Abbreviations

AASM: American Academy of Sleep Medicine
ACC: anterior cingulate cortex
Ach: acetylcholine
ACTH: adrenocorticotropic hormone
AD-ACL: Activation-Deactivation Adjective Check List
ADHD: attention-deficit-hyperactivity disorder
AHI: apnea-hypopnea index
AIM: ancestry informative marker
AMPA: α-amino-3hydroxy-5-methylisozazole-4-propionic acid
AMPK: adenosine-monophosphate-activated protein kinase
AMS: acute mountain sickness
ANS: autonomic nervous system
ASPS: advanced sleep phase syndrome
ASPT: advanced sleep phase type
AW: active wakefulness
BA: Brodman area
BAC: blood alcohol content
BCOPS: Buffalo Cardio-Metabolic occupational Police Stress
BF: basal forebrain
BMAL1: brain and muscle ARNT-like
BMI: body mass index
BNST: bed nucleus of the stria terminalis
BPD: biliopancreatic diversion
BPDDS: Biliopancreatic diversion with duodenal switch
BzRA: benzodiazepine receptor agonist
CAD: coronary artery disease
CAPS: cyclic alternating pattern sequence(s)
CBT: cognitive behavior therapy
CHF: congestive heart failure
CI: confidence interval
CPS/HHPRI: Calgary Police Service Health and Human Performance Research Initiative
COMT: catechol-*O*-methyltransferase
COPD: chronic obstructive pulmonary disease
CPAP: continuous positive airway pressure
CRP: C-reactive protein
CRY: cryptochrome
CSN: cold-sensitive neuron
CYP: cytochrome P-450
DA: dopamine
DAT: dopamine transporter
DBP: D-element binding protein
DD: constant dark
DIM: digital integration mode
DLMO: dim-light melatonin onset
DLPFC: dorsolateral prefrontal cortex
DMD: Duchenne's muscular dystrophy
DSISD: Duke Structured Interview for Sleep Disorders
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition
DSPS: delayed sleep phase syndrome
DSPT: delayed sleep phase type
DTs: delirium tremens
DU: duodenal ulcer
ECG: electrocardiogram/electrocardiographic
EDS: excessive daytime sleepiness
EEG: electroencephalogram, electroencephalographic
EMG: electromyogram
ENS: enteric nervous system
EOG: electrooculogram
EPS: extrapyramidal side effects (s)
EPSP: excitatory postsynaptic potential
ERP: event-related potential
ESS: Epworth Sleepiness Scale
FAID: Fatigue Audit InterDyne
^{18}FDG: 2-deoxy-2-[^{18}F]fluoro-D-glucose
F-DOPA: 6-[^{18}F]fluoro-L-dopa
FEV_1: forced expiratory volume in 1 second
FIRST: Ford Insomnia Response to Stress Test
fMRI: functional magnetic resonance imaging
FOQA: flight operations quality assurance
FOSQ: Functional Outcomes of Sleep Questionnaire
FRA: Federal Railroad Administration
FRC: functional residual capacity
FSIVGTT: frequently sampled intravenous glucose tolerance test
GABA: gamma-aminobutyric acid
GAD: generalized anxiety disorder
GAHMS: genioglossus advancement, hyoid myotomy, and suspension
GCD: global cessation of dreaming
GER: gastroesophageal reflux
GHB: gamma-hydroxybutyrate
GHRH: growth hormone-releasing hormone
GWA: genome wide association
5-HIAA: 5-hydroxyindole acetic acid
5-HT: hydroxytryptamine (serotonin)
HAPE: high-altitude pulmonary edema
Hcrt: hypocretin
HDI: hypnotic-dependent insomnia
HDL: high density lipoprotein
HIF: hypoxia inducible factor
HIV: human immunodeficiency virus
HLA: human leukocyte antigen
HOMA: homeostasis model assessment
HPA: hypothalamic-pituitary-adrenal axis
HRV: heart rate variability
HVA: homovanillic acid
HWHSGPS: Harvard Work Hours and Safety Group Police Study

ICD: International Classification of Diseases
ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification
ICS-10: International Classification of Diseases, 10th revision
ICSD-2: International Classification of Sleep Disorders, Revised
ICV: intracerebroventricular
IEG: immediate early gene
IGL: intergeniculate leaflet
IL: interleukin
ILD: interstitial lung disease
IPSP: inhibitory postsynaptic potential
ISI: Insomnia Severity Index
kd: kilodalton
KSS: Karolinska Sleepiness Scale
LAUP: laser-assisted uvulopalatoplasty
LD: light-dark
LDL: low density lipoprotein
L-dopa: L-dihydroxyphenylalanine, levodopa
LG: lateral geniculate
LL: constant light
LOC: left outer canthus
LPA (or LPOA): lateral preoptic area
LSAT: lowest oxyhemoglobin saturation
LTIH: long-term intermittent hypoxia
MAO: monoamine oxidase
MAOI: monamine oxidase inhibitor
MDA: methylenedioxyamphetamine
MDD: major depressive disorder
MDMA: methylenedioxymethamphetamine ("ecstasy")
MDP-LD: muramyl dipeptide *N*-actyl-muramyl-L-alanyl-D-isoglutamine
MEG: magnetoencephalography
MI: myocardial infarction
MMC: migrating motor complex
MMO: maxillary and mandibular osteotomy
MnPN: median preoptic nucleus
MNSA: muscle nerve sympathetic vasomotor activity
MPA or (MPOA): medial preoptic area
MPA: medroxyprogesterone acetate
MRA: mandibular repositioning appliance
MSLT: Multiple Sleep Latency Test
MWT: Maintenance of Wakefulness Test
NAD: nicotinamide adenine nucleotide
NAMPT: nicotinamide phosphoribosyltransferase
NASH: nonalcoholic steatohepatitis
NCEP: National Cholesterol Education Program
NCSDR: National Center on Sleep Disorders Research
NE: norepinephrine
NET: norepinephrine transporter
NFLD: nonalcoholic fatty liver disease
NFκB: nuclear factor kappa B
NHANES: national Health and Nutrition Examination Survey
NIH: National Institutes of Health
NIPPV: nasal intermittent positive-pressure ventilation
NK: natural killer [cell]
NMDA: *N*-methyl-D-aspartate
NO: nitric oxide
NPPV: noninvasive positive-pressure ventilation
NPT: nocturnal penile tumescence
NREM: non–rapid eye movement, non-REM
OCD: obsessive-compulsive disorder
OFC: orbitofrontal cortex
6-OHDA: 6-hydroxydopamine
OHS: obesity-hypoventilation syndrome
OR: odds ratio
OSA: obstructive sleep apnea
OSAHS: obstructive sleep apnea–hypopnea syndrome
OSAS: obstructive sleep apnea syndrome
PACU: postanesthesia care unit
PCOS: polycystic ovary syndrome
PEEP: positive end-expiratory pressure
PER: period
PET: positron emission tomography
PGO: ponto-geniculo-occipital [spike]
PIA: pontine inhibitory area
PLMS: periodic limb movements during sleep (or PLM)
PMDD: premenstrual dysphoric disorder
PNI: people not having insomnia
POA: preoptic area
POMS: Profile of Mood States
POSSR: Patrol Officers Shift Schedule Review
PR: prevalence ratio
PRC: phase–response curve
PSG: polysomnography, polysomnographic
PSQI: Pittsburgh Sleep Quality Index
PTSD: posttraumatic stress disorder
PVN: paraventricular nucleus
PVT: psychomotor vigilance test
PWI: people with insomnia
PWOP: people who did not report having the medical problem
PWP: people who reported have the medical problem
QTL: quantitative trait loci (or locus)
QW: quiet wakefulness
RBD: REM sleep behavior disorder
RDC: research diagnostic criteria
RDI: respiratory disturbance index
REM: rapid eye movement
RERA: respiratory effort related arousal
RFA: radiofrequency ablation
RHT: retinohypothalamic tract
RI: recombinant inbred
R_{in}: membrane input resistance
RIP: respiratory inductive plethysmography
RLS: restless legs syndrome
RMMA: rhythmic masticatory motor activity
ROC: right outer canthus
ROS: reactive oxygen species (sing. and pl.)
RR: risk ratio
RT: reaction time
RYGB: Roux-en-Y gastric bypass
SAFTE: Sleep, Activity, Fatigue, and Task Effectiveness (model)
SCD: stearoyl coenzyme A desaturase
SCID: Structured Clinical Interview for Diagnosis
SCN: suprachiasmatic nucleus
SCT: sleep compression therapy
SDB: sleep-disordered breathing
SE%: sleep efficiency percentage
SEMs: small eye movements
SIDS: sudden infant death syndrome

SIT: suggested immobilization test
SND: synucleinopathic disorders
SNP: single nucleotide polymorphism
SOL: sleep-onset latency
SOREM: sleep-onset REM
SOREMP: sleep-onset REM period
SP: sleep paralysis
SPM: statistical parametric mapping
SRE: sleep-related erection
SREBP: sterol regulatory element binding proteinSRED: sleep-related eating disorder
SRT: sleep restriction therapy
SSEP: somatosensory evoked potential
SSS: Stanford Sleepiness Scale
SSRI: selective serotonin reuptake inhibitor
SWA: slow wave activity
SWD: shift work disorder/shift work sleep disorder
SWS: slow wave sleep
T_a: ambient temperature
TAT: time above threshold
TCA: tricyclic antidepressant
THH: terrifying hypnagogic hallucination
TLR: Toll-like receptor
TMJ: temporomandibular joint
TNF: tumor necrosis factor
TRD: tongue-retaining device
UARS: upper airway resistance syndrome
UNS: Ullanlinna Narcolepsy Scale
UPF: uvulopalatal flap
UPPP: uvulopalatopharyngoplasty
VIP: vasoactive intestinal peptide
VLDL: very low density lipoprotein
VLPO: ventrolateral POA (preoptic area)
VMAT2: vascular monoamine transporter-2
VTA: ventral tegmental area
WASO: wake after sleep onset
WSN: warm-sensitive neuron
ZCM: zero crossing mode

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—Meir H. Kryger, Thomas Roth, and William C. Dement

Normal Sleep and Its Variations

Section 1

Timothy Roehrs

History of Sleep Physiology and Medicine

Chapter 1

William C. Dement

Abstract

There has been great scientific interest in sleep for well over a century, with the discoveries of the electrical activity of the brain, the arousal systems, the circadian system, and rapid eye movement sleep. In spite of these discoveries, the field of sleep medicine has existed for only about 4 decades. The evolution of the field required clinical research, development of clinical services, and changes in society and public policy that recognized the impact of sleep disorders on society. The field is still evolving as new disorders are being discovered, new treatments are being delivered, and basic science is helping us understand the complexity of sleep and its disorders.

Interest in sleep and dreams has existed since the dawn of history. Perhaps only love and human conflict have received more attention from poets and writers. Some of the world's greatest thinkers, such as Aristotle, Hippocrates, Freud, and Pavlov, have attempted to explain the physiologic and psychological bases of sleep and dreaming. However, it is not the purpose of this chapter to present a scholarly review across the ages about prehistoric, biblical, and Elizabethan thoughts and concerns regarding sleep or the history of man's enthrallment with dreams and nightmares. This has been reviewed by others.[1] What is emphasized here for the benefit of the student and the practitioner is the evolution of the key concepts that define and differentiate sleep research and sleep medicine, crucial discoveries and developments in the formative years of the field, and those principles and practices that have stood the test of time.

SLEEP AS A PASSIVE STATE

"Sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension."[2]

The foregoing is the first sentence of *The Philosophy of Sleep*, a book by Robert MacNish, a member of the faculty of physicians and surgeons of Glasgow; the first American edition was published in 1834 and the Scottish edition somewhat earlier. This sentence exemplifies the overarching historical conceptual dichotomy of sleep research and sleep medicine, which is sleep as a passive process versus sleep as an active process. Until the discovery of rapid eye movements and the duality of sleep, sleep was universally regarded as an inactive state of the brain. With one or two exceptions, most thinkers regarded sleep as the inevitable result of reduced sensory input with the consequent diminishment of brain activity and the occurrence of sleep. Waking up and being awake were considered a reversal of this process, mainly as a result of bombardment of the brain by stimulation from the environment. No real distinction was seen between sleep and other states of quiescence such as coma, stupor, intoxication, hypnosis, anesthesia, and hibernation.

The passive to active historical dichotomy is also given great weight by the modern investigator J. Allan Hobson.[3] In the first sentence of his book, *Sleep*, published in 1989, he stated that "more has been learned about sleep in the past 60 years than in the preceding 6,000." He went on, "In this short period of time, researchers have discovered that sleep is a dynamic behavior. Not simply the absence of waking, sleep is a special activity of the brain, controlled by elaborate and precise mechanisms."

Dreams and dreaming were regarded as transient, fleeting interruptions of this quiescent state. Because dreams seem to occur spontaneously and sometimes in response to environmental stimulation (e.g., the well-known alarm clock dreams), the notion of a stimulus that produces the dream was generalized by postulating internal stimulation from the digestive tract or some other internal source. Some anthropologists have suggested that notions of spirituality and the soul arose from primitive peoples' need to

explain how their essence could leave the body temporarily at night in a dream and permanently at death.

In addition to the mere reduction of stimulation, a host of less popular theories were espoused to account for the onset of sleep. Vascular theories were proposed from the notion that the blood left the brain to accumulate in the digestive tract, and from the opposite idea that sleep was due to pressure on the brain by blood. Around the end of the 19th century, various versions of a "hypnotoxin" theory were formulated in which fatigue products (toxins and the like) were accumulated during the day, finally causing sleep, during which they were gradually eliminated. It had, of course, been observed since biblical times that alcohol would induce a sleeplike state. More recently, these observations included other compounds such as opium. Finally, it was noted that caffeine had the power to prevent sleep.

The hypnotoxin theory reached its zenith in 1907 when French physiologists, Legendre and Pieron,[4] did experiments showing that blood serum from sleep-deprived dogs could induce sleep in dogs that were not sleep deprived. The notion of a toxin causing the brain to sleep has gradually given way to the notion that there are a number of endogenous "sleep factors" that actively induce sleep by specific mechanisms.

In the 1920s, the University of Chicago physiologist Nathaniel Kleitman carried out a series of sleep-deprivation studies and made the simple but brilliant observation that individuals who stayed up all night were generally less sleepy and impaired the next morning than in the middle of their sleepless night. Kleitman argued that this observation was incompatible with the notion of a continual buildup of a hypnotoxin in the brain or blood. In addition, he felt that humans were about as impaired as they would get, that is, very impaired, after about 60 hours of wakefulness, and that longer periods of sleep deprivation would produce little additional change. In the 1939 (first) edition of his comprehensive landmark monograph "Sleep and Wakefulness" Kleitman[5] summed up by saying, "It is perhaps not sleep that needs to be explained, but wakefulness, and indeed, there may be different kinds of wakefulness at different stages of phylogenetic and ontogenetic development. In spite of sleep being frequently designated as an instinct, or global reaction, an actively initiated process, by excitation or inhibition of cortical or subcortical structures, there is not a single fact about sleep that cannot be equally well interpreted as a let down of the waking activity."

THE ELECTRICAL ACTIVITY OF THE BRAIN

As the 20th century got under way, Camillo Golgi and Santiago Ramón y Cajal had demonstrated that the nervous system was not a mass of fused cells sharing a common cytoplasm but rather a highly intricate network of discrete cells that had the key property of signaling to one another. Luigi Galvani had discovered that the nerve cells of animals produce electricity, and Emil duBois-Reymond and Hermann von Helmholtz found that nerve cells use their electrical capabilities for signaling information to one another. In 1875, the Scottish physiologist Richard Caton demonstrated electrical rhythms in the brains of animals. The centennial of his discovery was commemorated at the 15th annual meeting of the Association for the Psychophysiological Study of Sleep convening at the site of the discovery, Edinburgh, Scotland.

However, it was not until 1928 when the German psychiatrist Hans Berger[6] recorded electrical activity of the human brain and clearly demonstrated differences in these rhythms when subjects were awake or asleep that a real scientific interest commenced. Berger correctly inferred that the signals he recorded, which he called "electroencephalograms," were of brain origin. For the first time, the presence of sleep could be conclusively established without disturbing the sleeper, and, more important, sleep could be continuously and quantitatively measured without disturbing the sleeper.

All the major elements of sleep brain wave patterns were described by Harvey, Hobart, Davis, and others[7-9] at Harvard University in a series of extraordinary papers published in 1937, 1938, and 1939. Blake, Gerard, and Kleitman[10,11] added to this from their studies at the University of Chicago. On the human electroencephalogram (EEG), sleep was characterized by high-amplitude slow waves and spindles, whereas wakefulness was characterized by low-amplitude waves and alpha rhythm. The image of the sleeping brain completely "turned off" gave way to the image of the sleeping brain engaged in slow, synchronized, "idling" neuronal activity. Although it was not widely recognized at the time, these studies were some of the most critical turning points in sleep research. Indeed, Hobson[3] dated the turning point of sleep research to 1928, when Berger began his work on the human EEG. Used today in much the same way as they were in the 1930s, brain wave recordings with paper and ink, or more recently on computer screens, have been extraordinarily important to sleep research and sleep medicine.

The 1930s also saw one series of investigations that seemed to establish conclusively both the passive theory of sleep and the notion that it occurred in response to reduction of stimulation and activity. These were the investigations of Frederick Bremer,[12,13] reported in 1935 and 1936. These investigations were made possible by the aforementioned development of electroencephalography. Bremer studied brain wave patterns in two cat preparations. One, which Bremer called encéphale isolé, was made by cutting a section through the lower part of the medulla. The other, cerveau isolé, was made by cutting the midbrain just behind the origin of the oculomotor nerves. The first preparation permitted the study of cortical electrical rhythms under the influence of olfactory, visual, auditory, vestibular, and musculocutaneous impulses; in the second preparation, the field was narrowed almost entirely to the influence of olfactory and visual impulses.

In the first preparation, the brain continued to present manifestations of wakeful activity alternating with phases of sleep as indicated by the EEG. In the second preparation, however, the EEG assumed a definite deep sleep character and remained in this condition. In addition, the eyeballs immediately turned downward with a progressive miosis. Bremer concluded that in sleep there occurs a functional (reversible, of course) deafferentation of the cerebral

cortex. The cerveau isolé preparation results in a suppression of the incessant influx of nerve impulses, particularly cutaneous and proprioceptive, which are essential for the maintenance of the waking state of the telencephalon. Apparently, olfactory and visual impulses are insufficient to keep the cortex awake. It is probably misleading to assert that physiologists assumed the brain was completely turned off, whatever this metaphor might have meant, because blood flow and, presumably, metabolism continued. However, Bremer and others certainly favored the concept of sleep as a reduction of activity-idling, slow, synchronized, "resting" neuronal activity.

THE ASCENDING RETICULAR SYSTEM

After World War II, insulated, implantable electrodes were developed, and sleep research on animals began in earnest. In 1949, one of the most important and influential studies dealing with sleep and wakefulness was published: Moruzzi and Magoun's classic paper "Brain Stem Reticular Formation and Activation of the EEG."[14] These authors concluded that "transitions from sleep to wakefulness or from the less extreme states of relaxation and drowsiness to alertness and attention are all characterized by an apparent breaking up of the synchronization of discharge of the elements of the cerebral cortex, an alteration marked in the EEG by the replacement of high voltage, slow waves with low-voltage fast activity" (p. 455).

High-frequency electrical stimulation through electrodes implanted in the brainstem reticular formation produced EEG activation and behavioral arousal. Thus, EEG activation, wakefulness, and consciousness were at one end of the continuum; sleep, EEG synchronization, and lack of consciousness were at the other end. This view, as can be seen, is hardly different from the statement by MacNish quoted at the beginning of this chapter.

The demonstration by Starzl and coworkers[15] that sensory collaterals discharge into the reticular formation suggested that a mechanism was present by which sensory stimulation could be transduced into prolonged activation of the brain and sustained wakefulness. By attributing an amplifying and maintaining role to the brainstem core and the conceptual ascending reticular activating system, it was possible to account for the fact that wakefulness outlasts, or is occasionally maintained in the absence of, sensory stimulation.

Chronic lesions in the brainstem reticular formation produced persisting slow waves in the EEG and immobility. The usual animal for this research was the cat because excellent stereotaxic coordinates of brain structures had become available in this model.[16] These findings appeared to confirm and extend Bremer's observations. The theory of the reticular activating system was an anatomically based passive theory of sleep or an active theory of wakefulness. Figure 1-1 is from the published proceedings of a symposium entitled *Brain Mechanisms and Consciousness*, which published in 1954 and is probably the first genuine neuroscience bestseller.[17] Horace Magoun had extended his studies to the monkey, and the illustration represents the full flowering of the ascending reticular activating system theory.

EARLY OBSERVATIONS OF SLEEP PATHOLOGY

Insomnia has been described since the dawn of history and attributed to many causes, including a recognition of the association between emotional disturbance and sleep disturbance. Scholars and historians have a duty to bestow credit accurately. However, many discoveries lie fallow for want of a contextual soil in which they may be properly understood and in which they may extend the understanding of more general phenomena. Important early observations were those of von Economo on "sleeping sickness" and of Pavlov, who observed dogs falling asleep during conditioned reflex experiments.

Two early observations about sleep research and sleep medicine stand out. The first is the description in 1880 of narcolepsy by Jean Baptiste Edouard Gélineau (1859-1906), who derived the name narcolepsy from the Greek words narkosis (a benumbing) and lepsis (to overtake). He was the first to clearly describe the collection of components that constitute the syndrome, although the term cataplexy for the emotionally induced muscle weakness was subsequently coined in 1916 by Richard Henneberg.

Obstructive sleep apnea syndrome (OSAS), which may be called the leading sleep disorder of the 20th century, was described in 1836, not by a clinician but by the novelist Charles Dickens. In a series of papers entitled the "Posthumous Papers of the Pickwick Club," Dickens described Joe, a boy who was obese and always excessively sleepy. Joe, a loud snorer, was called Young Dropsy, possibly as a result of having right-sided heart failure. Meir Kryger[18] and Peretz Lavie[19,20] published scholarly accounts of many early references to snoring and conditions that were most certainly manifestations of OSAS. Professor Pierre Passouant[21] provided an account of the

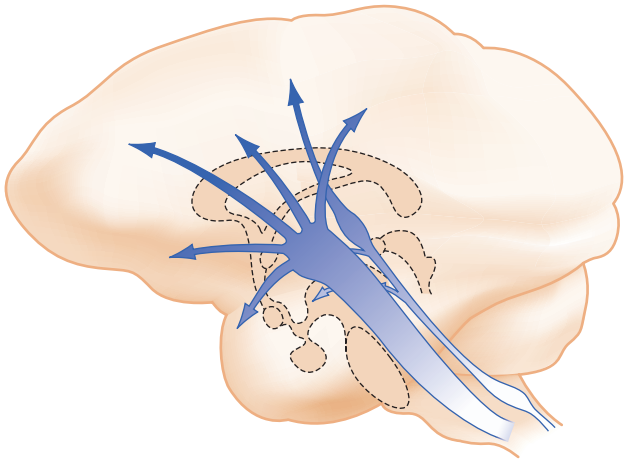

Figure 1-1 Lateral view of the monkey's brain, showing the ascending reticular activating system in the brainstem receiving collaterals from direct afferent paths and projecting primarily to the associational areas of the hemisphere. (Redrawn from Magoun HW: The ascending reticular system and wakefulness. In Adrian ED, Bremer F, Jasper HH [eds]. Brain mechanisms and consciousness. A symposium organized by the Council for International Organizations of Medical Sciences, 1954. (Courtesy of Charles C Thomas, Publisher, Springfield, Ill.)

life of Gélineau and his landmark description of the narcolepsy syndrome.

SIGMUND FREUD AND THE INTERPRETATION OF DREAMS

By far the most widespread interest in sleep by health professionals was engendered by the theories of Sigmund Freud, specifically about dreams. Of course, the interest was really in dreaming, with sleep as the necessary concomitant. Freud developed psychoanalysis, the technique of dream interpretation, as part of his therapeutic approach to emotional and mental problems. As the concept of the ascending reticular activating system dominated behavioral neurophysiology, so the psychoanalytic theories about dreams dominated the psychological side of the coin. Dreams were thought to be the guardians of sleep and to occur in response to a disturbance in order to obviate waking up, as exemplified in the classic alarm clock dream. Freud's concept that dreaming discharged instinctual energy led directly to the notion of dreaming as a safety valve of the mind. At the time of the discovery of rapid eye movements during sleep (circa 1952), academic psychiatry was dominated by psychoanalysts, and medical students all over America were interpreting one another's dreams.

From the vantage point of today's world, the dream deprivation studies of the early 1960s, engendered and reified by the belief in psychoanalysis, may be regarded by some as a digression from the mainstream of sleep medicine. On the other hand, because the medical–psychiatric establishment had begun to take dreams seriously, it was also ready to support sleep research fairly generously under the guise of dream research.

CHRONOBIOLOGY

Most, but not all, sleep specialists share the opinion that what has been called chronobiology or the study of biologic rhythms is a legitimate part of sleep research and sleep medicine. The 24-hour rhythms in the activities of plants and animals have been recognized for centuries. These biologic 24-hour rhythms were quite reasonably assumed to be a direct consequence of the periodic environmental fluctuation of light and darkness. However, in 1729, Jean Jacques d'Ortous de Mairan described a heliotrope plant that opened its leaves during the day even after de Mairan had moved the plant so that sunlight could not reach it. The plant opened its leaves during the day and folded them for the entire night even though the environment was constant. This was the first demonstration of the persistence of circadian rhythms in the absence of environmental time cues. Figure 1-2, which represents de Mairan's original experiment, is reproduced from *The Clocks That Time Us* by Moore-Ede and colleagues.[22]

Chronobiology and sleep research developed separately. The following three factors appear to have contributed to this:

1. The long-term studies commonly used in biologic rhythm research precluded continuous recording of brain wave activity. Certainly, in the early days, the latter was far too difficult and not really necessary. The measurement of wheel-running activity was a convenient and widely used method for demonstrating circadian rhythmicity.
2. The favorite animal of sleep research from the 1930s through the 1970s was the cat, and neither cats nor dogs demonstrate clearly defined circadian activity rhythms.
3. The separation between chronobiology and sleep research was further maintained by the tendency for chronobiologists to know very little about sleep, and for sleep researchers to remain ignorant of such biological clock mysteries as phase response curves, entrainment, and internal desynchronization.

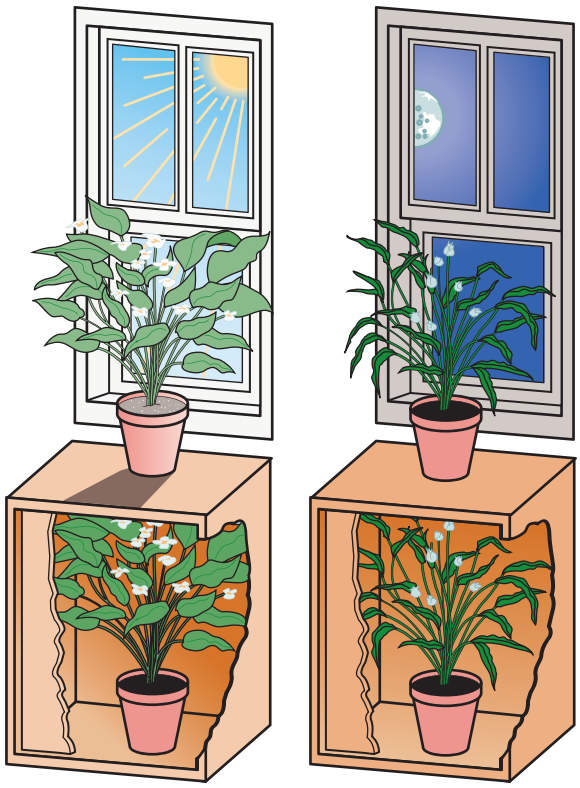

Figure 1-2 Representation of de Mairan's original experiment. When exposed to sunlight during the day (upper left), the leaves of the plant were open; during the night (upper right), the leaves were folded. De Mairan showed that sunlight was not necessary for these leaf movements by placing the plant in total darkness. Even under these constant conditions, the leaves opened during the day (lower left) and folded during the night (lower right). (Redrawn from Moore-Ede MC, Sulzman FM, Fuller CA. The clocks that time us: physiology of the circadian timing system. Cambridge, Mass: Harvard University Press; 1982. p. 7.)

THE DISCOVERY OF REM SLEEP

The characterization of rapid eye movement (REM) sleep as a discrete organismic state should be distinguished from the discovery that rapid eye movements occur during sleep. The historical threads of the discovery of rapid eye movements can be identified. Nathaniel Kleitman (Fig. 1-3, Video 1-1), a professor of physiology at the University of Chicago, had long been interested in cycles of activity and inactivity in infants and in the possibility that this cycle ensured that an infant would have an opportunity to

Figure 1-3 Nathaniel Kleitman (circa 1938), Professor of Physiology, University of Chicago, School of Medicine.

respond to hunger. He postulated that the times infants awakened to nurse on a self-demand schedule would be integral multiples of a basic rest-activity cycle. The second thread was Kleitman's interest in eye motility as a possible measure of "depth" of sleep. The reasoning for this was that eye movements had a much greater cortical representation than did almost any other observable motor activity, and that slow, rolling, or pendular eye movements had been described at the onset of sleep with a gradual slowing and disappearance as sleep "deepened."[23]

In 1951, Kleitman assigned the task of observing eye movement to a graduate student in physiology named Eugene Aserinsky. Watching the closed eyes of sleeping infants was tedious, and Aserinsky soon found that it was easier to designate successive 5-minute epochs as "periods of motility" if he observed any movement at all, usually a writhing or twitching of the eyelids, versus "periods of no motility."

After describing an apparent rhythm in eye motility, Kleitman and Aserinsky decided to look for a similar phenomenon in adults. Again, watching the eyes during the day was tedious, and at night it was even worse. Casting about, they came upon the method of electrooculography and decided (correctly) that this would be a good way to measure eye motility continuously and would relieve the human observer of the tedium of direct observations. Sometimes in the course of recording electrooculograms (EOGs) during sleep, they saw bursts of electrical potential changes that were quite different from the slow movements at sleep onset.

When they were observing infants, Aserinsky and Kleitman had not differentiated between slow and rapid movements. However, on the EOG, the difference between the slow eye movements at sleep onset and the newly discovered rapid motility was obvious. Initially, there was a great deal of concern that these potentials were electrical artifacts. With their presence on the EOG as a signal, however, it was possible to watch the subject's eyes simultaneously, and when this was done, the distinct rapid movement of the eyes beneath the closed lids was extremely easy to see.

At this point, Aserinsky and Kleitman made two assumptions:

1. These eye movements represented a "lightening" of sleep.
2. Because they were associated with irregular respiration and accelerated heart rate, they might represent dreaming.

The basic sleep cycle was not identified at this time, primarily because the EOG and other physiologic measures, notably the EEG, were not recorded continuously but rather by sampling a few minutes of each hour or half-hour. The sampling strategy was done to conserve paper (there was no research grant) and because there was not a clear reason to record continuously. Also, the schedule made it possible for the researcher to nap between sampling episodes.

Aserinsky and Kleitman initiated a small series of awakenings, both when rapid eye movements were present and when rapid eye movements were not present, for the purpose of eliciting dream recall. They did not apply sophisticated methods of dream content analysis, but the descriptions of dream content from the two conditions were generally quite different with REM awakenings yielding vivid complex stories and non-REM (NREM) awakenings often yielding nothing at all or very sparse accounts. This made it possible to conclude that rapid eye movements were associated with dreaming. This was, indeed, a breakthrough in sleep research.[24,25]

The occurrence of the eye movements was quite compatible with the contemporary dream theories that dreams occurred when sleep lightened in order to prevent or delay awakening. In other words, dreaming could still be regarded as the "guardian" of sleep. However, it could no longer be assumed that dreams were fleeting and evanescent.

ALL-NIGHT SLEEP RECORDINGS AND THE BASIC SLEEP CYCLE

The seminal Aserinsky and Kleitman paper was published in 1953. It attracted little attention, and no publications on the subject appeared from any other laboratory until 1959. Staying up at night to study sleep remained an undesirable occupation by anyone's standards. In the early 1950s, most previous research on the EEG patterns of sleep, like most approaches to sleep physiology generally, had either equated short periods of sleep with all sleep or relied on intermittent time sampling during the night. The notion of obtaining continuous records throughout typical nights of sleep would have seemed highly extravagant.

