosine injections into the RAS are known to decrease waking, while adenosine levels in the basal forebrain (but not in the thalamus) progressively increase during prolonged wakefulness and decrease during subsequent recovery of sleep [12].

The close relationship between sleep–wake regulation and other homeostatic control functions should be remembered. These systems, especially hypothalamic sleep–wake modulatory regions, interact with the regulation of food intake, metabolism, hormone release, and temperature [13]. This means that disorders of hypothalamic sleep–wake modulatory regions, or psychoactive agents that modulate them, can be expected to also affect homeostatic control systems. For example, Kleine–Levin syndrome is a postpubertal onset disorder characterized by episodes of hypersomnia, mood disturbances (especially depression), compulsive hyperphagia (especially carbohydrates), hypersexuality, and signs of dysautonomia. This disorder points to a pathological locus bridging sleep–wake control, mood control, and homeostatic control systems.
BLOOD FLOW DURING SLEEP AND WAKING

The state of slow-wave sleep is marked by decreases in regional cerebral blood flow throughout the brain, but more significantly in the RAS, thalamus, hypothalamus, and basal forebrain [14]. This state is characterized by decreased activity of cholinergic RAS and basal forebrain neurons, of LH orexinergic cells, and of TMN histaminergic cells. That is, the major excitatory projection systems decrease their outputs during slow-wave sleep. On the other hand, REM sleep is characterized by increased blood flow in the RAS, the thalamus, and the anterior cingulate cortex, among others, with decreases in blood flow in the dorsolateral prefrontal cortex [15]. It has been proposed that the unregulated activity of RAS cholinergic neurons is responsible for REM sleep and, via unknown mechanisms, for decreased frontal lobe blood flow, or “hypofrontality” [2]. The hypofrontality of REM sleep is thought to account for the lack of critical judgment during dreaming (and during hallucinations). This state is also characterized by the generation of PGO waves (triggered by descending cholinergic PPN projections to the pons), now thought to be involved in some aspects of sleep-dependent plasticity. Unlike sleep, the process of awakening entails two stages, a rapid (5 min) reestablishment of consciousness that is marked by increases in cerebral blood flow in the RAS and thalamus, followed by a slower (15 min) increase in cerebral blood flow, primarily in anterior cortical regions [16]. Therefore psychoactive agents that affect blood flow can be expected to alter sleep–wake states. It should also be noted that cholinergic RAS neurons have some of the highest concentrations of nitric oxide in the brain. Therefore wherever the PPN projects, a corollary effect may include vasodilation.

NEUROPHARMACOLOGY

The foregoing suggests that psychoactive agents that affect the function of sleep–wake regulating systems also can have profound effects on a host of processes, from higher cognitive performance to attention, learning, and memory, to homeostatic regulation and more. The following is a brief description of the effects of only the most common agents.

Alcohol

Alcohol appears to preferentially affect small neurons, particularly granule cells throughout the cerebral and cerebellar cortices and the hippocampus, perhaps by enhancing GABAergic transmission. Direct effects on sleep–wake control regions appear to also involve potentiation of GABAergic transmission. However, at high doses, its effects are neurotoxic, mainly on basal forebrain neurons, and thus may impair diffuse cholinergic input to the cortex. It should be noted that significant impairment in motor performance, such as driving, occurs at very low blood alcohol concentrations, an effect potentiated by sleep deprivation or sleep loss. Most alcoholic patients suffer from insomnia, which is clinically important since alcoholism can exacerbate the adverse consequences of insomnia, such as mood changes and anxiety, and because insomnia has been associated with alcohol relapse. In general, sleep loss has greater sedative effects than low doses of alcohol, but similar effects on psychomotor performance. Alcohol produces greater memory impairment than sleep loss, probably because of its marked effects on the hippocampus.

Alcohol, aside from its recreational uses, is the prototypical anxiolytic, having a calming effect on the stressed, or over-stressed, organism. It is evident that alcohol intake is a form of self-medication used as an anxiolytic by patients suffering from psychiatric disorders that involve hypervigilance, for example, schizophrenia, anxiety disorders, and depression. It is likely that alcohol treatment programs could increase their success rates if patients who ingest excessive amounts of alcohol, but are not true “alcoholics,” would be properly diagnosed and treated. Such patients, in the absence of appropriate treatment for their disorder, are certain to relapse into the alternative of self-medication. Because alcohol ingestion can lead to decreased frontal lobe blood flow, the ultimate effect will be to exacerbate the hypofrontality already evident in these psychiatric patients, further impairing decision-making capacity and lowering the threshold for uncritical action.

Anesthetics and Sedatives

The proposed mechanisms of action of anesthetics have typically involved a myriad of cellular effects at different sites by disparate drugs. Recent evidence suggests that the primary site of action of most anesthetics may be the sleep–wake control system [17]. The parallel manifestations between sleep and anesthesia suggest that anesthetics basically “hijack” the sleep–wake control system to induce anesthesia. This concept allows for a more rational characterization of traits that should be used to determine anesthetic level. That is, considering that arousal and alertness represent a continuum of levels from mania to coma, with physiological and behavioral concomitants, the monitoring of EEG, along with behavioral and autonomic signs, should be used routinely to assess level of anesthesia.

