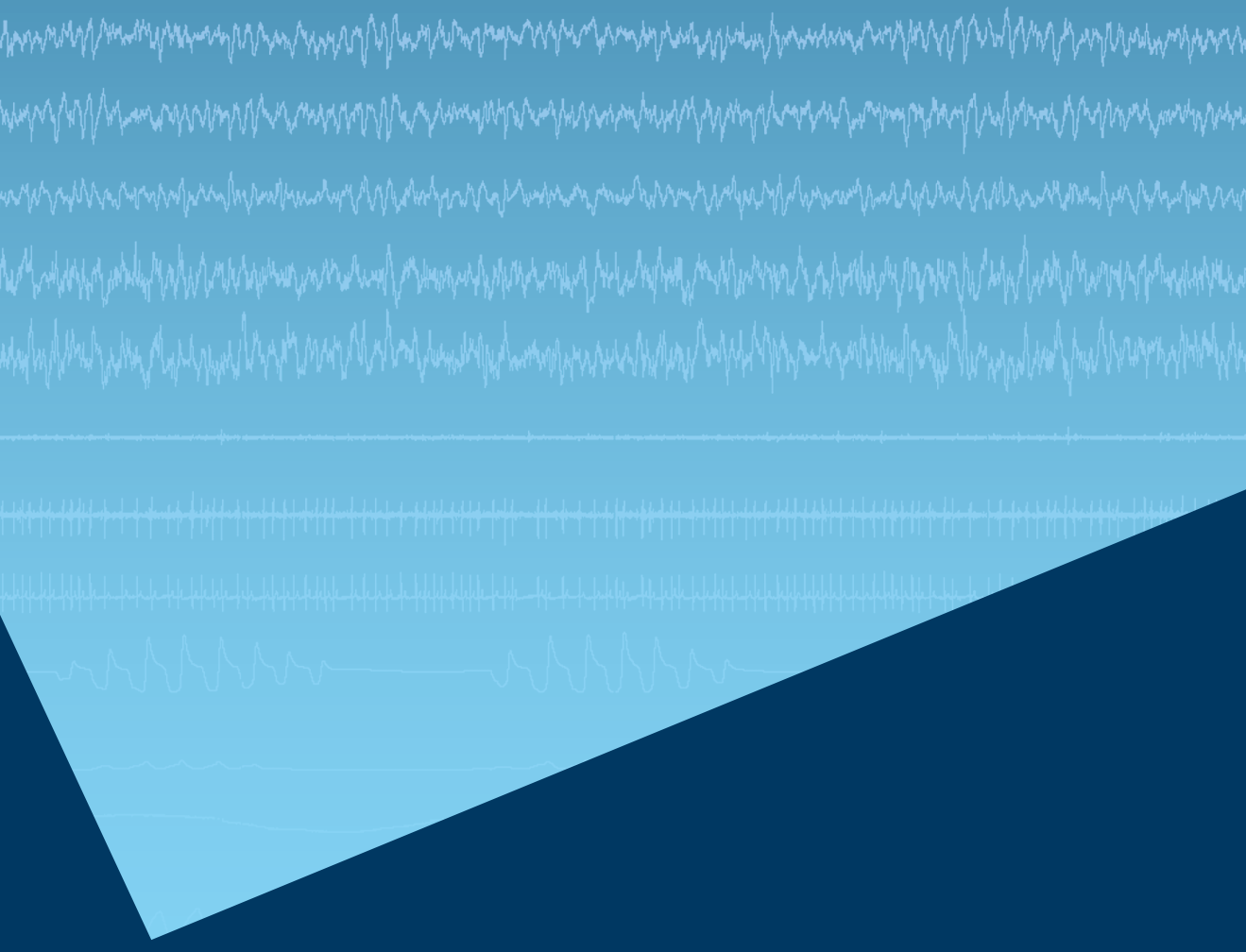
# Sleep Medicine in Clinical Practice

## Second Edition



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## Second Edition

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*Dr Silber dedicates this edition to his mother, Dr Leila Arens, and his late father, Prof Wolf (Bill) Silber, physician investigators, who taught him by example how to combine clinical research with compassionate patient care.*

*Dr Krahn dedicates this edition to her parents, Dr Henry and Mrs Frances Krahn, who have dedicated their lives to their family as well as to innumerable patients in New York, Manitoba, and Minnesota.*

*Dr Morgenthaler dedicates this edition to his parents, Dr George and Mrs Luella Morgenthaler, who inspired their sons to look beyond the horizons.*

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The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some of the indications suggested for drugs described in this book may not have been approved by the U.S. Food and Drug Administration (FDA). It is the responsibility of readers to ascertain which indications are "off label" and to decide whether the medications should be prescribed for these purposes. Some drugs and medical devices presented in this publication may have FDA clearance for limited use in restricted research settings. It is the responsibility of health care providers to ascertain the FDA status of each drug or device planned for use in their clinical practice.

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# Preface to the second edition

> And if tonight my soul may find her peace
> in sleep, and sink in good oblivion,
> and in the morning wake like a new-opened flower
> then I have been dipped again in God, and new-created.
>
> D.H. Lawrence: *Shadows*

Since the publication of the first edition of this book, much has changed in sleep medicine. Our knowledge of sleep science, especially neurobiology, has dramatically increased. New therapies for sleep disorders have been developed and old ones modified. Understanding of the adverse physiologic effects of sleep deprivation and sleep fragmentation has grown. Over 12,000 scientific papers with "sleep" in their titles have been indexed in the PubMed database in the past five years! The influential Institute of Medicine of the National Academies has completed two major reports on sleep and society: *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem* (1) and *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety* (2). The American Academy of Sleep Medicine (AASSM) has completed and published two seminal works, the second edition of the *International Classification of Sleep Disorders* (3) and the *AASM Manual for the Scoring of Sleep and Associated Events* (4). The U.S. Accreditation Council for Graduate Medical Education (ACGME) began accrediting sleep medicine fellowships and 71 programs had been accredited by October 2009. The American Board of Medical Specialties approved a multidisciplinary specialist examination in sleep medicine set jointly by representatives of six primary specialties. In 2007, 1882 candidates sat for the first examination (5). Thus, sleep medicine has not only developed scientifically in the past half decade, but has achieved recognition as a growing medical specialty whose practitioners can greatly enhance the quality of their patients' health.

As a result of these changes, we have extensively modified the second edition of this book. New developments in the science of sleep are incorporated. In particular, the chapter on the physiology of sleep has been essentially rewritten with special reference to the role of the preoptic nuclei and the hypocretin system. We emphasize advances in understanding the metabolic, cardiovascular, and behavioral consequences of sleep deprivation. We discuss new concepts in the pathogenesis of sleep disorders, such as the current understanding of autoimmunity in narcolepsy, the role neurodegenerative diseases play in REM sleep behavior disorder, and the genetic basis of restless legs syndrome. The chapters on the diagnosis of sleep disorders incorporate the technical recommendations and scoring rules set out in the AASM manual. We discuss current data on interpreting the multiple sleep latency and maintenance of wakefulness tests. The classification of sleep disorders follows the nosology described in the second edition of the *International Classification of Sleep Disorders*. Diagnostic controversies, such as the classification of idiopathic hypersomnia and the concept of complex sleep apnea, are explored. New diagnostic techniques and therapeutic advances are discussed, such as home sleep testing and the role of adaptive servoventilation in the management of sleep apnea. We have updated drug therapy for conditions such as narcolepsy, insomnia, parasomnias, and sleep-related movement disorders, with practical algorithms for patient management. We have paid attention to novel adverse reactions, such as impulse control disorders as a result of dopaminergic therapy, cardiac arrhythmias with use of stimulants and atypical neuroleptic agents, and parasomnias associated with short-acting hypnotics. Wherever possible, recommendations are evidence based and incorporate AASM standards of practice parameters. The bibliography has been thoroughly updated and includes references to new studies published in 2009. Tables and figures have been modified or redrawn. We believe the

second edition provides a state-of-the-art authoritative account of the practice of sleep medicine.

Although much has been modified, the basic structure of the book remains the same as the first edition. The content is still structured around sleep symptoms rather than disorders and is aimed at the practicing sleep clinician. The authors remain the same, still representing the different perspectives that specialists in neurology, psychiatry, and pulmonology bring to the field of sleep medicine. The book remains based on the way sleep medicine is practiced at the Mayo Clinic, a method that has formally grown over a quarter of a century with roots delving back to the 1930s and earlier. In Rochester, the comprehensive Center for Sleep Medicine now has 20 consultants, 4 sleep medicine fellows, and 28 laboratory beds. Active sleep medicine centers are also part of Mayo Clinic in Arizona and Florida. Multiple research and educational programs supplement the clinical practice. We hope the second edition will continue to be useful to a number of audiences, including sleep medicine fellows and other trainees, program directors of sleep medicine fellowships designing curricula, practicing sleep physicians who might like to explore how the specialty is practiced at a center different from theirs, and physicians in other specialties intrigued by the growth of this new area.

At Mayo Clinic we are committed to team work and interdisciplinary collegiality. Therefore, we thank our colleagues for their insights into the practice of sleep medicine and their contributions to the approaches discussed in this book. We include not only the physician staff, but also our nurses, technologists, and fellows from whom we continue to learn every day. Paul Honermann of the Mayo Section of Illustration and Design was responsible for much of the artwork. Roberta Schwartz of the Mayo Department of Publications shared her insights and wisdom. Susan Miller assisted with obtaining copyright permissions. We also thank Sandra Beberman, Aimee Laussen, and others at Informa Healthcare for their encouragement, assistance, and support. Finally, we thank our families for their forbearance and understanding while we worked long hours at completing this book.

*Michael H. Silber*
*Lois E. Krahn*
*Timothy I. Morgenthaler*

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# Preface to the first edition

Come, Sleep: O Sleep! The certain knot of peace,
The baiting place of wit, the balm of woe,
The poor man's wealth, the prisoner's release,
The indifferent judge between the high and low.
Philip Sidney: *Astrophel and Stella*

In late June of 1995, the ninth annual meeting of the Associated Professional Sleep Societies was held in Nashville. To the amazement of the attending physicians and scientists, a special appearance by Dr Nathaniel Kleitman, then in his 100th year of life, had been arranged. Forty two years had passed since the discovery of REM sleep at the University of Chicago by Kleitman and his graduate student, Eugene Aserinsky. Many of us present were not even aware that the father of sleep medicine was still alive, and to see and hear him was a spine chilling experience. Kleitman was the pioneer of sleep researchers in more ways than by discovering REM sleep. In 1938, he spent more than a month in Mammoth Cave, Kentucky to study biological rhythms and in 1939 he published the first modern book on sleep research, the classic "*Sleep and Wakefulness*." However, the discovery of REM sleep was the seminal event in the investigation of sleep and proved the beginning of an exponential explosion of knowledge that still continues. In a young field like this, the current generation of sleep physicians still can feel a direct link to the origins of our discipline.