However, motivated by the desire to expand and quantify the description of rapid eye movements, then graduate student William Dement and Kleitman[26] did just this over a total of 126 nights with 33 subjects and, by means of a simplified categorization of EEG patterns, scored the paper recordings in their entirety. When they examined these 126 records, they found that there was a predictable

sequence of patterns over the course of the night, such as had been hinted at by Aserinsky's study but entirely overlooked in all previous EEG studies of sleep. Although this sequence of regular variations has now been observed tens of thousands of times in hundreds of laboratories, the original description remains essentially unchanged.

The usual sequence was that after the onset of sleep, the EEG progressed fairly rapidly to stage 4, which persisted for varying amounts of time, generally about 30 minutes, and then a "lightening" took place. Whereas the progression from wakefulness to stage 4 at the beginning of the cycle was almost invariable through a continuum of change, the lightening was usually abrupt and coincident with a body movement or series of body movements. After the termination of stage 4, there was generally a short period of stage 2 or stage 3 which gave way to stage 1 and rapid eye movements. When the first eye movement period ended, the EEG again progressed through a continuum of change to stage 3 or 4, which persisted for a time and then lightened, often abruptly, with body movement to stage 2, which again gave way to stage 1 and the second rapid eye movement period (see p. 679 of Dement and Kleitman[26]).

Dement and Kleitman found that this cyclical variation of EEG patterns occurred repeatedly throughout the night at intervals of 90 to 100 minutes from the end of one eye movement period to the end of the next. The regular occurrences of REM periods and dreaming strongly suggested that dreams did not occur in response to chance disturbances.

At the time of these observations, sleep was still considered to be a single state. Dement and Kleitman characterized the EEG during REM periods as "emergent stage 1" as opposed to "descending stage 1" at the onset of sleep. The percentage of the total sleep time occupied by REM sleep was between 20% and 25%, and the periods of REM sleep tended to be shorter in the early cycles of the night. This pattern of all-night sleep has been seen over and over in normal humans of both sexes, in widely varying environments and cultures, and across the life span.

REM SLEEP IN ANIMALS

The developing knowledge of the nature of sleep with rapid eye movements was in direct opposition to the ascending reticular activating system theory and constituted a paradigmatic crisis. The following observations were crucial:

- Arousal thresholds in humans were much higher during periods of REM sleep that had a low-amplitude, relatively fast (stage 1) EEG pattern than during similar "light sleep" periods at the onset of sleep.
- Rapid eye movements during sleep were discovered in cats; the concomitant brain wave patterns (low-amplitude, fast) were indistinguishable from active wakefulness.
- By discarding the sampling approach and recording continuously, a basic 90-minute cycle of sleep without rapid eye movements, alternating with sleep with rapid eye movements, was discovered. This basic sleep-cycle characterized all episodes of nocturnal sleep. Continuous recording also revealed a consistent, low-amplitude EEG pattern during a precise interval of sleep always associated with bursts of REM, which were additionally established as periods of vivid dreaming.
- Observations of motor activity in both humans and animals revealed the unique occurrence of an active suppression of spinal motor activity and muscle reflexes.

Thus, sleep consists not of one state but rather of two distinct organismic states, as different from one another as both are from wakefulness. It had to be conceded that sleep could no longer be thought of as a time of brain inactivity and EEG slowing. By 1960, this fundamental change in our thinking about the nature of sleep was well established; it exists as fact that has not changed in any way since that time.

The discovery of rapid eye movements during sleep in humans, plus the all-night sleep recordings that revealed the regular recurrence of lengthy periods during which rapid eye movements occurred and during which brain wave patterns resembled light sleep, prepared the way for the discovery of REM sleep in cats, in spite of the extremely powerful bias that an "activated" EEG could not be associated with sleep. In the first study of cats, maintaining the insulation and, therefore, the integrity of implanted electrodes had not yet been solved, so an alternative, small pins in the scalp, was used. With this approach, the waking EEG was totally obscured by the electromyogram from the large temporal muscles of the cat. However, when the cat fell asleep, slow waves could be seen, and the transition to REM sleep was clearly observed because muscle potentials were completely suppressed. The cat's rapid eye movements and also the twitching of the whiskers and paws could be directly observed.

It is very difficult today, in 2010, to understand and appreciate the exceedingly controversial nature of these findings. The following note from a more personal account[27] illustrates both the power and the danger of scientific dogma. "I wrote them [the findings] up, but the paper was nearly impossible to publish because it was completely contradictory to the totally dominant neurophysiological theory of the time. The assertion by me that an activated EEG could be associated with unambiguous sleep was considered to be absurd. As it turned out, previous investigators had observed an activated EEG during sleep in cats[28,29] but simply could not believe it and ascribed it to arousing influences during sleep. A colleague who was assisting me was sufficiently skeptical that he preferred I publish the paper as sole author. After four or five rejections, to my everlasting gratitude, Editor-in-Chief Herbert Jasper accepted the paper without revision for publication in Electroencephalography and Clinical Neurophysiology." (see p. 23 of Dement[30])

It is notable, however, that I did not appreciate the significance of the absence of muscle potentials during the REM periods in cats. It remained for Michel Jouvet, working in Lyon, France, to insist on the importance of electromyographic suppression in his early papers,[31,32] the first of which was published in 1959. Hodes and Dement began to study the "H" reflex in humans in 1960, finding complete suppression of reflexes during REM sleep,[33] and Octavio Pompeiano and others in Pisa, Italy, worked out the basic mechanisms of REM atonia in the cat.[34]

THE DUALITY OF SLEEP

Even though the basic NREM sleep cycle was well established, the realization that REM sleep was qualitatively different from the remainder of sleep took years to evolve. Jouvet[35] and his colleagues performed an elegant series of investigations on the brainstem mechanisms of sleep that forced the inescapable conclusion that sleep consists of two fundamentally different organismic states. Among his many early contributions were clarification of the role of pontine brainstem systems as the primary anatomic site for REM sleep mechanisms and the clear demonstration that electromyographic activity and muscle tonus are completely suppressed during REM periods and *only* during REM periods. These investigations began in 1958 and were carried out during 1959 and 1960.

It is now an established fact that atonia is a fundamental characteristic of REM sleep and that it is mediated by an active and highly specialized neuronal system. The pioneering microelectrode studies of Edward Evarts[36] in cats and monkeys, and observations on cerebral blood flow in the cat by Reivich and Kety[37] provided convincing evidence that the brain during REM sleep is very active. Certain areas of the brain appear to be more active in REM sleep than in wakefulness. By now, the notion of sleep as a passive process was totally demolished although for many years there was a lingering attitude that NREM sleep was essentially inactive and quiet. By 1960, it was possible to define REM sleep as a completely separate organismic state characterized by cerebral activation, active motor inhibition, and, of course, an association with dreaming. The fundamental duality of sleep was an established fact.

PREMONITIONS OF SLEEP MEDICINE

Sleep research, which emphasized all-night sleep recordings, burgeoned in the 1960s and was the legitimate precursor of sleep medicine and particularly of its core clinical test, polysomnography. Much of the research at this time emphasized studies of dreaming and REM sleep and had its roots in a psychoanalytic approach to mental illness which strongly implicated dreaming in the psychotic process. After sufficient numbers of all-night sleep recordings had been carried out in humans to demonstrate a highly characteristic "normal" sleep architecture, investigators noted a significantly shortened REM latency in association with endogenous depression.[38] This phenomenon has been intensively investigated ever since. Other important precursors of sleep medicine were the following:

1. Discovery of sleep-onset REM periods in patients with narcolepsy
2. Interest in sleep, epilepsy, and abnormal movement–primarily in France
3. Introduction of benzodiazepines and the use of sleep laboratory studies in defining hypnotic efficacy

SLEEP-ONSET REM PERIODS AND CATAPLEXY

In 1959, a patient with narcolepsy came to the Mount Sinai Hospital in New York City to see Dr. Charles Fisher. At Fisher's suggestion, a sleep recording was begun. Within seconds after he fell asleep, the patient was showing the dramatic, characteristic rapid eye movements of REM sleep, and sawtooth waves as well, in the EEG. The first paper documenting sleep-onset REM periods in a single patient was published in 1960 by Gerald Vogel.[39] In a collaborative study between the University of Chicago and the Mount Sinai Hospital, nine patients were studied, and the important sleep-onset REM periods at night were described in a 1963 paper.[40] Subsequent research showed that sleepy patients who did not have cataplexy did not have sleep-onset REM periods (SOREMPs), and those with cataplexy always had SOREMPs.[41] It was clear that the best explanation for cataplexy was the normal motor inhibitory mechanisms of REM sleep occurring during wakefulness in a precocious or abnormal way.

THE NARCOLEPSY CLINIC: A FALSE START

In January 1963, after moving to Stanford University, Dement was eager to test the hypothesis of an association between cataplexy and SOREMPs. However, not a single narcoleptic patient could be identified. A final attempt was made by placing a "want ad," a few words about an inch high, in a daily newspaper, the San Francisco Chronicle. More than 100 people responded! About 50 of these patients were bona fide narcoleptics having both sleepiness and cataplexy.

The response to the ad was a noteworthy event in the development of sleep disorders medicine. With one or two exceptions, none of the narcoleptics had ever been diagnosed correctly. A responsibility for their clinical management had to be assumed in order to facilitate their participation in the research. The late Dr. Stephen Mitchell, who had completed his neurology training and was entering a psychiatry residency at Stanford University, joined Dement in creating a narcolepsy clinic in 1964, and they were soon managing well over 100 patients. Mostly, this involved seeing the patients at regular intervals and adjusting their medication. Nonetheless, the seeds of the typical sleep disorders clinic were sowed because at least one daytime polygraphic sleep recording was performed on all patients to establish the presence of SOREMPs, and patients were questioned exhaustively about their sleep. If possible, an all-night sleep recording was carried out. Unfortunately, most of the patients were unable to pay cash to cover their bills, and insurance companies declared that the recordings of narcoleptic patients were experimental. Because the clinic was unable to generate sufficient income, it was discontinued and most of the patients were referred back to local physicians with instructions about treatment.

EUROPEAN INTEREST

In Europe, a genuine clinical interest in sleep problems had arisen, and it achieved its clearest expression in a 1963 symposium held in Paris, organized by Professor H. Fischgold, and published as La Sommeil de Nuit Normal et Pathologique in 1965.[42] The primary clinical emphasis in this symposium was the documentation of sleep-related

epileptic seizures and a number of related studies on sleepwalking and night terrors. Investigators from France, Italy, Belgium, Germany, and the Netherlands took part.

BENZODIAZEPINES AND HYPNOTIC EFFICACY STUDIES

Benzodiazepines were introduced in 1960 with the marketing of chlordiazepoxide (Librium). This compound offered a significant advance in terms of safety over barbiturates for the purpose of tranquilizing and sedating. It was quickly followed by diazepam (Valium) and the first benzodiazepine introduced specifically as a hypnotic, flurazepam (Dalmane). Although a number of studies had been done on the effects of drugs on sleep, usually to answer theoretical questions, the first use of the sleep laboratory to evaluate sleeping pills was the 1965 study by Oswald and Priest.[43] An important series of studies establishing the role of the sleep laboratory in the evaluation of hypnotic efficacy was carried out by Anthony Kales and his colleagues at the University of California, Los Angeles.[44] The group also carried out studies of patients with hypothyroidism, asthma, Parkinson's disease, and somnambulism.[45-48]

THE DISCOVERY OF SLEEP APNEA

One of the most important events in the history of sleep disorders medicine occurred in Europe. Sleep apnea was discovered independently by Gastaut, Tassinari, and Duron[49] in France and by Jung and Kuhlo in Germany.[50] Both these groups reported their findings in 1965. As noted earlier, scholars have found references to this phenomenon in many places, but this was the first clear-cut recognition and description that had a direct causal continuity to sleep disorders medicine as we know it today. Peretz Lavie has detailed the historical contributions made by scientists and clinicians around the world in helping to describe and understand this disorder.[20]

These important findings were widely ignored in America (Video 1-2). What should have been an almost inevitable discovery by either the otolaryngologic surgery community or the pulmonary medicine community did not occur because there was no tradition in either specialty for carefully observing breathing during sleep. The well-known and frequently cited study of Burwell and colleagues[51]—although impressive in a literary sense in its evoking of the somnolent boy, Joe, from the "Posthumous Papers of the Pickwick Club"—erred badly in evaluating their somnolent obese patients only during waking and attributing the cause of the somnolence to hypercapnia.

The popularity of this paper further reduced the likelihood of discovery of sleep apnea by the pulmonary community. To this day, there is no evidence that hypercapnia causes true somnolence, although, of course, high levels of PCO_2 are associated with impaired cerebral function. Nonetheless, the term "pickwickian" became an instant success as a neologism and may have played a role in stimulating interest in this syndrome by the European neurologists who were also interested in sleep.

A small group of French neurologists who specialized in clinical neurophysiology and electroencephalography were in the vanguard of sleep research. One of the collaborators in the French discovery of sleep apnea, C. Alberto Tassinari, joined the Italian neurologist Elio Lugaresi in Bologna in 1970. These clinical investigators along with Giorgio Coccagna and a host of others over the years performed a crucial series of clinical sleep investigations and, indeed, provided a complete description of the sleep apnea syndrome, including the first observations of the occurrence of sleep apnea in nonobese patients, an account of the cardiovascular correlates, and a clear identification of the importance of snoring and hypersomnolence as diagnostic indicators. These studies are recounted in Lugaresi's book, *Hypersomnia with Periodic Apneas*, published in 1978.[52]

ITALIAN SYMPOSIA

In 1967, Henri Gastaut and Elio Lugaresi (Fig. 1-4) organized a symposium, published as *The Abnormalities of Sleep in Man*,[53] which encompassed issues across a full range of pathologic sleep in humans. This meeting took place in Bologna, Italy, and the papers presented covered many of what are now major topics in the sleep medicine field: insomnia, sleep apnea, narcolepsy, and periodic leg movements during sleep. It was an epic meeting from the point of view of the clinical investigation of sleep; the only major issues not represented were clear concepts of clinical practice models and clear visions of the high population prevalence of sleep disorders. However, the event that may have finally triggered a serious international interest in sleep apnea syndromes was organized by Lugaresi in 1972 and took place in Rimini, a small resort on the Adriatic coast.[54]

BIRTH PANGS

In spite of all the clinical research, the concept of all-night sleep recordings as a clinical diagnostic test did not emerge unambiguously. It is worth considering the reasons for this failure, partly because they continue to operate today as impediments to the expansion of the field, and partly to understand the field's long overdue development.

The first important reason was the unprecedented nature of an all-night diagnostic test, particularly if it was conducted on outpatients. The cost of all-night

Figure 1-4 Elio Lugaresi, Professor of Neurology, University of Bologna, at the 1972 Rimini symposium.

polygraphic recording, in terms of its basic expense, was high enough without adding the cost of hospitalization although hospitalization would have legitimized a patient's spending the night in a testing facility. To sleep in an outpatient clinic for a diagnostic test was a totally unprecedented, time-intensive, and labor-intensive enterprise and completely in conflict with the brief time required to go to the chemistry laboratory to give a blood sample, to breathe into a pulmonary function apparatus, to undergo a radiographic examination, and so forth.

A second important barrier was the reluctance of nonhospital clinical professionals to work at night. Although medical house staff are very familiar with night work, they do not generally enjoy it; furthermore, clinicians could not work 24-hour days, first seeing patients and ordering tests, and then conducting the tests themselves.

Finally, only a very small number of people understood that complaints of daytime sleepiness and nocturnal sleep disturbance represented something of clinical significance. Even narcolepsy, which was by the early 1970s fully characterized as an interesting and disabling clinical syndrome requiring sleep recordings for diagnosis, was not recognized in the larger medical community and had too low a prevalence to warrant creating a medical subspecialty. A study carried out in 1972 documented a mean of 15 years from onset of the characteristic symptoms of excessive daytime sleepiness and cataplexy to diagnosis and treatment by a clinician. The study also showed that a mean of 5.5 different physicians were consulted without benefit throughout that long interval.[55]

THE EARLY DEVELOPMENT OF SLEEP MEDICINE CLINICAL PRACTICE

The practice of sleep medicine developed in many centers in the 1970s, often as a function of the original research interests of the center. The sleep disorders clinic at Stanford University is in many ways a microcosm of how sleep medicine evolved throughout the world. Patients complaining of insomnia were enrolled in hypnotic efficacy research studies. This brought the Stanford group into contact with many insomnia patients and demolished the notion that the majority of such patients had psychiatric problems. An early question was how reliable the descriptions of their sleep by these patients were. The classic all-night sleep recording gave an answer and yielded a great deal of information. Throughout the second half of the 1960s, as a part of their research, the Stanford group continued to manage patients with narcolepsy. As the group's reputation for expertise in narcolepsy grew, it began to receive referrals for evaluation from physicians all over the United States. Although sleep apnea had not yet been identified (or treated) as a frequent cause of severe daytime sleepiness, it was clear that a number of patients referred with the presumptive diagnosis of narcolepsy certainly did not possess narcolepsy's two cardinal signs, SOREMPs and cataplexy, and actually suffered from obstructive sleep apnea. True pickwickians were an infrequent referral at this time.

In January 1972, Christian Guilleminault, a French neurologist and psychiatrist, joined the Stanford group. He had extensive knowledge of the European studies of sleep apnea. Until his arrival, the Stanford group had not routinely used respiratory and cardiac sensors in their all-night sleep studies. Starting in 1972, these measurements became a routine part of the all-night diagnostic test. This test was given the permanent name of polysomnography in 1974 by Dr. Jerome Holland, a member of the Stanford group. Publicity about narcolepsy and excessive sleepiness resulted in a small flow of referrals to the Stanford sleep clinic, usually with the presumptive diagnosis of narcolepsy. During the first year or two, the goal for the Stanford practice was to see at least five new patients per week. To foster financial viability, the group did as much as possible (within ethical limits) to publicize its services. As a result, there was also a sprinkling of patients, often self-referred, with chronic insomnia. The diagnosis of obstructive sleep apnea in patients with profound excessive daytime sleepiness was nearly always completely unambiguous.

During 1972, the search for sleep abnormality in patients with sleep-related complaints continued; an attempt was made as well to conceptualize the pathophysiologic process both as an entity and as the cause of the presenting symptom. With this approach, a number of phenomena seen during sleep were rapidly linked to the fundamental sleep-related presenting complaints.

Toward the end of 1972, the basic concepts and formats of sleep disorders medicine were sculpted to the extent that it was possible to offer a daylong course through Stanford University's Division of Postgraduate Medicine. The course was titled "The Diagnosis and Treatment of Sleep Disorders." The topics covered were normal sleep architecture; the diagnosis and treatment of insomnia with drug-dependent insomnia, pseudoinsomnia, central sleep apnea, and periodic leg movement as diagnostic entities; and the diagnosis and treatment of excessive daytime sleepiness or hypersomnia, with narcolepsy, NREM narcolepsy, and obstructive sleep apnea as diagnostic entities.

The disability and cardiovascular complications of severe sleep apnea were severe and alarming. Unfortunately, the treatment options at this time were limited to usually ineffective attempts to lose weight and chronic tracheostomy. The dramatic results of chronic tracheostomy in ameliorating the symptoms and complications of obstructive sleep apnea had been reported by Lugaresi and coworkers[56] in 1970. However, the notion of using such a treatment was strongly resisted at the time by the medical community, both in the Stanford University medical community and elsewhere. One of the first patients referred to the Stanford sleep clinic for investigation of this severe somnolence and who eventually had a tracheostomy was a 10-year-old boy. The challenges that were met to secure the proper management of this patient can be seen in this account by Christian Guilleminault (personal communication, 1990).

In addition to medical skepticism, a major obstacle to the practice of sleep disorders medicine was the retroactive denial of payment by insurance companies, including the largest one in the United States. A 3-year period of educational efforts directed toward third-party carriers finally culminated in the recognition of polysomnography as a reimbursable diagnostic test in 1974. Another issue was

that outpatient clinics that offered overnight testing in polysomnographic testing bedrooms needed to obtain state licensure in order to avoid the licensing requirements of hospitals. This, too, was finally accomplished in 1974.

CLINICAL SIGNIFICANCE OF EXCESSIVE DAYTIME SLEEPINESS

Christian Guilleminault, in a series of studies, had clearly shown that excessive daytime sleepiness was a major presenting complaint of several sleep disorders as well as a pathologic phenomenon unto itself.[57] However, it was recognized that methods to quantify this symptom and the underlying condition were not adequate to document the degree of improvement as a result of treatment. The subjective Stanford Sleepiness Scale, developed by Hoddes and colleagues,[58] did not give reliable results. The problem was not a crisis, however, because patients with severe apnea and overwhelming daytime sleepiness improved dramatically after tracheostomy, and the reduction in daytime sleepiness was unambiguous. Nonetheless, the less urgent need to document the pharmacologic treatment of narcolepsy and the objective improvement of sleepiness in patients with less severe sleep apnea continued to be a problem.

The apparent lack of interest in daytime sleepiness by individuals who were devoting their careers to the investigation of sleep at that time has always been puzzling. There is no question but that the current active investigation of this phenomenon is the result of the early interest of sleep disorders specialists. The early neglect of sleepiness is all the more difficult to understand because it is now widely recognized that sleepiness and the tendency to fall asleep during the performance of hazardous tasks is one of the most important problems in our society. A number of reasons have been put forward. One is that sleepiness and drowsiness are negative qualities. A second is that the societal failure to confront the issue was fostered by language ambiguities in identifying sleepiness. A third is that the early sleep laboratory studies focused almost exclusively on REM sleep and other nighttime procedures with little concern for the daytime except for psychopathology. Finally, the focus with regard to sleep deprivation was on performance from the perspective of human factors rather than on sleepiness as representing a homeostatic response to sleep reduction.

An early attempt to develop an objective measure of sleepiness was that of Yoss and coworkers[59] who observed pupil diameter directly by video monitoring and described changes in sleep deprivation and narcolepsy. Subsequently designated pupillometry, this technique has not been widely accepted. Dr. Mary Carskadon deserves most of the credit for the development of the latter-day standard approach to the measurement of sleepiness called the Multiple Sleep Latency Test (MSLT). She noted that subjective ratings of sleepiness made before a sleep recording not infrequently predicted the sleep latency. In the spring of 1976, she undertook to establish sleep latency as an objective measurement of the state of sleepiness-alertness by measuring sleep tendency before, during, and after 2 days of total sleep deprivation.[60] The protocol designed for this study has become the standard protocol for the MSLT. The choices of a 20-minute duration of a single test and a 2-hour interval between tests were essentially arbitrary and dictated by the practical demands of that study. This test was then formally applied to the clinical evaluation of sleepiness in patients with narcolepsy[61] and, later, in patients with OSAS.[62]

Carskadon and her colleagues then undertook a monumental study of sleepiness in children by following them longitudinally across the second decade of life, which happens to also be the decade of highest risk for the development of narcolepsy. Using the new MSLT measure, she found that 10-year-old children were completely alert in the daytime, but by the time they reached sexual maturity, they were no longer fully alert even though they obtained almost the same amount of sleep at night as at age ten. Results of this remarkable decade of work and other studies are summarized in an important review.[63]

Early MSLT research established the following important advances in thinking:

1. Daytime sleepiness and nighttime sleep are an interactive continuum, and the adequacy of nighttime sleep absolutely cannot be understood without a complementary measurement of the level of daytime sleepiness or its antonym, alertness.
2. Excessive sleepiness, also known as impaired alertness, was sleep medicine's most important symptom.

FURTHER DEVELOPMENT OF SLEEP MEDICINE

As the decade of the 1970s drew to a close, the consolidation and formalization of the practice of sleep disorders medicine was largely completed. What is now the American Academy of Sleep Medicine was formed and provided a home for professionals interested in sleep and, particularly, in the diagnosis and treatment of sleep disorders. This organization began as the Association of Sleep Disorders Centers with five members in 1975. The organization then was responsible for the initiation of the scientific journal *Sleep*, and it fostered the setting of standards through center accreditation and an examination for practitioners by which they were designated Accredited Clinical Polysomnographers.

The first international symposium on narcolepsy took place in the French Languedoc in the summer of 1975, immediately after the Second International Congress of the Association for the Physiological Study of Sleep in Edinburgh. The former meeting, in addition to being scientifically productive, had landmark significance because it produced the first consensus definition of a specific sleep disorder,[64] drafted, revised, and unanimously endorsed by 65 narcoleptologists of international reputation. The first sleep disorders patient volunteer organization, the American Narcolepsy Association, was also formed in 1975. The ASDC/APSS Diagnostic Classification of Sleep and Arousal Disorders was published in fall 1979 after 3 years of extraordinary effort by a small group of dedicated individuals who composed the "nosology" committee chaired by Howard Roffwarg.[65]

Before the 1980s, the only effective treatment for severe OSAS was chronic tracheostomy. This highly effective but personally undesirable approach was replaced by two new

procedures—one surgical,[66] the other mechanical.[67] The first was uvulopalatopharyngoplasty, which is giving way to more complex and effective approaches. The second was the widely used and highly effective continuous positive nasal airway pressure technique introduced by the Australian pulmonologist Colin Sullivan (Video 1-3). The combination of the high prevalence of OSAS and effective treatments fueled a strong expansion of centers and individuals offering the diagnosis and treatment of sleep disorders to patients.

The decade of the 1980s was capped by the publication of sleep medicine's first textbook, *Principles and Practice of Sleep Medicine*.[68] For many years there was only one medical journal devoted to sleep; by 2004 there were seven: *Sleep*, *Journal of Sleep Research*, *Sleep and Biological Rhythms*, *Sleep & Breathing*, *Sleep Medicine*, *Sleep Medicine Reviews*, and *Sleep Research Online*. Articles about sleep are now routinely published in the major pulmonary, neurology, and psychiatric journals.

The 1990s saw an acceleration in the acceptance of sleep medicine throughout the world.[69] In spite of that, adequate sleep medicine services are still not readily available everywhere.[70] In the United States, the National Center on Sleep Disorders Research (NCSDR) was established by statute as part of the National Heart, Lung, and Blood Institute of the National Institutes of Health.[71,72] The mandate of NCSDR is to support research, promote educational activities, and coordinate sleep-related activities throughout various branches of the U.S. government. This initiative led to the development of large research projects dealing with various aspects of sleep disorders and the establishment of awards to develop educational materials at all levels of training.

The 1990s also saw the establishment of the National Sleep Foundation[73] as well as other organizations for patients. This foundation points out to the public the dangers of sleepiness, and sponsors the annual National Sleep Awareness Week. As the Internet increases exponentially in size, so does the availability of sleep knowledge for physicians, patients, and the general public. The average person today knows a great deal more about sleep and its disorders than the average person did at the end of the 1980s.

THE TURN OF THE CENTURY AND BEYOND

Chapter 62 of this volume deals with public policy and public health issues. From today's vantage, the greatest challenge for the future is the cost-effective expansion of sleep medicine so that its benefits will be readily available. The major barrier to this availability is the continuing failure of sleep research and sleep medicine to effectively penetrate the educational system at any level. As a consequence, the majority of individuals remain unaware of important facts of sleep and wakefulness, biologic rhythms, and sleep disorders, and particularly of the symptoms that suggest a serious pathologic process. The management of sleep deprivation and its serious consequences in the workplace, particularly in those industries that depend on sustained operations, continue to need increased attention.

Finally, the education and training of all health professionals, including nurses, has far to go. This situation was highlighted by the recently published report of the Institute of Medicine.[74] Take heart! These problems are grand opportunities. Sleep medicine has come into its own (Videos 1-4 and 1-5). It has made concern for health a truly 24-hours-a-day enterprise, and it has energized a new effort to reveal the secrets of the healthy and unhealthy sleeping brain.

❖ Clinical Pearl

Recent advances in sleep science, sleep medicine, public policy, and communications will foster an educated public that will know a great deal about sleep and its disorders. Clinicians should expect that their patients may have already learned about their sleep disorders from the information sources that are readily available.

Case History

Raymond M. was a 10½ -year-old boy referred to the pediatrics clinic in 1971 for evaluation of unexplained hypertension, which had developed progressively over the preceding 6 months. There was a positive family history of high blood pressure, but never so early in life. Raymond was hospitalized and had determination of renin, angiotensin, and aldosterone, renal function studies including contrast radiographs, and extensive cardiac evaluation. All results had been normal except that his blood pressure oscillated between 140-170/90-100. It was noticed that he was somnolent during the daytime and Dr. S. suggested that I see him for this "unrelated" symptom.

I reviewed Raymond's history with his mother. Raymond had been abnormally sleepy "all his life." However, during the past 2 to 3 years, his schoolteachers were complaining that he would fall asleep in class and was at times a "behavioral problem" because he was not paying attention and was hyperactive and aggressive. His mother confirmed that he had been a very loud snorer since he was very young, at least since age 2, perhaps before.

Physical examination revealed an obese boy with a short neck and a very narrow airway. I recommended a sleep evaluation, which was accepted. An esophageal balloon and measurement of end-tidal CO_2 was added to the usual array. His esophageal pressure reached 80 to 120 cm H_2O, he had values of 6% end-tidal CO_2 at end of apnea, apneic events lasted between 25 and 65 seconds, and the apnea index was 55. His SaO_2 [oxygen saturation, arterial] was frequently below 60%.

I called the pediatric resident and informed him that the sleep problem was serious. I also suggested that the sleep problem might be the cause of the unexplained hypertension. The resident could not make

Continued

sense of my information and passed it to the attending physician. I was finally asked to present my findings at the pediatric case conference, which was led by Dr. S. I came with the recordings, showed the results, and explained why I believed that there was a relationship between the hypertension and the sleep problem. There were a lot of questions. They simply could not believe it. I was asked what treatment I would recommend, and I suggested a tracheostomy. I was asked how many patients had this treatment in the United States, and how many children had ever been treated with tracheostomy. When I had to answer "zero" to both questions, the audience was somewhat shocked. It was decided that such an approach was doubtful at best, and completely unacceptable in a child. However, they did concede that if no improvement was achieved by medical management, Raymond would be reinvestigated, including sleep studies.

That was spring 1972. In the fall, he was, if anything, worse in spite of vigorous medical treatment. At the end of 1972, Raymond finally had his tracheostomy. His blood pressure went down to 90/60 within 10 days, and he was no longer sleepy. During the 5 years we were able to follow Raymond, he remained normotensive and alert, but I had to fight continuously to prevent outside doctors from closing his tracheostomy. I do not know what has happened to him since then.

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Normal Human Sleep:
An Overview

Mary A. Carskadon and William C. Dement

Chapter 2

Abstract

Normal human sleep comprises two states—rapid eye movement (REM) and non–REM (NREM) sleep—that alternate cyclically across a sleep episode. State characteristics are well defined: NREM sleep includes a variably synchronous cortical electroencephalogram (EEG; including sleep spindles, K-complexes, and slow waves) associated with low muscle tonus and minimal psychological activity; the REM sleep EEG is desynchronized, muscles are atonic, and dreaming is typical. A nightly pattern of sleep in mature humans sleeping on a regular schedule includes several reliable characteristics: Sleep begins in NREM and progresses through deeper NREM stages (stages 2, 3, and 4 using the classic definitions, or stages N2 and N3 using the updated definitions) before the first episode of REM sleep occurs approximately 80 to 100 minutes later. Thereafter, NREM sleep and REM sleep cycle with a period of approximately 90 minutes. NREM stages 3 and 4 (or stage N3) concentrate in the early NREM cycles, and REM sleep episodes lengthen across the night.

Age-related changes are also predictable: Newborn humans enter REM sleep (called active sleep*) before NREM (called* quiet sleep*) and have a shorter sleep cycle (approximately 50 minutes); coherent sleep stages emerge as the brain matures during the first year. At birth, active sleep is approximately 50% of total sleep and declines over the first 2 years to approximately 20% to 25%. NREM sleep slow waves are not present at birth but emerge in the first 2 years. Slow-wave sleep (stages 3 and 4) decreases across adolescence by 40% from preteen years and continues a slower decline into old age, particularly in men and less so in women. REM sleep as a percentage of total sleep is approximately 20% to 25% across childhood, adolescence, adulthood, and into old age except in dementia. Other factors predictably alter sleep, such as previous sleep-wake history (e.g., homeostatic load), phase of the circadian timing system, ambient temperature, drugs, and sleep disorders.*

A clear appreciation of the normal characteristics of sleep provides a strong background and template for understanding clinical conditions in which "normal" characteristics are altered, as well as for interpreting certain consequences of sleep disorders. In this chapter, the normal young adult sleep pattern is described as a working baseline pattern. Normative changes due to aging and other factors are described with that background in mind. Several major sleep disorders are highlighted by their differences from the normative pattern.

