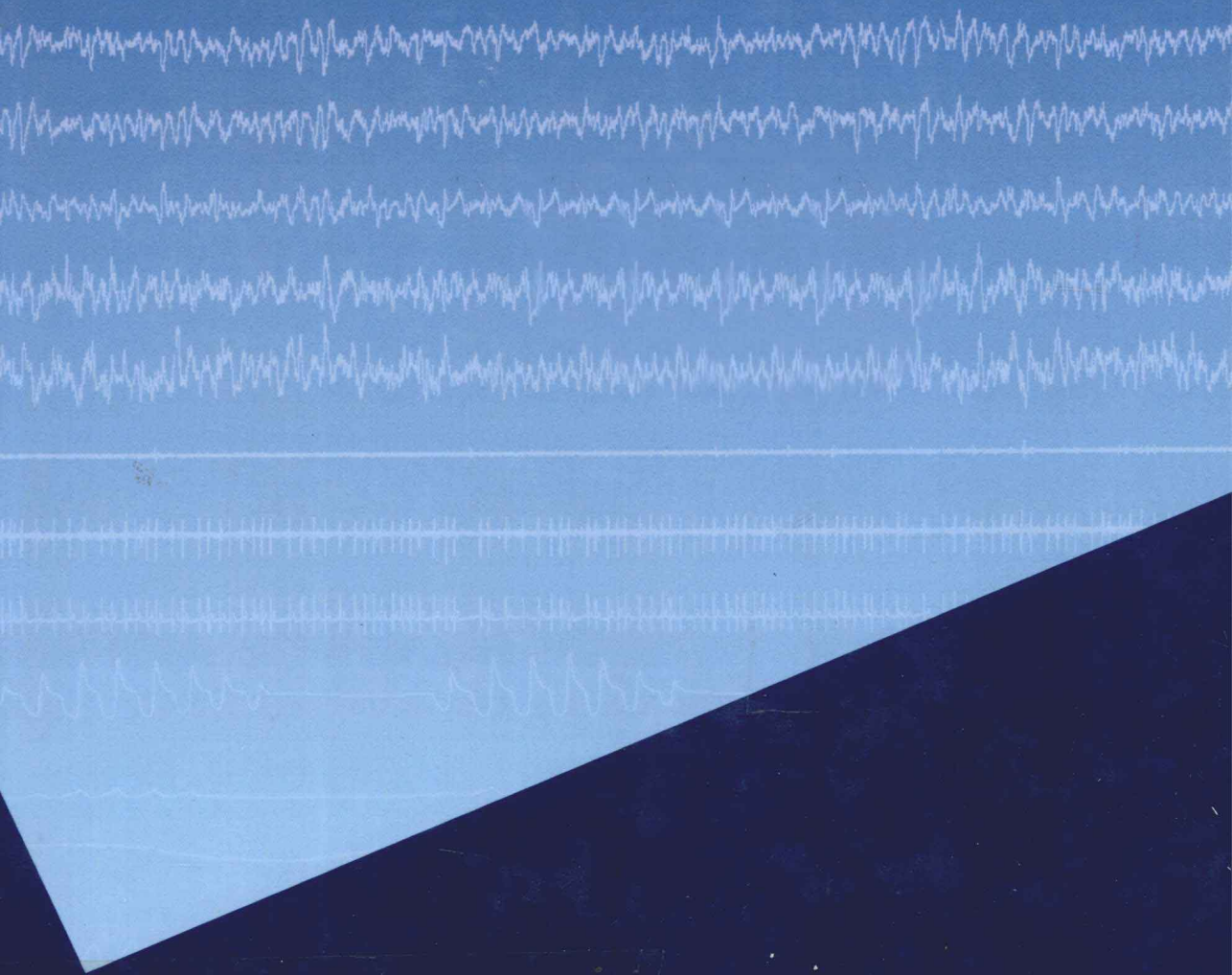
Sleep Medicine in Clinical Practice

Second Edition



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Sleep Medicine in Clinical Practice

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.