Sleep medicine also has a long history at Mayo Clinic. As early as 1934, Lumen Daniels published a comprehensive review of the Mayo experience with narcolepsy (1). In this lengthy paper, he not only delineated all the clinical features of the disorder but also described patients with what would later be called obstructive sleep apnea syndrome, although not recognizing its pathophysiology. In the 1950s, Dr Robert Yoss became one of the first specialists in narcolepsy, describing the tetrad of symptoms still recognized today, introducing pupillometry as the first test for the disorder and introducing methylphenidate as a treatment. Daytime sleep studies were performed in the 1970s, and in 1983 the Mayo Sleep Disorder Center was formally founded under the leadership of Dr Philip Westbrook. This center has remained a multidisciplinary clinic and laboratory with currently 16 laboratory beds and a consultant staff of 13. A one-year sleep medicine fellowship for physicians has been in place since 1990 as well as training programs for technologists. Active research continues in such fields as narcolepsy, the treatment of sleep apnea and parasomnias in neurodegenerative disorders.

Why have we chosen to write this book? There are already a number of large multiauthored textbooks of sleep medicine as well as smaller single-authored monographs. However, we felt we could add a new perspective by writing a book coauthored by three colleagues working closely together in a large academic sleep center and representing the different perspectives of neurology, psychiatry, and pulmonology. We have arranged the book around a clinical approach to the patient with a sleep disorder. We have included sufficient basic science to allow an understanding of the pathogenesis, diagnostic tools, and treatments of sleep disorders, but predominantly emphasize the role of the clinician in diagnosing and managing disease. We have used tables, algorithms, and figures to emphasize the approaches we advocate and have based these on what we hope has been a scholarly review of the literature as well as our own experience in a busy academic practice. We have used extensive case histories to personalize the text, describing both common and unusual clinical problems.

We have designed this book for a number of audiences. First, we hope it will be helpful to trainees studying sleep medicine as well as those in neurology, pulmonology, psychiatry, and other residencies who would like to explore the world of sleep in more depth than is

covered in general textbooks. We also considered the needs of practicing sleep physicians who might appreciate reading the approaches of a different sleep center, especially in areas aligned to a primary specialty different from their own. We also hope the book may be beneficial to the faculty of sleep medicine training programs as a basis for an organized curriculum. Finally, we would be delighted if the book were to spur the interest of medical students and physicians not working in sleep medicine, and stimulate them to make this enticing field a part of their professional lives.

We would like to thank many people who directly or indirectly made this book possible. We work in the most collegial of sleep centers and all of our colleagues have contributed to our thinking about sleep. We have also learned from our nurses, technologists, and trainees. In particular, we must thank Drs Peter Hauri and John Shepard, past directors of our center, for imparting their knowledge and wisdom. Cameron Harris, coordinator of the Mayo Sleep Disorders Center, and Dan Herold, supervisor of our sleep laboratory, shared their extensive technical expertise and helped in the production of many of the illustrations. Bryce Bergene of the Mayo Division of Media Support Services was responsible for the artwork. Les Ottjes, Annette Schmidt, and Julie Stamschror provided secretarial support. Dr Leila Arens read much of the manuscript and provided valuable advice. Roberta Schwartz of the Mayo Department of Publications guided us through the intricacies of producing a book. Finally, we must thank Jonathan Gregory of Parthenon Publishing Group who first suggested us to write this book, overcame our objections, and supported us through many months of hard but enjoyable work.

*Michael H. Silber*
*Lois E. Krahn*
*Timothy I. Morgenthaler*

## REFERENCE

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# Contents

# 1 Physiologic basis of sleep

I met at eve the Prince of Sleep,
His was a still and lovely face,
He wandered through a valley steep,
Lovely in a lonely place.
Dark in his pools clear visions lurk,
And rosy, as with morning buds,
Along his dales of broom and birk
Dreams haunt his solitary woods.
Walter de la Mare: *I met at Eve*

Sleep can be defined in behavioral terms as a normal, recurring, reversible state of loss of awareness with inability to perceive and respond to the external environment. Voluntary motor activity largely ceases and a quiescent posture, specific to each species, is adopted. Sleep is present in mammals and birds, probably in reptiles, amphibians, and fish, and likely in at least some invertebrate species such as fruit flies. It may be present in only one cerebral hemisphere at a time in dolphins, porpoises, whales, and some species of birds, presumably as a defense against predators. Sleep is generated by the brain but is associated with profound changes in physiology elsewhere in the body. Contrary to early belief, the neurophysiology of sleep involves active and dynamic changes in neural functioning and is far from a passive process of absence of wakefulness.

## ELECTROENCEPHALOGRAPHY

The human scalp electroencephalogram (EEG) was first recorded by Hans Berger of Germany in 1929. Understanding sleep physiology requires some knowledge of the basis of the EEG and the manner in which it is recorded. EEG is recorded by electrodes that are attached to multiple areas of the scalp. They record summated electrical activity from synapses in the uppermost levels of the cerebral cortex. Electrodes are applied according to the International 10–20 system, a method for finding the correct electrode sites measuring from certain anatomic landmarks. The electrodes used most often in monitoring sleep are discussed in chapter 4.

A single tracing of EEG is known as a derivation; in a full EEG, 16 or more derivations are recorded simultaneously from multiple areas of the scalp. Two forms of recording are used: bipolar and referential. In a bipolar derivation, the difference in electric potentials recorded by two adjacent electrodes is displayed, whereas in a referential derivation, the electric potential recorded from a single scalp electrode is compared to that recorded from a relatively inactive electrode at a distance from the scalp, such as over the mastoid process (Fig. 1.1). An arrangement of derivations in a specified order is known as a montage.

The various frequency ranges of electrical activity recorded on an EEG are arbitrarily divided into four categories (Table 1.1). Alpha rhythm consists of alpha frequency activity in sinusoidal trains recorded over the occipital head region during wakefulness when a subject's eyes are shut (Fig. 1.2). Opening the eyes attenuates alpha rhythm, as does the development of drowsiness.

## SLEEP STATES AND CYCLES

Human sleep is not a uniform process but comprises two states: non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. A night's sleep in an adult consists of between four and six sequential cycles, each lasting approximately 90 minutes, during which a longer period of NREM sleep is followed by a generally shorter period of REM sleep. NREM sleep is divided into three stages of increasing depth of unresponsiveness, known as stages N1

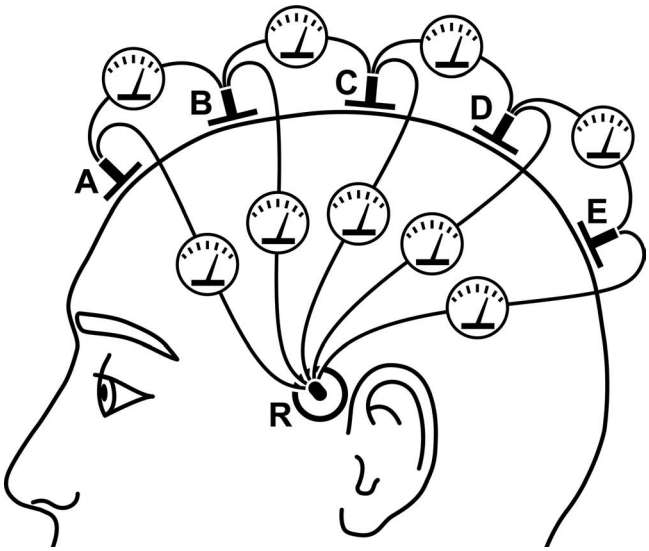


**Figure 1.1** Bipolar and referential EEG derivations. The difference between the scalp potentials underlying electrodes A and B are compared in a bipolar derivation, A–B. The chain of derivations A–B, B–C, C–D, and D–E comprise a bipolar montage. In contrast, the potential underlying electrode A is compared to the potential (assumed to be close to zero) recorded from the distant electrode R attached to the mastoid process. This derivation (A–R) is known as a referential derivation, and the chain of derivations A–R, B–R, C–R, D–R, and E–R comprise a referential montage.

**Table 1.1** Electroencephalogram Wave Frequencies

| |
|---|
| Beta: >13 Hz |
| Alpha: 8–13 Hz |
| Theta: 4–7.9 Hz |
| Delta: <4 Hz |

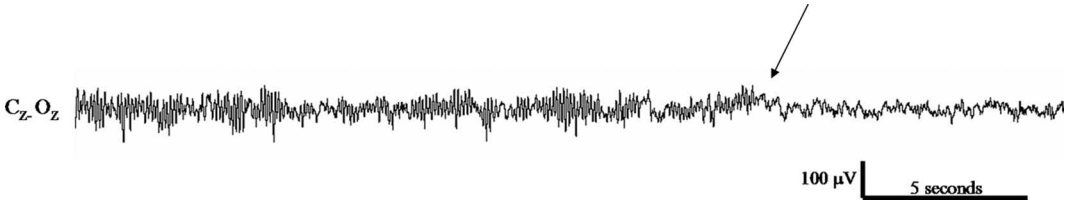


**Figure 1.2** Alpha rhythm. This tracing shows occipital alpha rhythm, attenuating with eye opening (*arrow*).

through N3 (1,2). Stage N3 is often referred to as slow-wave sleep. Figure 1.3 illustrates schematically the progression of sleep through the different states. It can be seen that most slow-wave sleep occurs during earlier sleep cycles, whereas most REM sleep occurs during later cycles. Transitions from NREM to REM sleep usually occur through stage N2. It is normal for sleep cycles to be interrupted by occasional brief arousals, often associated with position changes and usually without full return to consciousness. Approximately three-quarters of a night's sleep in a young adult comprises NREM sleep (5% stage N1, 50% stage N2, and 20% stage N3), whereas the other quarter consists of REM sleep (Fig. 1.4).