SLEEP DEFINITIONS

According to a simple behavioral definition, sleep is a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment. It is also true that sleep is a complex amalgam of physiologic and behavioral processes. Sleep is typically (but not necessarily) accompanied by postural recumbence, behavioral quiescence, closed eyes, and all the other indicators one commonly associates with sleeping. In the unusual circumstance, other behaviors can occur during sleep. These behaviors can include sleepwalking, sleeptalking, teeth grinding, and other physical activities. Anomalies involving sleep processes also include intrusions of sleep—sleep itself, dream imagery, or muscle weakness—into wakefulness, for example (Box 2-1).

Within sleep, two separate states have been defined on the basis of a constellation of physiologic parameters. These two states, rapid eye movement (REM) and non-REM (NREM), exist in virtually all mammals and birds yet studied, and they are as distinct from one another as each is from wakefulness.

NREM (pronounced "non-REM") sleep is conventionally subdivided into four stages defined along one measurement axis, the electroencephalogram (EEG). The EEG pattern in NREM sleep is commonly described as synchronous, with such characteristic waveforms as sleep spindles, K-complexes, and high-voltage slow waves (Fig. 2-1). The four NREM stages (stages 1, 2, 3, and 4) roughly parallel a depth-of-sleep continuum, with arousal thresholds generally lowest in stage 1 and highest in stage 4 sleep. NREM sleep is usually associated with minimal or fragmentary mental activity. A shorthand definition of NREM sleep is a relatively inactive yet actively regulating brain in a movable body.

REM sleep, by contrast, is defined by EEG activation, muscle atonia, and episodic bursts of rapid eye movements. REM sleep usually is not divided into stages, although tonic and phasic types of REM sleep are occasionally distinguished for certain research purposes. The distinction of tonic versus phasic is based on short-lived events such as eye movements that tend to occur in clusters separated by episodes of relative quiescence. In cats, REM sleep phasic activity is epitomized by bursts of ponto-geniculo-occipital (PGO) waves, which are accompanied peripherally by rapid eye movements, twitching of distal muscles, middle ear muscle activity, and other phasic events that correspond to the phasic event markers easily measurable in human beings. As described in Chapter 141, PGO waves are not usually detectable in human beings. Thus, the most commonly used marker of REM sleep phasic activity in human beings is, of course, the bursts of rapid eye movements (Fig. 2-2); muscle twitches and cardiorespiratory irregularities often accompany the REM bursts. The mental activity of human REM sleep is associated with dreaming, based on vivid dream recall reported after approximately 80% of arousals from this state of sleep.[1] Inhibition of spinal motor neurons by brainstem mechanisms mediates suppression of postural motor tonus in REM sleep. A shorthand definition of REM sleep, therefore, is an activated brain in a paralyzed body.

Box 2-1 Sleep Medicine Methodology and Nomenclature

In 2007, the American Academy of Sleep Medicine (AASM) published a new manual (see reference 50) for scoring sleep and associated events. This manual recommends alterations to recording methodology and terminology that the Academy will demand of clinical laboratories in the future. Although specification of arousal, cardiac, movement, and respiratory rules appear to be value added to the assessment of sleep-related events, the new rules, terminology, and technical specifications for recording and scoring sleep are not without controversy.

The current chapter uses the traditional terminology and definitions, upon which most descriptive and experimental research has been based since the 1960s.[17] Hence, where the AASM terminology uses the term N for NREM sleep stages and R for REM sleep stages, N1 and N2 are used instead of stage 1 and stage 2; N3 is used to indicate the sum of stage 3 and stage 4 (often called slow-wave sleep in human literature); R is used to name REM sleep. Another change is to the nomenclature for the recording placements. Hence, calling the auricular placements M1 and M2 (rather than A1 and A2) is unnecessary and places the sleep EEG recording terminology outside the pale for EEG recording terminology in other disciplines. Although these are somewhat trivial changes, changes in nomenclature can result in confusion when attempting to compare to previous literature and established data sets and are of concern for clinicians and investigators who communicate with other fields.

Of greater concern are changes to the core recording and scoring recommendations that the AASM manual recommends. For example, the recommended scoring montage requires using a frontal (F3 or F4) EEG placement for use with visual scoring of the recordings, rather than the central (C3 or C4) EEG placements recommended in the standard manual. The rationale for the change is that the frontal placements pick up more slow-wave activity during sleep. The consequence, however, is that sleep studies performed and scored with the frontal EEG cannot be compared to normative or clinical data and the frontal placements also truncate the ability to visualize sleep spindles. Furthermore, developmental changes to the regional EEG preclude the universal assumption that sleep slow-wave activity is a frontal event.

Other issues are present in this new AASM approach to human sleep; however, this is not the venue for a complete description of such concerns. In summary, the AASM scoring manual has not yet become the universal standard for assessing human sleep and might not achieve that status in its current form. Specifications for recording and scoring sleep are not without controversy.[51-56]

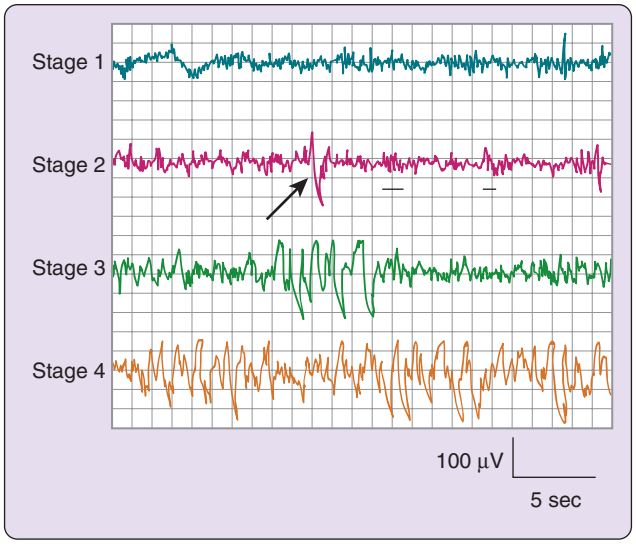

Figure 2-1 The stages of non–rapid eye movement sleep. The four electroencephalogram tracings depicted here are from a 19-year-old female volunteer. Each tracing was recorded from a referential lead (C3/A2) recorded on a Grass Instruments Co. (West Warwick, R.I.) Model 7D polygraph with a paper speed of 10 mm/sec, time constant of 0.3 sec, and ½ -amplitude high-frequency setting of 30 Hz. On the second tracing, the *arrow* indicates a K-complex and the *underlining* shows two sleep spindles.

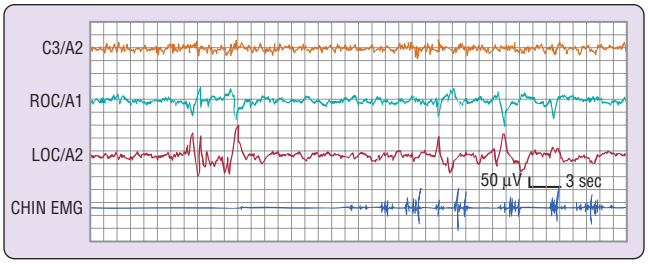

Figure 2-2 Phasic events in human rapid eye movement (REM) sleep. On the *left side* is a burst of several rapid eye movements (out-of-phase deflections in right outer canthus [ROC]/A1 and left outer canthus [LOC]/A2). On the *right side,* there are additional rapid eye movements as well as twitches on the electromyographic (EMG) lead. The interval between eye movement bursts and twitches illustrates tonic REM sleep.

SLEEP ONSET

The onset of sleep under normal circumstances in normal adult humans is through NREM sleep. This fundamental principle of normal human sleep reflects a highly reliable finding and is important in considering normal versus pathologic sleep. For example, the abnormal entry into sleep through REM sleep can be a diagnostic sign in adult patients with narcolepsy.

Definition of Sleep Onset

The precise definition of the onset of sleep has been a topic of debate, primarily because there is no single measure that is 100% clear-cut 100% of the time. For example, a change in EEG pattern is not always associated with a person's perception of sleep, yet even when subjects report that they are still awake, clear behavioral changes can indicate the presence of sleep. To begin a consideration of this issue, let us examine the three basic polysomnographic measures of sleep and how they change with sleep onset. The electrode placements are described in Chapter 141.

Electromyogram

The electromyogram (EMG) may show a gradual diminution of muscle tonus as sleep approaches, but rarely does

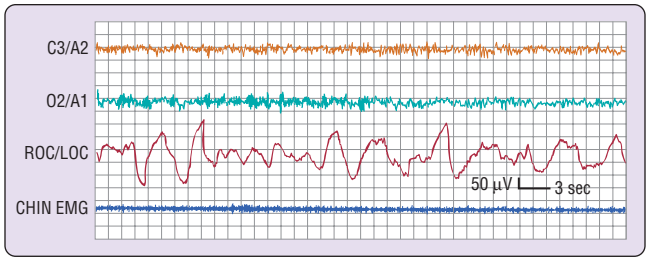

Figure 2-3 The transition from wakefulness to stage 1 sleep. The most marked change is visible on the two electroencephalographic (EEG) channels (C3/A2 and O2/A1), where a clear pattern of rhythmic alpha activity (8 cps) changes to a relatively low-voltage, mixed- frequency pattern at about the middle of the figure. The level of electromyographic (EMG) activity does not change markedly. Slow eye movements (right outer canthus [ROC]/left outer canthus [LOC]) are present throughout this episode, preceding the EEG change by at least 20 seconds. In general, the change in EEG patterns to stage 1 as illustrated here is accepted as the onset of sleep.

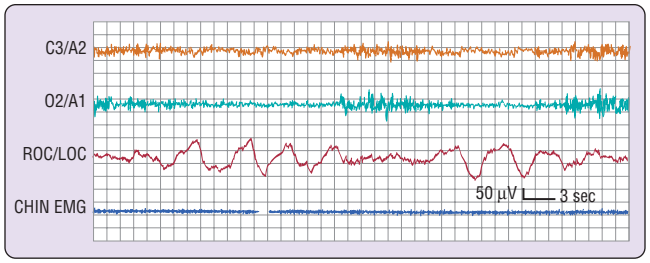

Figure 2-4 A common wake- to-sleep transition pattern. Note that the electroencephalographic pattern changes from wake (rhythmic alpha) to stage 1 (relatively low-voltage, mixed-frequency) sleep twice during this attempt to fall asleep. EMG, electromyogram; LOC, left outer canthus; ROC, right outer canthus.

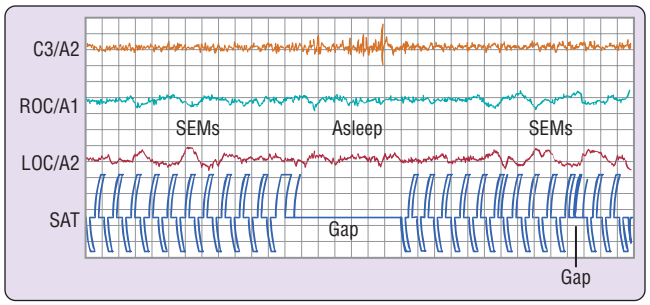

Figure 2-5 Failure to perform a simple behavioral task at the onset of sleep. The volunteer had been deprived of sleep overnight and was required to tap two switches alternately, shown as pen deflections of opposite polarity on the channel labeled SAT. When the electroencephalographic (EEG; C3/A2) pattern changes to stage 1 sleep, the behavior stops, returning when the EEG pattern reverts to wakefulness. LOC, left outer canthus; ROC, right outer canthus; SEMs, slow eye movements. (From Carskadon MA, Dement WC. Effects of total sleep loss on sleep tendency. Percept Mot Skills 1979;48:495-506. © Perceptual and Motor Skills, 1979.)

a discrete EMG change pinpoint sleep onset. Furthermore, the presleep level of the EMG, particularly if the person is relaxed, can be entirely indistinguishable from that of unequivocal sleep (Fig. 2-3).

Electrooculogram

As sleep approaches, the electrooculogram (EOG) shows slow, possibly asynchronous eye movements (see Fig. 2-3) that usually disappear within several minutes of the EEG changes described next. Occasionally, the onset of these slow eye movements coincides with a person's perceived sleep onset; more often, subjects report that they are still awake.

Electroencephalogram

In the simplest circumstance (see Fig. 2-3), the EEG changes from a pattern of clear rhythmic alpha (8 to 13 cycles per second [cps]) activity, particularly in the occipital region, to a relatively low-voltage, mixed-frequency pattern (stage 1 sleep). This EEG change usually occurs seconds to minutes after the start of slow eye movements. With regard to introspection, the onset of a stage 1 EEG pattern may or may not coincide with perceived sleep onset. For this reason, a number of investigators require the presence of specific EEG patterns—the K-complex or sleep spindle (i.e., stage 2 sleep)—to acknowledge sleep onset. Even these stage 2 EEG patterns, however, are not unequivocally associated with perceived sleep.[2] A further complication is that sleep onset often does not occur all at once; instead, there may be a wavering of vigilance before "unequivocal" sleep ensues (Fig. 2-4). Thus, it is difficult to accept a single variable as marking sleep onset. As Davis and colleagues[3] wrote many years ago (p. 35):

> Is "falling asleep" a unitary event? Our observations suggest that it is not. Different functions, such as sensory awareness, memory, self-consciousness, continuity of logical thought, latency of response to a stimulus, and alterations in the pattern of brain potentials all go in parallel in a general way, but there are exceptions to every rule. Nevertheless, a reasonable consensus exists that the EEG change to stage 1, usually heralded or accompanied by slow eye movements, identifies the transition to sleep, provided that another EEG sleep pattern does not intervene. One might not always be able to pinpoint this transition to the millisecond, but it is usually possible to determine the change reliably within several seconds.

Behavioral Concomitants of Sleep Onset

Given the changes in the EEG that accompany the onset of sleep, what are the behavioral correlates of the wake-to-sleep transition? The following material reviews a few common behavioral concomitants of sleep onset. Keep in mind that "different functions may be depressed in different sequence and to different degrees in different subjects and on different occasions" (p. 35).[3]

Simple Behavioral Task

In the first example, volunteers were asked to tap two switches alternately at a steady pace. As shown in Figure 2-5, this simple behavior continues after the onset of slow eye movements and may persist for several seconds after the EEG changes to a stage 1 sleep pattern.[4] The behavior then ceases, usually to recur only after the EEG reverts to a waking pattern. This is an example of what one may think of as the simplest kind of "automatic" behavior pattern. Because such simple behavior can persist past sleep onset

and as one passes in and out of sleep, it might explain how impaired, drowsy drivers are able to continue down the highway.

Visual Response

A second example of behavioral change at sleep onset derives from an experiment in which a bright light is placed in front of the subject's eyes, and the subject is asked to respond when a light flash is seen by pressing a sensitive microswitch taped to the hand.[5] When the EEG pattern is stage 1 or stage 2 sleep, the response is absent more than 85% of the time. When volunteers are queried afterward, they report that they did not see the light flash, not that they saw the flash but the response was inhibited. This is one example of the perceptual disengagement from the environment that accompanies sleep onset.

Auditory Response

In another sensory domain, the response to sleep onset is examined with a series of tones played over earphones to a subject who is instructed to respond each time a tone is heard. One study of this phenomenon showed that reaction times became longer in proximity to the onset of stage 1 sleep, and responses were absent coincident with a change in EEG to unequivocal sleep.[6] For responses in both visual and auditory modalities, the return of the response after its sleep-related disappearance typically requires the resumption of a waking EEG pattern.

Olfactory Response

When sleeping humans are tasked to respond when they smell something, the response depends in part on sleep state and in part on the particular odorant. In contrast to visual responses, one study showed that responses to graded strengths of peppermint (strong trigeminal stimulant usually perceived as pleasant) and pyridine (strong trigeminal stimulant usually perceived as extremely unpleasant) were well maintained during initial stage 1 sleep.[7] As with other modalities, the response in other sleep stages was significantly poorer: Peppermint simply was not consciously smelled in stages 2 and 4 NREM sleep or in REM sleep; pyridine was never smelled in stage 4 sleep, and only occasionally in stage 2 NREM and in REM sleep.[7] On the other hand, a tone successfully aroused the young adult participants in every stage. One conclusion of this report was that the olfactory system of humans is not a good sentinel system during sleep.

Response to Meaningful Stimuli

One should not infer from the preceding studies that the mind becomes an impenetrable barrier to sensory input at the onset of sleep. Indeed, one of the earliest modern studies of arousability during sleep showed that sleeping human beings were differentially responsive to auditory stimuli of graded intensity.[8] Another way of illustrating sensory sensitivity is shown in experiments that have assessed discriminant responses during sleep to meaningful versus nonmeaningful stimuli, with meaning supplied in a number of ways and response usually measured as evoked K-complexes or arousal. The following are examples.

- A person tends to have a lower arousal threshold for his or her own name versus someone else's name.[9] In light sleep, for example, one's own name spoken softly will produce an arousal; a similarly applied nonmeaningful stimulus will not. Similarly, a sleeping mother is more likely to hear her own baby's cry than the cry of an unrelated infant.
- Williams and colleagues[10] showed that the likelihood of an appropriate response during sleep was improved when an otherwise nonmeaningful stimulus was made meaningful by linking the absence of response to punishment (a loud siren, flashing light, and the threat of an electric shock).

From these examples and others, it seems clear that sensory processing at some level does continue after the onset of sleep. Indeed, one study has shown with functional magnetic resonance imaging that regional brain activation occurs in response to stimuli during sleep and that different brain regions (middle temporal gyrus and bilateral orbitofrontal cortex) are activated in response to meaningful (person's own name) versus nonmeaningful (beep) stimuli.[11]

Hypnic Myoclonia

What other behaviors accompany the onset of sleep? If you awaken and query someone shortly after the stage 1 sleep EEG pattern appears, the person usually reports the mental experience as one of losing a direct train of thought and of experiencing vague and fragmentary imagery, usually visual.[12] Another fairly common sleep-onset experience is hypnic myoclonia, which is experienced as a general or localized muscle contraction very often associated with rather vivid visual imagery. Hypnic myoclonias are not pathologic events, although they tend to occur more commonly in association with stress or with unusual or irregular sleep schedules.

The precise nature of hypnic myoclonias is not clearly understood. According to one hypothesis, the onset of sleep in these instances is marked by a dissociation of REM sleep components, wherein a breakthrough of the imagery component of REM sleep (hypnagogic hallucination) occurs in the absence of the REM motor inhibitory component. A response by the individual to the image, therefore, results in a movement or jerk. The increased frequency of these events in association with irregular sleep schedules is consistent with the increased probability of REM sleep occurring at the wake-to-sleep transition under such conditions (see later). Although the usual transition in adult human beings is to NREM sleep, the REM portal into sleep, which is the norm in infancy, can become partially opened under unusual circumstances.

Memory Near Sleep Onset

What happens to memory at the onset of sleep? The transition from wake to sleep tends to produce a memory impairment. One view is that it is as if sleep closes the gate between short-term and long-term memory stores. This phenomenon is best described by the following experiment.[13] During a presleep testing session, word pairs were presented to volunteers over a loudspeaker at 1-minute intervals. The subjects were then awakened either 30 seconds or 10 minutes after the onset of sleep (defined as EEG stage 1) and asked to recall the words presented before sleep onset. As illustrated in Figure 2-6, the

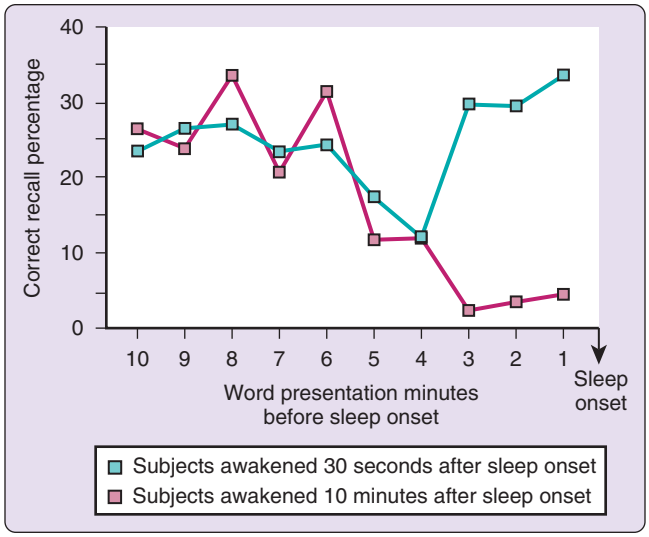

Figure 2-6 Memory is impaired by sleep, as shown by the study results illustrated in this graph. See text for explanation.

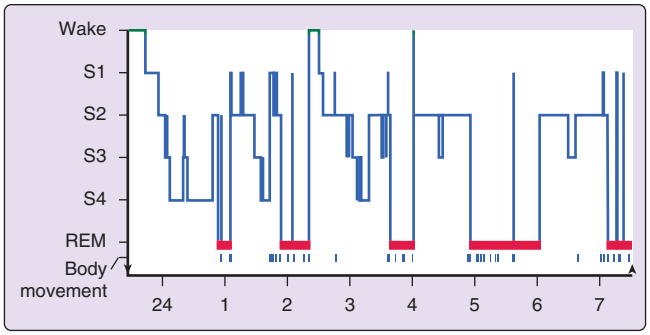

Figure 2-7 The progression of sleep stages across a single night in a normal young adult volunteer is illustrated in this sleep histogram. The text describes the ideal or average pattern. This histogram was drawn on the basis of a continuous overnight recording of electroencephalogram, electrooculogram, and electromyogram in a normal 19-year-old man. The record was assessed in 30-second epochs for the various sleep stages. REM, rapid eye movement.

30-second condition was associated with a consistent level of recall from the entire 10 minutes before sleep onset. (Primacy and recency effects are apparent, although not large.) In the 10-minute condition, however, recall paralleled that in the 30-second group for only the 10 to 4 minutes before sleep onset and then fell abruptly from that point until sleep onset.

In the 30-second condition, therefore, both longer-term (4 to 10 minutes) and shorter-term (0 to 3 minutes) memory stores remained accessible. In the 10-minute condition, by contrast, words that were in longer-term stores (4 to 10 minutes) before sleep onset were accessible, whereas words that were still in shorter-term stores (0 to 3 minutes) at sleep onset were no longer accessible; that is, they had not been consolidated into longer-term memory stores. One conclusion of this experiment is that sleep inactivates the transfer of storage from short- to long-term memory. Another interpretation is that encoding of the material before sleep onset is of insufficient strength to allow recall. The precise moment at which this deficit occurs is not known and may be a continuing process, perhaps reflecting anterograde amnesia. Nevertheless, one may infer that if sleep persists for approximately 10 minutes, memory is lost for the few minutes before sleep. The following experiences represent a few familiar examples of this phenomenon:

- Inability to grasp the instant of sleep onset in your memory.
- Forgetting a telephone call that had come in the middle of the night.
- Forgetting the news you were told when awakened in the night.
- Not remembering the ringing of your alarm clock.
- Experiencing morning amnesia for coherent sleeptalking.
- Having fleeting dream recall.

Patients with syndromes of excessive sleepiness can experience similar memory problems in the daytime if sleep becomes intrusive.

Learning and Sleep

In contrast to this immediate sleep-related "forgetting," the relevance for sleep to human learning—particularly for consolidation of perceptual and motor learning—is of growing interest.[14,15] The importance of this association has also generated some debate and skepticism.[16] Nevertheless, a spate of recent research is awakening renewed interest in the topic, and mechanistic studies explaining the roles of REM and NREM sleep more precisely are under examination (see Chapter 29).

PROGRESSION OF SLEEP ACROSS THE NIGHT

Pattern of Sleep in a Normal Young Adult

The simplest description of sleep begins with the ideal case, the normal young adult who is sleeping well and on a fixed schedule of about 8 hours per night (Fig. 2-7). In general, no consistent male versus female distinctions have been found in the normal pattern of sleep in young adults. In briefest summary, the normal human adult enters sleep through NREM sleep, REM sleep does not occur until 80 minutes or longer thereafter, and NREM sleep and REM sleep alternate through the night, with an approximately 90-minute cycle (see Chapter 141 for a full description of sleep stages).

First Sleep Cycle

The first cycle of sleep in the normal young adult begins with stage 1 sleep, which usually persists for only a few (1 to 7) minutes at the onset of sleep. Sleep is easily discontinued during stage 1 by, for example, softly calling a person's name, touching the person lightly, quietly closing a door, and so forth. Thus, stage 1 sleep is associated with a low arousal threshold. In addition to its role in the initial wake-to-sleep transition, stage 1 sleep occurs as a transitional stage throughout the night. A common sign of severely disrupted sleep is an increase in the amount and percentage of stage 1 sleep.

Stage 2 NREM sleep, signaled by sleep spindles or K-complexes in the EEG (see Fig. 2-1), follows this brief

episode of stage 1 sleep and continues for approximately 10 to 25 minutes. In stage 2 sleep, a more intense stimulus is required to produce arousal. The same stimulus that produced arousal from stage 1 sleep often results in an evoked K-complex but no awakening in stage 2 sleep.

As stage 2 sleep progresses, high-voltage slow-wave activity gradually appears in the EEG. Eventually, this activity meets the criteria[17] for stage 3 NREM sleep, that is, high-voltage (at least 75 μV) slow-wave (2 cps) activity accounting for more than 20% but less than 50% of the EEG activity. Stage 3 sleep usually lasts only a few minutes in the first cycle and is transitional to stage 4 as more and more high-voltage slow-wave activity occurs. Stage 4 NREM sleep—identified when the high-voltage slow-wave activity comprises more than 50% of the record—usually lasts approximately 20 to 40 minutes in the first cycle. An incrementally larger stimulus is usually required to produce an arousal from stage 3 or 4 sleep than from stage 1 or 2 sleep. (Investigators often refer to the combined stages 3 and 4 sleep as slow-wave sleep [SWS], delta sleep, or deep sleep.)

A series of body movements usually signals an "ascent" to lighter NREM sleep stages. A brief (1- or 2-minute) episode of stage 3 sleep might occur, followed by perhaps 5 to 10 minutes of stage 2 sleep interrupted by body movements preceding the initial REM episode. REM sleep in the first cycle of the night is usually short-lived (1 to 5 minutes). The arousal threshold in this REM episode is variable, as is true for REM sleep throughout the night. Theories to explain the variable arousal threshold of REM sleep have suggested that at times, the person's selective attention to internal stimuli precludes a response or that the arousal stimulus is incorporated into the ongoing dream story rather than producing an awakening. Certain early experiments examining arousal thresholds in cats found highest thresholds in REM sleep, which was then termed *deep sleep* in this species. Although this terminology is still often used in publications about sleep in animals, it should not be confused with human NREM stages 3 plus 4 sleep, which is also often called deep sleep. One should also note that SWS is sometimes used (as is synchronized sleep) as a synonym for all of NREM sleep in other species and is thus distinct from SWS (stages 3 plus 4 NREM) in human beings.

NREM-REM Cycle

NREM sleep and REM sleep continue to alternate through the night in cyclic fashion. REM sleep episodes usually become longer across the night. Stages 3 and 4 sleep occupy less time in the second cycle and might disappear altogether from later cycles, as stage 2 sleep expands to occupy the NREM portion of the cycle. The average length of the first NREM-REM sleep cycle is approximately 70 to 100 minutes; the average length of the second and later cycles is approximately 90 to 120 minutes. Across the night, the average period of the NREM-REM cycle is approximately 90 to 110 minutes.

Distribution of Sleep Stages across the Night

In the young adult, SWS dominates the NREM portion of the sleep cycle toward the beginning of the night (the first one third); REM sleep episodes are longest in the last one third of the night. Brief episodes of wakefulness tend to intrude later in the night, usually near REM sleep transitions, and they usually do not last long enough to be remembered in the morning. The preferential distribution of REM sleep toward the latter portion of the night in normal human adults is thought to be linked to a circadian oscillator, which can be gauged by the oscillation of body temperature.[18,19] The preferential distribution of SWS toward the beginning of a sleep episode is not thought to be mediated by circadian processes but shows a marked response to the length of prior wakefulness.[20] The SWS pattern reflects the homeostatic sleep system, highest at sleep onset and diminishing across the night as sleep pressure wanes. Thus, these aspects of the normal sleep pattern highlight features of the two-process model of sleep as elaborated on in Chapter 37.

Length of Sleep

The length of nocturnal sleep depends on a great number of factors—of which volitional control is among the most significant in human beings—and it is thus difficult to characterize a "normal" pattern. Most young adults report sleeping approximately 7.5 hours a night on weekday nights and slightly longer, 8.5 hours, on weekend nights. The variability of these figures from person to person and from night to night, however, is quite high. Sleep length also depends on genetic determinants,[21] and one may think of the volitional determinants (staying up late, waking by alarm, and so on) superimposed on the background of a genetic sleep need. Length of prior waking also affects how much sleeps, although not in a one-for-one manner. Indeed, the length of sleep is also determined by processes associated with circadian rhythms. Thus, *when* one sleeps helps to determine *how long* one sleeps. In addition, as sleep is extended, the amount of REM sleep increases, because REM sleep depends on the persistence of sleep into the peak circadian time in order to occur.

Generalizations about Sleep in the Normal Young Adult

A number of general statements can be made regarding sleep in the normal young adult who is living on a conventional sleep-wake schedule and who is without sleep complaints:

- Sleep is entered through NREM sleep.
- NREM sleep and REM sleep alternate with a period near 90 minutes.
- SWS predominates in the first third of the night and is linked to the initiation of sleep and the length of time awake.
- REM sleep predominates in the last third of the night and is linked to the circadian rhythm of body temperature.
- Wakefulness in sleep usually accounts for less than 5% of the night.
- Stage 1 sleep generally constitutes approximately 2% to 5% of sleep.
- Stage 2 sleep generally constitutes approximately 45% to 55% of sleep.
- Stage 3 sleep generally constitutes approximately 3% to 8% of sleep.

- Stage 4 sleep generally constitutes approximately 10% to 15% of sleep.
- NREM sleep, therefore, is usually 75% to 80% of sleep.
- REM sleep is usually 20% to 25% of sleep, occurring in four to six discrete episodes.

Factors Modifying Sleep Stage Distribution

Age

The strongest and most consistent factor affecting the pattern of sleep stages across the night is age (Fig. 2-8). The most marked age-related differences in sleep from the patterns described earlier are found in newborn infants. For the first year of life, the transition from wake to sleep is often accomplished through REM sleep (called *active sleep* in newborns). The cyclic alternation of NREM-REM sleep is present from birth but has a period of approximately 50 to 60 minutes in the newborn compared with approximately 90 minutes in the adult. Infants also only gradually acquire a consolidated nocturnal sleep cycle, and the fully developed EEG patterns of the NREM sleep stages are not present at birth but emerge over the first 2 to 6 months of life. When brain structure and function achieve a level that can support high-voltage slow-wave EEG activity, NREM stages 3 and 4 sleep become prominent.

SWS is maximal in young children and decreases markedly with age. The SWS of young children is both qualitatively and quantitatively different from that of older adults. For example, it is nearly impossible to wake youngsters in the SWS of the night's first sleep cycle. In one study,[22] a 123-dB tone failed to produce any sign of arousal in a group of children whose mean age was 10 years. In addition, children up to midadolescence often "skip" their first REM episode, perhaps due to the quantity and intensity of slow-wave activity early in the night. A similar, although less profound qualitative difference distinguishes SWS occurring in the first and later cycles of the night in a given person. The quantitative change in SWS may best be seen across adolescence, when SWS decreases by nearly 40% during the second decade, even when length of nocturnal sleep remains constant.[23] Feinberg[24] hypothesized that the age-related decline in nocturnal SWS might parallel loss of cortical synaptic density. By midadolescence, youngsters no longer typically skip their first REM, and their sleep resembles that described earlier for young adults. By age 60 years, SWS might no longer be present, particularly in men. Women appear to maintain SWS later into life than men.

REM sleep as a percentage of total sleep is maintained well into healthy old age; the absolute amount of REM sleep at night has been correlated with intellectual functioning[25] and declines markedly in the case of organic brain dysfunctions of the elderly.[26]

Arousals during sleep increase markedly with age. Extended wake episodes of which the individual is aware and can report, as well as brief and probably unremembered arousals, increase with aging.[27] The latter type of transient arousals may occur with no known correlate but are often associated with occult sleep disturbances, such as periodic limb movements during sleep (PLMS) and sleep-related respiratory irregularities, which also become more prevalent in later life.[28,29]

Perhaps the most notable finding regarding sleep in the elderly is the profound increase in interindividual variability,[30] which thus precludes generalizations such as those made for young adults.