Most anesthetics, including barbiturates, etomidate, propofol, neuroactive steroids, and volatile anesthetics, act on GABAa receptors among other receptors [18]. Sedation and natural sleep occur greatly as a result of enhanced GABAergic transmission, which in turn affects the release of a number of excitatory transmitters such as acetylcholine, excitatory amino acids, and histamine. That is, these
actions may take place specifically in such regions as the RAS, TMN, and basal forebrain (all of which have local circuit GABAergic neurons and receive GABAergic input from VLPO, as described earlier), thereby regulating the level of arousal.

Most barbiturates are dangerous drugs with a narrow therapeutic index between the dose required for sedation and the dose that will cause coma and death. These agents typically decrease cerebral blood flow, although regional differences between agents are evident. Volatile and steroid anesthetics also are known to reduce cerebral blood flow along with cerebral oxygen metabolism, an effect that maintains the coupling between metabolism and flow.

The benzodiazepines act by binding to a site that modulates GABA receptors, especially GABAα receptors. These agents produce sedative, hypnotic, anxiolytic, and anticonvulsant activities. They act generally by amplifying GABAergic transmission, such that short-acting agents have been used to promote sleep in insomnia patients, although more recently, effective nonbenzodiazepine hypnotics have been developed. These agents also act to facilitate GABAα receptor function (e.g., zolpidem and zaleplon). Insomnia is a very common symptom, especially in the elderly, and has a number of causes, including physical, social, and psychiatric. Treatment of such causes, rather than symptomatic alleviation of insomnia, obviously is more desirable. Similarly, use of benzodiazepines as anxiolytic agents represents symptomatic treatment, requiring the assessment of the underlying causes in order to prevent prolonged treatment with potential for leading to dependence. Some psychiatric conditions are characterized by insomnia, mainly due to the nighttime manifestation of hypervigilance, increased REM sleep drive (decreased REM sleep latency, increased REM sleep duration, sleep fragmentation due to frequent awakenings, etc.). Identification of the underlying mechanism allows for the design of a more rational therapeutic strategy.

A naturally occurring metabolite of GABA, gammahydroxybutyrate (GHB), is a potent CNS depressant, and acute intoxication with GHB or its analogs can lead to respiratory depression and even death. Like most hypnotics, GHB can induce tolerance and produce dependence. In pharmacological doses, it is used as a sedative/anesthetic, in alcohol/opiate detoxification, and for the treatment of cataplexy in narcolepsy. Narcolepsy is a disorder marked by significant daytime sleepiness, hypnagogic hallucinations, and episodes of cataplexy, loss of consciousness, and postural collapse, which sometimes occur with affective incitement. These episodes are reminiscent of the loss of consciousness and of postural muscle tone that accompanies REM sleep, almost as if the patient transitions directly from waking to REM sleep without passing through the requisite slow-wave sleep state. Narcolepsy is thought to arise from degeneration of excitatory orexinergic neurons in the LH. How does GHB act to decrease cataplexy? The cellular mechanisms are unknown, but one possible mechanism may be through direct or indirect activation of GABAb receptors, which can inhibit PPN neurons (which induce REM sleep) and elicit slow-wave activity, including spike and wave activity via the thalamus, a form of nonconvulsive epilepsy. This agent, when administered before bedtime, appears to induce the symptoms of narcolepsy and contain them at night [19]. High doses of GHB can decrease glucose metabolism but, surprisingly, do not significantly alter global blood flow.

Antihistamines

Pathology and lesions of the TMN cause hypersomnia (recall that these neurons are highly active during waking). Histaminergic inputs to the RAS suppress slow-wave sleep and promote waking, although they do not affect REM sleep significantly [20]. Administration of antihistamines (histamine receptor blockers) results in sedation. Such an effect may result from blockade of histaminergic inputs to the RAS, basal forebrain, and/or LH. It should be noted that the cortex has the highest concentration of histamine receptors, so that widespread changes in cortical excitability are also possible through that mechanism. Antihistamines reduce blood flow in frontal cortex and midbrain, which could also account for the cognitive impairments and decrement in psychomotor function observed. Some tolerance can develop over time that can decrease such impairments. In children, first- and second-generation antihistamine intoxication can induce coma, although the newer (third-generation) pediatric formulations (e.g., fexofenadine, loratadine, cetirizine) appear to be safer.