Disclaimer

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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.

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.

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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

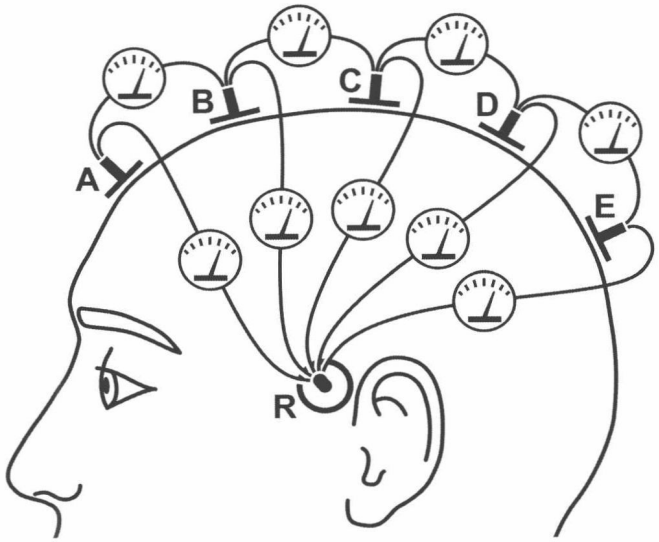

Figure 1.1 Bipolar and referential EEG derivations. The difference between the scalp potentials underlying electrodes A and B are compared in a bipolar derivation, A–B. The chain of derivations A–B, B–C, C–D, and D–E comprise a bipolar montage. In contrast, the potential underlying electrode A is compared 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

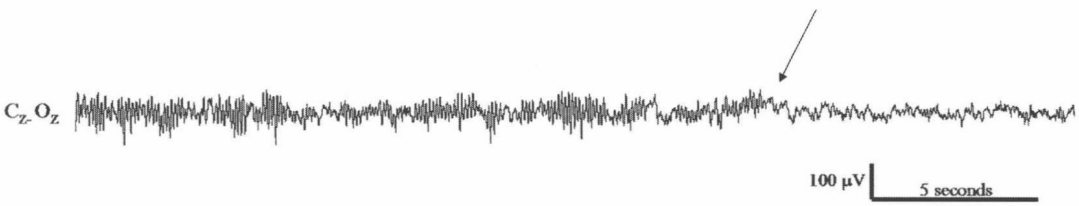

Figure 1.2 Alpha rhythm. This tracing shows occipital alpha rhythm, attenuating with eye opening (*arrow*).

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

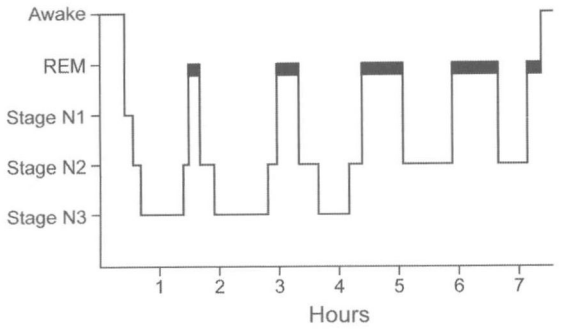

Figure 1.3 Schematic representation of the cycles of a night's sleep. This figure is a representation of a typical night's sleep in a young adult, demonstrating five sleep cycles with most slow-wave sleep in earlier cycles and most REM sleep in later cycles. Brief periods of wakefulness, which are normally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

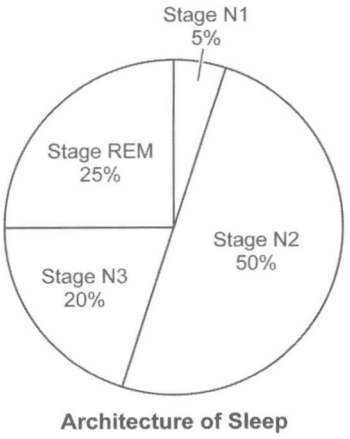

Figure 1.4 Percentage of sleep stages in a young adult. *Source*: From Ref. 3.