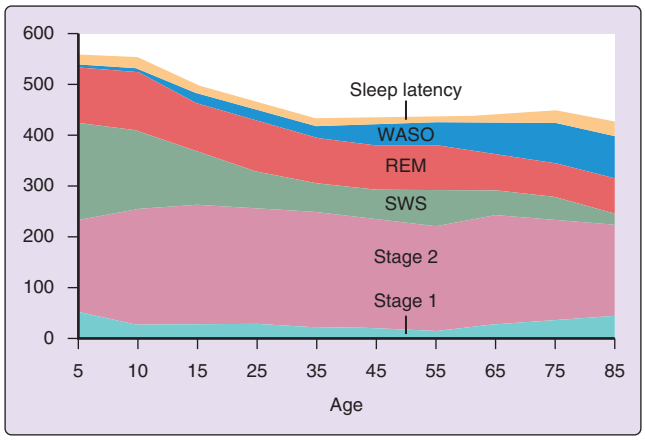

Figure 2-8 Changes in sleep with age. Time (in minutes) for sleep latency and wake time after sleep onset (WASO) and for rapid eye movement (REM) sleep and non-REM (NREM) sleep stages 1, 2, and slow wave sleep (SWS). Summary values are given for ages 5 to 85 years. (Ohayon M, Carskadon MA, Guilleminault C, et al. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004;27:1255-1273.)

Prior Sleep History

A person who has experienced sleep loss on one or more nights shows a sleep pattern that favors SWS during recovery (Fig. 2-9). Recovery sleep is also usually prolonged and deeper—that is, having a higher arousal threshold throughout—than basal sleep. REM sleep tends to show a rebound on the second or subsequent recovery nights after an episode of sleep loss. Therefore, with total sleep loss, SWS tends to be preferentially recovered compared with REM sleep, which tends to recover only after the recuperation of SWS.

Cases in which a person is differentially deprived of REM or SWS—either operationally, by being awakened each time the sleep pattern occurs, or pharmacologically (see later)—show a preferential rebound of that stage of sleep when natural sleep is resumed. This phenomenon has particular relevance in a clinical setting, in which abrupt withdrawal from a therapeutic regimen can result in misleading diagnostic findings (e.g., sleep-onset REM periods [SOREMPs] as a result of a REM sleep rebound) or could conceivably exacerbate a sleep disorder (e.g., if sleep apneas tend to occur preferentially or with greater intensity in the rebounding stage of sleep).

Chronic restriction of nocturnal sleep, an irregular sleep schedule, or frequent disturbance of nocturnal sleep can result in a peculiar distribution of sleep states, most commonly characterized by premature REM sleep, that is, SOREMPs. Such episodes can be associated with hypnagogic hallucinations, sleep paralysis, or an increased

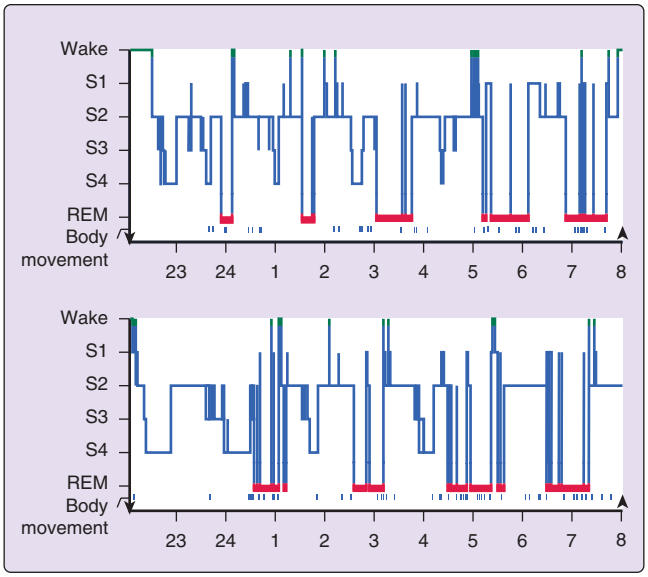

Figure 2-9 The *upper histogram* shows the baseline sleep pattern of a normal 14-year-old female volunteer. The *lower histogram* illustrates the sleep pattern in this volunteer for the first recovery night after 38 hours without sleep. Note that the amount of stage 4 sleep on the lower graph is greater than on baseline, and the first rapid eye movement (REM) sleep episode is markedly delayed.

incidence of hypnic myoclonia in persons with no organic sleep disorder.

Although not strictly related to prior sleep history, the first night of a laboratory sleep evaluation is commonly associated with a disruption of the normal distribution of sleep states, characterized chiefly by a delayed onset of REM sleep.[31] Often this delay takes the form of skipping the first REM episode of the night. In other words, the NREM sleep stages progress in a normal fashion, but the first cycle ends with an episode of stage 1 or a brief arousal instead of the expected brief REM sleep episode. In addition, REM sleep episodes are often disrupted, and the total amount of REM sleep on the first night in the sleep laboratory is also usually reduced from the normal value.

Circadian Rhythms

The circadian phase at which sleep occurs affects the distribution of sleep stages. REM sleep, in particular, occurs with a circadian distribution that peaks in the morning hours coincident with the trough of the core body temperature rhythm.[18,19] Thus, if sleep onset is delayed until the peak REM phase of the circadian rhythm—that is, the early morning—REM sleep tends to predominate and can even occur at the onset of sleep. This reversal of the normal sleep-onset pattern is commonly seen in a normal person who acutely undergoes a phase shift, either as a result of a work shift change or as a change resulting from jet travel across a number of time zones. Studies of persons sleeping in environments free of all cues to time have shown that the timing of sleep onset and the length of sleep occur as a function of circadian phase.[32,33] Under these conditions, sleep distribution with reference to the circadian body temperature phase position shows that sleep onset is likeliest to occur on the falling limb of the temperature cycle. A secondary peak of sleep onsets, corresponding to afternoon napping, also occurs; the offset of sleep occurs most often on the rising limb of the circadian body temperature curve.[34]

Temperature

Extremes of temperature in the sleeping environment tend to disrupt sleep. REM sleep is commonly more sensitive to temperature-related disruption than is NREM sleep. Accumulated evidence from human beings and other species suggests that mammals have only minimal ability to thermoregulate during REM sleep; in other words, the control of body temperature is virtually poikilothermic in REM sleep.[35] This inability to thermoregulate in REM sleep probably affects the response to temperature extremes and suggests that such conditions are less of a problem early during a night than late, when REM sleep tends to predominate. It should be clear, as well, that such responses as sweating or shivering during sleep under ambient temperature extremes occur in NREM sleep and are limited in REM sleep.

Drug Ingestion

The distribution of sleep states and stages is affected by many common drugs, including those typically prescribed in the treatment of sleep disorders as well as those not specifically related to the pharmacotherapy of sleep disorders and those used socially or recreationally. Whether changes in sleep stage distribution have any relevance to health, illness, or psychological well-being is unknown; however, particularly in the context of specific sleep disorders that differentially affect one sleep stage or another, such distinctions may be relevant to diagnosis or treatment. A number of generalizations regarding the effects of certain of the more commonly used compounds on sleep stage distribution can be made.

- Benzodiazepines tend to suppress SWS and have no consistent effect on REM sleep.
- Tricyclic antidepressants, monoamine oxidase inhibitors, and certain selective serotonin reuptake inhibitors tend to suppress REM sleep. An increased level of motor activity during sleep occurs with certain of these compounds, leading to a pattern of REM sleep without motor inhibition or an increased incidence of PLMS. Fluoxetine is also associated with rapid eye movements across all sleep stages ("Prozac eyes").
- Withdrawal from drugs that selectively suppress a stage of sleep tends to be associated with a rebound of that sleep stage. Thus, acute withdrawal from a benzodiazepine compound is likely to produce an increase of SWS; acute withdrawal from a tricyclic antidepressant or monoamine oxidase inhibitor is likely to produce an increase of REM sleep. In the latter case, this REM rebound could result in abnormal SOREMPs in the absence of an organic sleep disorder, perhaps leading to an incorrect diagnosis of narcolepsy.
- Acute presleep alcohol intake can produce an increase in SWS and REM sleep suppression early in the night, which can be followed by REM sleep rebound in the latter portion of the night as the alcohol is metabolized.

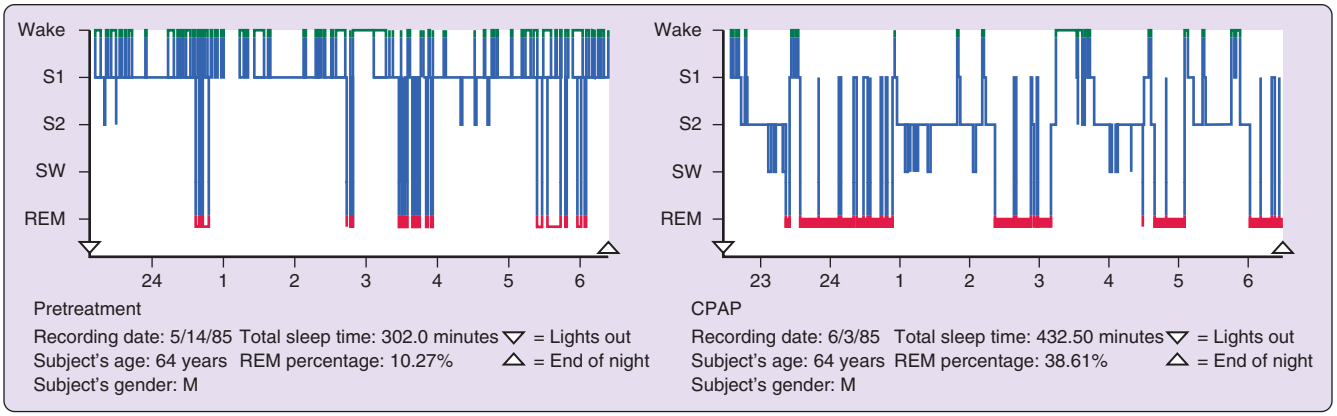

Figure 2-10 These sleep histograms depict the sleep of a 64-year-old male patient with obstructive sleep apnea syndrome. The *let graph* shows the sleep pattern before treatment. Note the absence of slow-wave sleep, the preponderance of stage 1 (S1), and the very frequent disruptions. The *right graph* shows the sleep pattern in this patient during the second night of treatment with continuous positive airway pressure (CPAP). Note that sleep is much deeper (more SWS) and more consolidated, and rapid eye movement (REM) sleep in particular is abnormally increased. The pretreatment REM percentage of sleep was only 10%, versus nearly 40% with treatment. (Data supplied by G. Nino-Murcia, Stanford University Sleep Disorders Center, Stanford, Calif.)

Low doses of alcohol have minimal effects on sleep stages, but they can increase sleepiness late at night.[36,37]

- Acute effects of marijuana (tetrahydrocannabinol [THC]) include minimal sleep disruption, characterized by a slight reduction of REM sleep. Chronic ingestion of THC produces a long-term suppression of SWS.[38]

Pathology

Sleep disorders, as well as other nonsleep problems, have an impact on the structure and distribution of sleep. As suggested before, these distinctions appear to be more important in diagnosis and in the consideration of treatments than for any implications about general health or illness resulting from specific sleep stage alterations. A number of common sleep-stage anomalies are commonly associated with sleep disorders.

Narcolepsy

Narcolepsy is characterized by an abnormally short delay to REM sleep, marked by SOREMPs. This abnormal sleep-onset pattern occurs with some consistency, but not exclusively; that is, NREM sleep onset can also occur. Thus, the preferred diagnostic test consists of several opportunities to fall asleep across a day (see Chapter 143). If REM sleep occurs abnormally on two or more such opportunities, narcolepsy is extremely probable. The occurrence of this abnormal sleep pattern in narcolepsy is thought to be responsible for the rather unusual symptoms of this disorder. In other words, dissociation of components of REM sleep into the waking state results in hypnagogic hallucinations, sleep paralysis, and, most dramatically, cataplexy.

Other conditions in which a short REM sleep latency can occur include infancy, in which sleep-onset REM sleep is normal; sleep reversal or jet lag; acute withdrawal from REM-suppressant compounds; chronic restriction or disruption of sleep; and endogenous depression.[39] Reports have indicated a relatively high prevalence of REM sleep onsets in young adults[40] and in adolescents with early rise times.[41] In the latter, the REM sleep onsets on morning (8:30 AM and 10:30 AM) naps were related to a delayed circadian phase as indicated by later onset of melatonin secretion.

Sleep apnea syndromes

Sleep apnea syndromes may be associated with suppression of SWS or REM sleep secondary to the sleep-related breathing problem. Successful treatment of this sleep disorder, as with nocturnal continuous positive airway pressure, can produce large rebounds of SWS or REM sleep (Fig. 2-10).

Sleep fragmentation

Fragmentation of sleep and increased frequency of arousals occur in association with a number of sleep disorders as well as with medical disorders involving physical pain or discomfort. PLMS, sleep apnea syndromes, chronic fibrositis, and so forth may be associated with tens to hundreds of arousals each night. Brief arousals are prominent in such conditions as allergic rhinitis,[42,43] juvenile rheumatoid arthritis,[44] and Parkinson's disease.[45] In upper airway resistance syndrome,[46] EEG arousals are important markers because the respiratory signs of this syndrome are less obvious than in frank obstructive sleep apnea syndrome, and only subtle indicators may be available.[47] In specific situations, autonomic changes, such as transient changes of blood pressure,[48] can signify arousals; Lofaso and colleagues[49] indicated that autonomic changes are highly correlated with the extent of EEG arousals. Less well studied is the possibility that sleep fragmentation may be associated with subcortical events not visible in the cortical EEG signal. These disorders also often involve an increase in the absolute amount of and the proportion of stage 1 sleep.

Acknowledgments

The authors thank Joan Mancuso for preparing the figures.

❖ Clinical Pearls

The clinician should expect to see less slow-wave sleep (stages 3 and 4) in older persons, particularly men.

Clinicians or colleagues might find themselves denying mid-night communications (nighttime calls) because of memory deficits that occur for events proximal to sleep onset. This phenomenon might also account for memory deficits in excessively sleepy patients.

Many medications (even if not prescribed for sleep) can affect sleep stages, and their use or discontinuation alters sleep. Thus, REM-suppressant medications, for example, can result in a rebound of REM sleep when they are discontinued.

Certain patients have sleep complaints (insomnia, hypersomnia) that result from attempts to sleep or be awake at times not in synchrony with their circadian phase.

Patients who wake with events early in the night might have a disorder affecting NREM sleep; patients who wake with events late in the night may have a disorder affecting REM sleep.

When using sleep restriction to build sleep pressure, treatment will be more effective if sleep is scheduled at the correct circadian phase. The problem of napping in patients with insomnia is that naps diminish the homeostatic drive to sleep.

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Normal Aging

Donald L. Bliwise

Chapter 3

Abstract

Numerous factors challenge the integrity of sleep in the older human. Intrinsic lightening and fragmentation of sleep, reflecting changes in circadian and, even more so, homeostatic processes characterize aging, as do numerous medical and psychiatric comorbidities. Specific disorders such as sleep-disordered breathing and restless legs syndrome can demonstrate age-dependence and contribute to sleep problems. Descriptive data continue to accrue to suggest that sleep disturbance in late life might carry its own morbidity and should not be dismissed by the sleep medicine specialist. New data suggest that the breakdown of sleep in the aged organism might reflect physiologic age and reflect alterations in function present at the genomic level.

As the populations of industrialized societies age, knowledge of defining how sleep is affected by age will assume greater importance. Within the United States, the average current life expectancy of 77 years means that 80% of residents now live to be at least 65; the fastest growing segment of the population is those who are 85 years and older. These huge numbers force the sleep medicine specialist to confront the definition of what is *normal*. Researchers often use the term to connote a variety of meanings. In sleep medicine, confusion often occurs because the term is used descriptively, to indicate representativeness, as well as clinically, to indicate absence of disease.

Aging is also subject to semantic confusion. Chronologic age has been shown repeatedly only to approximate physiologic (biological) age. The decline in slow-wave sleep, for example, can occur at a chronological age (at least in men) far earlier than most age-related declines in other biological functions. Some researchers in gerontology have noted that distance from death may be a far better approximation of the aging process, but too few longitudinal sleep studies in humans exist to yield these types of findings. However, studies of invertebrates and have shed new light on relationships between physiologic age and sleep that can affect the functional significance of age-dependent changes (see Basic Science Considerations, later).

In addition to the issue of physiologic age, subjective age must be considered. Because the practice of sleep disorders medicine in geriatrics relies heavily on the increased self-reports of sleep disturbance seen in aging, subjective appraisal of the older person's symptoms must be considered. Whether an aged person views 75% sleep efficiency as insomnia or merely accepts this as a normal part of aging may depend largely on that person's perspective on growing old and what that means to him or her. It has been reported that older people are more likely to perceive themselves as having sleep problems if they have difficulty falling asleep rather than staying asleep, even though the latter continues to be a generally more commonly endorsed symptom.(See reference 1 for review) In addition, some have suggested that self-reports of sleep measured by polysomnography (PSG) are inherently less accurate and valid in older relative to younger subjects, although evidence for such age differences in other studies is decidedly mixed and varies according to the variables under consideration or the subject's sex.

Finally, normal aging must be viewed in counterpoint to pathologic aging (see Chapter 136). Although the prevalence of dementing illnesses is high in late life, determination of the number of normal elderly persons who may be in incipient stages of dementia has seldom been addressed. Additionally, recognition of mental impairments in the more limited domains of memory, executive function, language, attention, and visuospatial ability characterized as of lesser severity has led to the use of an intermediate diagnostic category termed *mild cognitive impairment* (MCI).[2] Few sleep studies of normal aging rely on extensive diagnostic work to eliminate persons in the earliest stages of mental impairment, and polysomnographic studies in well-defined MCI patients have yet to occur.

The point here is not to dismiss all that is known about sleep patterns in normal aging as inadequate but rather to point out the complexities of defining normal aging. Normal aging can never be defined without some arbitrary criteria. Throughout this chapter I will refer to aging across several species, encompassing both what in humans may be considered "middle-aged" (approximately 40 to 65 years) and "elderly" (older than 65 years). We recognize fully the otherwise arbitrary nature of these verbal and numeric descriptors of processes that are most assuredly gradual, are continuous, and vary widely across individuals. It is also important to recognize that the age-dependent alterations in sleep may simply be secondary manifestations of senescence.

SLEEP ARCHITECTURE

Although age-dependent alterations in sleep architecture have been described for many years,[3] only recently have attempts been made to summarize this large body of cross-sectional data using meta-analytic techniques.[4,5] Results from the first of these analyses[4] indicated that although sleep efficiency showed clear age-dependent declines up to and beyond age 90 years, the vast majority of age-dependent changes in sleep architecture occurred before age of 60 years, with few changes in slow-wave sleep (SWS, now referred to as N3 sleep in the revised American Academy of Sleep Medicine [AASM] nomenclature[6]; see later), rapid eye movement (REM) sleep, and stage 1 percentage (N1) occurring after that.[4] Some variables (total sleep time, REM) appeared best characterized as linear decline, whereas others (SWS, wake after sleep onset) followed a more exponential course. Sleep latency showed no clear age effect after age 60 years, although it increased up

Table 3-1 Sleep Architecture as a Function of Age

	Percentage of Time Spent in Stage—Mean (95% CI)							
	STAGE 1		**STAGE 2**		**STAGE 3 + 4**		**REM SLEEP**	
AGE (YR)	***MEN***	***WOMEN***	***MEN***	***WOMEN***	***MEN***	***WOMEN***	***MEN***	***WOMEN***
37-54	5.8 (5.2-6.5)	4.6 (4.1-5.3)	61.4 (60.0-62.8)	58.5 (57.1-60.0)	11.2 (9.9-12.6)	14.2 (12.7-15.9)	19.5 (18.8-20.2)	20.9 (20.0-21.8)
55-60	6.3 (5.6-7.0)	5.0 (4.4-5.7)	64.5 (63.2-65.9)	56.2 (54.5-57.8)	8.2 (7.1-9.5)	17.0 (15.2-18.9)	19.1 (18.4-19.8)	20.2 (19.3-21.1)
61-70	7.1 (6.4-7.9)	5.0 (4.4-5.7)	65.2 (63.9-66.5)	57.3 (55.7-58.9)	6.7 (5.7-7.7)	16.7 (14.8-18.6)	18.4 (17.8-19.1)	19.3 (18.4-20.2)
>70	7.6 (6.8-8.5)	4.9 (4.3-5.6)	66.5 (65.1-67.8)	57.1 (55.6-58.7)	5.5 (4.5-6.5)	17.2 (15.5-19.1)	17.8 (17.1-18.5)	18.8 (18.0-19.6)

CI, confidence interval; REM, rapid eye movement.
From Redline S, Kirchner HL, Quan SF, et al. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch Intern Med 2004;164:406-418.

to that point. A second meta-analysis focused only on REM percentage and noted a cubic trend, with REM apparently increasing after age 75 years and then demonstrating an even steeper drop after age 90 years.[5] The meaning of the latter data is unclear and raises many questions as to the extent of the precision of chronologic age to capture biological processes in these upper age ranges. Published population-based longitudinal data on sleep architecture would assist in addressing many of these uncertainties.

Although meta-analyses can provide cumulative information on age-dependent values across many laboratories, enormous variability in parameter values exists across studies,[4] and much of the sleep architecture was not scored blindly to the patient's chronologic age or sex. This might limit the value of meta-analytic approaches for extrapolation of readily usable, age-dependent laboratory norms. By contrast, the systematically collected, rigorously acquired data derived from the centralized scoring center for the Sleep Heart Health Study (SHHS), although subject to survivor effects and based on single-night data derived from composite cohorts, offer detailed appreciation of how comorbidities, demographics, and sleep-disordered breathing (SDB) can affect observed sleep architecture values employing traditional Rechtschaffen and Kales rules.[7] Some have viewed the SHHS sleep architecture data as broadly representative of the elderly population generally because persons with a wide variety of medical conditions were not excluded.[8]

Percentage of Time Spent in Each Sleep Stage

Table 3-1 provides sleep architecture values for 2685 SHHS participants ages 37 to 92 years, excluding persons who use psychotropic medications and who have high alcohol intake, restless legs syndrome symptoms and systemic pain conditions. About a third of these participants were hypertensive and about 10% had histories of cardiovascular disease or chronic pulmonary disease. Results clearly show that although age effects are apparent in some measures, gender occupied a far more dramatic role in sleep architecture, in some cases showing considerable divergence when comparing women and men. Most notable in this regard is percentage of time spent in sleep stages 3 plus 4, which shows enormous gender differences at every age and, in fact, shows no appreciable decline with aging in women, relative to men.

Men demonstrate a marked cross-sectional decline with aging, as well as huge individual differences in every age group. In fact, the extent of these individual differences is emphasized by the fact that even within men as a group, coefficients of variation (ratio of variance to mean) in percentage of time spent in sleep stages 3 plus 4 far exceeded those for all other sleep variables in both men and women. Although gender differences in SWS have been noted previously (see reference 3 for review), the fact that the age-dependent decline may be confined only to men suggests a more limited utility of this often-characterized aging biomarker for women.

In contrast to the results of the SHHS, these gender differences in SWS were not confirmed meta-analytically.[4] At least one study has proposed that gender differences in delta activity are more likely to be a function of overall lower EEG amplitude in men relative to women.[9] When corrected for overall amplitude, the decreased growth hormone secretion seen in postmenopausal women was accompanied by lower delta amplitude than in comparably aged men.[10] A decline in the amplitude and the incidence of the evoked K-complex over the age range of 19 to 78 years has been reported in both women and men, suggesting that similar deficits in delta synchronization processes operate equally in both sexes.[11] Gender did not play a significant role when assessed as the homeostatic response of nighttime delta power to daytime napping in either young or elderly subjects.[12]

Percentage of time spent in sleep stage 1 also showed similar gender-related effects in SHHS, and age-dependent increases in this sleep stage, usually considered to represent a feature of fragmented, transitional sleep, were confined only to men. By contrast, percentage of time spent in REM sleep showed a modest decline with age, but the effect was detected in both men and women. REM percentages of 18% to 20% in 75- to 85-year-olds were derived from curve smoothing in another meta-analysis

focused on only REM sleep measures in normal aging,[5] which were slightly lower than, but essentially similar to, SHHS data (see Table 3-1). In SHHS, sleep efficiency also declined with age, with mean values of 85.7 (standard deviation [SD] = 8.3) in the 37- to 54-year-old group, 83.3 (SD = 8.9) in the 55- to 60-year-old group, 80.6 (SD = 11.7) in the 61- to 70-year-old group, and 79.2 (SD = 10.1), in the over-70-year-old group, but without differential effects of gender, findings corroborated meta-analytically in persons older than 60 years.[4] However, the declines in percentage of time spent in REM sleep and the (male-specific) increases in percentage of time spent in sleep stage 1 seen in SHHS were not confirmed meta-analytically in persons older than 60 years.[4] The density of eye movements in REM is reduced with aging,[13] but lack of standardization across laboratories precludes examination of this aspect of REM using meta-analytic techniques.

Arousals during Sleep

Brief arousals during sleep, representing one component of the microarchitecture of sleep, continues to attract considerable interest as a metric, with particular relevance for the aged population. When examined in the laboratory, healthy older persons wake up from sleep more frequently than younger persons do, regardless of circadian phase, but they have no greater difficulty falling back to sleep.[14] Failure to maintain continuous sleep has, as its basic science counterpart, short bout lengths, a feature highly characteristic of sleep in many aged mammalian species.[3] In elderly humans without SDB, arousal indices from 18 to 27 events per hour have been reported.[15] Among the predominantly elderly subjects (mean age, 61 years) in SHHS, the mean (SD) Arousal Index showed significant but relatively small increases with age: 16.0 (8.2) for 37- to 54-year-olds, 18.4 (10.0) for 55- to 61-year-olds, 20.3 (10.5) for 62- to 70-year-olds, and 21.0 (11.6) for subjects older than 70 years.[7] Values approximating these have been reported[16] in another group of subjects without sleep apnea or periodic leg movements, thus further corroborating these SHHS values.

Other phasic events of non-REM (NREM) sleep, such as K-complex and spindle density, also decrease with age.[17] Spindle density is thought to reflect, at least partially, the corticothalamic functional integrity of gamma-aminobutyric acid–ergic (GABAergic) systems.

Although, like other metrics of impaired sleep quality, brief arousals show a male predominance (also seen meta-analytically using Wake after Sleep Onset[4]), the influences of age and gender are not as pronounced as the effects of breathing events (Table 3-2). In fact, when accounting for the presence of brief arousals in the elderly, the Respiratory Disturbance Index (RDI) predicts 10-fold more variance than age and 5-fold more variance than gender. Higher levels of RDI were also associated with slightly lower percentage of time spent in REM sleep in both men and women and with lower percentages of time spent in sleep stages 3 plus 4 in men. The latter result is consistent with the hypothesis that at least some SDB in both elderly men and women might reflect ventilatory control instability and that SWS may be protective (see the later section on SDB).

Table 3-2 Brief Arousal Index in Elderly Subjects as a Function of Sleep-Disordered Breathing

	Arousal Index: Brief Arousals per Hour of Sleep (±SD)	
RDI	**MEN**	**WOMEN**
≤5	16.7 (7.7)	14.7 (7.1)
>5 to 15	20.5 (8.7)	17.9 (7.8)
>15 to 30	25.2 (10.3)	23.2 (10.4)
>30*	39.4 (14.7)	29.7 (13.6)

*Estimated weighted values.
RDI, respiratory disturbance index (apneas plus hypopneas per hour of sleep), a measure of sleep-disordered breathing; SD, standard deviation.
From Redline S, Kirchner HL, Quan SF, et al. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch Intern Med 2004;164:406-418.

Comorbidities

Insofar as comorbidities are concerned, SHHS sleep architecture data showed substantial convergence with meta-analytically derived data. In SHHS, selected medical comorbidities (a positive history of cardiovascular disease, hypertension, and stroke) were associated with disturbed sleep architecture, as was smoking, although, curiously, these results were not seen with chronic obstructive pulmonary disease. Consistent with results suggesting that reduced sleep amounts or quality might predispose to the metabolic syndrome in old age, diabetic patients had smaller percentages of time in stages 3 plus 4 sleep, lower sleep efficiencies, and higher numbers of brief arousals and percentage of time spent in sleep stage 1. In most cases, however, these effects appeared to less salient (i.e., predicted less variance) for sleep architecture than demographic variables such as gender, age (to a lesser extent), and, in some cases, ethnicity,[7] except for the arousal index, where RDI was by far the single most powerful predictor. Less-disease-specific moderator effects from meta-analytic approaches also suggested that across the entire life span, age effects were reduced substantially when persons with medical and psychiatric conditions were included.[4] The inclusion of persons with sleep apnea showed some evidence of reducing the effects of age in sleep efficiency, wake after sleep onset, and SWS when considered across the entire adult life span,[4] data that are compatible with SHHS.

Slow-Wave Sleep

The gender differences in SWS reported by SHHS notwithstanding, several aspects of these data must be viewed in the context of prior literature on age-dependent changes in architecture. When analyzed with period-amplitude analyses, the major change in SWS ascribed to aging has been a decline in delta wave amplitude rather than wavelength (Fig. 3-1).(See reference 3 for review) The decrease in delta amplitude simply may be a more readily identifiable visual change of the sleep EEG, which is present at frequencies up to about 10 Hz, though it is difficult to see above this.[18] When scored visually using central derivations and

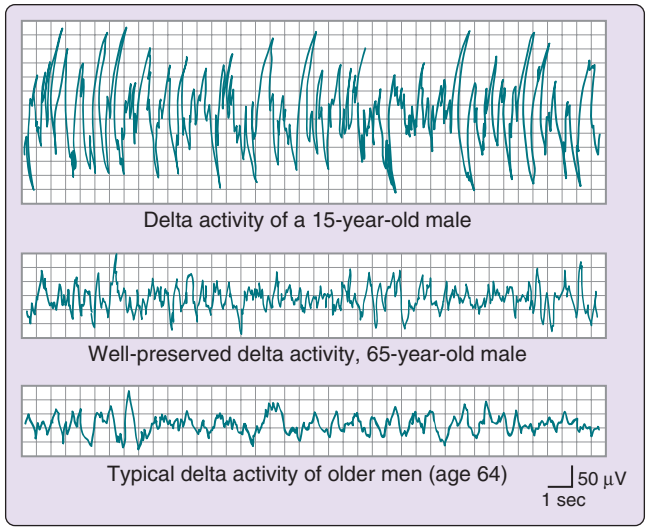

Figure 3-1 Age differences in delta activity. The *top tracing* shows typically abundant high-amplitude delta in an adolescent. The *middle tracing* shows particularly well-preserved delta in an older man. Note the marked decrease in amplitude relative to the adolescent. The *bottom tracing* is a more typical example of delta activity in an older man. Note the number of waves failing to meet the 75-μV amplitude criterion. (From Zepelin H. Normal age related change in sleep. In: Chase MH, Weitzman ED, editors. Sleep disorders: basic and clinical research. New York: Spectrum; 1983. pp. 431-445.)

employing a 75-μV threshold, typical figures for the amount stages 3 plus 4 sleep in the elderly have often been considered to fall in the 5% to 10% range. Thus, the figures reported by SHHS, particularly for women, are somewhat higher than these conventionally accepted figures. Whether these values represent a more precise rendering of delta activity within sleep, perhaps engendered by the visual analyses of EEG waveforms on digital display or the simultaneous availability of precise calibration of the 75 microvolt criterion for delta waves stipulated by the Rechtschaffen and Kales guidelines, is unclear. Nonetheless, the strictly controlled and exquisitely refined visual analyses conducted by SHHS are likely to represent a standard of polysomnographic technology aspired to by the field of sleep medicine, thus arguing that these newly published metrics may well replace existing data and supplant our current understanding of how sleep architecture measures should be benchmarked.

Given the new AASM guidelines for sleep stage scoring,[6] much of the foregoing normative data on sleep architecture may have limited relevance for laboratories that elect to adopt such changes. For example, slow-wave activity has higher amplitude when recorded from frontal derivations relative to central derivations. This would be expected to result in increased levels of visually scored slow-wave (i.e., N3) sleep. Indeed a recent study comparing recordings scored with both revised AASM and traditional Rechtschaffen and Kales criteria have shown a number of significant differences in resulting measures.[19] Predictably, particularly in older persons, the revised scoring system resulted in higher percentages in N3 sleep. Beyond creating the need to establish new normative data, the mechanistic and functional significance or the diagnostic and therapeutic importance of such a revisionary approach remain obscure. Much the same effect could be obtained by adopting alternative scoring thresholds of less than 75 μV for defining delta wave activity. Such proposals were put forth in the 1990s(See reference 3 for review) but have not led to enhanced understanding of the age-dependent changes in SWS. Eventually, digitized indices of delta activity (e.g., fast Fourier transform, zero-crossing, or hybrid techniques) might come to replace such conventional measures; however, considerable controversy regarding filtering, sampling rates, and data-storage formatting leaves formal adoption of such approaches dubious for routine clinical purposes at this time,[20] though such efforts at signal processing are yielding important new clues regarding the significance of sleep-related delta activity for aging.