## NREM Sleep

NREM sleep is characterized by synchronized, rhythmic EEG activity, partial relaxation of voluntary muscles, and reduced cerebral blood flow. Heart rate, blood pressure, and respiratory

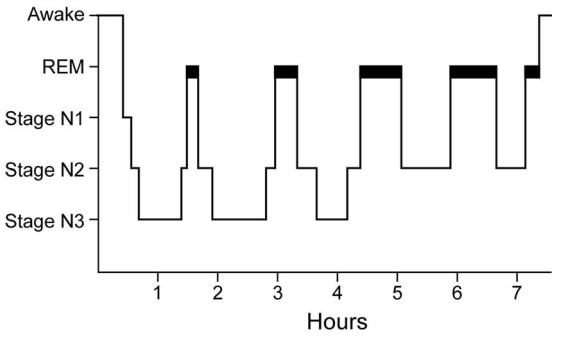


**Figure 1.3** Schematic representation of the cycles of a night's sleep. This figure is a representation of a typical night's sleep in a young adult, demonstrating five sleep cycles with most slow-wave sleep in earlier cycles and most REM sleep in later cycles. Brief periods of wakefulness, which are normally present during the night, have been omitted. *Source:* From Ref. 3.

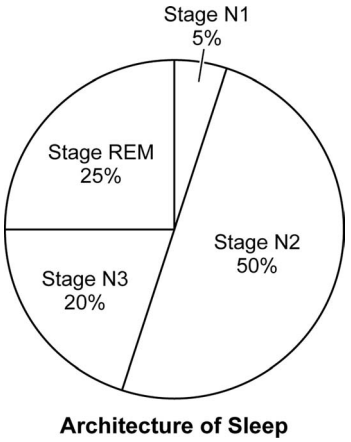


**Figure 1.4** Percentage of sleep stages in a young adult. *Source*: From Ref. 3.

tidal volume fall. Some mental imagery persists during NREM sleep, but on waking is more often described as fragmentary thoughts or simple images than as vivid dreams.

Stage N1 sleep is characterized by the disappearance of occipital alpha rhythm and its replacement by low-amplitude theta activity (Fig. 1.5). Sharply contoured vertex waves (V waves) may appear over the central head regions, and positive occipital sharp transients of sleep (POSTS) may be seen posteriorly. Slow horizontal roving eye movements develop, voluntary muscles relax, and response to environmental sensory stimuli lessens or ceases. The onset of sleep is usually preceded by a poorly defined period of drowsiness (chap. 5). The onset of behavioral sleep differs from the arbitrarily defined onset of electrophysiologic sleep, with responsiveness to the environment progressively declining from drowsiness preceding stage N1 sleep to early stage N2 sleep.

Two EEG phenomena, K complexes and sleep spindles, characterize stage N2 sleep (Fig. 1.6). K complexes are high-amplitude diphasic waves, and sleep spindles are chains of rhythmic 11- to 16-Hz activity, usually 12 to 14 Hz. Both are recorded over the vertex, but K complexes are usually maximal over the frontal region, whereas sleep spindles are maximally represented over the central head region. Both K complexes and sleep spindles have a duration of at least 0.5 seconds. Although they may occur independently, often a K complex is followed by a spindle. K complexes occur both spontaneously with a periodicity of about 30 seconds and in response to external auditory stimuli. They are associated with transient increases in sympathetic activity and may have evolved as a mechanism for inducing protective partial arousals during sleep in hazardous environments. However, controversy exists whether K complexes result in consolidation or fragmentation of sleep (4). Slow eye movements and

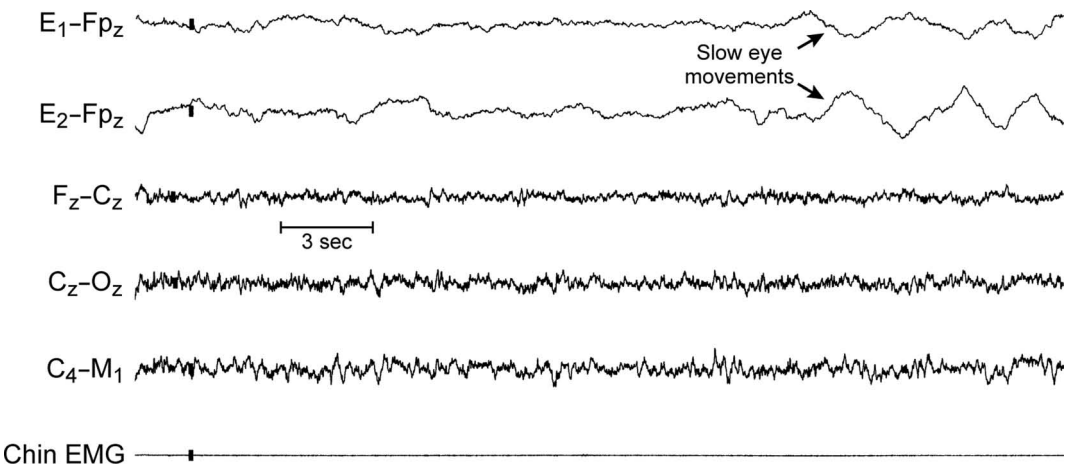


**Figure 1.5** Stage N1 sleep. This 30-second epoch shows the characteristics of stage 1 NREM sleep. The LOC-Fpz and ROC-Fpz derivations record eye movements. The Fpz-Cz, Cz-Oz, and C4-M1 derivations record EEG activity. All these derivations are explained in more detail in chapter 4. The EEG is low-amplitude, mixed frequency. Slow rolling horizontal eye movements of drowsiness are present on the eye movement channels. EMG amplitude is low. *Abbreviations*: EEG, electroencephalogram; EMG, electromyogram. *Source*: From Ref. 3.

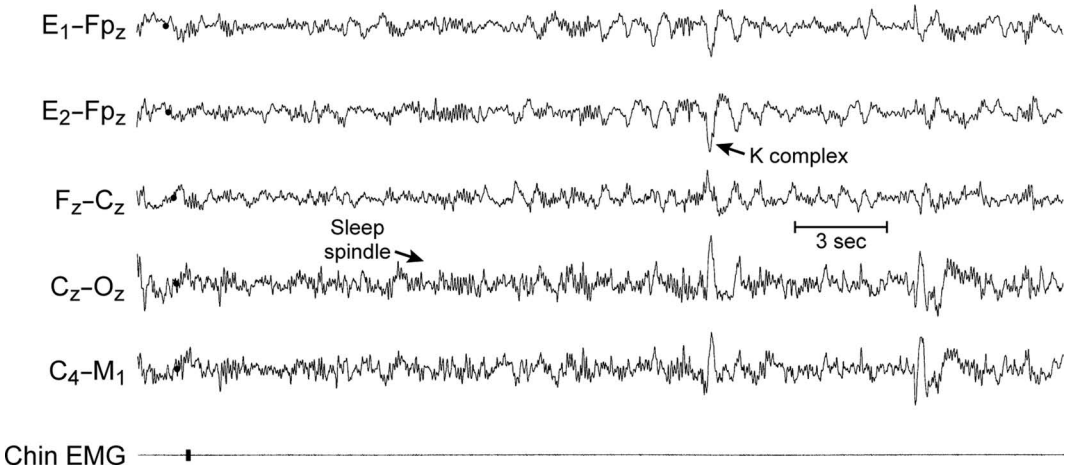


**Figure 1.6** Stage N2 sleep. This 30-second epoch shows the characteristics of stage N2 NREM sleep. Derivations are described in Figure 1.5 and in chapter 4. Eye movements have ceased. K complexes (high-amplitude diphasic waves maximal over the vertex) and sleep spindles predominantly 12- to 14-Hz activity) are indicated. *Source*: From Ref. 3.

POSTS may sometimes persist into stage N2 sleep. Stage N3 sleep (slow-wave sleep) is characterized by increasing quantities of synchronized, high-amplitude slow-wave activity with frequency of 0.5 to 2 Hz occurring over wide areas of the cortex, but maximal frontally (Fig. 1.7). This is the deepest stage of sleep, requiring the greatest sensory stimuli to induce an arousal.

### REM Sleep (Fig. 1.8)

REM sleep, also known as paradoxical sleep, can be conceptualized as a state of internal arousal, sharing some features of NREM sleep and some of wakefulness. REM sleep phenomena can be classified as tonic and phasic—tonic persisting throughout an REM sleep period and phasic occurring intermittently (Table 1.2). The tonic phenomena include a desynchronized,

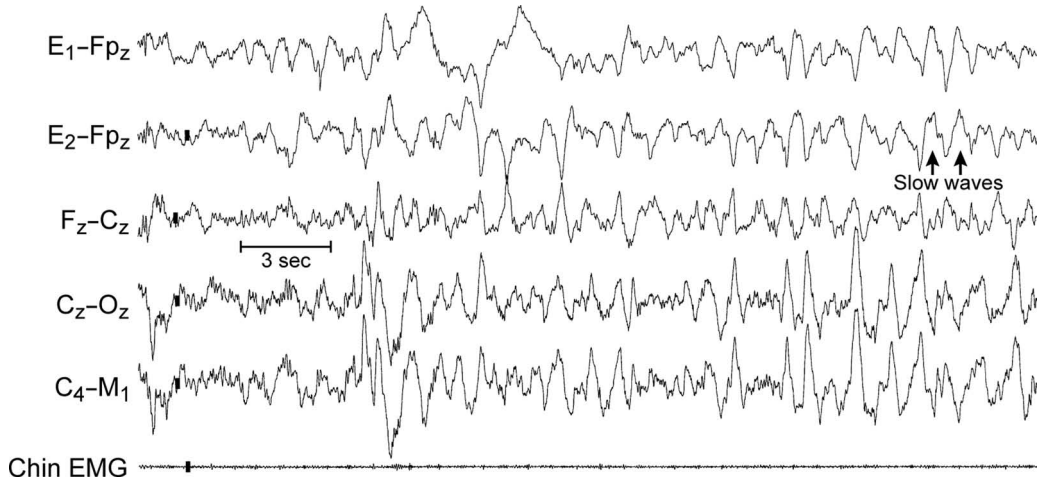


**Figure 1.7** Stage N3 sleep. This 30-second epoch shows the characteristics of stage N3 NREM sleep. Derivations are described in Figure 1.5 and in chapter 4. High-amplitude slow waves are the predominant finding. *Source*: From Ref. 3.