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

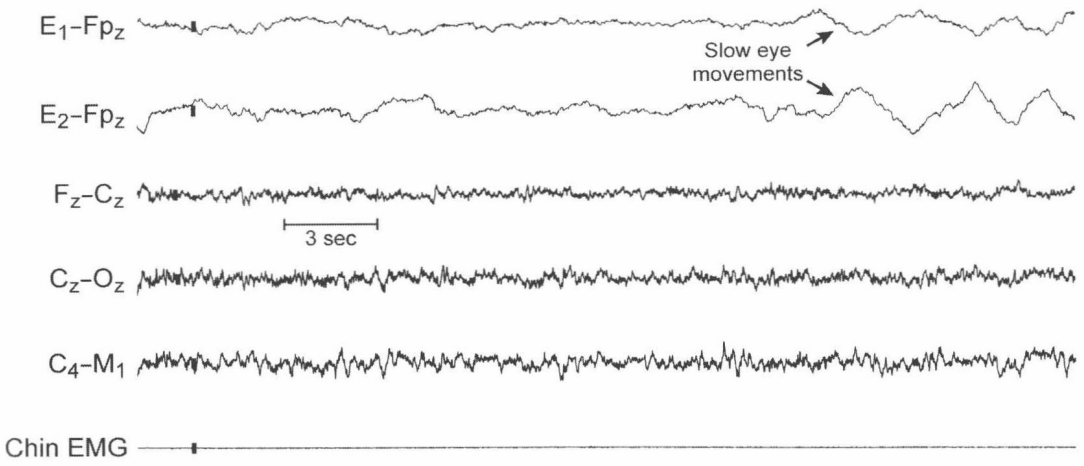

Figure 1.5 Stage N1 sleep. This 30-second epoch shows the characteristics of stage 1 NREM sleep. The LOC-Fpz and ROC-Fpz derivations record eye movements. The Fpz-Cz, Cz-Oz, and C4-M1 derivations record EEG activity. All these derivations are explained in more detail in chapter 4. The EEG is low-amplitude, 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.

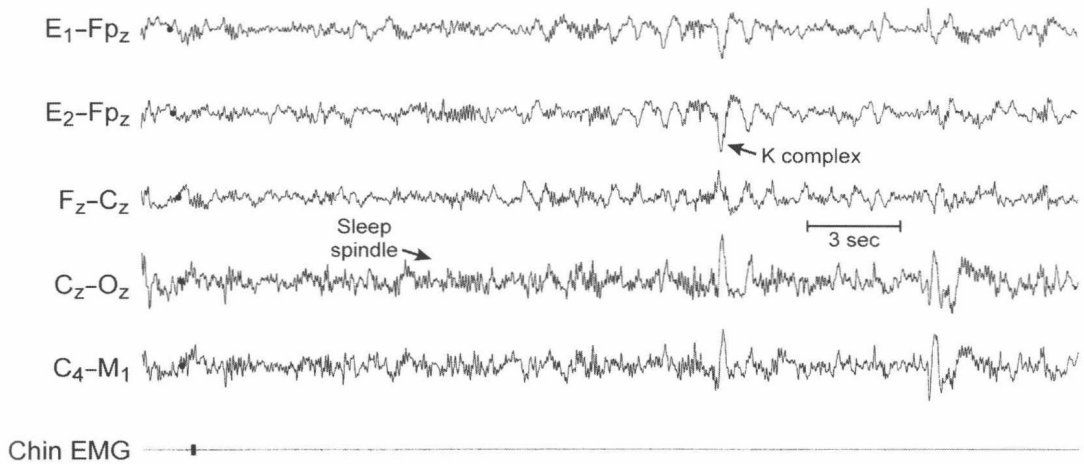

Figure 1.6 Stage N2 sleep. This 30-second epoch shows the characteristics of stage N2 NREM sleep. Derivations are described in Figure 1.5 and in chapter 4. Eye movements have ceased. K complexes (high-amplitude diphasic waves maximal over the vertex) and sleep spindles predominantly 12- to 14-Hz activity)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