Caffeine

The popularity of caffeine is related to its stimulant properties, which are mediated by its ability to reduce adenosine release in the brain. Caffeine appears to block adenosine A1 and A2a receptors, producing a psychomotor stimulant effect. Because of the high levels of A2a receptors in the striatum, the potential use of caffeine for the treatment of Parkinson’s disease has been advanced. Since adenosine A2a receptor blockade appears to protect dopaminergic neurons from toxic agents, a neuroprotective role has been proposed for caffeine in the treatment of Parkinson’s disease. Caffeine intake has also been associated with a decreased risk of Alzheimer’s disease, again presumably acting as a neuroprotective agent.

Caffeine is known to lower cerebral blood flow while simultaneously inducing an increase in metabolism through inhibition of adenosine receptors, leading to a state of relative hypoperfusion for prolonged periods of time. However, its alerting effects are obviously mediated by inhibition of
adenosinergic inputs to RAS and basal forebrain cholinergic neurons (see earlier discussion).

**Nicotine**

Inhaled nicotine in cigarette smoke is known to permeate the lungs where more than 80% of the available nicotine is absorbed into the bloodstream. The short delivery time and elimination half-lives (8 min and 2 h, respectively) assure that, within a short time, the effect can be reproduced by smoking another cigarette [21]. After absorption into the blood, nicotine readily crosses the blood–brain barrier and appears to be rapidly partitioned into brain tissue. Concentrations of nicotine in the brain have been reported to be 5–7 times higher than blood concentrations. Smokers assert that, in addition to its positive effects on concentration and attention, the primary positive effect of smoking is that it calms and relaxes. Recent findings suggest that one of the sites of action of nicotine may be in the RAS, specifically, on PPN neurons. One study found that systemic administration of nicotine, or localized injection of a nicotinic receptor agonist into the PPN, led to a dose-dependent decrease in the amplitude of the P13 potential in the rat, the rodent equivalent of the sleep state-dependent P50 potential in the human [22]. These results suggest that nicotinic agonists, at least initially, may reduce the level of arousal, as manifested by the amplitude of this waveform.

Figure 9.2 is from a study that used intracellular recordings from PPN neurons in brainstem slices. Application of a nicotinic agonist (1,1-dimethyl-4-phenyl-piperazinium—DMPP) directly (in the presence of tetrodotoxin—TTX) hyperpolarized 20% of PPN cholinergic neurons, an effect blocked by pretreatment with the nicotinic receptor blocker mecamylamine (MEC). DMPP also directly depolarized 10%, and indirectly depolarized 70%, of PPN neurons. These results suggest that nicotine, at least initially, has an inhibitory effect on cholinergic RAS neurons, which could produce the calming effect reported upon inhalation of cigarette smoke. Additional effects on other populations of cells also imply that there is a complex interaction between nicotine and the RAS. Some of the indirect effects appear to be mediated by nicotine’s ability to presynaptically modulate the release of a number of transmitter systems.

The proposed inhibitory effect of nicotine on the RAS is in keeping with clinical evidence. The majority of cigarettes are consumed by the mentally ill, especially those with disorders involving hypervigilance or hyperarousal, such as schizophrenia, anxiety disorders, and depression [23]. That is, smoking may be a form of self-medication, presumably because of its calming effects. This effect inhibition of cholinergic RAS neurons) appears to differ from the role of smoking in reducing the incidence of Parkinson’s disease, which appears to be manifested as a neuroprotective action on dopaminergic neurons by nicotine.

Cerebral vasodilation is seen immediately after smoking, but chronic smokers show global reductions in cerebral blood flow. Considering that hypofrontality is present in...
schizophrenia, anxiety disorders, and depression, the initial beneficial, calming effects of nicotine may be followed by deleterious consequences on cortical blood flow. Such an effect may drive craving for the next cigarette, creating a vicious cycle of continuous self-administration.

**Stimulants**

The most common stimulant, amphetamine, induces release of monoamines, especially dopamine, but also blocks reuptake and may have neurotoxic effects on nigral neurons [24] and, more recently, is suspected of inducing degeneration of certain striatal neurons [25]. Unfortunately, this agent is abused for recreational purposes and continues to be prescribed for the treatment of attention deficit disorder (ADD). Fortunately, methylphenidate does not appear to have such neurotoxic effects, although its use has decreased. The difference between these agents appears to be that methylphenidate is mainly a dopamine uptake inhibitor without major influence on release. While any psychotropic agent can have deleterious effects on brain cells, particularly if abused, great care is required when using amphetamine, especially in the young. Amphetamine psychosis occurs in two forms—acute intoxication after a single large dose (characterized by confusion and disorientation), and chronic abuse after repeated use that produces a schizophrenia-like syndrome [26]. The increased release of dopamine by amphetamine is considered a model for schizophrenia and contributed to the “dopamine theory” of schizophrenia (see later discussion).