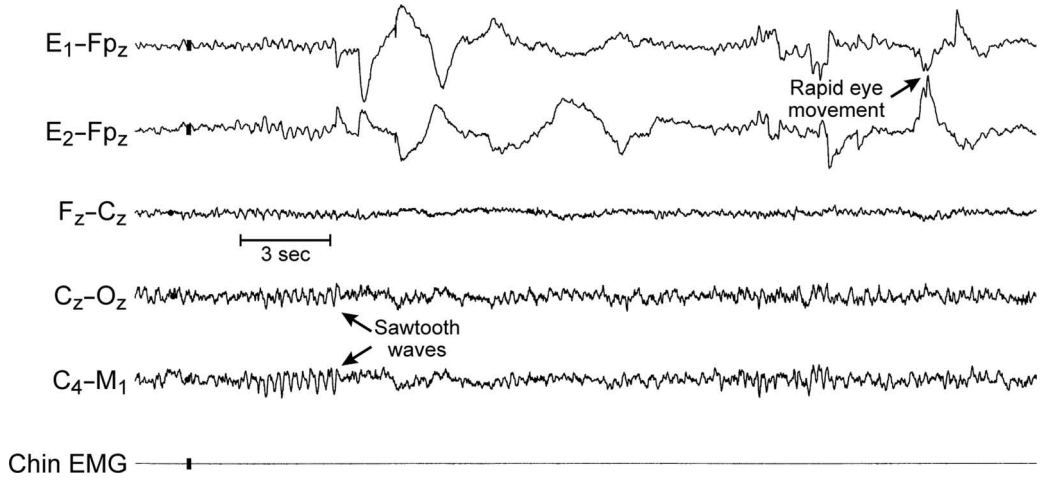


**Figure 1.8** REM sleep. This 30-second epoch shows the characteristics of stage R (REM) sleep. Derivations are described in Figure 1.5 and in chapter 4. Irregular, conjugate, horizontal rapid eye movements are present in the eye movement channels. Sawtooth waves precede rapid eye movements, but the remainder of the EEG consists of low-amplitude, mixed frequency rhythms. Electromyogram tone is absent. *Source*: From Ref. 3.

low-amplitude, mixed frequency cortical EEG resembling the EEG of wakefulness with the eyes open, and rhythmic hippocampal theta activity. Voluntary muscles become largely atonic with only the extraocular muscles and diaphragm retaining activity. Cerebral blood flow increases relative to NREM sleep. Thermal regulation is impaired, resulting in near poikilothermia. Penile erections occur in men and clitoral engorgement in women. The most characteristic REM sleep phenomenon is that of dreaming. Subjects woken during REM sleep will report dreaming in about 85% of awakenings, but dreams are rarely recalled after a period of REM sleep has ended. REM dreams are vivid, surrealistic, emotionally charged, multicolor experiences with frequent auditory accompaniments, and perceptions of movement.

Superimposed phasic events include rapid eye movements. These are conjugate, irregular, predominantly horizontal or oblique, sharply peaked eye movements that occur in clusters during a period of REM sleep. Superimposed on the skeletal muscle atonia are

**Table 1.2** Phenomena of REM Sleep

| |
|---|
| Tonic phenomena |
| Desynchronized, mixed frequency EEG |
| Hippocampal theta activity |
| Atonic voluntary muscles |
| Increased cerebral blood flow |
| Impaired thermal regulation |
| Penile erections and clitoral engorgement |
| Dreams |
| Phasic phenomena |
| Rapid eye movements |
| Transient muscle activity |
| Irregular accelerations of heart and respiratory rate |
| Ponto-geniculo-occipital waves |
| Sawtooth waves |

irregular short bursts of transient muscle activity, sometimes termed phasic muscle twitches. Irregular accelerations of heart rate and respiration occur. In animals, intermittent ponto-geniculo-occipital (PGO) waves can be recorded from the pontine tegmentum, the lateral geniculate body of the thalamus, and the cerebral cortex, especially the occipital lobe. The human scalp EEG may show sawtooth waves, trains of triangular 2- to 6-Hz waves recorded over the vertex, often preceding bursts of rapid eye movements.

The transition between NREM and REM sleep is not an abrupt process. Experimental studies with intracellular electrodes in pontine reticular formation neurons show that there is a gradual membrane depolarization of these cells before the onset of REM sleep. This is mirrored in the human polysomnogram by such phenomena as K complexes or spindles intruding into early REM sleep or muscle atonia developing several seconds before any other REM sleep phenomena. In obstructive sleep apnea syndrome (chap. 8), it is common to see a distinct worsening of apneas as the first sign that REM sleep is approaching. In patients with neurodegenerative disorders, periods of sleep can be recorded with intermixture of NREM and REM phenomena, often referred to as ambiguous sleep. The most extreme form of this (status dissociatus) occurs when it is impossible to distinguish wakefulness and NREM and REM sleep on a polysomnogram.

**Case 1.1**

A 68-year-old man presented with a four-year history of nocturnal hallucinations. He would wake from sleep seeing vivid images of snakes, spiders, or Arabian palaces in his bedroom. On one occasion, he was convinced he saw the dead body of his wife next to him and was actually phoning for help when his wife walked into the bedroom. The images lasted several minutes, and at times he would jump out of bed to avoid them. The patient was aware of mild short-term memory problems. Neurologic examination confirmed difficulties with learning and recall, but was otherwise normal. A polysomnogram showed markedly abnormal sleep architecture. During most of the night, alpha rhythm with variable amounts of theta and delta activity was seen. Occasional sleep spindles were present. No REM sleep was recorded, but at one time rapid eye movements were seen coincident with sleep spindles and not associated with muscle atonia. The patient aroused from sleep once and reported seeing a bear. Initially a definitive diagnosis was not possible, but with passage of time moderate cognitive impairment developed, and a diagnosis of dementia with Lewy bodies was made.

This case illustrates dissociation of the phenomena of wake and NREM and REM sleep, resulting in ambiguous sleep states and manifesting clinically by vivid nocturnal hallucinations. Severe sleep abnormalities preceded other manifestations of a neurodegenerative illness. These issues are discussed at greater length in chapters 16 and 17.

## CHANGES IN SLEEP PHYSIOLOGY WITH AGE

The two states of sleep are present in neonates, but are known as quiet (NREM) and active (REM) sleep. Active sleep may comprise 50% of total sleep time with a shorter cyclical periodicity of 50 to 60 minutes and frequent transitions from wakefulness directly into active

sleep. Daily total sleep time in a neonate is at least 16 hours. Sleep spindles develop by two to three months of age and K complexes by five to six months (5). Sleep spindles in the first year of life may be asynchronous, occurring alternately over each hemisphere. During the first decade, the percentage of REM sleep falls, and the timing of the first REM sleep period from sleep onset (REM latency) lengthens.

REM sleep latency again shortens in the elderly. The percentage of slow-wave sleep begins to fall in adolescence and continues to decline with advancing age. Sleep after middle age is also characterized by increased wake time after sleep onset and reduced total sleep time (6) (Fig. 1.9). Periodic limb movements of sleep (chap. 16) become more common, and an increased tendency to sleep-disordered breathing is noted.

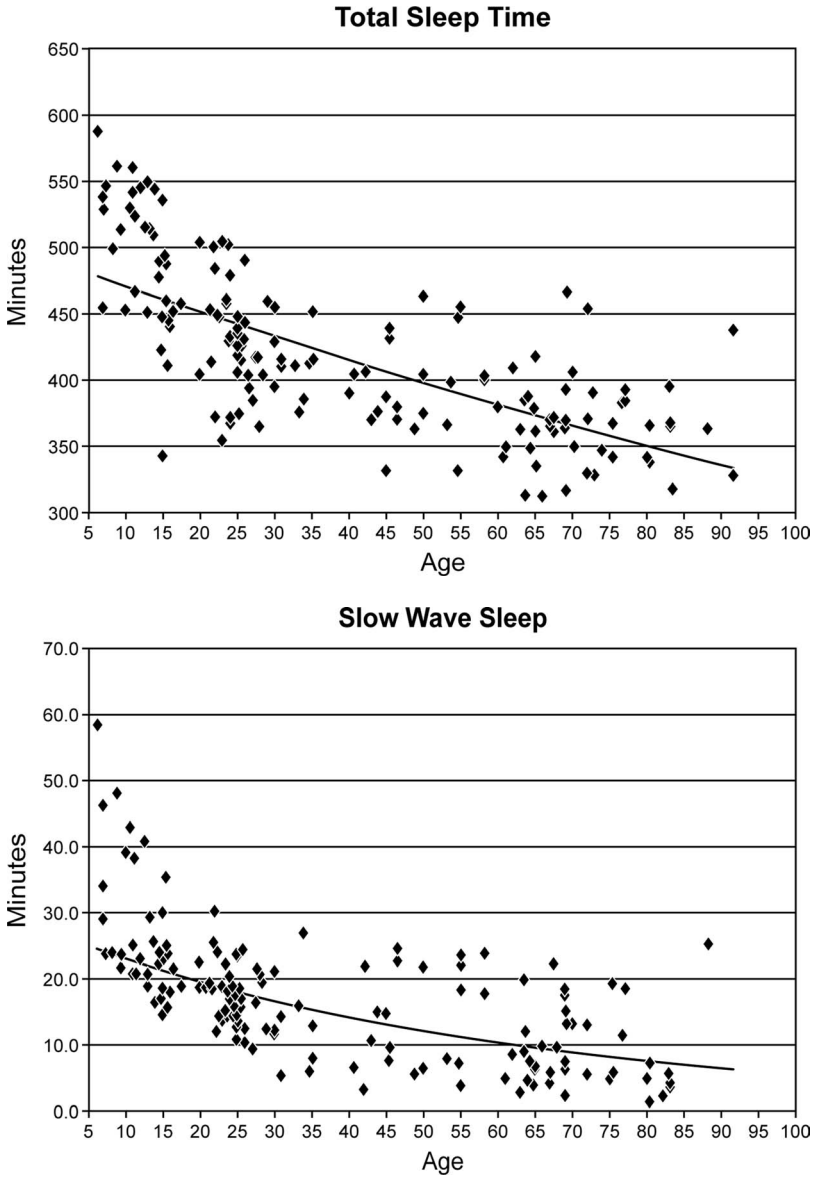


**Figure 1.9** Changes in total sleep time and slow-wave sleep time with age. These graphs, based on a meta-analysis of many studies, indicate changes in total sleep time and slow-wave sleep time with age. *Source*: Modified from Ref. 6.