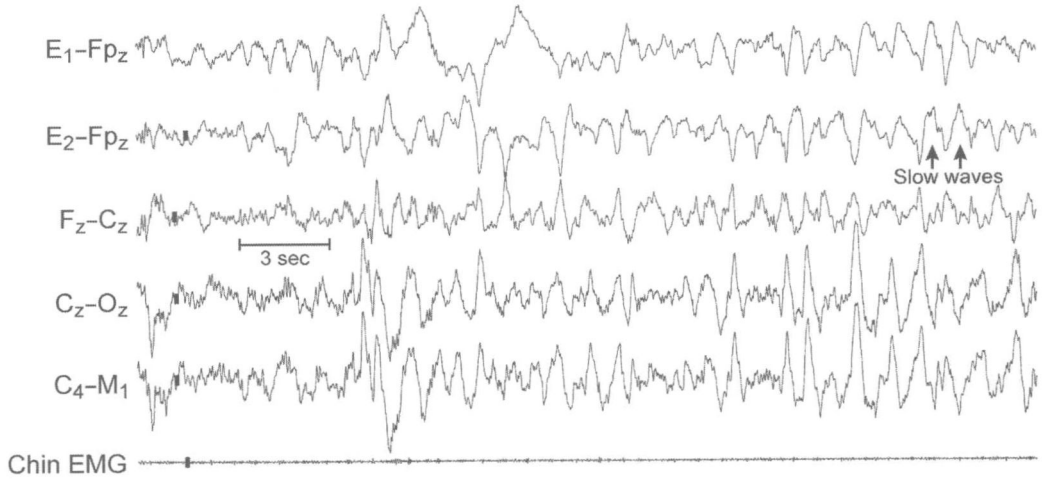

Figure 1.7 Stage N3 sleep. This 30-second epoch shows the characteristics of stage N3 NREM sleep. Derivations are described in Figure 1.5 and in chapter 4. High-amplitude slow waves are the predominant finding. *Source*: From Ref. 3.

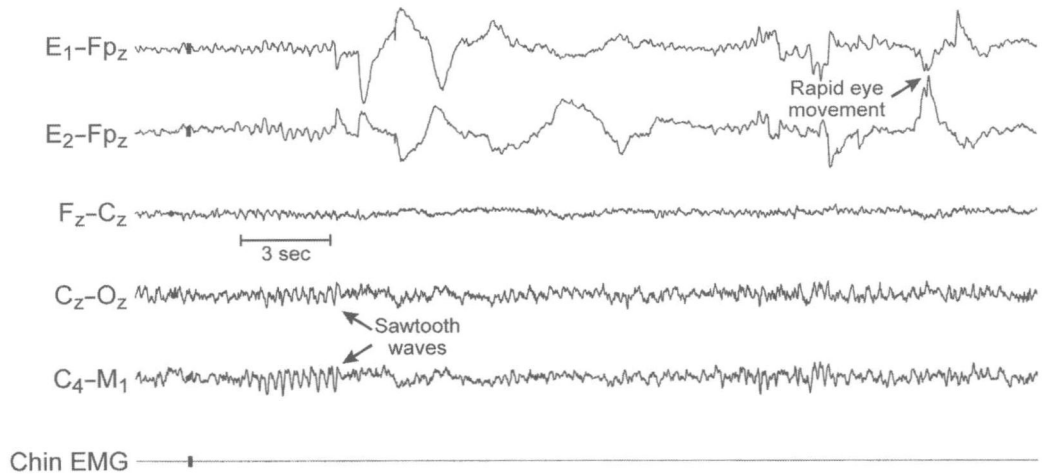

Figure 1.8 REM sleep. This 30-second epoch shows the characteristics of stage R (REM) sleep. Derivations are described in Figure 1.5 and in chapter 4. Irregular, conjugate, horizontal rapid eye movements are present in the eye movement channels. Sawtooth waves precede rapid eye movements, but the remainder 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