Methamphetamine, a popular street drug similar to amphetamine, has become widely abused and probably has severe neurotoxic effects. One potential mechanism via which these agents promote hypervigilance is through activation of the striatum and disinhibition of cholinergic RAS neurons. A more direct effect would be induced release of dopamine and noradrenaline at the level of the cortex. These effects are accompanied by transient increases in cerebral blood flow (midbrain, thalamus, and frontal cortex), but abistent abusers are known to have decreased blood flow in basal ganglia and certain cortical areas; that is, long-term effects on blood flow may be deleterious. MDMA (3,4-methylenedioxymethamphetamine) or “ecstasy” is another recreational abused amphetamine that is even more neurotoxic, has hallucinogenic properties at high doses, and has been linked to a number of deaths.

Modafinil is a newer stimulant that does not appear to act through dopaminergic mechanisms, like amphetamine. Modafinil does seem to affect structures involved in the regulation of sleep–wake states [27] and to affect a number of transmitter systems, including noradrenergic, histaminergic, and orexinergic, as well as excitatory amino acid and serotonin release. In addition, it may block GABAa receptors [28]. Modafinil has been found to be effective in the treatment of daytime sleepiness in patients with narcolepsy [29]. This agent was recently reported to block “spatial neglect” resulting from cortical stroke [30]. This revolutionary finding suggests that sensory neglect arising from stroke (right hemisphere strokes typically lead to persistent neglect of the left spatial field, whereas left hemisphere strokes lead to only transient neglect of the contralateral spatial field) can be treated successfully by “waking up” the involved cortex, implying that the consequences of stroke may be to decrease activity, blood flow, or metabolism, one or more of which modafinil may counteract. It should be noted that the potential blockade of GABAa receptors may make it undesirable for use in patients whose condition includes epilepsy or heightened susceptibility to seizures.

However, the wake-promoting property of modafinil may make it beneficial for the treatment of other disorders involving decreased activity, blood flow, or metabolism. For example, the hypofrontality in various psychiatric disorders may be amenable to such therapy, as long as the hypervigilance present in these conditions is not exacerbated by using low doses. In addition, cocaine abusers show reduced frontal cortex blood flow, a mechanism thought to promote risky or erroneous decision-making [31]. Therefore the hypofrontality of drug abuse also may be amenable to correction using modafinil, perhaps also at low doses. The RAS is thought to be damaged in about 85% of cases of coma, with the rest accounted for by hypothalamic damage. While the use of amphetamine or methylphenidate has been advocated in patients with coma, a better alternative that does not induce significant cardiovascular effects could be modafinil.

**SCHIZOPHRENIA, ANXIETY DISORDER, AND DEPRESSION**

The connectivity of the RAS described earlier is reviewed in Figure 9.3, including the potential sites of action of therapeutic agents aimed at alleviating some of the symptoms of these disorders, especially those related to hypervigilance and sleep dysregulation, along with hypofrontality. The serotonergic RN is known to inhibit the PPN and LC, with the cholinergic PPN exciting the LC and the noradrenergic LC inhibiting, via alpha-2 adrenergic receptors, the PPN. The PPN sends excitatory cholinergic projections to the substantia nigra (SN), which, in turn, sends dopaminergic projections to the striatum.

The treatment of depression previously included tricyclic antidepressants such as amitryptiline, imipramine, and clomipramine, agents that mainly blocked reuptake of noradrenaline and serotonin, and blocked histamine and acetylcholine release, thus accounting for increased sleepiness. The selective serotonin reuptake inhibitors (SSRIs) more selectively affect the RAS by increasing the inhibition
at site “a” in Figure 9.3, thus downregulating arousal levels, especially through promoting inhibition of the PPN and LC. It is not clear if the etiology of depression is related to disinhibition of the PPN and LC by a decrement in serotonegic tone, although this would seem a likely origin for the sleep–wake symptomatology of depression.

The treatment of anxiety disorder, as mentioned earlier, has involved the use of benzodiazepine amplification of GABAAergic inhibition. In addition, the use of the alpha-2 noradrenergic receptor agonist clonidine produces anxiolytic effects, probably by inhibiting autoreceptors in the LC and postsynaptic receptors in the PPN (site “b” in Figure 9.3), thus downregulating vigilance. Because of the peripheral cardiovascular effects of clonidine, alpha-2 adrenergic receptor agonists without such actions would be more desirable. One study provided strong evidence for the use of the alpha-2 adrenergic receptor agonist dexmedetomidine as an anxiolytic for the treatment of anxiety disorders like post-traumatic stress disorder, panic attacks, and general anxiety disorder [32]. The etiology of anxiety disorder has been proposed to include downregulation or degeneration of LC outputs (possibly induced by stress hormones), which would act to release, or disinhibit, PPN neurons at site “b” in Figure 9.3.