Slow-wave activity during sleep is thought to represent synaptic downscaling, which is viewed as critical for forming memories.[21] Broadly viewed, given at least some data suggesting decreased SWS with age, such findings might fit with mild impairments in cognition that characterize normal aging. Extremely low frequency (<1.0 Hz) slow wave activity in NREM sleep has been thought to hold particular significance as a more immediate reflection of cellular processes than conventionally defined delta activity.[22] In dementia, the integrity of the normal auditory evoked response (K-complex) may be impaired,[23] whereas in normal aging, there is some suggestion that spectral power at frequencies below 0.7 Hz might demonstrate fewer age differences than at between 0.7 and 3.0 Hz.[24] Other attempts to examine NREM sleep in old age using nonlinear, dynamic EEG approaches yield broadly compatible findings. The sleep EEG of healthy older adults in the first NREM period may resemble patterns of compensatory activation similar to those seen in young adults during sleep subsequent to sleep deprivation.[25] Whether such phenomenological parallels of altered functional connectivity in sleep deprivation and aging hold prognostic or practical significance at the individual case level is unknown but certainly plausible. Nonlinearity of the NREM sleep EEG increases with normal aging[25] and sample entropy, a novel measure reflecting dynamic probabilities of state,[26] also changes with age.

CIRCADIAN RHYTHMS IN AGING

In humans, most descriptive data collected under entrained conditions have suggested that the amplitude of the sleep-wake rhythm, body temperature (Fig. 3-2),[27] and some hormones decrease with aging. Sex differences in such phenomena have also been reported (see reference 28 for review). However, in exceptionally healthy older adults such differences might not always appear,[29] and a study of centenarians indicated relatively robust neuroendocrine profiles.[30] A phase advance of aging has often been ascribed to the timing of sleep patterns in older adults. Many sleep medicine specialists use this designation as an abbreviation for indicating that older persons go to bed earlier in the evening and wake up earlier in the morning than younger persons, findings corroborated in age differences in the timing of bedtimes and wakeup times in dozens of cross-sectional surveys(See reference 3 for review) and even longitudinally.[31]

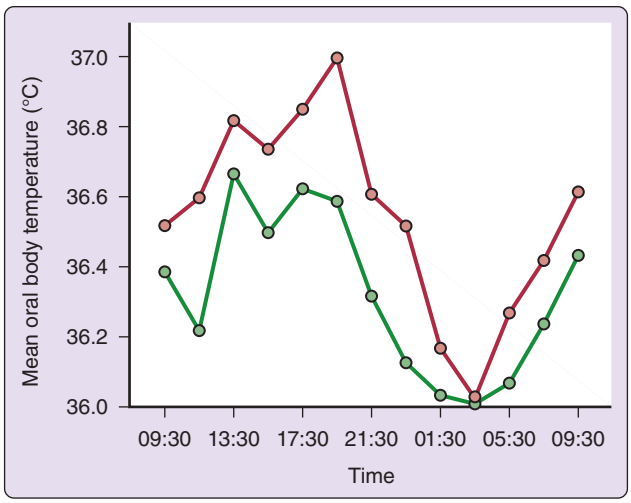

Figure 3-2 Oral temperatures in young *(open circles)* and old *(dark circles)* subjects, showing apparent decreased amplitude and earlier phase in body temperature cycle as a function of aging. Data were obtained under entrained conditions. (From Richardson GS, Carskadon MA, Orav EJ. Circadian variation of sleep tendency in elderly and young adult subjects. Sleep 1982;5[Suppl. 2]:S82-S94.)

However, the reader should be aware that fundamental changes in phase relationships in human circadian rhythms might not always substantiate the notion of such an advance. For example, in the constant routine protocol, older subjects' typical earlier bedtimes and wakeup times relative to younger subjects actually were more phase delayed, rather than phase advanced, relative to their peaks in melatonin.[32] The implication of this finding is that the earlier bedtimes and wakeup times may be due to homeostatic factors. Studies using 28-hour forced desynchrony, an experimental protocol that requires subjects to sleep on a 2:1 wake-to-sleep ratio outside the limits of entrainment of the circadian system, have shown absence of age differences in estimates of tau, the endogenous period length of the human core temperature rhythm.[33] Again, these results implicate factors other than circadian ones that may be responsible for the earlier bedtimes of older humans. Further evidence of interaction between circadian and homeostatic factors comes from a study of age differences in the melatonin rhythm under the constant routine protocol, during which younger subjects showed elevated melatonin levels during the higher homeostatic pressure induced by this procedure, whereas older subjects did not.[34]

The interaction between homeostatic and circadian influences in older humans has been described elegantly in the forced desynchrony protocol, which has shown that throughout the assigned (9.33-hour) sleep period, elderly subjects awakened more frequently than younger subjects, regardless of circadian phase.[35] The duration of awakenings was virtually identical in young and old subjects, but the largest differences in the frequency of awakenings between young and older subjects were detected early, rather than late, in the sleep period. These results appear incompatible with the broadly defined phase-advanced hypothesis of sleep in the elderly, in which differences in sleep consolidation would be predicted to be most pronounced late in the sleep period (corresponding to early morning awakening) and least pronounced just after sleep onset (corresponding to early evening sleepiness). This study also analyzed sleep structure immediately before awakenings from consolidated periods of sleep. With circadian phase controlled, older subjects were far less likely to awaken from stage 1 and far more likely to awaken from stage 2 than were young subjects, suggesting that awakenings in the older subjects probably represented abrupt transitions from NREM sleep rather than gradual lightening of sleep.[35] These findings can be interpreted as an indication of a reduced homeostatic pressure for continuous bouts of sleep independent of circadian phase in the sleep of older persons.

A well-described feature of the circadian system in the aged organism is the relative impairment in the ability to phase shift. This may in part reflect loss of rhythmic function within the suprachiasmatic nucleus.[36] In humans, the sleep-wake system appears particularly vulnerable to such changes in phase shifting[37] and might account for the some of the apparent self-selection out of shift work typically seen in older people (see reference 38 for review). In rodents, such impairments in phase shifting have also been described.[39] Although both photic and nonphotic influences on impaired phase-shifting ability have been described in aging,(See reference 38 for review) the ability to phase shift and entrain to light in old age might be expected to be particularly impaired because of challenges to the visual system that occur as a part of human aging (e.g., cataracts, macular degeneration). Perhaps as a consequence, in epidemiologic studies, elderly persons with visual impairments were 30% to 60% more likely to have impaired nighttime sleep relative to visually unimpaired elderly subjects.[40] In the laboratory setting, however, disagreement exists as to whether, among persons without visual impairment, responsiveness of the circadian system, as indexed by melatonin rhythms, is decreased[41] or unchanged[42] by light exposure. Finally, another study examined the ability of a nonphotic stimulus (evening exercise) to phase shift melatonin onset in young and elderly humans and found comparable phase delays subsequent to exercise in both groups, arguing for the importance of entraining factors other than bright light to affect rhythms in the elderly.[43]

Invertebrate models in studies of sleep and aging have been broadly confirmatory for many of the changes described in mammals, such as the decline in nocturnal sleep durations.[44] Several studies in the fruit fly (*Drosophila melanogaster*)[45] and in the honeybee (*Apis mellifera*)[46] have indicated a dispersal of sleep around the 24-hour day occurring with aging. Perhaps more noteworthy is that these studies have also implied that total amount of sleep per 24 hours does not merely redistribute (via shorter bout length and increased number of bouts) but might also increase in quantity with advanced physiologic age. These changes appeared particularly pronounced in male fruit flies[45] and female honeybees[46] near the end of life. Because an avowed function of the mammalian master clock, located in the suprachiasmatic nucleus, is to provide clock-dependent alerting, these data are consistent with early studies that demonstrated such a role for the suprachiasmatic nucleus in primates using lesion models.[47] Although studies involving neurodegenerative disease in aged

humans have shown increased sleep per 24 hours consistent with level of dementia (see Chapter 136), the invertebrate data imply that increased rather than decreased sleep-durations hours would be likely to occur in aged humans normatively on a population-wide basis. In this regard, it is noteworthy that the largest single compilation of human sleep durations ever published (more than 1 million subjects), shows that reported sleep durations increase, rather than decrease, with age.[48] Taken together, these data broadly suggest that increased sleep durations in aged humans might fundamentally represent biological rather than sociocultural factors.

Among lower vertebrates, aged zebrafish (*Danio rerio*) have been shown to demonstrate reduced rest-activity rhythm and shorter nocturnal sleep durations across the lifespan (from 1 to 4 years), and these were associated with decreased brain melatonin during the dark period.[49] Melatonin administration was shown to partially restore sleep durations and simple measures of learning in this species. Zebrafish aging was also shown to be associated with gene expression in several clock genes (*Bmal1*, *PER 1*),[49] although the translation of this finding back to older humans might not be clear.[50] Additionally, in rodents, age-effects in the expression of several clock genes may occur equally in both wild-type and mutant lines.[51]

CAUSES AND CONSEQUENCES OF POOR SLEEP IN OLD AGE

Causes

The prevalence of insomnia in the aged varies across studies, but figures between approximately 20% and 40% are typically reported. In one of the largest surveys of an American population (the Established Populations for Epidemiologic Studies of the Elderly [EPESE], with more than 9000 participants), 29% of the over-65 population had difficulty maintaining sleep.[52] Relative to sleep maintenance, sleep latency is less likely to be problematic for the elderly population, with prevalence figures on the order of 10% to 19% typically seen, although one study[53] reported a relatively high prevalence of sleep latency problems (36.7%) in a largely rural aged population. In nearly all studies, elderly women have a greater probability of sleep complaints and sedative-hypnotic use than elderly men do (see reference 1 for review). Conflicting data exist on racial differences in sleep complaints,[54] though health disparities in sleep durations did not appear to depend on age.[55] Figures for regular use of sedative-hypnotics in elderly populations range from as low as 5% per year to as high as 16% over 4.5 years, 29% over 8 years, 34% over 1 year and 62% over 3 years.(See reference 1 for review) Although subjective reports of poor sleep invariably increased with age and numerous changes in sleep architecture have been frequently noted (see earlier), the relationship between these two domains are significant, though relatively weak, with women showing slightly higher levels of association relative to men.[56]

Disturbed sleep is thought to both contribute to and reflect allostatic load of illness in old age and might reflect physiologic age of the organism. When other causes of poor sleep are taken into account, chronological age might explain little of the observed higher prevalence in the elderly. Psychiatric conditions have always been considered to play a major role in the insomnia of old age. A study of more than 3000 older men reported that depressive symptoms were associated with difficulties in falling asleep, but not lower sleep efficiency or total sleep time.[57] Among women, although the caregiving role per se was not associated with poor sleep, for women who were depressed, caregiving was associated with reported sleep problems.[58] Regardless of caregiving status, anxiety appeared to play a larger role in predicting poor sleep quality in these older women, even relative to depressed mood per se.[59] However, poor sleep, left untreated, appears to be a risk factor for incident depression in the elderly.[60]

Limitations in mobility, visual impairment, lack of regular exercise, alcohol use, and smoking all contribute to declining sleep quality in older persons, as do chronic pain conditions, such as arthritis, hip fracture, fibromyalgia, headache, and back pain; cardiovascular diseases such as hypertension, myocardial infarction, stroke, congestive heart failure, and angina; respiratory conditions such as asthma and bronchitis; and other systemic diseases such as diabetes, gastroesophageal reflux, and duodenal ulcer (see reference 61 for review). When persons with such comorbidities are eliminated from consideration, the resulting insomnia prevalence in elderly populations may be only 1% to 3%,[62] reiterating the decreased significance of chronologic age per se in predicting poor sleep. In women, some evidence suggests that menopause may also be associated with declining sleep quality (see Chapter 140). Additionally, in both women and men, the otherwise mundane occurrence of nocturia (nightly awakenings to void) appears to be associated with poor sleep,[63] even when other factors such as pain and medical comorbidity are taken into account. In fact, nocturia may be the single most common factor associated with poor sleep in the elderly.[63]

The role of SDB as a cause for insomnia in older adults has been debated over the years. Although a carefully performed case-control study suggested that SDB frequency was no higher (and might even have been lower) in older persons with poor sleep than in those who slept well, there was evidence that for persons who demonstrated both SDB and poor-quality sleep, the impact on day-to-day function was quite substantial,[64] even exceeding those in persons with comparable levels of SDB but no insomnia.

Several longitudinal studies examining the incidence (development of new cases) of insomnia over periods of up to 10 years have been reported. The single best predictor of insomnia continuing longer than 10 years was insomnia at a previous time, although cardiovascular and pulmonary comorbidities conferred risk as well in the over-65 population.[65] Reported remissions were less likely in older subjects than in younger ones.[66] The EPESE data indicated a yearly incidence of insomnia complaints in the aged population of about 5%, with a spontaneous remission rate of about 50% over 3 years.[67] In these data, incident insomnia was related to heart disease, stroke, hip fracture, and new-onset depression. Spontaneous remission of insomnia was related to the resolution of depression, physical illness, and physical disability affecting activities of daily living,[67] whereas in the Cardiovascular Health Study, persistence of insomnia was associated with unresolved depression.[68] Important from the standpoint of prevention, another

study reported that higher levels of physical activity were protective for incident insomnia over an 8-year period.[69]

Potential Consequences

A major question regarding the frequent complaints of poor sleep among the elderly involves whether these have an impact on the health of older persons. If the poor sleep of old age, although annoying and distressing for many, represents primarily a quality-of-life issue, albeit one modifiable by medical or behavioral interventions, it might cast a different perspective on this problem, than for a medical disorder such as SDB, where negative outcomes may be better defined and quantified. There is no question that almost universally, poor nocturnal sleep is distressing and related to lower quality of life of many older persons. This has been demonstrated in elderly populations in the United States,[70] in Canada,[71] across Europe[72] and in Asia.[73] Interestingly, some have questioned the extent to which such observations may be tempered by older persons' qualitative perceptions of sleep satisfaction[74] or sleep insufficiency,[75] which might not change with aging.

Most work relating poor sleep quality or duration to putative adverse outcomes has been observational, which, although often provocative, lacks the definitive element of proof of causation that is afforded by randomized clinical trials. Unfortunately, with few exceptions, most pharmacologic and nonpharmacologic randomized clinical trials attempting to treat poor sleep in elderly persons seldom rely on outcomes other than conventional subjective and polysomnographic measures of nocturnal sleep per se. Rare exceptions to the latter have been several insomnia treatment studies among older adults that have demonstrated increases in selected quality-of-life measures such as the SF-36[76] or decreased daytime napping.[77] Interventional data relevant for other medical outcomes in old age (e.g., hypertension, insulin resistance) have yet to be published.

Among observational studies, the association between nocturia and insomnia has led to speculation that the more likely a person is to rise from bed during the night to use the bathroom, the more likely the person is to fall.[63] Considerable evidence for this association exists at the population level, where studies have shown associations between insomnia and falls.[78] Sleep durations of less than 5 hours were associated with an increased risk for falls of more than 50%.[79] Risk for increased falls with short duration of sleep or poor quality of sleep (or both) is also consistent with data suggesting that insomnia is associated with impaired physical function. For example, lower sleep efficiencies were associated with lower grip strength and slower walking speed in a population of elderly men.[80] Short sleep durations were associated with a slightly different set of markers of physical impairment in elderly women, primarily consisting of chair-to-stand speed.[81] Although the increased risk for falls in the older populations has been typically ascribed to psychotropic and sedative-hypnotic medications, reanalyses of some of these databases have suggested that poor sleep per se may be a more relevant predictive factor.[82]

Population-based studies also have suggested that poor sleep may be linked to lower cognition in old age. In the Study of Osteoporotic Fractures, a population of older women were noted to have scored lower on the Mini Mental State Examination, a general examination of mental function and orientation, and take more time to complete the Trail Making Test, part B, a paper-and-pencil test of psychomotor speed, as sleep efficiencies decreased and sleep latencies increased.[83] In another report from that same population, cognitive decline over 15 years was more likely to be associated with sleep efficiency of less than 70% at follow-up.[84] In the Nurses' Health Study cohort, poorer performances on a more-comprehensive battery of cognition, including immediate and delayed verbal memory, category fluency, and attention, were associated with sleep durations of less than 5 hours.[85] In an older French population, the likelihood of cognitive problems derived on a self-reported telephone-derived questionnaire was increased by 50% for those reporting 4.5 to 6.0 hours of sleep, and it more than doubled in respondents reporting less than 4.5 hours of sleep.[86]

Relative to poor-quality sleep, at least some data suggest adverse outcomes associated with short sleep durations in older populations. Gangwisch and colleagues[87] reported that sleep durations of less than 5 hours were associated with higher rates of all-cause mortality in subjects 60 years and older, a finding that was not present in persons ages 32 to 59 years. Sleep durations of less than 5 hours per night in even older populations (67 to 99 years old) were associated with obesity as well,[88] a finding otherwise well acknowledged in populations younger than 65 years in women in one study[89] and in men and women in another.[90] Hypertension has also been associated with short sleep durations in elderly persons,[91] but other studies of older populations indicated that neither short sleep durations[92] nor complaints of poor sleep[93] were associated with this morbidity. Diabetes and impaired glycemic control were associated with sleep durations of less than 6 hours (but not insomnia complaints) across the age range 53 to 93 years[94] and were independent of age across an even broader age range.[95] As mentioned earlier, these are all observational studies, which, although impressive by size of the samples studied and control over confounding variables, did not manipulate sleep quality or sleep duration to demonstrate improvement in any of these putative adverse outcomes in older persons.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS IN SLEEP

One specific cause of insomnia in the elderly is restless legs syndrome (RLS) (see Chapter 90). This condition, characterized by an urge to move the legs, which is usually accompanied by sensations of discomfort, aggravation of symptoms by rest and temporary relief of symptoms by movement, and worsening during the evening or nocturnal hours, is exceedingly common in elderly populations. Estimates vary, but the condition appears to be more prevalent in northern European[96] relative to Asian populations,[97] and several genotypes have been identified (see Chapter 90). Peak prevalence was noted in the group ages 60 to 69 years for women (16.3%) and 50 to 59 years for men (7.8%),[96] though the population sampled included persons up to age 90 years. Another European study including subjects up to

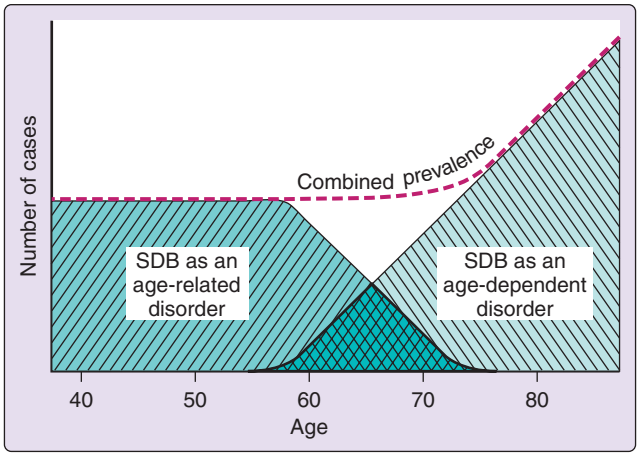

Figure 3-3 Heuristic model suggesting that sleep-disordered breathing (SDB) is both an age-related and an age-dependent condition with potential overlap of distributions in the 60- to 70-year-old age range. Cross-sectionally, note that the number of cases observed can remain high and increase with age, despite a presumed decrease in age-related SDB.

their 80s also showed similar gender differences (14.7% in women; 6.8% in men) with peak prevalence for both genders in the 50- to 59-year-old range.[98] Thus, in some respects, RLS prevalence appears to be more age related than age dependent (see later and Fig. 3-3), although at least one study of a Dutch population noted that prevalence was highest in the oldest subjects (80 to 100 years of age).[99]

Periodic limb movements in sleep (PLMS) are stereotypic, repetitive, nonepileptiform movements of the legs usually consisting of dorsiflexion of the ankle but occasionally limited to flexion of the great toe or incorporating flexion at the level of knee or hip. They often, but not invariably, occur in conjunction with RLS. The intermovement interval has been reported to decrease with age from about 24 to 28 seconds before the age of 55 years to about 14 to 16 seconds after the age of 65 years.[100] Age-dependent increases in the occurrence of PLMS have been noted cross-sectionally in series without a drop in the oldest (e.g., older than 80 years) groups.[101] Curiously, longitudinal follow-up of elderly subjects did not show increases consistently,[102] perhaps owing to inherent variability in PLMS. Prevalence, defined as a PLM Index of 15 movements or more per hour, has been estimated as high as 52% in a population of older women.[103] When measured with wrist actigraphy in that population, the presence of PLMS was associated with sleep durations of less than 5 hours of sleep,[104] though earlier population-based studies have presented conflicting data as to whether PLMS, in the absence of frank RLS symptoms, were associated with poor sleep.[101] One study of men ages 40 to 60 years noted poorer sleep quality when the PLM index exceeded 10.[105] Other studies demonstrating the mixed pattern of results correlating PLMS with sleep complaints have been reviewed elsewhere.[106]

One possible explanation for the variability of results across studies is that PLMS may vary considerably from night to night. A 15-night study suggested that estimated prevalence for PLMS might stabilize only after multiple nights of measurement.[107] The discrepancy between the higher prevalence of PLMS relative to RLS and the failure of a number of studies to show associations between their presence and specific symptoms suggests that in many elderly persons, PLMS may be an incidental finding.[106]

The worsening of RLS and PLMS with aging suggests that this syndrome may be associated with other conditions known to be common in older populations. Given the likelihood of anemia among the elderly, current attention has focused largely on iron transport and storage deficiencies.[108] Elderly RLS patients with serum ferritin levels of less than 45 mg/mL showed subjective improvement following use of ferrous sulfate, although their total iron levels were no different.[108] These findings were later replicated by the same research group.[109] Because iron represents a key component of production of dopamine, it could play a role in presence of RLS in some elderly subjects. One population-based study could not confirm the ferritin finding,[110] although another report indicated that higher serum-soluble transferrin-receptor levels (often characteristic of early-stage anemia) and lower serum iron were associated with RLS.[96] An interesting perspective on iron metabolism and aging was based on examination of ferritin levels in the cerebrospinal fluid of elderly RLS patients. Older patients had higher CSF ferritin levels than did younger patients; however, for elderly patients whose RLS had been long-standing, lower levels were associated with a more-severe condition.[111]

SLEEP-DISORDERED BREATHING

Specific considerations related to diagnosis and treatments of SDB in the elderly are covered in Chapter 134. This section deals with more general issues involving age-dependence.

The previously proposed heuristic model for SDB (Fig. 3-3) posits that SDB represents both an age-related phenomenon (with a specific vulnerability confined to middle age) and an age-dependent phenomenon (with a prevalence that steadily increases throughout the human life course).[1] The articulation and differentiation of these two presumably separate, but chronologically overlapping, distributions represents a major challenge to clinicians. Practically, if the health consequences of SDB in elderly populations are diminished, the necessity to treat the enormous numbers of elderly persons who have the condition is reduced. Age dependence implies that SDB risk factors might be best considered markers of physiologic or biological age.[112] Chronologic age may thus serve only as a proxy for other risk factors that are themselves age-dependent.

Risk Factors

Risk factors for SDB in the older population may differ to some extent from those in middle-aged populations. In SHHS, several markers of obesity that were significant cross-sectional predictors of SDB in middle-aged populations (neck circumference and waist-to-hip ratio), were no longer significant predictors by age 70 years and 80 years,

respectively,[113] although body mass index continued to be correlated with SDB, even past age 80 years, albeit with a somewhat diminished effect. Although the male predominance in SDB is thought to equalize in old age, this was not the case within SHHS.[113] Other cohort studies including older subjects suggested roughly equal prevalence in elderly men and women.[114,115]

The prevailing view for many decades was that most SDB in the elderly consisted of central (i.e., diaphragmatic) events, whereas in the middle-aged population obstructive events predominated; however this is unsubstantiated by both descriptive studies, showing the predominance of obstructive apneas, and by pathophysiologic studies, which show increased tendency for upper airway collapse with aging (see reference 116 for review). Upper airway resistance has been reported to be higher in both REM and NREM sleep in older men relative to younger men,[117] and closing pressures during sleep were higher in older subjects in N2 sleep relative to younger subjects.[118] Aging has been associated with lengthening of the soft palate and with upper airway fat pad deposition, both of which may contribute to oropharygeal collapse during sleep.[119] Lower lung volumes have been shown to predict incident SDB in elderly persons over time,[120] perhaps by providing less caudal traction on the trachea and hastening upper airway collapse during sleep. In older animals, the pharyngeal muscles appear to have a worse profile for endurance relative to the diaphragm, which may enhance susceptibility to collapse,[121] and a shift from type IIa to IIb fibers occurred in the genioglossus in 24-month-old rats, a finding interpreted as conferring susceptibility to fatigue.[122]

Predisposing influences on SDB in elderly human populations are not limited to neuromuscular factors. Ventilatory control instability,[123] which may be accentuated by the decrease of N3 sleep with age, might also predispose to SDB in the elderly, though not all studies report high loop gain in older subjects.[124] These and other potential age-dependent risk factors for SDB are shown in Figure 3-4.

Outcomes

Potential outcomes relevant to SDB in old age include mortality, cardiovascular and neurobehavioral morbidities, and morbidities related to other potential end-organ damage (see Fig. 3-4). In the absence of large-scale prospective randomized clinical trials specifically targeting SDB treatments in geriatric populations, definitive causal associations with adverse outcomes in the aged remain uncertain. The prevailing viewpoint in sleep medicine has been that SDB demonstrates weakened associations with morbidities in elderly, relative to middle-aged, persons. Offered here is a brief description of studies in older populations suggesting otherwise.

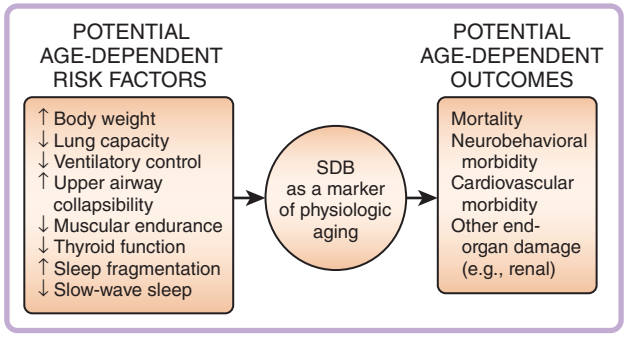

Figure 3-4 Sleep-disordered breathing (SDB) in older adults as an age-dependent condition. Other potentially associated age-dependent risk factors and outcomes are shown.

In the elderly, SDB has been associated cross-sectionally with clinically defined hypertension,[125] a nondipping blood pressure pattern,[126] composite cardiovascular disease history (in men),[127] stroke,[128] reduced kidney function (in men),[129] poorer physical function (in men),[80] nocturia,[130] overactive bladder,[131] and impaired cognition (in women).[132] Longitudinal data have shown a relationship between declining mental status test scores and the development of SDB.[133] Additionally, higher health care costs were associated with sleep apnea in both middle-aged and elderly persons.[134] An important association between SDB and frailty has also been noted in older women,[135] which is particularly important given the fact that, as a well-acknowledged geriatric syndrome, frailty is highly predictive of other morbidities and of mortality.[136]

In SHHS, when subjects with prevalent cardiovascular disease were excluded, relationships between SDB (as measured by quartiles of the apnea-hypopnea index) and various morbidities (including diabetes and hyperlipidemia) were clearly lower in the over-65-year-old population than in the under-65-year-old population, but only in men, not women, where the associations were similar.[137] By contrast, Haas and colleagues[138] reported that isolated systolic hypertension was unrelated to SDB in any age range, but that systolic and diastolic hypertension were related to SDB in only those younger than 60 years. In another report examining associations between multiple measures of SDB and more broadly defined cardiovascular disease (including coronary heart disease, congestive heart failure, and stroke), relationships with SDB, although reduced to some extent by age, were still age-independent.[139]

Despite this suggestive evidence, other studies continue to minimize the significance of SDB for elderly populations. For example, it has been contended that sleep apnea has little impact upon quality of life in the elderly,[140] and others have argued that ischemic preconditioning essentially renders the SDB of old age innocuous, because some component of protective adaptation is likely to have occurred.[141] Goff and colleagues[142] have shown that cardiovascular responses (elevations in heart rate and blood pressure) to auditory stimulation are reduced in older relative to younger persons, and they have interpreted this as consistent with the reduced associations between SDB and systemic hypertension that has been reported in older persons. Because the study was performed in older persons without SDB, the results are difficult to reconcile with the ischemic preconditioning hypothesis, and it remains unclear whether such presumed sympathetic downregulation might underlie the presumably reduced impact of SDB in the elderly. The consequences of SDB in older

populations thus remain an area of considerable controversy, and the sleep medicine specialist should be cognizant of these issues. For further discussion, the reader is directed elsewhere(See references 1 and 116 for review) and to other chapters in this volume (Chapters 134 and 136).

WHY DO OLDER PEOPLE NAP?

A time-honored question, asked by both professionals and the lay public, involves the significance of napping in old age. From the layperson's perspective the question is most typically: "Is it normal to nap?" or "Are naps good or bad for my health?" The sleep medicine specialist may ask fundamentally similar, though more diagnostically inclined questions such as: "What is the probability that daytime naps in a 75-year-old indicate SDB?" "Does excessive sleepiness during the day in an older person portend dementia?" or "To what extent does daytime napping adversely effect sleep at night?" These are highly relevant questions that are made even more difficult to answer by cultural issues related to napping, the complexities in relying on self-reports to derive estimates of the physiologic tendency of sleep during the daytime hours, and the fact that, overarching all other issues, sleeping during the daytime hours in old age is most assuredly a multidetermined phenomenon.

Elsewhere I have reviewed the complex matrix of results that suggest that napping is both a beneficial and potentially protective event in the life of an older person as well as an identifiable risk factor for numerous morbidities and even mortality.[1] Perhaps the most direct approach to answer the question of why older persons are sleepy during the day is a case-control design that compares otherwise demographically well-matched, community-dwelling elderly persons, some of whom are sleepy during the day and some of whom are not.[143] Key to such a design is the incorporation of a diverse array for variables that have been thought to account for sleepiness in older persons, including subjective and polysomnographically defined measures of nocturnal sleep fragmentation, careful assessment of comorbid medical disease, psychopathology, medication use that might induce sleepiness, alcohol use, smoking status, measurements of SDB and PLMS, and specific conditions known to disrupt nocturnal sleep, such as nocturia and physical pain. Results from such a study indicated that male sex, poor sleep quality, sleep interruptions due to nocturnal pain or bathroom trips, and medications known to induce sleepiness differentiated cases and controls. Only severe SDB (more than 30 events per hour) predicted sleepiness, but PLMS did not.[143] Several unanticipated findings (positive relationship to percentage of time spent in REM sleep, negative relationship to alcohol consumption) were also noted. Taken together, these findings suggest there are many factors that predict why an older person may be sleepy during the day.

Napping has also been associated with falls[144] and incipient cognitive decline[84] in a population of older women and with depression,[145] nocturia,[146] diabetes,[147] and lower quality of life[148] in both men and women. On the other hand, evidence continues to accrue that naps may be protective for cardiovascular events,[149] might improve daytime function,[150] do not adversely affect nocturnal sleep,[151] and might even be associated with longer sleep duration the previous night.[152] Other studies suggest that naps and hypersomnolence portend mortality[153] or ischemic heart disease[154] and that daytime fatigue or anergy predict diverse morbidities[155] or all-cause mortality.[156] Again, however, not all population-based studies concur, and some suggest absence of excess mortality risk associated with napping,[157] particularly in elderly persons.[149] Clearly, the many reasons for daytime napping and sleepiness in older populations continue to be elusive and outcomes associated with the phenomenon are disparate.(See reference 1 for review) Additionally, the methodologic issues involved in defining napping are substantial and undoubtedly effect lack of comparability across studies.[158]

BASIC SCIENCE CONSIDERATIONS

Beyond the aforementioned rich description of the complex and interrelated changes in human sleep with advancing years outlined in this chapter, the ultimate significance of such alterations remains enigmatic. If one views such changes in sleep merely as epiphenomenal to components of the aging process, they may be merely a consequence of more fundamental changes in the biology of the organism operating at the system, cellular, or molecular levels. On the other hand, might age-dependent alterations in sleep and rhythms themselves be potential influences on physiologic aging per se? If that is indeed the case, then manipulations or interventions that alter sleep might modify disease course, change fundamental processes of aging, or perhaps even contribute to the longevity of the organism. Research in this exciting area is only just beginning, but certain provocative clues are emerging, particularly as we learn more about sleep function.