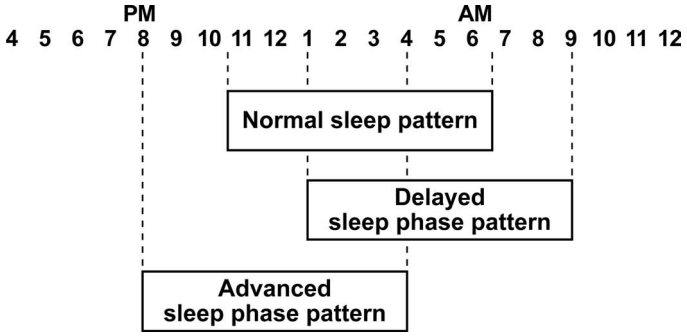


**Figure 1.10** Different sleep phase patterns. This diagram illustrates different sleep phase patterns with alterations in the timing of sleep in the 24-hour cycle.

Sleep disturbances also accompany lifecycle changes in women. Pregnancy is associated with disrupted sleep from a combination of hormonal changes, the increasing size of the fetus, anxiety, and medical conditions such as gastroesophageal reflux, restless legs syndrome (chap. 16), and obstructive sleep apnea. Sleep in the postpartum period may be compromised by the needs of the baby or depression. Perimenopausal women experience insomnia, often associated with hot flashes and night sweats, whereas the risk of obstructive sleep apnea (chap. 8) rises after menopause.

The timing of sleep also varies with age. First-decade children tend to go to sleep earlier than adults and often wake earlier as well. During adolescence, sleep onset becomes delayed, with 15- to 25-year-olds preferring to sleep from after midnight to late in the morning. This delayed sleep phase pattern is a physiologic change and is not simply due to social factors (7). Some older persons develop an advanced sleep pattern, with sleep onset at 7 to 8 p.m. and waking in the early hours of the morning (Fig. 1.10).

## FUNCTIONS OF SLEEP

We sleep for almost one-third of our lives and yet the functions of sleep remain enigmatic. Many functions have been proposed (Table 1.3), and all may be partially correct. It has been proposed that sleep, especially NREM sleep, is necessary for protein synthesis, cell division, and growth, thus allowing for repair of the body or brain. REM sleep appears to consolidate memory and may serve a role in deleting unnecessary memory files (8). Sleep may be necessary to maintain immunocompetence (9). Species with high metabolic rate have longer sleep times, suggesting that sleep may be required to conserve energy (10,11). However, there is no accepted model linking these varied effects, and the fundamental role of sleep at cellular and molecular levels is still uncertain. One hypothesis, supported by experimental evidence in mammals and fruit flies, suggests that sleep down-modulates synapses by reducing synaptic number and levels of several synaptic proteins in the brain. This homeostatic process may result in energy conservation, reduction in space occupied by synapses, and preparation for new learning during the next waking period (12).

**Table 1.3** Functions of Sleep: Proposed Hypotheses

- Body repair
- Brain restoration
- Memory and learning
- Unlearning
- Immunocompetence
- Thermoregulation and energy conservation
- Synaptic homeostasis

## NEUROBIOLOGY OF WAKEFULNESS AND SLEEP

### Wakefulness

There are two sets of neural systems mediating wakefulness (13). First, ascending neurons, predominantly from the brainstem reticular formation, project to the thalamus and cortex, and second, neurons located in the posterolateral hypothalamus stabilize the wake state. Each of these systems is now discussed in more detail (Table 1.4).

The ascending neurons release acetylcholine or monoamines (Fig. 1.11). The cholinergic system originates in the pontine tegmentum (pedunculopontine and laterodorsal tegmental nuclei) with axons projecting to the thalamus. This facilitates transmission of sensory information to the cortex, an essential characteristic of the wake state. Cholinergic neurons are active in wakefulness and in REM sleep, but silent during NREM sleep (Table 1.5). The monoamine system has several nuclei of origin, depending on the specific neurotransmitter released. Neurons releasing norepinephrine arise from locus coeruleus, ventral to the floor of

**Table 1.4** Neural Systems Mediating Wakefulness

| System | Neurotransmitter | Cells of origin |
|---|---|---|
| Ascending | Acetylcholine | Pontine tegmentum |
| | Monoamines | |
| | Norepinephrine | Locus coeruleus |
| | Serotonin | Raphe nuclei |
| | Dopamine | Periaqueductal gray |
| | Histamine | Tuberomammillary nuclei |
| Stabilizing | Hypocretin (orexin) | Posterolateral hypothalamus |

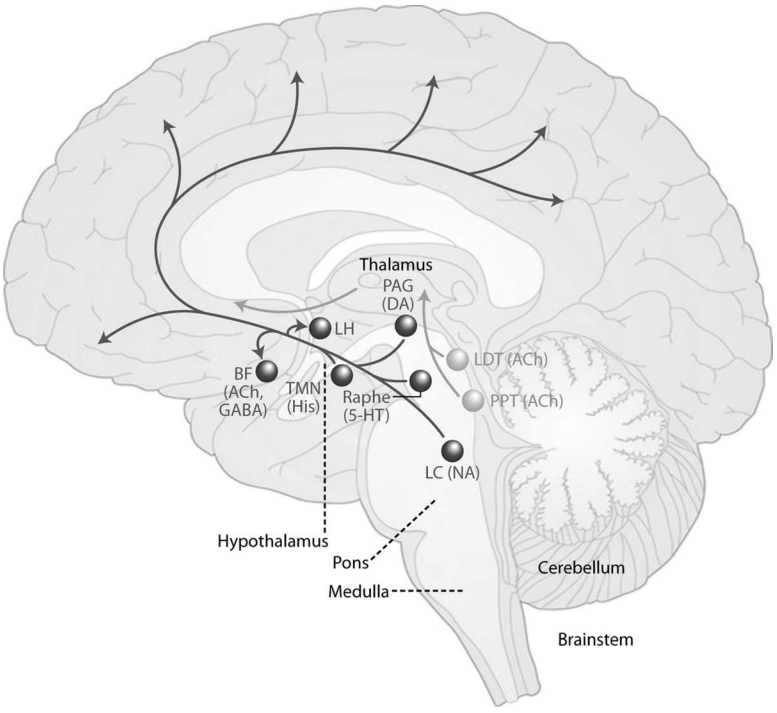


**Figure 1.11** Ascending arousal pathways. This diagram demonstrates the cholinergic and monoaminergic ascending pathways mediating alertness. *Abbreviations*: LDT, lateral dorsal tegmental nucleus; PPT, pedunculopontine nucleus; LC, locus coeruleus; TMN, tuberomammillary nucleus; BF, basal forebrain; LH, lateral hypothalamus; PAG, periaqueductal gray; DA, dopamine; ACh, acetylcholine; NA, norepinephrine; His, histamine; GABA, gamma aminobutyric acid. *Source*: Modified from Ref. 13.

**Table 1.5** Neurotransmitter Systems in Sleep and Wakefulness

| | Wake | NREM sleep | REM sleep |
|---|---|---|---|
| Cholinergic neurons | Active | Silent | Active |
| Noradrenergic neurons | Active | Partially active | Silent |
| Serotoninergic neurons | Active | Partially active | Silent |
| Hypocretinergic neurons | Active | Silent | Silent |

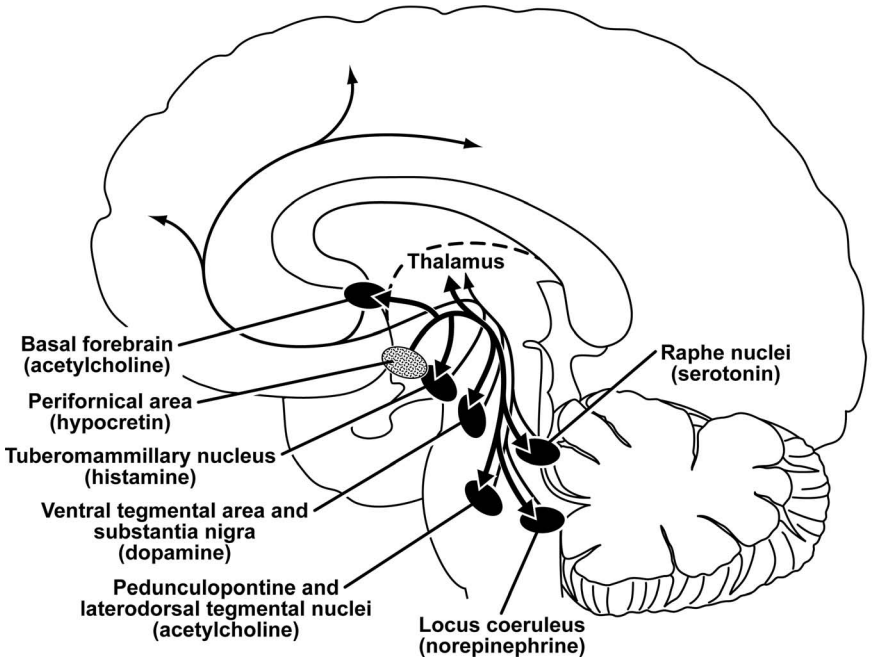


**Figure 1.12** Widespread projections of hypocretin (orexin)-synthesizing neurons. The figure demonstrates how hypocretin (orexin)-synthesizing neurons from the perifornical area of the hypothalamus project to many other neurons involved in a wide range of neurotransmitter systems. *Source*: Modified from Ref. 15.

the fourth ventricle, whereas those releasing serotonin are found in the midline raphe nuclei. Dopaminergic neurons are located in the periaqueductal gray (PAG) surrounding the cerebral aqueduct and neurons releasing histamine originate in the hypothalamic tuberomammillary nuclei. Axons from these monoaminergic neurons terminate on cells in the cerebral cortex, the preoptic and basal frontal regions, and the posterolateral hypothalamus. They activate cortical neurons, inhibit sleep-generating areas, and stimulate release of hypocretin (see later in text). Monoaminergic neurons are active in wakefulness, partially active in NREM sleep, and silent in REM sleep (Table 1.5). Drugs increasing catecholamines at the synaptic cleft, including amphetamines and cocaine, cause cortical activation. In contrast, sedation is a major side effect of the histamine-1 antagonists.