The treatment of schizophrenia previously involved the use of the dopaminergic receptor blocker haloperidol, which induced tardive dyskinesia, among other serious side effects. Newer antipsychotics such as risperidone and quetiapine appear to block dopaminergic, noradrenergic, and serotonergic receptors. More striking antipsychotic effects were provided by the use of clozapine, which was designed as a muscarinic cholinergic blocker for the treatment of Parkinson’s disease. The serious side effect of agranulocytosis made this a dangerous agent. However, one later-generation agent that has maintained anticholinergic activity without this side effect is olanzapine. These agents appear to have partial penetration at serotonergic, cholinergic, and dopaminergic receptors, basically reducing muscarinic cholinergic activation of the SN (at site “c” in Figure 9.3), as well as partially blocking dopaminergic actions in the striatum (at site “d” in Figure 9.3). The etiology of schizophrenia has been suggested to include increased PPN output, accounting for marked hypervigilance and hallucinations. Excessive PPN output would overactivate the SN and, in turn, increase striatal release of dopamine [33], that is, complying with the “dopamine theory” of schizophrenia. A recent review describes some of these, and additional, medications that affect sleep [34].

ADDITIONAL CONSIDERATIONS

Particular attention to hormonal conditions is warranted. After all, the first sign of puberty is pulsatile hormone (LH) release during sleep. For example, narcolepsy is tightly linked with certain human leukocyte antigen (HLA) haplotypes, suggesting that it is an autoimmune disorder. Kleine–Levin syndrome, discussed earlier, is linked to similar haplotypes, which suggests an autoimmune etiology [35]. Interestingly, in most cases of narcolepsy, Kleine–Levin syndrome, as well as schizophrenia, panic attacks, obsessive–compulsive disorder, and other disorders, the age of onset is soon after puberty. Along other lines, in about 20% of schizophrenic patients, the mother had an influenza attack during the second trimester, while narcoleptics are born predominantly during the late winter–early spring, that is, after influenza season. It has been suggested that developmental dysregulation, either pre- or perinatally (initial insult), becomes pathologically manifest after exposure to puberty and its hormonal onslaught [2, 36]. These considerations point to complex interactions between development, environment, and hormonal status, all of which seem to affect sleep–wake regulation in as yet unknown ways. These findings suggest that the effects of hormones, either prescribed or taken as dietary supplements, or abused, need to be more closely studied and considered in the design of therapeutic interventions.

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REFERENCES


INTRODUCTION

Each of us will spend about 27 years of his or her lifetime sleeping. This fact alone explains why neuroanatomists and neurophysiologists have been studying sleep for over a century. The epidemiology of sleep, however, is a relatively young field of study, although physicians have always been interested in knowing how widespread abnormal sleep phenomena are in the population. How does the population at large sleep? Well or poorly? Do we sleep too much or too little? Where is the cutoff between normal and abnormal sleep? Does sleep remain the same over the life span? Is it different between men and women and across cultures? These are some of the fundamental questions that the epidemiology of sleep disorders has been trying to answer.

THE HAZARDS OF SLEEP CLASSIFICATIONS

Classifications represent the advancement of our knowledge and understanding of sleep disorders. They are attempts to provide operationalized criteria to delineate abnormal sleep in all its forms. Abnormality, however, exists relative to a norm. This would imply that we know what constitutes normal sleep, but not abnormal sleep. Yet, the contrary is true. At this point in time, we can only say what does not constitute normal sleep. The International Classification of Sleep Disorders [1] was the first exhaustive attempt to classify abnormal sleep.

The difficulty in distinguishing between normal and abnormal sleep is reflected in the evolution of the classifications and definitions of symptomatology. For example, insomnia was defined by the American Institute of Medicine in 1979 as unsatisfactory sleep [2]. In the same year, the Association of Sleep Disorders Centers published its first classification [3] in which insomnia was referred to as a “heterogeneous group of conditions . . . considered to be responsible for inducing disturbed sleep or diminished sleep”.

In 1987, the American Psychiatric Association for the first time devoted a section in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) to sleep disorders [4]. The section was essentially divided into dyssomnias (insomnia, hypersomnia and sleep–wake disorders) and parasomnias (sleepwalking, sleep terrors, and nightmares). Insomnia was defined as difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS)—be it in the form of disrupted sleep (DS) or early morning awakening (EMA)—or nonrestorative sleep (NRS) lasting at least one month, occurring at least three times a week, and causing either distress or daytime repercussions.

In 1990, efforts by an international group of sleep researchers and sleep specialists produced the International Classification of Sleep Disorders (ICSD-90) [1], which listed nearly 80 sleep disorder diagnoses. In this classification, insomnia was more stringently defined by taking into account severity, frequency of symptoms, and impact on social and occupational functioning. In the DSM-IV, the latest edition of its classification published in 1994 [4], the American Psychiatric Association decided to harmonize its sleep disorder criteria and diagnoses with those of the ICSD-90. Insomnia was defined as a complaint of DIS,
DYSSOMNIAS

Insomnia and Related Disorders

To date, there is no consensus on how to define and to measure insomnia in epidemiology. As a consequence, epidemiological findings largely varied depending on the definition used. We shall take the problem of insomnia as an example of the way epidemiologic results may be collected and divided.