Invertebrate models have proved invaluable in understanding more about how sleep is related to the aging process. The relative strength of the sleep–wake cycle and the length of sleep bouts have been shown to breakdown with age in *Drosophila*, and the extent of the disruption was magnified under higher temperatures (29°C) relative to more moderate (25°C) or cooler (18°C) temperatures,[45] an important observation because *Drosophila* are known to have a longer life span in cooler temperatures. Additionally, incorporation of paraquat, an herbicide known to induce oxidative stress, into the flies' food supply produced similar results.

Examination of sleep in *Drosophila* mutants with exceedingly short sleep durations and rapid physiologic aging (i.e., shortened life span) also suggested that sleep may indeed play a vital role in survival.[158a] In the first of these, the *minisleep (MNS)* line, derived from an exhaustive search of 9000 mutant lines, homozygous flies showed reductions in sleep durations of 37% of female flies and 32% of male flies relative to wild-type flies.[159] Genotyping suggested that the *MNS* line was characterized by a point mutation in the *Shaker* gene, thought to regulate potassium channel repolarization and broadly defined neuronal excitability. Perhaps most importantly from the standpoint of aging, survivorship to very old age in these flies (defined in this study as 56 days), was substantially lower than in flies with other *Shaker* locus mutations or in wild-type controls; in

some cases the effects approached a fivefold reduction in life span.[159] A different fly line, called *sleepless (sss)*, which overexpresses another *Shaker*-related protein involved in the downregulation of potassium influx, has been shown to be associated with even more dramatic reductions in sleep amount (85% for males, 80% for females).[160] In this mutant, reductions in survivorship were even more profound, with virtually none of the *sss* flies surviving beyond 50 days (median about 30 days) relative to the median survival of control flies (about 70 days).[160] These data certainly imply that absence of sleep is associated with more rapid aging, though they do not suggest what function ascribed to sleep may be related to acceleration of such aging processes. By contrast, studies of sleep deprivation in mammals might afford a broader perspective on such issues.

Sleep deprivation studies in humans over the last 25 years have shown repeatedly that sleep loss interacts with aging in several key ways. Homeostatic pressure for sleep may be somewhat diminished in humans and in some rodent species, particularly when recovery sleep is characterized by changes in both sleep duration and delta activity pressure. In humans, the behavioral consequences of sleep loss, framed in terms of both greater daytime sleepiness and more impaired waking performances, appear diminished, rather than enhanced, with aging (see references 1 and 28 for reviews of this area). These facts imply, but cannot prove, that sleep might have less significance and, as a corollary, loss of sleep may be of less consequence—or at very least, no more consequence—as the organism ages. The data presented throughout this chapter notwithstanding, such results might be interpreted hastily as suggesting *less* of a need to intervene in the sleep of older persons.

By contrast, important new molecular evidence suggests that at the subcellular level, sleep deprivation may be *more* detrimental for function in aging animals than in young animals. More specifically, the unfolded protein response within the endoplasmic reticulum occurring after sleep deprivation[161] may be modified substantially by aging. Protein aggregation is a well-acknowledged feature of many neurodegenerative conditions in late life and appears to occur as one of the earliest signs of impending neuronal death. The unfolded protein response, which consists of a host of molecular changes involving attenuation of translation of adverse proteins, degradation of misfolded proteins, and promotion of factors (chaperones) protective for normal function of the endoplasmic reticulum, shows synergistic age and sleep-deprivation effects. For example, expression of a major chaperone, BiP/GRP78, is known to be downregulated in both brain and liver of aged animals, but it showed major upregulation following sleep deprivation in young, but not old, mice.[161,162] Perhaps even more relevant were changes in proapoptotic proteins (e.g., caspase-12). Aging was associated with greater expression of these markers of apoptosis, and sleep deprivation in the mouse activated this pathway as well. Strikingly, sleep deprivation in the older animal further accentuated such markers of preprogrammed cell death beyond those seen in normal aging and beyond those in sleep deprivation.[162] If these findings are in any way translatable to the human condition, they would suggest a *greater*, rather than *lesser*, necessity to attend to the myriad number of sleep problems in old age.[163]

SUMMARY

Defining normality in elderly populations remains a challenging task. However, an ever-increasing database informs the sleep medicine specialist about potential morbidities that may be associated with poor sleep and various sleep disorders in old age. Multiple factors contribute to poor sleep at night and excessive sleepiness during the day in the aged human. Although most studies have been observational and descriptive, the examination of sleep in lower animals might allow greater understanding of age-dependent changes in sleep as an indicator of biological or physiologic age and sheds new light on the importance of treating sleep problems in human aging.

Acknowledgment

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❖ Clinical Pearls

In old age, in particular, the sleep medicine specialist should always remember that there are numerous overlapping and contributing reasons why the elderly patient has disrupted sleep at night or may be sleepy during the day. Napping should never be assumed to be innocuous, nor should excessive sleepiness during the day be attributed unequivocally to active or subclinical disease. Sleep-disordered breathing may be associated with adverse outcomes in elderly populations as well as middle-aged populations and might warrant treatment. Poor sleep might not only reduce the quality of life of the older person, it might also portend adverse health consequences.

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Daytime Sleepiness and Alertness

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Chapter 4

Abstract

Sleepiness is a problem reported by 10% to 25% of the population, depending on the definition of sleepiness used and the population sampled. It is more frequent in young adults and elderly people. Sleepiness is a physiological need state with its intensity evident by how rapidly sleep onset occurs, how easily sleep is disrupted, and how long sleep endures. Validated self-rated scales and physiological measures are available to assess the presence and degree of sleepiness. Relative to sleepy, healthy adults, the chronicity and irreversibility of sleepiness is indicative of its clinical and pathological significance. Sleepiness is caused by reduced sleep time as often seen in otherwise healthy adults, by fragmented and disrupted sleep as found in patients with primary sleep disorders, by administration of sedating drugs and discontinuation of alerting drugs, and by various neurological disorders. Sleepiness has a normal circadian rhythm that is increased in circadian rhythm misalignments such as those occurring in shift work or jet lag. Excessive and persistent sleepiness is life-threatening, but when its presence is recognized and its etiology identified, it can be successfully treated or at least minimized.

INTRODUCTION

Scientific and clinical attention to sleepiness arose from the recognition of excessive daytime sleepiness (EDS) as a symptom associated with serious life-threatening medical conditions. In the late 1960s, this symptom—which earlier had been ignored, attributed to lifestyle excesses, viewed as a sign of laziness and malingering, or at best, seen as a sign of narcolepsy–began to be seriously studied by scientist–clinicians. Methods to detect and quantify sleepiness were developed. The result has been a growing scientific literature on the nature of sleepiness and its determinants in clinical populations, selected populations of healthy volunteers, and the general population.

This chapter will review information regarding the prevalence of sleepiness in the population. The various methods used to measure sleepiness in the population and laboratory will be described and guidelines regarding clinical assessment of sleepiness will be offered. The nature and neurobiological substrates of sleepiness will be discussed and the known determinants of sleepiness will be described. Finally, the clinical and public health significance of persistent complaints of sleepiness will be discussed.

EPIDEMIOLOGY OF SLEEPINESS

Prevalence estimates of sleepiness in the population vary widely depending on the definition of sleepiness used and the type of population sampled. Surveys and questionnaires have queried regarding the experience of a mood or feeling state of sleepiness, fatigue, or tiredness; about falling asleep unintentionally; or about struggling to stay awake and fighting sleep onset. New developments in the epidemiology of sleepiness have included the use of standardized sleepiness scales and physiological assessments of sleepiness that measure the behavior of falling asleep, its estimated likely occurrence or the speed of its actual occurrence. While another important focus has been on sleepiness in children and adolescents, this chapter only will address sleepiness in adults.

Sleepiness in Limited Populations or Populations of Convenience

In surveys of relatively small, selected populations, 0.3% to 36% of respondents reported excessive sleepiness. Surveys with reported excessive sleepiness rates of less than 3% generally are from earlier studies that focused on hypersomnia.[1] In later studies, in which 4% to 9% rates were reported, more specific questions about excessive sleepiness during the day or relative to one's peers were asked.[2] In some surveys, postprandial, or midday, sleepiness was distinguished from sleepiness at other times of the day, a distinction discussed later in regard to the circadian correlates of sleepiness. Somewhat higher rates are reported in other selected populations using sleepiness scales. For example, the Epworth Sleepiness Scale (ESS), a scale that requires one to estimate the likelihood of falling asleep in different situations, was completed by 740 day workers in 8 industrial plants in Israel and 23% of respondents had ESS scores indicative of excessive sleepiness (i.e., scores >10).[3]

Prevalence rates for sleepiness of 15% and greater also have been found for specific age groups that are consistent with smaller laboratory studies using the physiological measure of sleepiness, the Multiple Sleep Latency Test (MSLT), which is described later. Young adults were sleepier, on average, than a comparison group of middle-aged adults, and about 20% of the young adults had mean daily sleep latencies of less than 5 minutes, a level of sleepiness considered pathological.[4] Healthy elderly also were found to be physiologically sleepier than middle-aged adults.[5] In surveys of the work force engaged in shift or night work, complaints of excessive sleepiness during waking hours are more frequent than among day workers, and continuous ambulatory electroencephalographic (EEG) field monitoring has confirmed the sleepiness.[6]

Sleepiness in Representative Populations

Representative survey studies of national populations have been done. In a study representative of the Finnish

population, 11% of women and 7% of men reported daytime sleepiness almost every day.[7] In another survey, representative of a large geographical area in Sweden, 12% of respondents thought their sleep was insufficient.[8] In that survey, insufficient sleep, and not its consequent daytime sleepiness, was the focus of the questions. Two studies representative of the United States population used the MSLT to assess sleepiness. Given the necessary time commitment required of participants in MSLT studies, the representative integrity of study results is critically dependent on the recruitment response rate. From a large southeastern Michigan random sample (n = 1648) representative of the U.S. population, a subsample (n = 259) with a 68% response rate was recruited to undergo a nocturnal polysomnogram (NPSG) and MSLT the following day. The prevalence of excessive sleepiness, defined as a MSLT average sleep latency of less than 6 minutes, was 13%.[9] In another probability sample of 6,947 Wisconsin state employees, a subsample (n = 632), collected with a 52% response rate, slept at home and then completed a MSLT in the laboratory the next day. Twenty-five percent had an average sleep latency of less than 5 minutes.[10] These two studies also used the ESS to assess sleepiness; in the Michigan study 20% had ESS scores greater than 10, and in the Wisconsin study 25% had scores greater than 11. The higher prevalence in the Wisconsin study, despite the more stringent definition of sleepiness (MSLT of 5 vs. 6 minutes and ESS of 11 vs. 10), could be attributed to an age difference in the samples (51 vs. 42 yr on average) or the previous night's sleep time and circumstances (habitual at home, on average 7.1 hr vs. standard laboratory 8.5 hr). In Figure 4-1 the distribution of sleepiness, defined as average sleep latency on the MSLT, is illustrated for the Michigan population representative sample. The average sleep latency of various clinical samples and experimental sleep time manipulations is provided for comparisons.

Risk Factors for Sleepiness

The risk factors for sleepiness identified in the various surveys includes hours of daily sleep, employment status, marital status, snoring, and depression. Among 26- to 35-year-old members of a large health maintenance organization in Michigan, respondents reported 6.7 hours of sleep on weekdays and 7.4 hours on weekend days, on average.[11] The hours of sleep were inversely related to daytime sleepiness scores on the Sleep–Wake Activity Inventory (SWAI). Both these variables were related to employment and marital status, with full employment and being single predictive of less sleep time and more sleepiness. Self-reported snoring and depression, as measured by a structured diagnostic interview, were also associated with increased sleepiness. In the Finnish study cited earlier, sleepiness was associated with moderate to severe depression and with snoring more than three times per week.[7]

NATURE OF SLEEPINESS

Physiological Need State

Sleepiness, according to a consensus among sleep researchers and clinicians, is a basic physiological need state.[12]

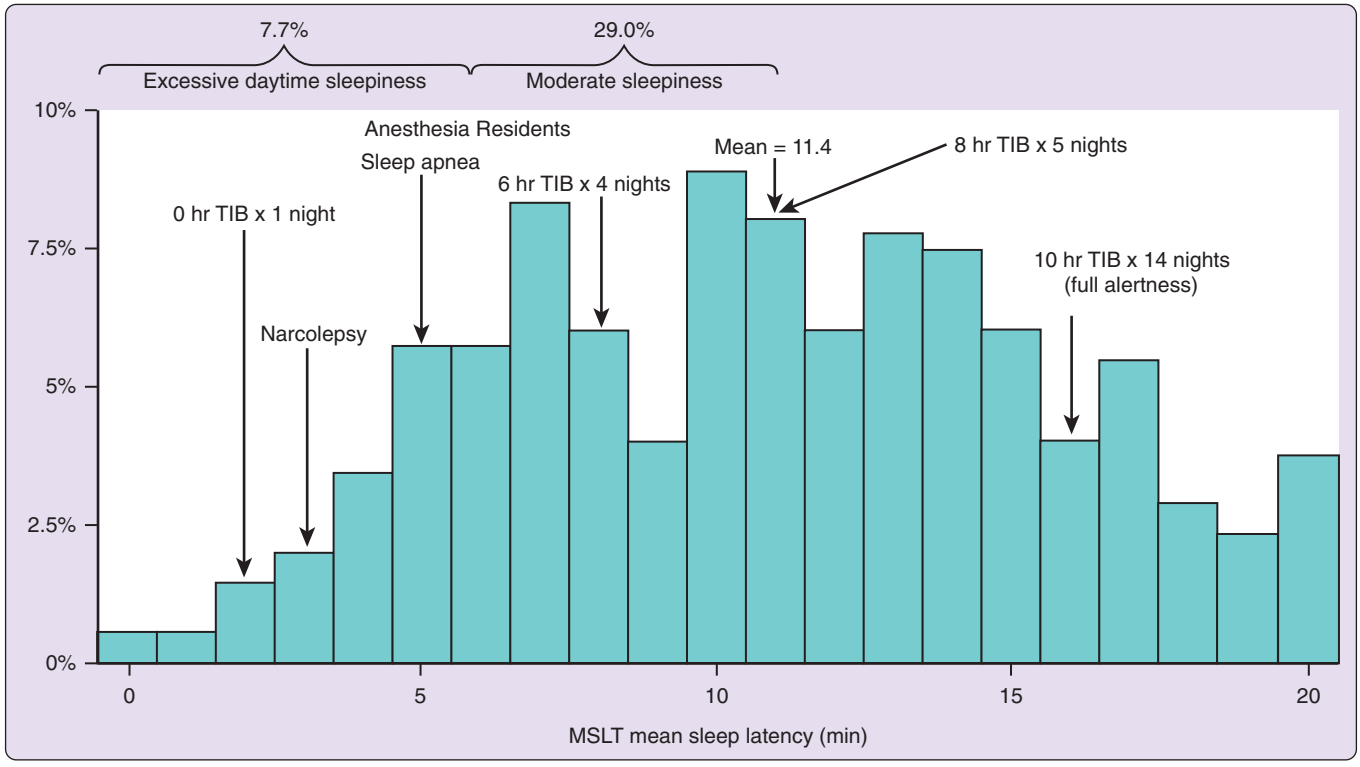

Figure 4-1 The distribution of mean daily sleep latency (min) on the multiple sleep latency test in a subsample (n = 259) recruited (68% response rate) from a large Southeastern Michigan random sample (N = 1648) representative of the U.S. population. The population mean is 11.4 minutes and this is compared to means reported for various patient groups[60,70,71] and the means found in healthy normals after various bedtime manipulations.[23,62] TIB, time in bed.

It may be likened to hunger or thirst, which are physiological need states basic to the survival of the individual organism. The presence and intensity of this state can be inferred by how readily sleep onset occurs, how easily sleep is disrupted, and how long sleep endures. Deprivation or restriction of sleep increases sleepiness, and as hunger or thirst is reversible by eating or drinking, sleep reverses sleepiness. In the organism's daily homeostatic economy, severe deprivation states do not normally occur and hence are not routinely responsible for regulating eating or drinking; other factors (i.e., taste, smell, time-of-day, social factors, biological variables) modulate these behaviors before severe deprivation states develop. Similarly, routine consumption of sleep is not purely homeostatic, but is greatly influenced by social (i.e., job, family, and friends) and environmental (i.e., noise, light, and bed) factors.

The subjective experience of sleepiness and its behavioral indicators (yawning, eye rubbing, nodding) can be reduced under conditions of high motivation, excitement, exercise, and competing needs (e.g., hunger, thirst); that is, physiological sleepiness may not necessarily be manifest. The expression of mild to moderate sleepiness can be masked by any number of factors that are alerting, including motivation, environment, posture, activity, light, or food intake. Studies have shown that average sleep latency on the MSLT is increased by 6 minutes when sitting versus lying in bed and also by 6 minutes when immediately preceded by a 5-minute walk.[13] However, when physiological sleepiness is most severe and persistent, the ability to reduce its impact on overt behavior wanes. The likelihood of sleep onset increases and the intrusion of microsleeps into ongoing behavior occurs. On the other hand, a physiologically alert (*sleepiness* and *alertness* are used here as antonyms) person does not experience sleepiness or appear sleepy even in the most soporific situations. Heavy meals, warm rooms, boring lectures, and the monotony of long-distance automobile driving unmask physiological sleepiness when it is present, but they do not cause it.

Within a conventional 24-hour sleep and wake schedule, maximum sleepiness ordinarily occurs in the middle of the night when the individual is sleeping, and consequently this sleepiness typically is not experienced or remembered. When forced to be awake in the middle of the night, one experiences loss of energy, fatigue, weariness, difficulty concentrating, and memory lapses. When significant physiological sleepiness (as a result of reduced sleep quantity or quality) intrudes on one's usual waking activities during the day, similar symptoms are experienced.

Adaptation to the chronic experience of sleepiness most probably occurs. Clinicians have reported anecdotally that successfully treated patients will frequently comment that they had forgotten the experience of complete alertness. Reduced sensitivity to chronic sleepiness is a likely explanation for the disparities between subjective assessments, even when done with validated scales and the MSLT.[5,14] Typically, it is the most sleepy individuals that show the greatest disparity in subjective versus objective assessments.[5,14] Such individuals deny sleepiness despite significant objective indicators of sleepiness. On the other hand, basally alert individuals (ESS mean 5.6, SEM 0.3) after a one night acute sleep restriction were quite accurate in estimating their sleepiness relative to the increases in EEG theta activity shown during a simulated driving task.[15] Studies have also shown that compensation occurs to the cognitive and behavioral effects of experimental sleep restriction and increased sleepiness, particularly when the sleep loss is mild and accumulates at a slow rate.[16] The absence of a readily apparent behavioral deficiency probably also contributes to the subjective-objective disparity seen in chronically sleepy individuals. Finally, findings from a general population study suggest that subjective sleepiness has multiple dimensions, beyond an increased tendency to fall asleep.[17] Consequently, patients often mistake chronic debilitating fatigue for sleepiness.[18]

The specific nature of this physiological need state is unclear. Whether sleepiness is one-dimensional, varying only in severity, or multidimensional, varying as to etiology or chronicity, has been discussed.[19] If it is one-dimensional, whether or not sleepiness and alertness are at opposite poles of the dimension is also an issue. Earlier, it was noted that sleepiness and alertness are being used as antonyms, which suggests a unipolar state. However, it is possible that sleepiness varies from presence to absence and is distinct from alertness. It was noted that sleepiness may be multidimensional, and among the different types of sleepiness cited are rapid eye movement (REM) versus non–rapid eye movement (NREM) and core versus optional sleepiness.[19] A complete discussion of the heuristic value and evidence to support these distinctions is beyond the scope of this chapter. Nonetheless, the point must be made that these theoretical perspectives may be colored by different measures, experimental demands, populations studied, and subject or patient motivations (i.e., sensitivity to and capacity to counteract sleepiness).

Neural Substrates of Sleepiness

The substrates of sleepiness have yet to be determined. It is assumed that sleepiness is a central nervous system (CNS) phenomenon with identifiable neural mechanisms and neurochemical correlates. Various electrophysiological events suggestive of incipient sleep processes appear in behaviorally awake organisms undergoing sleep deprivation. In sleep-deprived animals, ventral hippocampal spike activity, which normally is a characteristic of NREM sleep, increases during behavioral wakefulness and in the absence of the usual changes in cortical EEG indicative of sleep.[20] Human beings deprived, or restricted, of sleep show identifiable microsleep episodes (brief intrusions of EEG indications of sleep) and increased amounts of alpha and theta activity while behaviorally awake.[21] The evidence suggests that these electrophysiological events are indicants of sleepiness.

An emerging literature of neuroimaging studies, both structural and functional, have suggested specific brain systems that may be involved in sleepiness. Sleep deprivation in young healthy volunteers reduced regional cerebral glucose metabolism, as assessed by positron emission tomography, in thalamic, basal ganglia, and limbic regions of the brain.[22] Functional magnetic resonance imaging (fMRI) after chlorpheniramine (a sedating antihistamine) compared with placebo showed increased frontal and temporal activation.[23] Because fMRI was conducted while the subject was performing cognitive tasks, the authors interpreted the observed brain activation to have resulted from

the increased mental effort, due to sleepiness, required to perform the task. Two groups of patients with severe or slight hypersomnia associated with paramedian thalamic stroke on an MRI showed lesions involving dorso- and centromedial thalamic nuclei, bilateral lesions in the severe group and unilateral in the slight group.[24] As yet, these imaging data are not conclusive. They do suggest it may be possible to identify brain regions and functions that vary with sleepiness. But the nature of the alteration may depend on the behavioral load imposed on the sleepy subject as well as the cause of the sleepiness.

The neurochemistry of sleepiness and alertness involves critical and complex issues that have not yet been fully untangled (see Chapters 18, 37, 42, and 44). First, a basic issue concerns whether sleepiness and alertness have a neurochemistry specific and unique from that associated with the sleep process, per se. Second, it is not clear whether sleepiness and alertness are controlled by separate neurochemicals or by a single substance or system. Third, the relation of the neurochemistry of sleepiness and alertness to circadian mechanisms has not yet been determined. Given the number of questions, it should be of no surprise that these are areas of active research.

Neurophysiological studies of sleep and wake mechanisms have implicated histamine, serotonin, the catecholamines, and acetylcholine in control of wake and gamma-aminobutyric acid (GABA) for sleep.[25] Evidence from animal studies is emerging that suggests extracellular adenosine is the homeostatic sleep factor, with brain levels accumulating during prolonged wakefulness and declining during sleep.[26] The peptide hypocretin/orexin has received much attention for its role in the pathophysiology of narcolepsy.[27] It is considered to be a major wake-promoting hypothalamic neuropeptide and a hypocretin/orexin deficiency has been found in human narcolepsy. Its interactive role in the homeostatic control of sleep and sleepiness has yet to be determined. It is discussed in greater detail in Chapters 18, 37, 42, and 44.

Pharmacological studies provide other interesting hypotheses regarding the neurochemistry of sleepiness-alertness. For example, the benzodiazepines induce sleepiness and facilitate GABA function at the $GABA_A$ receptor complex, thus implicating this important and diffuse inhibitory neurotransmitter.[25] Another example involves histamine, which is now considered to be a CNS neurotransmitter and is thought to have CNS-arousing activity.[25] Antihistamines that penetrate the CNS produce sleepiness.[28] A functional neuroimaging study of histamine H_1 receptors in human brain found that the degree of sleepiness associated with cetirizine (20 mg) was correlated to the degree of H_1 receptor occupancy.[29]

Stimulant drugs suggest several other transmitters and neuromodulators. The mechanism of action of one class of drugs producing psychomotor stimulation and arousal, the amphetamines, is blockade of catecholamine uptake.[30] Another class of stimulants, the methylxanthines, which include caffeine and theophylline, are adenosine receptor antagonists. Adenosine, considered the key neurochemical in the homeostatic regulation of sleep, has inhibitory activity on the two major excitatory neurotransmitters acetylcholine and glutamate. It may be a biomarker of sleepiness.[26] On the other hand, some contradictory evidence limits making definitive conclusions. The space here is too limited to discuss all the evidence in detail. In conclusion, although it is widely held that sleepiness is a physiological state, its physiological substrates are as yet not fully defined.

ASSESSMENT OF SLEEPINESS

Quantifying Sleepiness

The behavioral signs of sleepiness include yawning, ptosis, reduced activity, lapses in attention, and head nodding. An individual's subjective report of his or her level of sleepiness also can be elicited. As noted earlier, a number of factors such as motivation, stimulation, and competing needs can reduce the behavioral manifestation of sleepiness. Thus, behavioral and subjective indicators often underestimate physiological sleepiness.

Assessment problems were evident early in research on the daytime consequences of sleep loss. Sleep loss compromises daytime functions; virtually everyone experiences dysphoria and reduced performance efficiency when not sleeping adequately. But a majority of the tasks used to assess the effects of sleep loss are insensitive.[31] In general, only long and monotonous tasks are reliably sensitive to changes in the quantity and quality of nocturnal sleep. An exception is a 10-minute visual vigilance task, completed repeatedly across the day, during which lapses (response times greater than or equal to 500 milliseconds) and declines in the best response times are increasingly observed as sleep is lost, either during total deprivation or cumulatively over nights of restricted bedtimes.[32]

In various measures of mood, including factor analytic scales, visual analogue scales, and scales for specific aspects of mood, subjects have shown increased fatigue or sleepiness with sleep loss. Among the various subjective measures of sleepiness, the Stanford Sleepiness Scale (SSS) is the best validated.[33] Yet clinicians have found that chronically sleepy patients may rate themselves alert on the SSS even while they are falling asleep behaviorally.[34] Such scales are state measures that query individuals about how they feel at the present moment. Another perspective is to view sleepiness behaviorally, as in the likelihood of falling asleep, and thus ask individuals to rate that likelihood in different social circumstances and over longer periods. The Epworth Sleepiness Scale (ESS) has been validated in clinical populations showing a 74% sensitivity and 50% specificity relative to the MSLT in a study of sleep disorders patients.[35] It asks about falling asleep in settings in which patients typically report falling asleep (e.g., while driving, at church, in social conversation). The time frame over which ratings are to be made is 2 to 4 weeks.

The standard physiological measure of sleepiness, the MSLT, similarly conceptualizes sleepiness as the tendency to fall asleep by measuring the speed of falling asleep. The MSLT has gained wide acceptance within the field of sleep and sleep disorders as the standard method of quantifying sleepiness.[36] Using standard polysomnographic techniques, this test measures, on repeated opportunities at 2-hour intervals throughout the day, the latency to fall asleep while lying in a quiet, dark bedroom. The MSLT is based on the assumption, as outlined earlier, that sleepiness is a

physiological need state that leads to an increased tendency to fall asleep. The metric typically used to express sleepiness has been average daily sleep latency (i.e., mean of the four or five tests conducted), but survival analyses have also been successfully used.[37] The reliability and validity of this measure have been documented in a variety of experimental and clinical situations.[38] In contrast to tests of performance, motivation does not seem to reduce the impact of sleep loss as measured by the MSLT. After total sleep deprivation, subjects can compensate for impaired performance, but they cannot stay awake long while in bed in a darkened room, even if they are instructed to do so.[39]

An alternative to the MSLT, suggested by some clinical investigators, is the Maintenance of Wakefulness Test (MWT). This test requires that subjects lie in bed or sit in a chair in a darkened room and try to remain awake.[40] Like the MSLT, the measure of ability to remain awake is the latency to sleep onset. The test has not been standardized: there are 20-minute and 40-minute versions, and the subject is variously sitting upright in a chair, lying in bed, or semirecumbent in bed. The reliability of the MWT has not been established either. One study reported sensitivity to the therapeutic effects of continuous positive airway pressure (CPAP) in patients with sleep apnea,[41] and several studies reported sensitivity to the therapeutic effects of stimulants in narcolepsy.[42] A study attempted to tease apart the critical factors being measured by the MWT and concluded that, unlike the MSLT which measures level of sleepiness, the MWT measures the combined effects of level of sleepiness and the degree of arousal as defined by heart rate.[43]

The rationale for the MWT is that clinically the critical issue for patients is how long wakefulness can be maintained. A basic assumption underlying this rationale, however, may not be valid: it assumes that a set of circumstances can be evaluated in the laboratory that will reflect an individual's probability of staying awake in the real world. Such a circumstance is not likely because environment, motivation, circadian phase, and any competing drive states all affect an individual's tendency to remain awake. Stated simply, an individual crossing a congested intersection at midday is more likely to stay awake than an individual driving on an isolated highway in the middle of the night. The MSLT, on the other hand, addresses the question of the individual's risk of falling asleep by establishing a setting to maximize the likelihood of sleep onset: all factors competing with falling asleep are removed from the test situation. Thus, the MSLT identifies sleep tendency or clinically identifies maximum risk for the patient. Obviously, the actual risk will vary from individual to individual, from hour to hour, and from environment to environment.

Relation of Sleepiness to Behavioral Functioning

Given that the MSLT is a valid and reliable measure of sleepiness, the question arises as to how this measure relates to an individual's capacity to function. Direct correlations of the MSLT with other measures of performance under normal conditions have not been too robust. Several studies have found, however, that when sleepiness is at maximum levels, correlations with performance are high. For example, MSLT scores after sleep deprivation,[44] after administration of sedating antihistamines,[45] and after benzodiazepine administration[46] correlate with measures of performance and even prove to be the most sensitive measure. Studies also have compared levels of sleepiness to the known performance-impairing effects of alcohol.[47] A study relating performance lapses on a vigilance task to the cumulative effects of sleep restriction found a function comparable to that of the MSLT under a similar cumulative sleep restriction (Fig. 4-2).[48] The reason many studies have found weak correlations between performance and MSLT at normal or moderate levels of sleepiness is that laboratory performance and MSLT are differentially affected by variables such as age, education, and motivation.

For the most part, the literature relating sleepiness and behavioral functioning has focused on psychomotor and attention behaviors with the major outcomes being response slowing and attentional lapses. These impairments can be attributed to slowed processing of information and microsleeps, that is intrusion of sleep preparation and sleep onset behaviors. Research has focused on other behavioral domains not as clearly associated with sleep-mediated behaviors, including decision-making and pain sensation. Several studies have shown that increased sleepiness is associated with poor risk-taking decisions.[49] Sleep loss and its associated sleepiness have also been shown to increase pain sensitivity.[50]

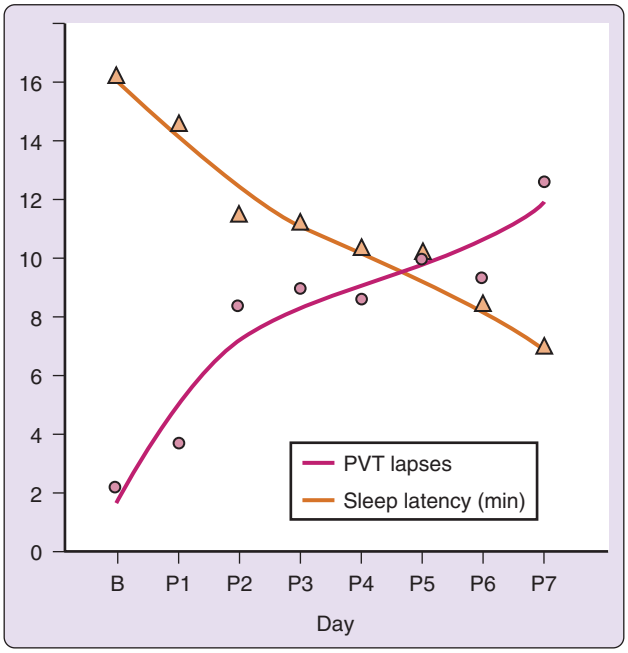

Figure 4-2 Similar functions relating mean daily sleep latency on the multiple sleep latency test (MSLT) and mean daily lapses on the visual psychomotor vigilance test (PVT) to the cumulative effects of sleep restriction (about 5 hours of bedtime nightly) across 7 consecutive nights (P1 to P7). (Redrawn from Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep 1997;20:275.)