The wakefulness stabilizing system is mediated by the hypocretins (also known as orexins), peptide neurotransmitters secreted by a small group of cells in the posterolateral hypothalamus (14). Hypocretin-releasing axons project widely to the limbic system, thalamus, brainstem reticular core, and neocortex (Fig. 1.12). Hypocretin neurons fire actively in wakefulness but are silent in NREM and REM sleep (Table 1.5). A precursor molecule, preprohypocretin, is converted into hypocretin-1 (hcrt-1) (orexin A) and hypocretin-2 (hcrt-2) (orexin B). There are two hypocretin receptors: hypocretin receptor 1 with a high affinity for

hcrt-1 and hypocretin receptor 2 with a high affinity for both hcrt-1 and hcrt-2. The first indication of a relationship of the hypocretin system to sleep and alertness was the discovery that narcolepsy in dogs, an autosomal recessive disorder, was due to a deletion in the hcrt-2 receptor gene (16). At about the same time, researchers studying hypocretin knockout mice noted that they developed sleep attacks and falls very reminiscent of cataplexy (17). Most human narcoleptics tested have shown undetectable levels of hcrt-1 in the cerebrospinal fluid (18) (chap. 7). Intraventricular infusion of hypocretins in rats causes increased alertness. The hypocretin system appears to act primarily to stabilize wakefulness by facilitating the release of wake-producing monoamines and inhibiting the release of sleep-inducing inhibitory neurotransmitters.

## NREM Sleep

*NREM Sleep Generation*

It has long been known that electrical stimulation of the anterior hypothalamic and preoptic areas results in sleep. In the encephalitis lethargica outbreak associated with the influenza pandemic following the World War I, patients with severe insomnia were found to have lesions in these areas. Today it is recognized that the primary generator of NREM sleep is the preoptic area in the anterior hypothalamus (Fig. 1.13). The ventrolateral preoptic (VLPO) area has been most thoroughly studied, but the median preoptic nucleus (MnPN) may be equally important (19). VLPO neurons release the inhibitory neurotransmitters gamma aminobutyric acid (GABA) and galanin (13). Their axons project onto the neurons-mediating arousal: brainstem cholinergic neurons, monoaminergic neurons, and hypocretin-synthesizing neurons (Fig. 1.14). The VLPO, in turn, receives inhibitory input from the ascending monoaminergic axons. VLPO neurons discharge throughout NREM sleep, whereas MnPN neurons are active early in NREM sleep, especially after periods of prolonged waking, and discharge less during stable NREM sleep.

Transitions between wake and NREM sleep are mediated by the mutually inhibitory interactions between the preoptic area and the ascending monoaminergic neurons. These interactions can be modeled as a flip-flop switch, an engineering concept consisting of two connected poles, each inhibiting the other (Fig. 1.15). Such a system produces sharp transitions between two discrete states. The presence of hypocretin results in stabilization of wakefulness, and its absence allows sleep. Hypocretin, released when the VLPO becomes inactive during wakefulness, stimulates the monoamine pole of the switch that in turn further inhibits the VLPO. In contrast, discharges from the VLPO pole of the switch during NREM sleep prevent hypocretin release and thus further inhibit monoamine release. Lesions in the posterior hypothalamus were found in encephalitis lethargica patients with symptoms of persistent hypersomnia, presumably in what is today recognized as the cells of origin of hypocretin neurons.

Anterior to the preoptic nuclei lies the basal forebrain area, including the nucleus of the diagonal band and the substantia innominata (Fig. 1.13). Electrical stimulation here also produces sleep, and single-unit recordings demonstrate a population of cells that fire more

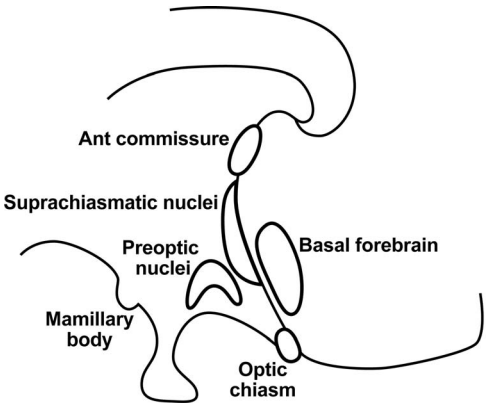


**Figure 1.13** Midline sagittal section through the hypothalamus and basal forebrain. This figure illustrates the anatomy of the preoptic nuclei and basal forebrain nuclei involved in the generation of NREM sleep.

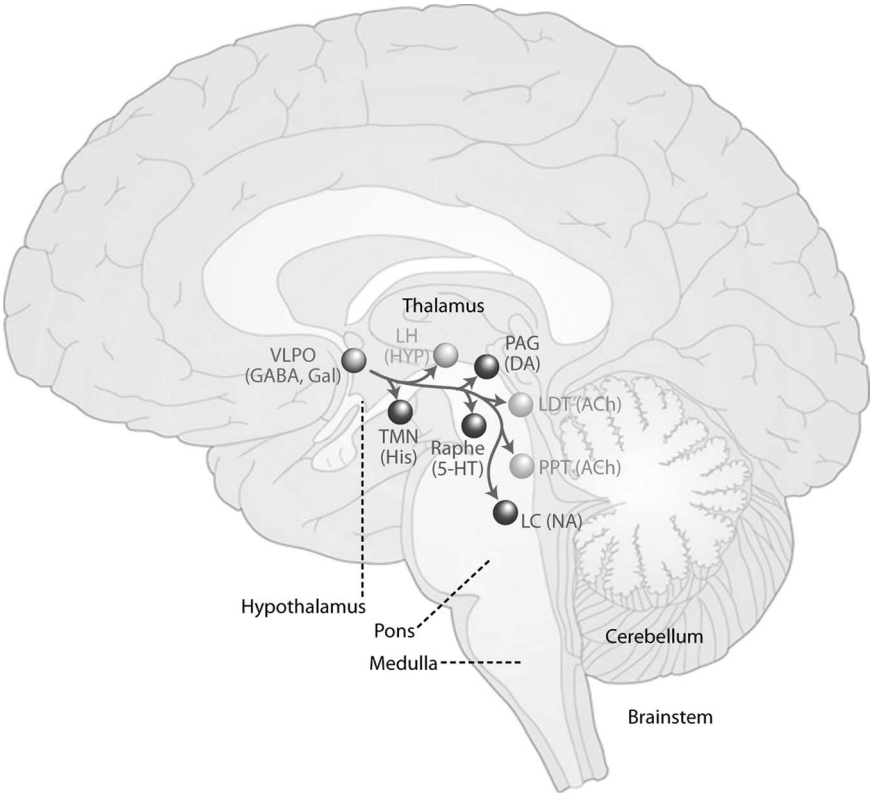


**Figure 1.14** Outflow connections of the VLPO. This diagram demonstrates the outflow connections from the VLPO, the major generator of NREM sleep. *Abbreviations*: VLPO, ventrolateral preoptic nuclei; LDT, lateral dorsal tegmental nucleus; PPT, pedunculopontine nucleus; LC, locus coeruleus; HYP, hypocretin; TMN, tuberomammillary nucleus; LH, lateral hypothalamus; PAG, periaqueductal gray; DA, dopamine; ACh, acetylcholine; NA, norepinephrine; His, histamine; Gal, galanin; GABA, gamma aminobutyric acid. *Source*: Modified from Ref. 13.

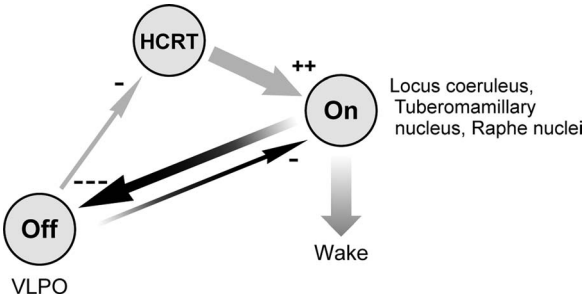


**Figure 1.15** The wake–NREM flip-flop switch and the hypocretin stabilizer. The ventrolateral preoptic nuclei (VLPO) and the major monoaminergic nuclei serve as opposite poles of a flip-flop switch, controlling wakefulness and NREM sleep. This diagram illustrates the condition of wakefulness. Hypocretin (HCRT) results in stabilization of the wake state. *Source*: Modified from Ref. 13.

rapidly during NREM sleep than during wakefulness. Like VLPO neurons, basal forebrain neurons also inhibit hypocretin synthesizing wake centers in the posterolateral hypothalamus.

*Spindle Generation and Cortical Synchronization*

One of the characteristic electrophysiologic characteristics of NREM sleep is the presence of highly synchronized cortical activity in the form of sleep spindles and high-amplitude slow

waves. Spindle activity depends on some unusual properties of thalamic neurons. During waking and REM sleep, thalamic reticular neurons show tonic activity, but with the inhibition of brainstem cholinergic neurons in NREM sleep, they alter their electrical activity to produce a burst-firing pattern. The mechanism involves initial hyperpolarization with superimposed depolarization resulting in bursts of rhythmic action potentials at the frequency of sleep spindles. Reticular neurons project to other thalamic nuclei and by releasing GABA induce widespread hyperpolarization and subsequent rhythmic burst firing. These thalamic nuclei in turn project to the cortex and initiate cortical spindle activity. Similar mechanisms are thought to play a role in slow-wave generation in slow-wave sleep. The important role of the thalamus in the initiation of sleep is illustrated by the rare prion disorder, fatal familial insomnia, in which degeneration of the anteroventral and dorsomedial thalamic nuclei results in profound insomnia (chap. 10).

## REM Sleep

*The REM Sleep Generator*

The search for the generator of REM sleep has included many different mammalian experimental models, involving transection, tissue ablation, and unit recording studies (20). After transection of the midbrain, electrophysiologic features of REM sleep can be recorded caudal, but not rostral, to the transection. In contrast, after transection at the junction between the medulla and the pons, REM phenomena can be recorded rostral, but not caudal, to the transection. Following transections both above and below the pons, REM sleep can be recorded from the isolated pons but not from structures rostral or caudal to it. Thus, transection experiments demonstrate that the principal REM sleep generator is localized in the pons (Fig. 1.16).

The dorsal portion of the pons (pontine tegmentum) contains a network of neurons and ascending fiber tracts known as the ascending reticular formation. Ablation of the more rostral portion of the pontine tegmentum, known as the nucleus reticularis pontis oralis (NRPO), eliminates REM sleep. More precise experiments have shown that the critical area for REM sleep generation consists of a small area in the lateral portions of the NRPO ventral to the locus coeruleus, known as the subcoeruleus region (Fig. 1.17). Application of kainic acid, a cytotoxin, to this area has demonstrated that cell loss rather than nerve fiber damage is responsible for the disruption of REM sleep.