Since the end of the 1970s, more than 50 epidemiological studies have assessed the prevalence of insomnia symptomatology in the general population. Methodologies have included face-to-face interviews, postal questionnaires, telephone interviews, or a combination of two of the above.

The definition of insomnia also varied considerably from one survey to another. Earlier studies evaluated insomnia based on the presence of DIS or DMS regardless of the frequency or severity of the symptom or daytime consequences. It was done simply by asking about the presence of these symptoms. Subsequently, DIS and DMS were assessed using the frequency of the symptom, an occurrence of 3 nights or more per week being necessary for the symptom to be present. Other studies asked about the severity of the symptoms, for example, being bothered “a lot” or “not at all” by the symptom.

Other studies, in addition to assessing the presence of insomnia symptoms, inquired about daytime repercussions of these symptoms such as daytime sleepiness, irritability, depressive or anxious mood, or needing to seek help. Finally, other studies inquired about dissatisfaction with sleep quantity or quality.

Table 10.1 gives the definitions used in epidemiological studies and the prevalence of insomnia.

Prevalence of Insomnia

In epidemiological studies, the binary query about the presence of insomnia symptoms gave high prevalence rates with an average around 33%. One of the earliest epidemiological surveys on insomnia symptoms was carried out by Bixler et al. [25] in the metropolitan area of Los Angeles with 1006 respondents aged 18 years or over. The overall prevalence of insomnia symptoms was 32.2% (DIS, 14.4%; DS, 22.9%; and EMA, 13.8%). Subsequent studies [13, 26–29] found a similar prevalence in the general population when inquiries were made about the presence of insomnia symptoms (Table 10.1).

Epidemiological studies using frequency to determine the prevalence of insomnia symptoms are the most common [8–11, 15, 23, 30–33]. In some studies, the subjects had to make a subjective assessment of the frequency of the symptom on a four- or five-point scale [8, 31–33]: for example, never, sometimes, often, or always; often or always being the cutoff point to determine the presence of insomnia. Mostly, however, frequency of the symptom is assessed on a weekly basis [9–11, 14, 23, 30]: for example, never, one or two nights, three or four nights, five nights or more per week; a frequency of three nights or more per week being the cutoff used to conclude the presence of insomnia. The prevalence of insomnia symptoms drops to around 16–21% when frequency is used to determine the presence of insomnia and has similar rates among countries (Table 10.1).

Epidemiological studies using severity of the symptoms (e.g., being bothered a lot; having great or very great DIS or DMS or a major complaint) gave prevalence of insomnia between 10% and 28% of the general population [34–37].

In most of the studies that assessed the prevalence of insomnia symptoms accompanied with daytime consequences, the prevalence was much lower, being about 10% [9, 10, 15, 18, 38–40]. One study provided a higher prevalence than the other studies mainly because the rate was based on lifetime estimation [38].

Dissatisfaction with the quantity of sleep can be expressed as a complaint of sleeping not enough or sleeping too much. Sleeping not enough has been reported with prevalence ranging from 20% to 41.7% in the general population [10, 41–43]. Sleeping too much is far less frequent with prevalence ranging between 2.8% and 9.5% [25, 39].

Dissatisfaction with quality of sleep had various definitions. In some studies, participants were asked to assess their level of satisfaction with their sleep. The prevalence of individuals reporting being dissatisfied with their sleep ranged from 8% to 18.5% [17, 18, 20–22, 44]. Other studies have inquired about perception of sleep as being poor or subjects considering themselves as being insomniac. Between 10% and 18.1% of the population reported being poor sleepers or being insomniacs [6, 11].
Unfortunately, most of these studies did not provide any information about the chronicity of these symptoms. Studies that measured it, showed that insomnia is mostly chronic [18, 22, 44, 45]. Only 4% of subjects with insomnia symptoms reported a duration of 1 month or less. About 6% of these subjects evaluated the duration being between 1 and 6 months; 5% said the duration is between 6 and 12 months, and 85% mentioned a duration of 1 year or more (68% said it lasted 5 years or more) [45].
Factors Associated with Insomnia

There are many causes of insomnia. It can be divided in three main categories (Figure 10.1): (1) secondary to another physical and/or mental illness, (2) induced by use of psychoactive substances or because of life style, or (3) without apparent cause.

Figure 10.2 displays the proportions for most common causes of insomnia. Sleep-related breathing disorders such as obstructive sleep apnea syndrome or hypoventilation account for 5–9% of insomnia complaints [40, 46, 47]. Periodic limb movement disorders and/or restless legs syndrome are found in about 15% of individuals with insomnia complaints [46–49]. Medical or neurological conditions are observed in 4–11% of insomnia complaints [23, 40, 46, 47, 50]. Poor sleep hygiene or environmental factors account for about 10% of insomnia complaints and substance-induced for 3–7% [22, 23, 40, 46, 47].