Clinical Assessment of Sleepiness

Assessing the clinical significance of a patient's complaint of excessive sleepiness can be complex for an inexperienced clinician. The assessment depends on two important factors: chronicity and reversibility. Chronicity can be explained simply. Although a healthy normal individual may be acutely sleepy, the patient's sleepiness is persistent and unremitting. As to reversibility, unlike the healthy normal person, increased sleep time may not completely or consistently ameliorate a patient's sleepiness. Patients with excessive sleepiness may not complain of sleepiness per se, but rather its consequences: loss of energy, fatigue, lethargy, weariness, lack of initiative, memory lapses, or difficulty concentrating.

To clarify the patient complaint, it is important to focus on soporific situations in which physiological sleepiness is more likely to be manifest, as was discussed earlier. Such situations might include watching television, reading, riding in a car, listening to a lecture, or sitting in a warm room. Table 4-1 presents the commonly reported "sleep-inducing" situations for a large sample of patients with sleep apnea syndrome. After clarifying the complaint, one should ask the patient about the entire day: morning, midday, and evening. In the next section, it will become clear that most adults experience sleepiness over the midday. However, patients experience sleepiness at other times of the day as well, and often throughout the day. Whenever possible, objective documentation of sleepiness and its severity should be sought. As indicated earlier, the standard and accepted method to document sleepiness objectively is the MSLT.

Guidelines for interpreting the results of the MSLT are available (see Fig. 4-1).[36] A number of case series of patients with disorders of excessive sleepiness have been published with accompanying MSLT data for each diagnostic classification.[51] These data provide the clinician with guidelines for evaluating the clinical significance of a given patient's MSLT results. Although these data cannot be considered norms, a scheme for ranking MSLT scores to indicate degree of pathology has been suggested.[41] An average daily MSLT score of 5 minutes or fewer suggests pathological sleepiness, a score of more than 5 minutes but fewer than 10 minutes is considered a diagnostic gray area, and a score of more than 10 minutes is considered to be in the normal range (see Fig. 4-1 for MSLT results in the general population). The MSLT is also useful in identifying sleep-onset REM periods (SOREMPs), which are common in patients with narcolepsy.[52] The American Academy of Sleep Medicine Standards of Practice Committee has concluded that the MSLT is indicated in the evaluation of patients with suspected narcolepsy.[52] MSLT results, however, must also be evaluated with respect to the conditions under which the testing was conducted. Standards have been published for administering the MSLT, which must be followed to obtain a valid, interpretable result.[36]

Table 4-1 Sleep-Inducing Situations for Patients with Apnea*

SITUATION	PERCENTAGE OF PATIENTS
Watching television	91
Reading	85
Riding in a car	71
Attending church	57
Visiting friends and relatives	54
Driving	50
Working	43
Waiting for a red light	32

*N = 384 patients.

DETERMINANTS OF SLEEPINESS

Quantity of Sleep

The degree of daytime sleepiness is directly related to the amount of nocturnal sleep. The performance effects of acute and chronic sleep deprivation are discussed in Chapters 5 and 6. As to sleepiness, partial or total sleep deprivation in healthy normal subjects is followed by increased daytime sleepiness the following day.[38] Therefore, modest nightly sleep restriction accumulates over nights to progressively increase daytime sleepiness and performance lapses (see Fig. 4-1).[53] However, the speed at which sleep loss is accumulated is critical, as studies have shown adaptation to a slow accumulation of 1 to 2 hours nightly occurs, which then increases the duration of the subsequent recovery process.[23] Increased sleep time in healthy, but sleepy, young adults by extending bedtime beyond the usual 7 to 8 hours per night produces an increase in alertness (i.e., reduction in sleepiness).[54] Further, the pharmacological extension of sleep time by an average of 1 hour in elderly people produces an increase in mean sleep latency on the MSLT (i.e., increased alertness).[55]

Reduced sleep time explains the excessive sleepiness of several patient and nonpatient groups. For example, a subgroup of sleep clinic patients has been identified whose excessive daytime sleepiness can be attributed to chronic insufficient sleep.[56] These patients show objectively documented excessive sleepiness, "normal" nocturnal sleep with unusually high sleep efficiency (time asleep–time in bed), and report about 2 hours more sleep on each weekend day than each weekday. Regularizing bedtime and increasing time in bed produces a resolution of their symptoms and normalized MSLT results.[57] The increased sleepiness of healthy young adults also can be attributed to insufficient nocturnal sleep. When the sleepiest 25% of a sample of young adults is given extended time in bed (10 hours) for as long as 5 to 14 consecutive nights, their sleepiness is reduced to a level resembling the general population mean.[54]

Individual differences in tolerability to sleep loss have been reported.[58] These differences can be attributed to a number of possible factors. A difference in the basal level of sleepiness at the start of a sleep time manipulation is quite possible given the range of sleepiness in the general population (see Fig. 4-1). The basal differences may reflect insufficient nightly sleep relative to ones' sleep need.[54] There also may be differences in the sensitivity and responsivity of the sleep homeostat to sleep loss, that is how large

a sleep deficit the system can tolerate and how robustly the sleep homeostat produces sleep when detecting deficiency. Finally, genetic differences in sleep need, the set point around which the sleep homeostat regulates daily sleep time, have long been hypothesized and one study has suggested a gene polymorphism may mediate vulnerability to sleep loss.[59] These all are fertile areas for research.

Quality of Sleep

Daytime sleepiness also relates to the quality and the continuity of a previous night's sleep. Sleep in patients with a number of sleep disorders is punctuated by frequent, brief arousals of 3 to 15 second durations. These arousals are characterized by bursts of EEG speeding or alpha activity and, occasionally, transient increases in skeletal muscle tone. Standard scoring rules for transient EEG arousals have been developed.[60] A transient arousal is illustrated in Figure 4-3. These arousals typically do not result in awakening by either Rechtschaffen and Kales sleep staging criteria or behavioral indicators, and the arousals recur in some conditions as often as 1 to 4 times per minute. The arousing stimulus differs in the various disorders and can be identified in some cases (apneas, leg movements, pain) but not in others. Regardless of etiology, the arousals generally do not result in shortened sleep but rather in fragmented or discontinuous sleep, and this fragmentation produces daytime sleepiness.[61]

Correlational evidence suggests a relation between sleep fragmentation and daytime sleepiness. Fragmentation, as indexed by number of brief EEG arousals, number of shifts from other sleep stages to stage 1 sleep or wake, and the percentage of stage 1 sleep correlates with EDS in various patient groups.[61] Treatment studies also link sleep fragmentation and excessive sleepiness. Patients with sleep apnea syndrome who are successfully treated by surgery (i.e., number of apneas are reduced) show a reduced frequency of arousals from sleep as well as a reduced level of sleepiness, whereas those who do not benefit from the surgery (i.e., apneas remain) show no decrease in arousals or sleepiness, despite improved sleeping oxygenation.[62] Similarly, CPAP, by providing a pneumatic airway splint, reduces breathing disturbances and consequent arousals from sleep and reverses EDS.[63] The reversal of daytime sleepiness following CPAP treatment of sleep apnea syndrome is presented in Figure 4-4. The hours of nightly CPAP use predicts both subjective and objective measures of sleepiness.[64]

Experimental fragmentation of the sleep of healthy normal subjects has been produced by inducing arousals with an auditory stimulus. Several studies have shown that subjects awakened at various intervals during the night demonstrate performance decrements and increased sleepiness on the following day.[65] Studies have also fragmented sleep without awakening subjects by terminating the stimulus on EEG signs of arousal rather than on behavioral response. Increased daytime sleepiness (shortened latencies on the MSLT) resulted from nocturnal sleep fragmentation in one study,[66] and in a second study, the recuperative effects (measured as increased latencies on the MSLT) of a nap following sleep deprivation were compromised by fragmenting the sleep on the nap.[67]

One nonclinical population in which sleep fragmentation is an important determinant of excessive sleepiness is the elderly. Many studies have shown that even elderly people without sleep complaints show an increased number of apneas and periodic leg movements during sleep.[68] As noted earlier, the elderly as a group are sleepier than other groups.[5] Furthermore, it has been demonstrated that elderly people with the highest frequency of arousal during sleep have the greatest daytime sleepiness.[69]

Circadian Rhythms

A biphasic pattern of objective sleep tendency was observed when healthy, normal young adult and elderly subjects were tested every 2 hours over a complete 24-hour day.[70] During the sleep period (11:30 PM to 8:00 AM) the latency

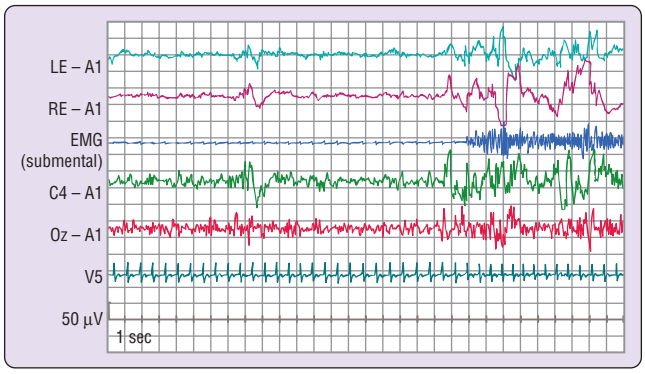

Figure 4-3 A transient arousal (on right side of figure) fragmenting sleep. The preexistence of sleep is evident by the K-complex at second 9 of the epoch preceding the arousal. LE-A1, Left electrooculogram referenced to A1; RE-A1, right electrooculogram referenced to A1; EMG, electromyogram from submental muscle; C4-A1, electroencephalogram referenced to A1 from C4 placement; Oz-A1, electroencephalogram referenced to A1 from Oz placement; V5, electrocardiogram from V5 placement. (Redrawn from American Sleep Disorders Association. EEG arousals: scoring rules and examples. Sleep 1992; 15:173-184.)

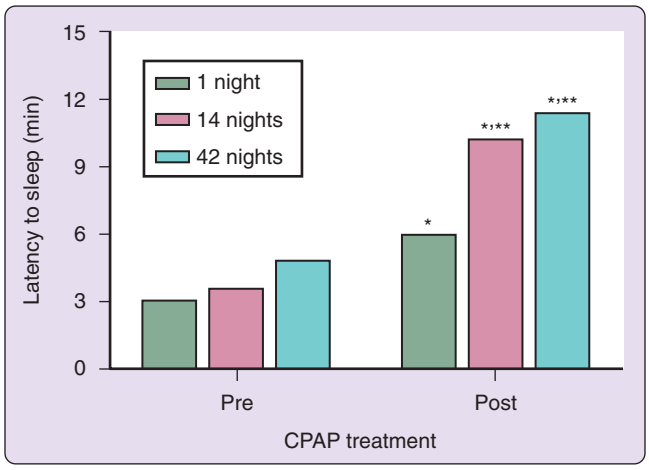

Figure 4-4 Mean daily sleep latency on the multiple sleep latency test (MSLT) in patients with obstructive sleep apnea syndrome before (pre) and after (post) 1, 14, and 42 nights of continuous positive airway pressure (CPAP) treatment.
*, $P < .05$; **, $P < .01$. (Redrawn from Lamphere J, Roehrs T, Wittig R, et al. Recovery of alertness after CPAP in apnea. Chest 1989;96:1364-1367.)

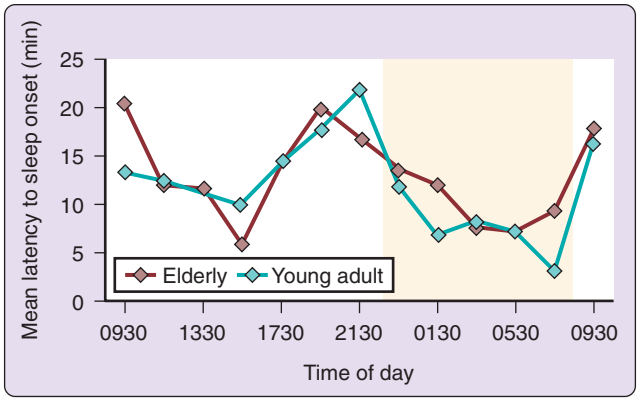

Figure 4-5 Latency to sleep at 4-hour intervals across the 24-hour day. Testing during the daytime followed standard multiple sleep latency test (MSLT) procedures. During the night, from 11:30 PM to 8:00 AM (shaded area), subjects were awakened every 2 hours for 15 minutes, and latency of return to sleep was measured. Elderly subjects (n = 10) were 60 to 83 years old; young subjects (n = 8) were 19 to 23 years old. (Redrawn from Carskadon MA, Dement WC: Daytime sleepiness: Quantification of a behavioral state. Neurosci Biobehav Rev 1987;111:307-317. Copyright 1987, Elsevier Science.)

testing was accomplished by awakening subjects for 15 minutes and then allowing them to return to sleep. Two troughs of alertness—one during the nocturnal hours (about 2:00 to 6:00 AM) and another during the daytime hours (about 2:00 to 6:00 PM)—were observed. Figure 4-5 shows the biphasic pattern of sleepiness–alertness.

Other research protocols have yielded similar results. In constant routine studies, where external environmental stimulation is minimized and subjects remain awake, superimposed on the expected increase in self-rated fatigue resulting from the deprivation of sleep is a biphasic circadian rhythmicity of self-rated fatigue similar to that seen for sleep latency.[71] In another constant routine study in which EEG was continuously monitored, a biphasic pattern of "unintentional sleep" was observed.[72] In studies with sleep scheduled at unusual times, the duration of sleep periods has been used as an index of the level of sleepiness. A pronounced circadian variation in sleep duration is found with the termination of sleep periods closely related to the biphasic sleep latency function in the studies cited earlier.[73] If individuals are permitted to nap when they are placed in time-free environments, this biphasic pattern becomes quite apparent in the form of a midcycle nap.[74]

This circadian rhythm in sleepiness is part of a circadian system in which many biological processes vary rhythmically over 24 hours. The sleepiness rhythm parallels the circadian variation in body temperature, with shortened latencies occurring in conjunction with temperature troughs.[70] But these two functions, sleep latency and body temperature, are not mirror images of each other; the midday body temperature decline is relatively small compared with that of sleep latency. Furthermore, under free-running conditions, the two functions become dissociated.[75] However, no other biological rhythm is as closely associated with the circadian rhythm of sleepiness as is body temperature.

Earlier, it was noted that shift workers are unusually sleepy, and jet travelers experience sleepiness acutely in a new time zone. The sleepiness in these two conditions results from the placement of sleep and wakefulness at times that are out of phase with the existing circadian rhythms. Thus, not only is daytime sleep shortened and fragmented but also wakefulness occurs at the peak of sleepiness or trough of alertness. Several studies have shown that pharmacological extension and consolidation of out-of-phase sleep can improve daytime sleepiness (see Chapters 42, 73, and 81 for more detail).[76] Yet, the basal circadian rhythm of sleepiness remains, although the overall level of sleepiness has been reduced. In other words, the synchronization of circadian rhythms to the new sleep–wake schedule is not hastened.

CNS Drugs

Sedating Drug Effects

Central nervous system (CNS) depressant drugs, as expected, increase sleepiness. Most of these drugs act as agonists at the $GABA_A$ receptor complex. The benzodiazepine hypnotics hasten sleep onset at bedtime and shorten the latency to return to sleep after an awakening during the night (which is their therapeutic purpose), as demonstrated by a number of objective studies.[77] Long-acting benzodiazepines continue to shorten sleep latency on the MSLT the day following bedtime administration.[77] Finally, ethanol administered during the daytime (9:00 AM) reduces sleep latency in a dose-related manner as measured by the MSLT.[78]

Second generation antiepileptic drugs, including gabapentin, tiagabine, vigabatrin, pregabalin, and others, enhance GABA activity through various mechanisms that directly or indirectly involve the $GABA_A$ receptor.[79] The sedating effects of these various drugs have not been thoroughly documented, but some evidence indicates they do have sedative activity. $GABA_B$ receptor agonists are being investigated as treatments for drug addictions and the preclinical animal research suggests these drugs may have sedative activity as well.[80]

Antagonists acting at the histamine H_1 receptor also have sedating effects. One of the most commonly reported side effects associated with the use of H_1 antihistamines is daytime sleepiness. Several double-blind, placebo-controlled studies have shown that certain H_1 antihistamines, such as diphenhydramine, increase sleepiness using sleep latency as the objective measure of sleepiness, whereas others, such as terfenadine or loratadine do not.[81] The difference among these compounds relates to their differential CNS penetration and binding. Others of the H_1 antihistamines (e.g., tazifylline) are thought to have a greater peripheral compared with central H_1 affinity, and, consequently, effects on daytime sleep latency are found only at relatively high doses.[81]

Antihypertensives, particularly beta adrenoreceptor blockers, are also reported to produce sedation during the daytime.[82] These CNS effects are thought to be related to the differential liposolubility of the various compounds. However, we are unaware of any studies that directly measure the daytime sleepiness produced by beta-blockers; the information is derived from reports of side effects. As noted earlier, it is important to differentiate sleepiness

from tiredness or fatigue. Patients may be describing tiredness or fatigue resulting from the drugs' peripheral effects (i.e., lowered cardiac output and blood pressure), not sleepiness, a presumed central effect.

Sedative effects of dopaminergic agonists used in treating Parkinson's disease have been reported as adverse events in clinical trials and in case reports as "sleep attacks" while driving.[83] It is now clear these "sleep attacks" are not attacks per se, but are the expression of excessive sleepiness. Whereas the dose-related sedative effect of these drugs has been established, the mechanism by which the sedative effects occur is unknown. The dopaminergic agonists are also known to disrupt and fragment sleep.[84] Thus, the excessive sleepiness may be secondary to disturbed sleep, or to a combination of disturbed sleep and direct sedative effects.

Alerting Drug Effects

Stimulant drugs reduce sleepiness and increase alertness. The drugs in this group differ in their mechanisms of action. Amphetamine, methylphenidate, and pemoline block dopamine reuptake and to a lesser extent enhance the release of norepinephrine, dopamine, and serotonin. The mechanism of modafinil is not established; some evidence suggests that modafinil has a mechanism distinct from the classical stimulants. Amphetamine, methylphenidate, pemoline, and modafinil are used to treat the EDS associated with narcolepsy and some have been studied as medications to maintain alertness and vigilance in normal subjects under conditions of sustained sleep loss (e.g., military operations). Studies in patients with narcolepsy using MSLT or MWT have shown improved alertness with amphetamine, methylphenidate, modafinil, and pemoline.[85] There is dispute as to the extent to which the excessive sleepiness of narcoleptics is reversed and the comparative efficacy of the various drugs. In healthy normal persons restricted or deprived of sleep, both amphetamine and methylphenidate increase alertness on the MSLT and improve psychomotor performance.[86,87] Caffeine is an adenosine receptor antagonist. Caffeine, in doses equivalent to 1 to 3 cups of coffee, reduced daytime sleepiness on the MSLT in normal subjects after 5 hours of sleep the previous night.[88]

Influence of Basal Sleepiness

The preexisting level of sleepiness–alertness interacts with a drug to influence the drug's behavioral effect. In other words, a drug's effect differs when sleepiness is at its maximum compared to its minimum. As noted previously, the basal level of daytime sleepiness can be altered by restricting or extending time in bed[58]; this in turn alters the usual effects of a stimulating versus a sedating drug. A study showed comparable levels of sleepiness–alertness during the day following 5 hours in bed and morning (9:00 AM) caffeine consumption compared to 11 hours in bed and morning (9:00 AM) ethanol ingestion. Follow-up studies explored the dose relations of ethanol's interaction with basal sleepiness.[89] Dose-related differences in daytime sleepiness following ethanol and 8 hours of sleep were diminished after even 1 night of 5 hour sleep, although the measured levels of ethanol in breath were consistent day to day. In other words, sleepiness enhanced the sedative effects of ethanol. In contrast, caffeine and methylphenidate produced a similar increase in alertness, regardless of the basal level of sleepiness. Clinically, these findings imply, for example, that a sleepy driver with minimal blood ethanol levels may be as dangerous as an alert driver who is legally intoxicated.[89]

The basal state of sleepiness also influences drug-seeking behavior. The likelihood that a healthy normal person without a drug abuse history will self-administer methylphenidate is greatly enhanced after 4 hours of sleep the previous night compared to 8 hours of sleep (see Fig. 4-4). Though not experimentally demonstrated as yet, self administration of caffeine also is probably influenced by basal state of sleepiness. The high volume of caffeine use in the population probably relates to the high rate of self medication for sleepiness due to chronic insufficient sleep in the population.

CNS Pathologies

Pathology of the CNS is another determinant of daytime sleepiness. The previously noted hypocretin/orexin deficiency is thought to cause excessive sleepiness in patients with narcolepsy.[90] Another sleep disorder associated with excessive sleepiness due to an unknown pathology of the CNS is idiopathic CNS hypersomnolence. A report of a series of rigorously diagnosed cases (n = 77) found moderate MSLT scores (8.5 minutes mean latency) relative to narcoleptics (4.1 minutes mean latency).[91] As yet hypocretin/orexin deficiency has not been shown in this disorder. These two conditions are described in detail in Chapters 84 and 86.

Excessive sleepiness is reported in other neurological diseases. A study in patients with myotonic dystrophy, type 1 reported excessive sleepiness on the MSLT and reduced cerebrospinal levels of hypocretin/orexin.[92] "Sleep attacks" have been reported in Parkinson's disease and assessment with the MSLT suggests these attacks are the expression of excessive daytime sleepiness.[93] What remains unresolved in the excessive sleepiness of Parkinson's disease is the relative contribution of the disease itself, the fragmentation of sleep due to periodic leg movement or apnea , and the dopaminergic drugs used in treating Parkinson's disease.[94] The previously cited study found no differences in sleepiness as a function of prescribed drug or sleep fragmentation, although further assessment in larger samples is necessary to confirm this finding. Sleepiness may be prominent after traumatic brain injury.[94a,94b]

CLINICAL AND PUBLIC HEALTH SIGNIFICANCE OF SLEEPINESS

Although the patients at sleep disorders centers are not representative of the general population, they do provide some indications regarding the clinical significance of sleepiness. Their sleep–wake histories directly indicate the serious impact excessive sleepiness has on their lives.[95] Nearly half the patients with excessive sleepiness report automobile accidents; half report occupational accidents, some life threatening; and many have lost jobs because of their sleepiness. In addition, sleepiness is considerably disruptive of family life.[96] An elevated automobile accident rate (i.e., sevenfold) among patients with excessive sleepi-

ness has been verified through driving records obtained from motor vehicle agencies.[97]

Population-based information regarding traffic and industrial accidents also suggests a link between sleepiness and life-threatening events. Verified automobile accidents occurred more frequently in a representative sample of people with MSLT scores of 5 minutes or less.[98] The highest rate of automobile accidents occurs in the early morning hours, which is notable because the fewest automobiles are on the road during these hours. Also during these early morning hours, the greatest degree of sleepiness is experienced.[99] Long-haul truck drivers have accidents most frequently (even corrected for hours driving before the accident) during the early morning hours, again when sleepiness reaches its zenith.[100]

Workers on the graveyard shift were identified as a particularly sleepy subpopulation. In 24-hour ambulatory EEG recordings of sleep and wakefulness, workers (20% in one study) were found to actually fall asleep during the night shift.[8] Not surprisingly, the poorest job performance consistently occurs on the night shift, and the highest rate of industrial accidents is usually found among workers on this shift.[101] Medical residents are another particularly sleepy subpopulation. In surveys those reporting five or fewer hours of sleep per night were more likely to make medical errors, report serious accidents, and were two times more likely to be named in medical malpractice suits.[102,103] In a survey of medical house-staff, 49% reported falling asleep while driving and 90% of the episodes occurred postcall compared to 13% fall-asleep episodes reported by the medical faculty and 20 of the 70 house-staff were involved in automobile accidents compared to 11 of the 85 faculty.[104]

Cognitive function is also impaired by sleepiness. Adults with various disorders of excessive sleepiness have cognitive and memory problems.[105] The memory deficiencies are not specific to a certain sleep disorder but rather specific to the sleepiness associated with the disorder. When treated adequately, sleepiness is rectified and the memory and cognitive deficits similarly improve.[106] Results of sleep deprivation studies in healthy normal patients support the relation between sleepiness and memory deficiency. Even modest reductions of sleep time are associated with cognitive deficiencies.[107]

Sleepiness also depresses arousability to physiological challenges: 24-hour sleep deprivation decreases upper airway dilator muscle activity[108] and decreases ventilatory responses to hypercapnia and hypoxia.[109] In a canine model of sleep apnea, periodic disruption of sleep with acoustic stimuli (i.e., sleep fragmentation, in contrast to sleep deprivation) resulted in lengthened response times to airway occlusion, greater oxygen desaturation, increases in inspiratory pressures, and surges in blood pressure.[110] Depressed physiological responsivity due to sleepiness is clinically significant for patients with sleep apnea and other breathing disorders as they are all exacerbated by sleepiness. The emerging data on sleepiness and pain threshold, cited earlier, is also clinically significant in the management of both acute and chronic pain conditions.

Finally, life expectancy data directly link excessive sleep (not specifically sleepiness) and mortality. A 1976 study found that men and women who reported sleeping more than 10 hours of sleep a day were about 1.8 times more likely to die prematurely than those sleeping between 7 and 8 hours daily.[111] This survey, however, associated hypersomnia and increased mortality and not necessarily EDS, for which the relation is currently unknown.

❖ Clinical Pearl

Sleepiness, when most excessive and persistent, is a signal to the individual to stop operating because it is dangerous and life-threatening to continue without sleep. It is also a signal to the clinician that there may be some underlying pathology that can be successfully treated, or in the very least minimized, as to its vital, life-threatening impact.

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Acute Sleep Deprivation

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Chapter 5

Abstract

Sleep deprivation is extremely common in modern society. Sleep loss is accompanied by significant and increasingly apparent alterations in mood, alertness, and performance. This chapter reviews the behavioral effects of sleep deprivation, including both sleep/circadian influences and arousal system influences such as activity, light, noise, posture, motivation, and drugs. The effects of sleep loss are broad, and numerous systems are affected. Work showing similar changes after alcohol ingestion provides one means of comparatively describing the effects of sleep loss. A number of relatively mild physiologic changes accompany total sleep deprivation in man. However, several new means of assessing sleep deprivation effects, including brain scans, genetic assessment, and animal models, show promise for a better understanding of sleep and sleep loss. Studies have also shown that high-frequency periodic sleep fragmentation produces nonrestorative sleep that results in a state of sleepiness and decreased performance that is similar in many dimensions to sleepiness after total sleep deprivation. Recovery sleep after sleep loss or sleep fragmentation shows a characteristic pattern of elevated slow-wave sleep (SWS) with elevated sensory thresholds followed by elevated rapid eye movement (REM) sleep.

Sleep deprivation is both extremely common and critically relevant in our society. As a clinical entity, sleep deprivation is recognized by the diagnosis of insufficient sleep syndrome (International Classification of Diseases [ICD]-2, #307.44). As an experimental methodology, sleep deprivation serves as a major tool in understanding the function of sleep. A broad range of physiologic responses and behavioral abilities have been examined after varying periods without sleep, and lawful relationships have been described. These relationships and the theory they represent are important in their own right, but the findings also serve as an extensive guide to symptoms associated with insufficient sleep. Furthermore, methods developed to lessen the impact of sleep deprivation also serve as possible clinical treatments for disorders related to insufficient sleep or excessive sleepiness.

This chapter will review behavioral, physiologic, and theoretical implications of acute sleep deprivation. Chronic partial sleep deprivation is examined in Chapter 6. Studies of sleep deprivation can suffer from some common methodological problems that require consideration. The most important control issue is that one cannot perform a blinded sleep deprivation study. Both experimenter and subject motivation can have an impact on results, particularly in the behavioral and subjective domains. Motivation effects are frequently apparent near the end of sleep deprivation studies (where performance improvement is sometimes found) and may account for the difficulty in showing early decrements. Animal studies are less susceptible to subject expectation effects, but they may contain additional elements of stress that may interact with sleep loss, so these studies may not be directly comparable with stress control conditions. In addition, almost all sleep loss experiments involve more than simple loss of sleep. Maintenance of wakefulness usually includes upright posture, light, movement, cognition, and all the underlying physiologic processes implied by these activities. The experimental setting itself is usually far from routine. Some studies have attempted to control some of these factors during sleep loss, but trying to control all variables in a single experiment is daunting.

Over a thousand studies of sleep deprivation have been published during the past 10 years, and the resulting knowledge database has been remarkably consistent. However, new techniques and increasingly sensitive tests continue to add both theoretical and practical understanding of the impact of sleep loss. This review includes sections on total sleep deprivation, sleep fragmentation, and recovery from sleep deprivation.

TOTAL SLEEP DEPRIVATION

The first published studies of total sleep loss date to 1894 for puppies[1] and 1896 for humans.[2] The puppy study indicated that prolonged sleep loss in animals could be fatal, an idea reinforced by numerous, more recent animal studies. The human study included a range of physiologic and behavioral measurements and remains a model study.

Behavioral Effects

The most striking effect of sleep loss is sleepiness, and this can be inferred from subjective reports, the multiple sleep latency test (MSLT), electroencephalographic (EEG) change, or simply looking at the face of the participant. The variables that determine the impact of sleep loss can be divided into four categories: sleep/circadian influences, arousal system influences, individual characteristics, and test characteristics (Box 5-1).

Sleep/Circadian Influences

Sleep deprivation, like nutritional status, is a relative concept. How an individual responds to sleep loss depends on the prior sleep amount and distribution. Performance during a period of sleep loss is also directly dependent on the length of time awake and the circadian time, and predictive models support these factors. Experiments usually try to control prior wakefulness and sleep amount by requiring "normal" nights of sleep before initiation of a sleep loss episode. Data from multiple regression analyses of behavioral and EEG data during 64 hours of sleep loss[3] suggest that time awake accounts for 25% to 30% of the variance in alertness, and that circadian time

Box 5-1 Determinants of the Impact of Sleep Loss

Sleep/Circadian Influences
- Prior sleep amount and distribution
- Length of time awake
- Circadian time

Arousal Influences
- Activity
- Bright light
- Noise
- Temperature
- Posture
- Motivation or interest
- Drugs
- Group effects
- Repeated exposure to sleep loss

Individual Characteristics
- Age
- Individual sensitivity
- Personality and psychopathology

Test Characteristics and Types
- Length of test
- Knowledge of results
- Test pacing
- Proficiency level
- Difficulty or complexity of test
- Memory requirement
- Executive function measures
- Subjective (versus objective) measures
- Electroencephalographic measures—multiple sleep latency test (MSLT)

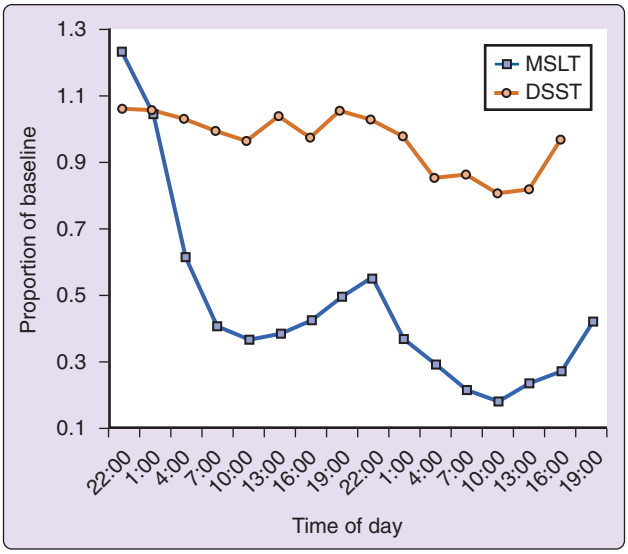

Figure 5-1 Latency to stage 2 sleep *(boxes)* and number of correctly completed symbol substitutions in repeated 5-minute test sessions *(dots)* over a period of 64 hours of sleep deprivation, both expressed as a proportion of baseline values. (Data from Bonnet MH, Gomez S, Wirth O, et al. The use of caffeine versus prophylactic naps in sustained performance. Sleep 1995;18:97-104.) DSST, digit symbol substitution task; MSLT multiple sleep latency test.

accounts for about 6% of the variance. When prophylactic naps of varying length were interjected early in a period of sleep loss, it was found that the prophylactic nap sleep accounted for about 5% of the variance in alertness during the sleep deprivation period. In terms of reducing the effect of sleep loss, the overall effect of increasing the prophylactic nap period was linear for additional sleep amounts ranging up to 8 hours in length. Figure 5-1 displays the effects of time awake and the circadian rhythm on objective alertness as measured by the MSLT and the ability to complete correct symbol substitutions during 64 hours of sleep loss.