Unit recording studies with microelectrodes have detected a population of neurons in the subcoeruleus region that has a high rate of discharge only during REM sleep (REM sleep-on cells). At least some of these cells produce acetylcholine. REM sleep-off cells have been found in other areas of the lateral pontine tegmentum and in the ventrolateral PAG surrounding the cerebral aqueduct rostral to the fourth ventricle. Neurons in the noradrenergic locus coeruleus and in the serotonergic raphe system that discharge regularly during wakefulness and slowly during NREM sleep are also silent during REM sleep.

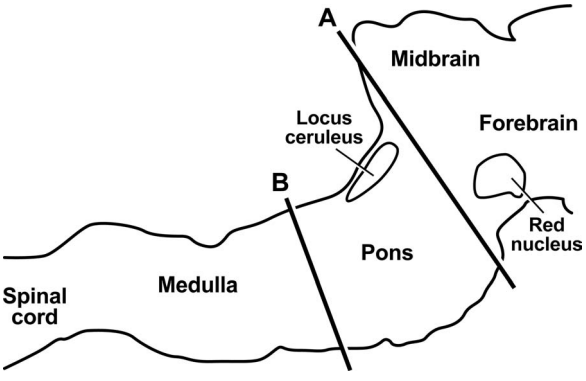


**Figure 1.16** Brainstem transection experiments to determine the generator of REM sleep. Transections at point B result in REM phenomena being recorded only rostral to the cut. Transections at point A result in REM phenomena only caudal to the cut, whereas transections at both points A and B result in REM phenomena only recordable from the pons. *Source*: Modified from Ref. 20.

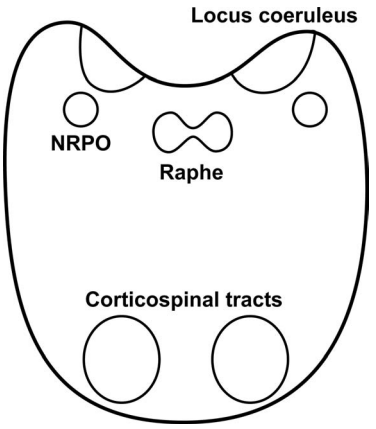


**Figure 1.17** Schematic transverse section through the pons. Dorsal is at the top of the figure, ventral at the bottom.

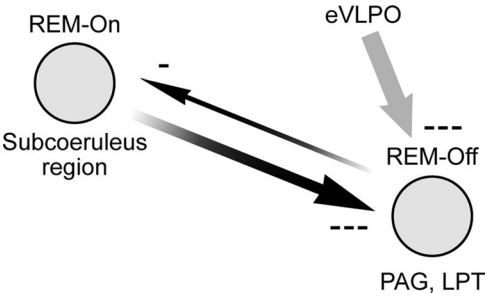


**Figure 1.18** Control of REM sleep. This diagram illustrates the control of REM sleep through a flip-flop switch. Neural impulses from the eVLPO trigger initiation of periods of REM sleep. *Abbreviations*: eVLPO, extended ventrolateral preoptic area; PAG, periaqueductal gray; LPT, lateral pontine tegmentum. *Source*: Modified from Ref. 21.

The onset and termination of periods of REM sleep appears to be controlled through a brainstem flip-flop switch with poles consisting of REM-on cells in the subcoeruleus region and REM-off cells in the PAG and lateral pontine tegmentum (21). GABAergic neurons in the extended VPLO (an area adjacent to the VLPO in the hypothalamus) inhibit REM-off cells that in turn disinhibit REM-on cells, allowing REM sleep to occur (Fig. 1.18). Periods of REM sleep terminate when excitatory stimuli from the posterior hypothalamic hypocretin-synthesizing neurons, the noradrenergic locus coeruleus, and the serotoninergic raphe nuclei activate REM-off cells, inhibiting REM-on cells.

*Effector Pathways in REM Sleep*

With the principal REM sleep generator being localized to a small number of cells in the rostral pontine tegmentum, extensive axonal pathways are required to produce the range of REM sleep phenomena, such as skeletal muscle atonia, rapid eye movements, and dreams. Muscle atonia can be produced by electrical stimulation of a number of areas in the brainstem, including the pedunculopontine nucleus of the pons, the retrorubral nucleus of the lower midbrain, and the nucleus magnocellularis of the medial medulla. In cats the pathway involves axons probably arising from the dorsolateral pedunculopontine nucleus, which travel in the tegmentoreticular tract to synapse on cell bodies in the nucleus magnocellularis of the ventromedial medulla (Fig. 1.19). The neurotransmitters released by these axons are believed to be glutamate and acetylcholine. Axons from these nuclei run in the ventrolateral reticulospinal tract, terminating on spinal cord anterior horn cells. Release of glycine or GABA produces hyperpolarization and thus postsynaptic inhibition, resulting in muscle atonia. In rats, the pathway appears to bypass medullary relay nuclei, ending on short interneurons in the spinal cord. The exact pathway in humans has not been determined (22).

This physiology helps explain the pathogenesis of some of the pathologic phenomena associated with REM sleep. Atonia without other phenomena of REM sleep can be produced experimentally by the injection of cholinergic agonists into the dorsal pons or by electrical

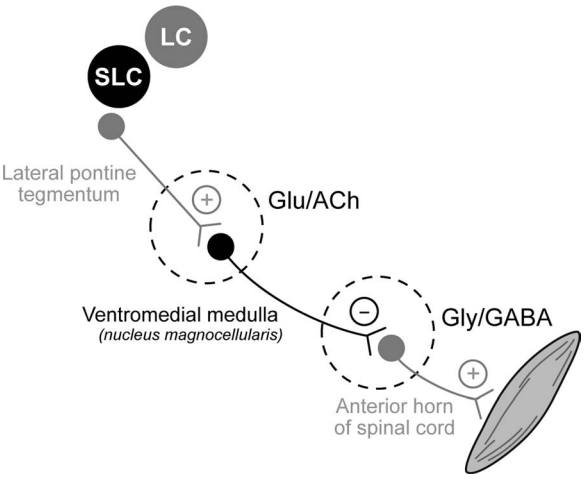


**Figure 1.19** Schematic diagram of the neural pathways mediating REM sleep atonia. This diagram illustrates schematically the neural pathways mediating skeletal muscle atonia in REM sleep. *Abbreviations*: LC, locus coeruleus; SLC, sublocus coeruleus; Glu, glutamate; ACh, acetylcholine; Gly, glycine; GABA, gamma aminobutyric acid; +, excitatory neurotransmitter; −, inhibitory neurotransmitter.

stimulation or injection of glutamate into the medial medulla. This is a model of cataplexy, the sudden loss of muscle tone with emotion occurring in the patients with narcolepsy (chap. 7). A population of medullary cells has been detected in narcoleptic dogs that fire only during REM sleep and cataplectic attacks. In contrast, REM sleep without atonia can be produced by lesions of the dorsal pons in cats, which presumably interrupt the tegmentoreticular tract. Depending on the exact site of the lesion, the animal's behavior ranges from slight raising of the head to elaborate aggressive motor activity (23). This experimental preparation is a model for the condition of REM sleep behavior disorder, in which patients lose the muscle atonia of REM sleep and act out their dreams, often in a violent manner (chap. 16).

PGO waves, generated in the cholinergic peribrachial area of the pontine tegmentum, project to the lateral geniculate body and other thalamic nuclei as well as the occipital cortex. They serve as the physiologic correlate of the neural pathways mediating REM phenomena rostral to the pons. PGO waves precede rapid eye movements and may play a role in the generation of dream imagery in the occipital cortex.

## HOMEOSTATIC AND CIRCADIAN CONTROL

The timing of sleep and wakefulness within the 24-hour day is determined by an interaction of two physiologic processes: homeostatic (known as process-S) and circadian (known as process-C) (Fig. 1.20). The concept of homeostatic regulation of sleep depends on the observation that sleep drive increases linearly with increased time awake and dissipates following subsequent sleep. Considerable evidence indicates that this effect is predominantly mediated by the concentration of extracellular adenosine, a byproduct of DNA metabolism. Adenosine concentration in the brain increases during prolonged wakefulness and decreases with subsequent recovery sleep. During wakefulness, active metabolic processes in neurons or astrocytes may result in increasing release of adenosine, which binds to adenosine receptors (24). The site of action of adenosine is uncertain (11), but the basal forebrain, median preoptic nuclei, and the posterior hypothalamus have been postulated. The exact mechanism by which adenosine induces sleep is also uncertain; hypotheses include a decrease in glutamate release, inhibition of cholinergic arousal neurons, and inhibition of hypocretin release. Caffeine produces alertness by blocking adenosine receptors. The effects of sleep deprivation and recovery sleep are further discussed in chapter 5.

Many other humoral substances found within the brain or cerebrospinal fluid appear to modulate sleep, possibly by a homeostatic mechanism. Prostaglandin D2 promotes sleep, whereas prostaglandin E2 inhibits sleep. A number of substances enhance slow-wave sleep,

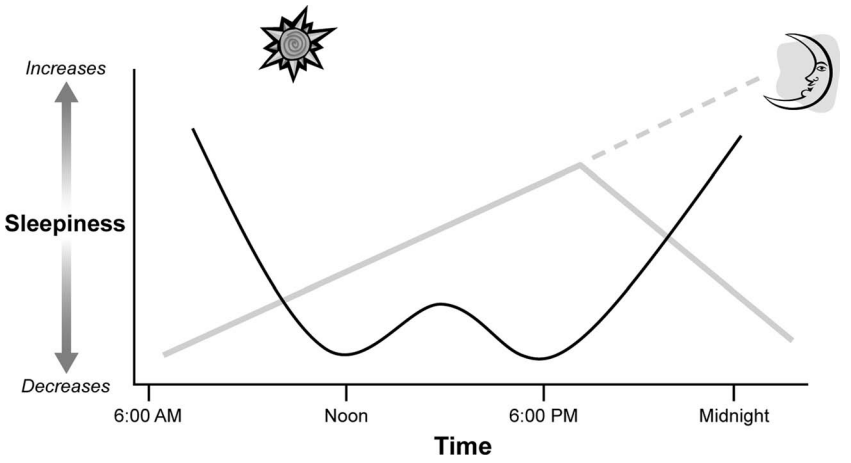


**Figure 1.20** Homeostatic and circadian control of sleep. This schematic diagram shows how the homeostatic drive (*thick line*) increases sleepiness from the time of waking in the morning until it is relieved by sleep at night. The circadian rhythm (*thin line*) shows a minor peak of sleepiness in the early afternoon and a major peak in the night.