Sociodemographic Factors

Gender

Women are more likely than men to report insomnia symptoms [11, 15, 31–33, 37, 50–52], daytime consequences [9,10,15,39], and dissatisfaction with sleep [15, 44] and to have insomnia diagnoses [18, 23, 24]. Women/men ratios for insomnia symptoms are about 1.4. The difference between women and men increases with age, the ratio of women/men being about 1.7 after 45 years of age. Women are twice more likely than men to have an insomnia diagnosis. Some studies have found that the prevalence of insomnia increases in menopausal women as compared to their younger counterparts [53–55].

Age

Almost all epidemiological studies reported an increased prevalence of insomnia symptoms with age, reaching close to 50% in elderly individuals (≥65 years old) [8–11, 18, 25, 26, 28, 44, 50, 52]. However, the prevalence of insomnia with daytime consequences and the prevalence of sleep dissatisfaction have mixed results. Other studies found lower rates in middle-aged individuals [56], while still other studies reported an increasing prevalence with age [10, 11, 15, 39, 44].

Insomnia in the elderly noninstitutionalized population has been the subject of several epidemiological studies [5, 12, 16, 17, 21, 38, 57–62]. Most of these studies were limited to insomnia symptoms; only two studies assessed sleep
dissatisfaction [12, 17]. Prevalence based on presence/absence of insomnia symptoms gave a very high rate (up to 65%). In elderly community-based samples, the prevalence of insomnia symptoms and sleep dissatisfaction do not significantly increase with age [7, 12, 17, 59, 60] but is higher in women than in men [7, 12, 58–60, 62]. Some studies found that insomnia symptoms without sleep dissatisfaction have a weak association with physical diseases and mental disorders [15, 41, 42].

Income and Education Prevalence of insomnia is higher in individuals with lower incomes [25, 52, 62] and in those with lower education [8, 25, 61]. However, these associations can be the result of other factors such as age. Use of the poverty index will provide a better indication of the association between insomnia and poverty.

Physical Illnesses
In the general population, subjects with insomnia symptoms were consistently found to perceive their health as being poorer than the rest of the population [7, 12, 16, 18, 22, 57, 60, 61]. Up to half of subjects with insomnia symptoms have recurrent, persistent, or multiple health problems [25, 37]. Most frequently reported associations were with upper airway diseases [18, 26, 34], rheumatic diseases [18, 34, 63, 64], chronic pain [64, 65], and cardiovascular diseases [7, 18, 66].

Mental Disorders
Epidemiological studies have consistently reported that a mental disorder is associated with 30–40% of insomnia complaints (Table 10.2). Up to 60% of subjects with insomnia symptoms were reported to have symptoms of mental disorders [37, 68]. In individuals with a current major depressive episode, the presence of insomnia symptoms was found in nearly 80% of the subjects [33, 54, 69]. Four longitudinal studies examined the relationship between the persistence of insomnia symptoms and the appearance of mental disorders (Table 10.2).

Ford and Kamerow [39] found a high co-occurrence of insomnia complaints and mental disorders (40%). Insomnia complaints were associated with a higher risk (odds ratio of 39.8) for developing a new major depressive illness if they persisted over two interviews within a 12 month interval, but were not a significant factor if they ceased by the second interview. Another study in young adults between 21 and 30 years of age [38] found that subjects with a history of insomnia were four times more likely to develop a new major depressive disorder in the 3.5 years following the initial interview. Another survey followed up 2164 individuals age 50 years and over in Alameda County (California) during a one year period [67]. The presence of major depression at the last assessment was eight times more likely to occur in individuals with insomnia on both assessments and ten times more likely to occur in those who reported insomnia only on the last assessment. However, insomnia was a less important predictor of future depression than other depressive symptoms (anhedonia, feelings of worthlessness, psychomotor agitation/retardation, mood disturbance, thoughts of death) [67].

Should the insomnia warrant a specific diagnosis? Should the insomnia be considered as part of the mental disorder manifestation? The first epidemiological study using a classification to categorize insomnia subjects was published

<table>
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<tr>
<th>TABLE 10.2 Exploration of Association Between Mental Disorders and Insomnia in Epidemiological Studies</th>
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<tr>
<td><strong>Descriptive Studies</strong></td>
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<tr>
<td>Mellinger et al., 1985, USA [37]</td>
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<tr>
<td>Henderson et al., 1995, Australia</td>
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<tr>
<td>(Canberra and Queanbeyan) [60]</td>
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<tr>
<td>Foley et al., 1995, USA (E. Boston, New Haven, Iowa, Washington counties) [66]</td>
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<tr>
<td>Newman et al., 1997, USA (Forsyth (NC), Sacramento (CA), Washington counties, Maryland and Pittsburg) [62]</td>
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<td>Ohayon, 1997, France [40]</td>
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<td>Maggi et al., 1998, Italy (Veneto region) [7]</td>
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<tr>
<td>Hoffmann, 1999, Belgium [9]</td>
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<td>Hetta et al., 1999, Sweden [10]</td>
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<tr>
<td>Ohayon et al., 2000, Canada [50]</td>
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<tr>
<td>Ohayon et al., 2003, United-Kingdom, Germany, Italy, Portugal [45]</td>
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</tbody>
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30% to 60% of insomniacs have mental disorder symptoms, 36% psychiatric diagnosis

Persistence of insomnia = 4 to 8 times more likely of developing a mental disorder
in 1997 [40]. The differential diagnosis of insomnia was based on the DSM-IV classification. Overall, 5.6% of the sample had one of the DSM-IV insomnia diagnoses. “Insomnia Related to Another Mental Disorder” and “Primary Insomnia” were the most frequent diagnoses. Similar studies were conducted in the United Kingdom, Germany, Canada, Italy, and Finland [18, 22, 23, 40, 43, 45]. The European studies included 20,536 subjects age 15 years and over. The overall prevalence of insomnia symptoms accompanied by sleep dissatisfaction was 12.4%. Insomnia diagnoses were observed in 35% of the subjects with insomnia; noninsomnia sleep disorders accounted for an additional 5%. The final diagnosis resulted in a mental disorder diagnosis in 36% of the insomnia symptoms accompanied by sleep dissatisfaction.

**Life Style**

Epidemiological studies have reported higher risks of insomnia in individuals with high stress [18, 22–24] and among individuals without work [9, 52, 70, 71], with shift/night work [18, 22], or sleeping in a bedroom with inappropriate temperature [18].

**Psychoactive Substances**

Epidemiological studies have reported higher risks (odds of 1.2–2) of insomnia in individuals using tobacco [30, 72–74], antihypertensive drugs [34], and alcohol [8, 18, 75]. Alcohol was used as a sleeping aid in 4 out of 10 individuals with sleep disturbances [8, 76].

The epidemiological surveys described here clearly show that insomnia symptoms are very common in the general population. For a sizable portion of the population, these complaints represent serious sleep disorders that require medical attention.

We shall now present epidemiologic surveys on other sleep disorders.

**Excessive Daytime Sleepiness and Related Disorders**

Hypersomnia has reported rates varying from 0.3% to 16.3% in the United States [26, 38, 39, 77]. The Cardiovascular Health Study found a 20% prevalence of participants being “usually sleepy in the daytime” in a sample of 4578 adults aged 65 and older.

In Europe, various studies found a prevalence varying from 5% to 16% [7, 34, 78–80].

Excessive daytime sleepiness can be caused by various factors such as poor sleep hygiene, work conditions, and psychotrophic medication use [77, 81]. Excessive daytime sleepiness has been found to be associated also with sleep-disordered breathing [78, 79, 81], psychiatric disorders, especially depression [19, 38, 39, 81], and physical illnesses [78, 79].

**Narcolepsy**

Based on representative community samples, prevalence varies from 20 to 67 per 100,000 inhabitants in Europe and North America [82, 83]. In Japan the rate is between 160 and 590 per 100,000 inhabitants [84, 85]. In Hong Kong, prevalence is estimated to be between 1 and 40 narcoleptics per 100,000 inhabitants [86]; in Saudi Arabia it is 40 per 100,000 inhabitants [87].

**Sleep Breathing Disorders**

In the Finnish twin cohort study, 1.4% had an AHI greater than or equal to 10, with an oxygenation desaturation index (ODI) of at least 4% [7, 64]. In Spain, the prevalence of AHI ≥ 10 was at 19% among men and 14.9% among women [88]. In Italy, 4.8% of the population between 30 and 69 years of age had an AHI greater than 5, and 3.2% had an AHI greater than 10 [89]. In the Wisconsin Sleep Cohort study [90], the prevalence of sleep apnea syndrome (daytime sleepiness and/or nonrefreshing sleep and an AHI of 5 or greater) was estimated at 4% among men and 2% among women. In another U.S. study, the prevalence of sleep apnea, defined as AHI ≥ 10 accompanied by daytime symptoms, was estimated at 3.3% among men [57, 77]. In Australia [91], the rate of obstructive sleep apnea syndrome, based on an AHI of 15 or greater, was estimated at 3.6% overall, and at 5.7% for men and 1.2% for women, and a prevalence of AHI ≥ 5 at 3.7%. In Hong Kong [92], the rate was 2.1% with AHI ≥ 5 accompanied by daytime sleepiness.

**Restless Legs Syndrome (RLS)**

The prevalence of RLS in the general population in European studies oscillates between 5.8% and 9.8% [49, 71, 93–95].

**PARASOMNIAS**

Parasomnias are sleep disorders characterized by abnormal behavioral or physiological events occurring at different sleep stages or during sleep–wake transitions. These disorders have seldom been investigated in the adult general population.

**Arousal Parasomnias**

In the adult general population, prevalence of sleepwalking varied between 1.9% and 3.2% [77, 96–98]; a 2.2% prevalence of night terrors has been reported [97], and a prevalence of 2.9% for confusional arousal [99].