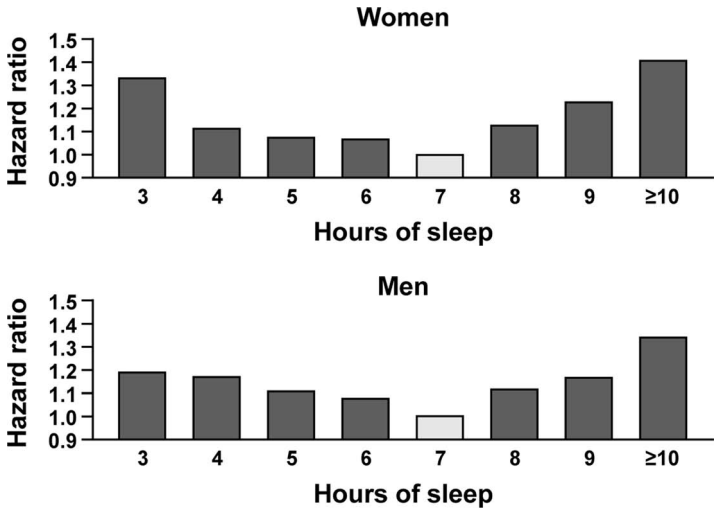


**Figure 1.21** The effect of self-reported sleep time on mortality. This graph shows the mortality hazard ratios associated with self-reported short and long sleep times in more than 1.1 million men and women. *Source*: Modified from Ref. 26.

including the cytokines interleukin-1 and tumor necrosis factor; a nonapeptide, delta sleep–inducing peptide; and growth hormone–releasing hormone.

Circadian control of sleep is determined by the biologic clock, localized in the suprachiasmatic nuclei of the hypothalamus. Melatonin, a peptide hormone secreted by the pineal gland, also plays a role in the control of the circadian system. The circadian control system is discussed at greater length in chapter 13.

How long should one sleep? Several large epidemiologic studies, some with more than a million participants, have demonstrated increased mortality associated with both self-reported sleep duration greater than eight hours and less than seven hours (25,26) (Fig. 1.21). Greatest effect has been with durations $\geq$9 hours or $\leq$4 hours. Although these results are robust and reproducible, causation has not been established and mechanisms of the increased mortality

remain obscure. A recent study shed some light on the problem by demonstrating increased coronary artery calcification with reduced sleep time, but failed to show increases with long sleep (27). Other effects of sleep deprivation are discussed in chapter 5.

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# 2 | Classification of sleep disorders

"The time has come," the Walrus said,
"To talk of many things;
Of shoes-and ships-and sealing wax-
Of cabbages-and kings-"

Lewis Carroll: *Through the Looking-Glass*

Sleep medicine is a young field and its nosology is far from fixed. The idea that the study of sleep physiology might evolve into a branch of medicine devoted to disorders of sleep arose during the 1960s. The first attempt to classify sleep disorders had its origin in a workshop at the 1972 annual meeting of the Association for the Psychophysiological Study of Sleep (APSS), resulting in the establishment of a Nosology Committee in 1976. Since then, three major classifications of sleep disorders have been published, the most recent in 2005. This ongoing process reflects a dynamic field of medicine, responsive to current practice and research.

## THE DIAGNOSTIC CLASSIFICATION OF SLEEP AND AROUSAL DISORDERS: 1979

In 1979, a 137-page classification of sleep disorders sponsored by the Association of Sleep Disorders Centers and the APSS was published in the newly formed journal *Sleep* (1). This remarkable document remained the framework for the study of sleep disorders for more than a decade. The authors, led by Dr Howard Roffwarg, readily admitted that this was a work in progress and predicted that there would be considerable changes as the field evolved. Like subsequent nosologies, the division of the subject was based on a combination of the best available scientific data and the shared judgment of experienced clinicians. Sleep and arousal disorders were divided into four categories (Table 2.1): the first two based on patient complaints, and the third and the fourth on presumed pathophysiology. The authors recognized that the harmoniously named DIMS (disorders of initiating and maintaining sleep) and DOES (disorders of excessive somnolence) were not clearly separable, with some conditions presenting at times with insomnia and at other times with excessive sleepiness.

## THE INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS

By 1985 it had become apparent that knowledge had progressed to the point that a new classification was needed. The American Sleep Disorders Association (ASDA) in collaboration with the European Sleep Research Society, the Japanese Society of Sleep Research, and the Latin American Sleep Society commissioned a new nosology that was published in 1990, under the leadership of Dr Michael Thorpy (2). The classification comprised 84 disorders and utilized a somewhat different grouping of topics based on pathophysiologic concepts (Table 2.2). The term "dyssomnia" was introduced to define disorders producing a complaint of either insomnia or sleepiness. The dyssomnias were subdivided into intrinsic sleep disorders (arising from dysfunction of the body or mind), extrinsic sleep disorders (arising from the external environment), and circadian rhythm disorders. Parasomnias were split into four categories, reflecting the states of sleep from which they arose. Two new categories were introduced: sleep disorders associated with other medical or psychiatric disorders and proposed sleep disorders. Formal diagnostic, severity, and duration criteria were devised. The nosology was revised in minor details in 1997, but remained essentially unchanged.

In 2002 the American Academy of Sleep Medicine, the successor to the ASDA, set up a committee to once again revise the classification of sleep disorders. More than 10 years had passed since the last major revision, and advances in the field had again dictated the need for a new approach. Under the direction of Dr Peter Hauri, the committee proposed a more pragmatic classification based on current clinical concepts of the grouping of sleep disorders (3). Table 2.3 presents a summary of the current nosology, published in 2005.

**Table 2.1** 1979 Classification of Sleep and Arousal Disorders

| |
|---|
| A. DIMS: Disorders of initiating and maintaining sleep (insomnias) |
| B. DOES: Disorders of excessive somnolence |
| C. Disorders of the sleep-wake schedule |
| D. Dysfunctions associated with sleep, sleep stages, or partial arousals (parasomnias) |

**Table 2.2** The International Classification of Sleep Disorders (1990)

- Dyssomnias
  - Intrinsic sleep disorders
  - Extrinsic sleep disorders
  - Circadian rhythm sleep disorders
- Parasomnias
  - Arousal disorders
  - Sleep-wake transition disorders
  - Parasomnias usually associated with REM sleep
  - Other parasomnias
- Sleep disorders associated with other medical or psychiatric disorders
  - Associated with mental disorders
  - Associated with neurological disorders
  - Associated with other medical disorders
- Proposed sleep disorders

**Table 2.3** The International Classification of Sleep Disorders-2 (ICSD-2) (2005)

- Insomnia
  - Adjustment insomnia
  - Psychophysiological insomnia
  - Idiopathic insomnia
  - Paradoxical insomnia
  - Inadequate sleep hygiene
  - Behavioral insomnia of childhood
  - Insomnia due to a mental disorder
  - Insomnia due to drug or substance
  - Insomnia related to medical condition
- Sleep-related breathing disorders
  - Obstructive sleep apnea
  - Central sleep apnea
    - Primary
    - Due to drug or substance
    - Cheyne–Stokes breathing pattern
    - High-altitude periodic breathing
    - Primary sleep apnea of infancy
  - Sleep-related hypoventilation
    - Central alveolar hypoventilation syndrome
      - Idiopathic
      - Congenital
    - Due to pulmonary pathology
    - Due to neuromuscular and chest wall disorders
- Hypersomnias of central origin not due to a circadian rhythm disorder or sleep-related breathing
  - Narcolepsy
    - With cataplexy
    - Without cataplexy
    - Due to medical conditions
  - Idiopathic hypersomnia
    - With long sleep time
    - Without long sleep time
  - Recurrent hypersomnia
  - Behaviorally induced insufficient sleep syndrome

(*Continued*)

**Table 2.3** The International Classification of Sleep Disorders-2 (ICSD-2) (2005) (*Continued*)

- Hypersomnia related to a medical condition
- Hypersomnia due to drug or substance
- Hypersomnia not due to substance or known physiological condition (nonorganic hypersomnia)

- Circadian rhythm sleep disorders
  - Delayed sleep phase disorder
  - Advanced sleep phase disorder
  - Irregular sleep-wake circadian rhythm sleep disorder
  - Free-running circadian rhythm sleep disorder (nonentrained type)
  - Jet lag disorder
  - Shift work disorder
- Parasomnias
  - Disorders of arousal (from NREM sleep)
    - Confusional arousals
    - Sleepwalking
    - Sleep terrors
  - Parasomnias associated with REM sleep
    - REM sleep behavior disorder
    - Recurrent isolated sleep paralysis
    - Nightmare disorder
  - Other parasomnias
    - Sleep-related dissociative disorders
    - Sleep enuresis
    - Sleep-related groaning (catathrenia)
    - Exploding head syndrome
    - Sleep-related hallucinations
    - Sleep-related eating disorder
- Sleep-related movement disorders
  - Restless legs syndrome
  - Periodic limb movement disorder
  - Sleep-related leg cramps
  - Sleep-related bruxism
  - Sleep-related rhythmic movement disorder
- Other sleep disorders
  - Environmental sleep disorder
- Isolated symptoms, apparently normal variants, and unresolved issues
  - Long sleeper
  - Short sleeper
  - Snoring
  - Sleep talking
  - Sleep starts (hypnic jerks)

Only some of the disorders in each category have been included.

## OVERVIEW OF SLEEP DISORDERS

This book discusses sleep disorders using a clinical approach to symptoms, rather than following a catalog of disorders. However, an overview of some of the disease categories is presented to provide a broad framework for the chapters that follow. This description follows the International Classification of Sleep Disorders-2 (ICSD-2) nosology as summarized in Table 2.3.

### Insomnia

Insomnia is a perceived reduction in the quantity or the quality of sleep resulting in daytime impairment, despite adequate time and opportunity for sleep. Certain causes of chronic insomnia are believed to be due to intrinsic disturbances of brain function and are sometimes grouped together as primary causes of insomnia (chap. 10). The commonest is *psychophysiological insomnia*, also known as learned or conditioned insomnia. This disorder generally originates following a period of stress associated with sleep difficulties, but despite the resolution of the stress, the insomnia persists as an abnormal conditioned response to going to bed. *Idiopathic insomnia* is a form of insomnia that starts in early childhood and persists through