Arousal Influences

Environmental and emotional surroundings have a large impact on the course of a period of sleep loss. In early stages of sleep deprivation, many intervening variables can easily reverse all measurable sleep loss decrements. These influences include activity, bright light, noise, temperature, posture, stress, and drugs.

Activity

A 5-minute walk immediately preceding MSLT evaluations had a large impact (about 6 minutes) on MSLT values, which masked the impact of a 50% reduction of nocturnal sleep (about a 2-minute reduction on MSLT) and continued for at least 90 minutes.[4] Exercise before performing tasks provided transient reversal of some psychomotor decrements resulting from sleep loss. However, more ambitious studies comparing high activity and low activity that continued over 40 to 64 hours of sleep deprivation have shown no beneficial effects of exercise on overall performance.[5] Perhaps, arousing stimuli act for only a discrete period of time that is decreased by increasing sleep loss.[6] There may also be a trade-off between production of arousal and production of physical fatigue.

Bright Light

Bright light can shift circadian rhythms. Some controversy exists concerning whether bright light can also act as a source of stimulation during a sleep-loss state to help to maintain alertness. Two of five studies found that periods of bright light immediately before sleep onset significantly increased sleep latencies. Other studies found improved nocturnal performance during bright light conditions, with elevated heart rate as a probable correlate.[7]

Noise

Noise, despite complex and occasionally negative effects on the performance of well-rested individuals, may produce small beneficial effects during sleep deprivation.[8] It is generally assumed that noise increases arousal level, and this may provide maximal benefit during sleep loss.

Temperature

Although temperature variation is commonly used as an acute stimulus to maintain alertness, little research supports ambient temperature as a large modulator of alertness. One study has shown that heat (92° F) was effective in improving performance during the initial minutes of a vigilance task during sleep deprivation.[9] However, another

study[10] showed only a small decrease in subjectively rated sleepiness for about 15 minutes after a car air-conditioner was turned on during simulated driving.

Posture

One study has shown a significant increase in sleep latency, as a measure of alertness, when subjects were asked to fall asleep in the sitting position (60-degree angle) as opposed to lying down.[11] Such a difference could be accounted for by increasing sympathetic nervous system activity, which occurs as one moves to the upright posture.

Drugs

Many drugs have been studied in conjunction with sleep loss, and an extensive review by the American Academy of Sleep Medicine has been published.[12] Most studies have examined stimulants, including amphetamine, caffeine, methylphenidate, modafinil, armodafinil, nicotine, and cocaine.

Numerous studies have shown that caffeine (dosages of 200 to 600 mg), modafinil (100 to 400 mg), and amphetamine (5 to 20 mg) can improve objective alertness and psychomotor performance for periods of time related to dosage, half-life, and hours of total sleep deprivation. However, head-to-head studies often provide the clearest comparison of compounds. One study[13] examined alertness and response speed hourly for 12 hours during the first night of sleep deprivation after administration of modafinil (100, 200, and 400 mg) in comparison with caffeine 600 mg. In that study, modafinil dosages of 200 and 400 mg were shown to be equivalent to caffeine (600 mg) in maintaining response speed consistently above placebo levels for 12 hours. The same group compared modafinil (400 mg), caffeine (600 mg), and dextroamphetamine (20 mg) given just before midnight of the second night of total sleep loss.[14] In this study, caffeine and dextroamphetamine significantly improved response speed only at midnight, 2:00 AM, and 4:00 AM, whereas modafinil improved response speed through 10 AM. The decreased sensitivity to caffeine probably reflects both the half-life of caffeine and the increased sleep pressure from the second night of deprivation. Side effects were fewest after modafinil at 400 mg. However, the authors concluded that (1) these stimulants all provided some benefits and had some associated costs, (2) caffeine, with efficacy, availability, and low cost, can be a first choice for alertness, and (3) modafinil, with good efficacy and few side effects, would be a good substitute if caffeine were ineffective (related to time course of available administration, tolerance, side effects, or degree of sleep loss).

Effects of stimulants can be enhanced by the use of naps or other sources of arousal. The beneficial effect of caffeine (300 mg) during periods of sleep loss was approximately equivalent to that seen after a 3- to 4-hour prophylactic nap before the sleep loss period.[15] The combination of a 4-hour prophylactic nap followed by 200 mg of caffeine at 1:30 AM and 7:30 AM resulted in significantly improved performance (remaining at baseline levels) compared with the nap alone, for 24 hours.[16] The combination of naps and caffeine was additive[16] and superior to the provision of 4 hours of nocturnal naps. The combination of 200 mg of caffeine administered at 10:00 PM and 2:00 AM and exposure to 2500-lux bright light had no impact beyond the effect of caffeine alone on the maintenance of wakefulness test but did provide significant benefit above caffeine alone on a vigilance task.[17]

Recent work has shown that armodafinil (the levorotatory R-enantiomer of modafinil), which has a 10- to 14-hour half-life, is effective in maintaining alertness and performance throughout 1 night of sleep deprivation.[18] Results with armodafinil (200 mg) appeared to be similar to those with modafinil (200 mg) but may have provided some additional benefit 11 to 13 hours after administration.[18]

Nicotine, infused intravenously at dosages of 0.25, 0.37 and 0.5 mg after 48 hours of wakefulness, had no significant impact on MSLT or psychomotor performance.[19] Cocaine (96 mg), like amphetamine, did not improve performance in subjects before sleep loss. However, reaction time and alertness, as measured by the Profile of Mood States, was improved after 24 and 48 hours of sleep loss.[20]

Alcohol use has been found to consistently reduce alertness.[21] Subjects were tested with the MSLT and simulated driving after 0.6 g/kg alcohol or placebo following normal sleep or 4 hours of sleep. There was a significant main effect for condition, and MSLT latencies were 10.7, 6.3, 6.1, and 4.7 minutes after placebo (normal sleep), placebo (4 hours sleep), ethanol (normal sleep), and ethanol (4 hours sleep), respectively. Similar results were found in the driving simulator, where there were three "crashes"—all in the reduced-sleep-with-ethanol condition. One difficulty in assessing the magnitude of performance effects associated with sleep loss is the lack of a clear standard of pathology for most measures. The fact that society has established very specific rules for blood alcohol content with respect to driving has led to the use of impairment associated with blood alcohol level as a standard reference for sleep deprivation as well. Several studies of alcohol use in direct comparison with sleep deprivation have shown decrements on different tasks. Response speed on the Mackworth task was reduced by approximately half a second by 3:45 AM (i.e., with sleep loss) and to a similar extent by a blood alcohol content (BAC) of 0.1%. Also, hand–eye coordination (in a visual tracking task) declined in a linear fashion during sleep loss and with increasing BAC, such that performance was equivalent at 3:00 AM to a blood alcohol level of 0.05% and equivalent at 8:00 AM (after a full night of sleep loss) to a blood alcohol level of 0.1%. In a third study,[22] performance was measured in a driving simulator after alcohol use or sleep deprivation. After a night of sleep deprivation (at 7:30 AM), subjects averaged one off-road (i.e., vehicle driving off the road) incident every 5 minutes. This same level of off-road driving was reached with a BAC of 0.08%. These studies suggest that the changes in response speed, visual tracking, and driving commonly found during the first night of total sleep deprivation are equivalent to changes associated with legal intoxication. Such metrics provide useful understanding of the consequences associated with short periods of sleep loss.

Motivation or interest

Motivation is relatively easy to vary by paying subjects and has therefore received attention. In one study, monetary

rewards for "hits" on a vigilance task and "fines" for false alarms[23] resulted in performance being maintained at baseline levels for the first 36 hours of sleep loss in the high-incentive group. Performance began to decline during the following 24 hours but remained significantly better than in the "no incentive" group. However, the incentive was ineffective in maintaining performance at a higher level during the third day of sleep loss. Knowledge of results—for example, the publication of daily test results—was sufficient to remove the effects of 1 night of sleep loss. In another variation, simple knowledge that a prolonged episode of sleep deprivation was going to end in a few hours was sufficient for performance to improve by 30% in a group of soldiers.[24]

Group effects

There are few studies, but interest is growing in how groups perform during sleep deprivation. Such studies are difficult because groups of individuals interact in many ways. One early study suggested that, if all group members were working at a similar task, greater deficits were seen as sleep deprivation progressed, compared with individual work. However, a more recent study that distributed work so that each individual added a unique component to task completion found that the deficits that accumulated during sleep deprivation were less pronounced in the group task.[25]

Repeated periods of sleep loss

Studies of repeated episodes of sleep loss have agreed that the magnitude of performance loss increases as a function of the number of exposures to sleep loss.[26] Increasingly poor performance may be secondary to decreased motivation or to familiarity with the sleep deprivation paradigm (resulting in decreased arousal).

Individual Characteristics

The impact of sleep loss on a given individual depends on characteristics that each participant brings to the sleep loss situation. For example, age and personality represent differences in physiologic or psychological function that may interact with the sleep loss event.

Age

Tests of performance and alertness in older subjects undergoing sleep loss reveal a decrease in performance and alertness similar to that seen in younger individuals. If anything, older men had a smaller decrease in psychomotor performance ability at nocturnal times during sleep loss[27,28] than younger men. Older individuals perform more poorly than young adults on a broad range of tasks, but, because of decreased amplitude of the circadian body temperature rhythm, this relationship may not be maintained across the night or during sleep loss.[27] The same flattened curve associated with lower temperatures and decreased performance during the day also produces relatively elevated temperatures that could be related to improved performance at night.

Sensitivity to sleep loss

A number of studies have now demonstrated consistent individual differences in both alertness and performance during sleep deprivation.[29] The studies have also shown that the reliable changes in subjective alertness, objective alertness, and performance are not related to one another. Performance consistently declined in the same subjects when sleep loss was repeated, but decrements did not generalize across performance tasks. This has led some to speculate that different brain areas could be responsible for different tasks. Some studies have begun to look for central predictors of performance loss. Early functional magnetic resonance imaging (fMRI) studies showed that subjects with higher levels of global brain activation (consistent at both baseline and during sleep loss) maintained better performance on a working memory task,[30] and a more recent study linked working memory during sleep loss with left frontal and parietal brain areas.[31] Other studies have shown that extroverts and caffeine-sensitive individuals were more sensitive to sleep loss.[32] Such findings imply individual trait ability to maintain higher levels of arousal in specific brain areas or systems to help to maintain performance during sleep loss.

In another approach, over 400 potential subjects were screened genetically, and groups were formed on the basis of the *PER3* polymorphism (*PER3[5/5]* versus *PER3[4/4]*) before a 40-hour constant routine. The *PER3(5/5)* group appeared sleepier by all measures (significantly shorter sleep latency, more slow-wave sleep (SWS), greater slow eye movements during sleep loss, and significantly worse performance during sleep loss, particularly on executive tasks done early in the morning [0600 to 0800]).[33,34]

Personality and psychopathology

Mood changes, including increased sleepiness, fatigue, irritability, difficulty in concentrating, and disorientation, are commonly reported during periods of sleep loss. Perceptual distortions and hallucinations, primarily of a visual nature, occur in up to 80% of normal individuals, depending on work load, visual demands, and length of deprivation.[35] Such misperceptions are normally quite easy to differentiate from the primarily auditory hallucinations of a schizophrenic patient, but normal individuals undergoing sleep loss may express paranoid thoughts. Two percent of 350 individuals sleep deprived for 112 hours experienced temporary states resembling acute paranoid schizophrenia. Some predisposition toward psychotic behavior existed in individuals who experienced significant paranoia during sleep loss, and the paranoid behavior tended to become more pronounced during the night, with partial recovery during the day and disappearance after recovery sleep. In a review of the area, Johnson concluded, "Each subject's response to sleep loss will depend on his age, physical condition, the stability of his mental health, expectations of those around him, and the support he receives."[36, p. 208] At a more general level, normal adults undergoing sleep deprivation typically express some increase in somatic complaints, anxiety, depression, and paranoia that do not reach clinical levels.[37]

In view of the commonly reported effects of sleep deprivation, it seems quite unusual that one would seek to treat depression by sleep deprivation. However, sleep deprivation has been used as a successful treatment for depression in 40% to 60% of cases for over 30 years. Imaging studies have shown that depressed patients have elevated metabolism in the prefrontal cortex and ventral anterior cingulate

cortex (possibly related to reduced transmission of dopamine and serotonin) that is normalized by sleep deprivation.[38] One theory proposes that sleep deprivation is more effective in depressed patients with high levels of activation or high central noradrenergic activity because it limits the effects of chronic hyperarousal. As a result, patients felt tired but also had improved mood and energy.

Test Characteristics and Types

Two meta-analyses of subtopics of sleep deprivation have been published.[39] Both analyses indicated that sleep deprivation has a significant impact on psychomotor performance. In general, longer periods of sleep loss had greater impact on performance, and decrements in speed of performance were greater than decreases in accuracy. Also, mood measures were more sensitive than cognitive tasks, which were more sensitive than motor tasks,[39] during sleep loss. Therefore, the measured response to sleep deprivation is critically dependent on the characteristics of the test used. To some extent, the type of test has also been used to infer specific brain area dysfunction. Sleep-deprived individuals appear most sensitive to the following dimensions.

Length of test

Individuals undergoing sleep loss can usually rally momentarily to perform at their non–sleep-deprived levels, but their ability to maintain that performance decreases as the length of the task increases. For example, subjects attempted significantly fewer addition problems than baseline after 10 minutes of testing following 1 night of sleep loss but reached the same criterion after 6 minutes of testing following the second night of sleep loss. It took 50 minutes of testing to show a significant decrease in percentage of correct problems after 1 night of sleep loss, and 10 minutes of testing to reach that criterion after the second night.[40] It is frequently difficult to show reliable differences during short-term sleep loss from almost any test that is shorter than 10 minutes in duration. Momentary arousal, even as minor as an indication that 5 minutes remained on a task, was sufficient to reverse 75% of the decrement accumulated over 30 minutes of testing.

Knowledge of results

Immediate performance feedback, possibly acting through motivation, has been shown to improve performance during sleep deprivation.[41] Simply not giving knowledge of results to subjects with normal sleep doubled their number of very long responses ("gaps") on a serial-reaction time test. One night of total sleep loss increased the number of gaps by 9.3 times the baseline level, but provision of immediate knowledge of results decreased the number of gaps back to baseline levels.[41]

Test pacing

Self-paced tasks are usually more resistant to the effects of sleep loss than tasks that are timed or in which items are presented by the experimenter. In a self-paced task, the subject can concentrate long enough to complete items correctly and not be penalized for lapses in attention that occur between items. When tasks are externally paced, errors occur if items are presented during lapses in attention.

Proficiency level

Sleep loss is likely to affect newly learned skills more than well-known activities, as long as arousal level remains constant. For example, in a study of the effects of sleep loss on doctors in training, significant performance decrements were found in postgraduate year (PGY)-1 surgical residents but not in PGY-2 to -5 surgical residents.[42]

Difficulty or complexity

Performance on simple tasks such as monitoring a light on a control panel (on/off) declines less than performance on more complex tasks such as mental subtraction[43] during sleep loss. Task difficulty can also be adjusted by increasing the speed at which the work must be performed. When 2 seconds was allowed to complete mental arithmetic problems, no significant performance decline was found after 2 nights of sleep loss, but when the rate of presentation was increased to 1.25 seconds, significant performance decline was found.

Memory requirement

Impairment of immediate recall for elements placed in short-term memory is a classic finding in sleep deprivation studies. Because subjects are usually required to write down each item as presented, the observed decrements, which can usually be seen after 1 night of sleep loss, do not result from impaired sensory registration of items. Observed decrements may result from decreased ability to encode,[44] from an increasing inability to rehearse old items (due to lapses) while the items are being presented, or from a combination of memory effects with reduced ability to respond. Deficits have been shown in both explicit/declarative memory and procedural/implicit memory.[44]

Executive function

Increasing behavioral and physiologic data implicate loss of function in prefrontal brain areas during sleep loss. Prefrontal areas are heavily involved in divergent thinking, temporal memory (planning, prioritization, organization), and novelty. Numerous studies have shown deficits on these tasks during sleep loss. One study[45] has shown decreased ability to make emotional judgments after total sleep loss. Another aspect of prefrontal behavior is related to risk taking. Studies have shown a shift toward accepting short-term rewards even when long-term consequences were more severe after sleep loss.[46]

Subjective (versus objective) measures

Measures of mood such as sleepiness, fatigue, and ability to think or concentrate are inversely correlated with performance and body temperature during sleep loss. Mood changes occur early, are easy to measure, and are prominent.

EEG measures

Clear EEG changes are seen during sleep loss (see Neurologic Changes, later). The MSLT, a standard test developed as an objective measure of sleepiness, was validated,

in part, by being shown to be sensitive to several types of partial and total sleep loss.[47] That the MSLT is more sensitive than psychomotor tasks can be seen in Figure 5-1, which displays performance changes in terms of the number of symbol substitutions correctly completed in 5-minute test periods and MSLT data.[15]

Summary

Tasks most affected by sleep loss are long, monotonous, without feedback, externally paced, newly learned, and have a memory component. One example of a task containing many of these elements is driving, which was discussed earlier in reference to the effects of alcohol. Since 1994, more than 20 studies have examined the impact of reduced sleep on various measures of driving ability or safety. One study,[48] for example, found that 49% of medical residents who worked on call and averaged 2.7 hours of sleep reported falling asleep at the wheel (90% of the episodes were after being on call). The residents also had 67% more citations for moving violations and 82% more car accidents than the control group.[48]

PHYSIOLOGIC EFFECTS OF SLEEP DEPRIVATION

Physiologic changes that occur during sleep loss can be categorized into neurologic (including EEG), autonomic, genetic, biochemical, and clinical changes. Physiologic and biochemical effects of sleep deprivation were extensively reviewed by Horne.[49]

Neurologic Changes

Although it is easy to identify a sleep-deprived individual by appearance and to demonstrate obvious behavioral changes, measurable neurologic changes during sleep loss are relatively minor and quickly reversible. In extended sleep loss studies (205 or more hours), mild nystagmus, hand tremor, intermittent slurring of speech, and ptosis have been noted.[50] Sluggish corneal reflexes, hyperactive gag reflex, hyperactive deep tendon reflexes, and increased sensitivity to pain were reported after deprivation that is more extensive. All of these changes reversed immediately after recovery sleep.

Sleep loss is consistently accompanied by characteristic EEG changes.[51] In careful studies, subjects have been required to stand or to be involved in tasks in an attempt to stabilize arousal level. Several studies have reported a generally linear decrease in alpha activity during sleep loss. Subjects were unable to sustain alpha activity for longer than 10 seconds after 24 hours of sleep loss, and this ability continued to decline to 4 to 6 seconds after 72 hours, and 1 to 3 seconds after 120 hours of sleep loss.[52] After 115 hours of sleep loss, eye closure failed to produce alpha activity. In another study, in which individuals were recorded standing with their eyes closed, the percentage of time spent with an alpha pattern in the EEG decreased from 65% in the early deprivation period to about 30% after 100 hours of sleep loss.[53] Delta and theta activity in the waking EEG were increased from 17% and 12% of the time to 38% and 26% of the time, respectively.[53] The increase in delta activity was most pronounced in frontal areas in younger subjects. Performance errors during sleep loss were usually accompanied by a slowing of the EEG[54] that was labeled a "microsleep."

Imaging Studies

Global decreases in brain activation correlated with increasing sleep loss have been found using positron emission tomography (PET). Larger decreases were found in prefrontal, parietal, and thalamic areas.[55] Several fMRI studies have examined the activity in prefrontal cortex and parietal lobes after sleep loss[56] that was measured while subjects performed various tasks. In some studies of verbal tasks, activity in these areas increases with task difficulty and after sleep loss as long as performance level is maintained, which has been interpreted as representing increased effort after sleep loss.[56] However, studies that have found declines in performance or examined subjects with poor performance after sleep loss have reported decreases in parietal activation during the performance.[31,57] These fMRI results suggest that imaging patterns could predict performance deficits during sleep loss.

Clinical EEG

Although the neurologic changes associated with significant sleep loss are relatively minor in normal young adults, sleep loss has repeatedly been shown to be a highly activating stress in individuals suffering seizure disorders, perhaps by reduction of central motor inhibition.[58] Using a period of sleep loss as a "challenge" to elicit abnormal EEG events is currently a standard neurologic test.[58]

Autonomic Changes

In humans, autonomic changes, even during prolonged periods of sleep loss, are relatively minor. Individual studies have reported either increases or decreases in systolic blood pressure, diastolic blood pressure, finger pulse volume, heart rate, respiration rate, and tonic and phasic skin conductance. However, the majority of 10 to 15 studies have reported no change in these variables during sleep loss in humans.[49] It has been suggested that these variable findings could be explained in part by measurement circumstances. Those studies that have had more strict activity controls and have made measurements from recumbent subjects have been more likely to find evidence for decreased or no change in activation, whereas studies of sitting or more active participants have tended to find increases in these parameters.[59]

There may be about a 20% reduction in response to hypoxia and hypercapnia[60] during sleep deprivation. However, this reduction was suggestive of a transient setpoint change rather than system failure. Sleep deprivation has been associated with small decreases in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in patients with pulmonary disease.[61] Both a study of infants[61a] and one of adults[62] have shown more apneic events[61a] and longer apneic events after sleep loss. Brooks and colleagues[63] have shown that apneas become longer as a function of the sleep fragmentation produced by the apneas (as opposed to the respiratory pathology).

Several studies in humans have found a small overall decrease (0.3° to 0.4°C) in body temperature during sleep loss.[2,64] Changes in thermoregulation have been described as heat retention deficits. Much larger changes

in thermoregulation producing huge increases in energy expenditure have been found in rats after longer periods of sleep deprivation (see Chapter 28).[65]

No sleep deprivation–related changes in whole-body metabolism were found at normal temperatures and in a cold-stress situation.[66] This finding in humans is of particular interest because a series of elegant studies in rats has shown that after a week of sleep loss, metabolic levels are greatly increased, increased food consumption is accompanied by significant weight loss, and significant difficulty with thermoregulation is apparent.[65] Several studies have examined aspects of brain metabolism in animals during short periods of sleep deprivation. Direct measures of brain metabolic rate were not different after a short period of sleep deprivation,[67] although several related enzymes did differ. However, some of the noted differences could have been related to stress rather than sleep deprivation.

Biochemical Changes

Several studies (10 or more for some variables) have examined various biochemical changes in humans during sleep loss. There is generally no significant change in cortisol,[68] adrenaline and related compounds, catecholamine output,[66,69] hematocrit,[70] plasma glucose,[70] creatinine,[66] or magnesium[66] during sleep loss.

Results from analyses of blood components largely parallel the results found in urine components. None of the adrenal or sex hormones (including cortisol, adrenaline, noradrenaline, luteinizing hormone, follicle-stimulating hormone, variants of testosterone, and progesterone) rises during sleep deprivation in humans.[68] Some of these hormones actually decreased somewhat during sleep loss, perhaps as a result of sleepiness and decreased physiologic activation. Thyroid activity, as indexed by thyrotropin, thyroxine, and triiodothyronine, was increased, probably as a result of the increased energy requirements of continuous wakefulness.[71] Studies appear about equally divided between those showing an increase in melatonin and no change in melatonin during sleep deprivation.[72] A finding of decreased melatonin in young adults after sleep deprivation suggested that earlier findings of increased melatonin may have been related to lack of control for posture, activity, and light.[73] Most studies have concluded that there is no significant change in hematocrit levels,[66] erythrocyte count, or plasma glucose during total sleep deprivation in humans.[70] As would be expected, hormones such as noradrenaline, prolactin, ghrelin, and growth hormone, which are dependent on sleep for their circadian rhythmicity or appearance, lose their periodic pattern of excretion during sleep loss (see reference 74 for review). Rebounds in growth hormone and adrenocorticotropic hormone (ACTH) during recovery sleep are seen after sleep loss or SWS deprivation.[75]

Gene Studies

A recent review of gene expression has described a number of changes that occur during wakefulness and extended wakefulness[76] (see Chapter 15). A number of genes expressed during wakefulness that regulate mitochondrial activity and glucose transport probably reflect increased energy use while awake. However, as sleep deprivation progresses, one gene, for the enzyme arylsulfotransferase (AST), showed stronger induction as a function of length of sleep deprivation. AST induction could reflect a homeostatic response to continuing central noradrenergic activity during sleep loss,[76] and this might imply a role for sleep in reversing activity of brain catecholaminergic systems.[77] In another approach, a gene named *Sleepless* was identified as required for sleep in *Drosophila*. Flies with significant reduction in Sleepless protein had reduced sleep and sleepiness before and after sleep deprivation.[78]

Clinical Changes

Immune Function

A number of studies in humans have examined various aspects of immune function after varying periods of partial or total sleep loss (see Chapter 25). Several studies have found decreases in natural killer (NK) cell numbers after short periods of sleep deprivation,[79] but increases after longer periods of sleep loss. Some studies have shown increases in interleukin (IL)-1[79] and IL-6[80] during total sleep loss. In general, immune function studies are difficult to compare because parameters measured, time and number of blood draws, and degree of sleep deprivation vary across studies.

At a more macroscopic level, one study reported the development of respiratory illness or asthma in three subjects after a 64-hour sleep deprivation protocol,[81] whereas another reported no incidence of illness after a similar protocol.[79] In longer studies involving strenuous exercise and other factors along with sleep loss, increased infection rates are reported about 50% of the time.[82]

One animal study has suggested that mice immunized against a respiratory influenza virus responded to that virus as if they had never been immunized, only when exposed after sleep loss.[83] However, in another study,[84] total sleep loss actually slowed the progression of a viral infection in mice. An extensive study of sleep loss in rats (7 to 49 days) was unable to show significant changes in spleen cell numbers, mitogen responses, or in vivo or in vitro splenic antibody-secreting cell responses.[85]

Pain

Increased sensitivity to pain has been an incidental finding in sleep deprivation research for many years, but 10 studies have now made specific pain measurements in several conditions of partial, sleep stage, or total sleep deprivation. Initial studies linked increased pain to SWS but not rapid eye movement (REM) deprivation. Later studies showed that total sleep deprivation decreased pressure pain or heat pain tolerance. However, the most recent studies[86,87] found effects for REM-stage deprivation not found earlier, and they split on the effectiveness of total sleep deprivation. One study,[87] which found increased pain sensitivity after disturbed sleep compared with reduced sleep, suggested that all of the pain findings associated with sleep-stage deprivation may actually have been caused by the sleep fragmentation necessary to produce sleep-stage deprivation. Another study has reported increased pain sensitivity to esophageal acid perfusion, specifically in patients with gastroesophageal reflux disease (but not controls) after sleep reduced to 3 hours or less for 1 night.[88]

This suggests that individual differences could also play a role in the modulation of pain. Animal studies have replicated findings of increasing pain sensitivity after REM deprivation and showed that pain sensitivity remained elevated even after low dosages of morphine and 24 hours of recovery sleep.[89]

Weight Control and Insulin

There are numerous reports of increased sympathetic activity, impaired glucose tolerance, and weight gain associated with chronic partial sleep deprivation (see Chapter 6), but, remarkably, these effects have not been replicated following total sleep deprivation. One study, in a small group of subjects, before and after 1 night of total sleep deprivation found no increase in cortisol, blood glucose, insulin, ACTH, catecholamines, or lactate.[90] This study did report a decrease in basal glucagon, possibly linked to pancreatic islet secretion and increased hunger. From such reports, it is unclear whether the results reported from chronic partial sleep deprivation are related to increased or chronic stress or whether time of sampling may play a role.

Exercise

Effects of sleep loss on the ability to perform exercise are subtle. Animal studies have consistently shown that sleep deprivation decreases spontaneous activity by up to 40%,[91] but most human studies have focused on maximal exercise ability, where large differences as a function of sleep loss are more difficult to demonstrate. For example, one study[92] reported a 7% decrease in maximum oxygen uptake ($\dot{V}O_2max$) during 64 hours of sleep loss. This change was not associated with heart rate, respiratory exchange ratio, or blood lactate, which remained unchanged. Recovery from exercise may be slowed by sleep loss. Studies are evenly divided between claims that the amplitude of the circadian rhythm of temperature is increased, decreased, or unchanged during sleep loss.[49]

Summary

A large number of studies have reported autonomic, biochemical, and immune function variables during sleep loss. Many of the older studies were based on single observation points before and after sleep loss. Many studies suffer from poor activity controls (use of activity to maintain wakefulness may produce or mask changes in underlying variables of interest). More recent studies have been able to make use of sampling as often as once per hour and have begun to consider circadian and activity effects. For example, NK cell numbers were increased[93] during the night when subjects remained awake (compared with a sleep control) but were then decreased on the following afternoon, with the result that numbers averaged across the entire study were the same in sleep loss and baseline conditions. This means that a study could find an increase, a decrease, or the same number of NK cells based on the time of sampling. In a similar manner, it has been found that IL-6 was decreased during a night of sleep deprivation compared with the sleep control but increased compared with control during the next day, so that numbers averaged across the entire study were, again, about the same.

SLEEP FRAGMENTATION

Sleep is a time-based cumulative process that can be impeded both by deprivation and by systematic disturbance. A number of studies have shown that very brief periodic arousals from sleep reduce the restorative power of sleep and leave deficits similar to those seen after total sleep deprivation.[94]

Experimental Sleep Fragmentation

Many studies have examined the relationship between various empiric schedules of sleep fragmentation and residual sleepiness on the following day. Data from eight studies are plotted in Figure 5-2. There is a strong relationship ($r = .775$, $P < .01$) between rate of fragmentation (plotted as minutes of sleep allowed between disturbances) and decrease in sleep latency on the following day as measured by MSLT.[94] As expected, increased sleepiness after sleep fragmentation was also associated with decreased psychomotor performance on a broad range of tasks,[95] and with degraded mood.[94]

Studies have been carefully designed to produce brief EEG arousals or even "nonvisible" EEG sleep disturbance, with the result that there are few[96] in standard sleep EEG parameters despite the periodic sleep fragmentation. With preservation of normal-EEG sleep amounts, participants were still significantly sleepier on the day after sleep fragmentation. In another approach, fragmentation rates, consolidated sleep periods, and SWS amounts were experimentally varied in participants in an attempt to tease out sleep stage versus fragmentation effects, with similar

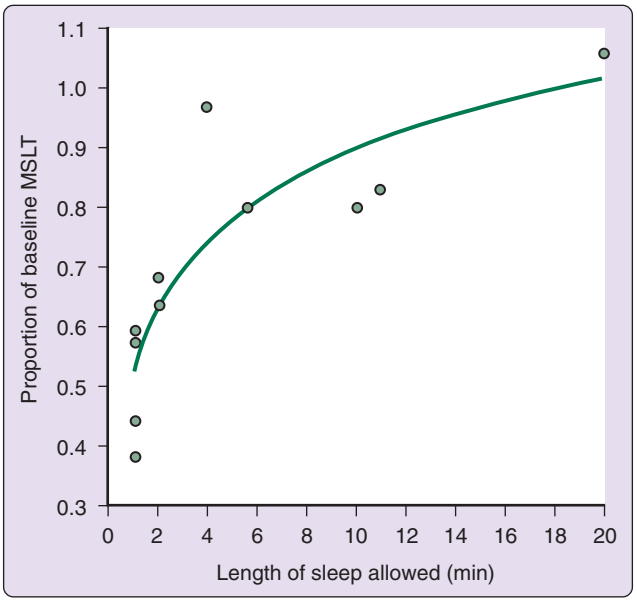

Figure 5-2 Proportion of baseline multiple sleep latency test (MSLT) value (i.e., sleep latency after fragmentation nights divided by sleep latency after baseline) in eight sleep fragmentation studies (two separate fragmentation conditions were identified in three studies), plotted as a function the amount of sleep time allowed until disturbance (e.g., "2" means that subjects were aroused briefly after each 2 minutes of sleep). (From Bonnet MH, Arand DL. Clinical effects of sleep fragmentation versus sleep deprivation. Sleep Med Rev 2003;7:297-310.)

conclusions—residual sleepiness was more related to the sleep fragmentation than to sleep-stage parameters.[94]

Other studies have directly compared the impact of relatively high rates of sleep fragmentation (usually disturbance every 1 to 2 minutes) with the effect of total sleep deprivation in the same study. In one study, profiles of cortisol and ACTH were similar during total sleep deprivation and sleep fragmentation.[97] In other studies,[94] MSLT was decreased to similar low values after both total sleep deprivation and high-frequency sleep fragmentation. A significant increase in apnea-hypopnea index was found after both sleep fragmentation and sleep deprivation, and this increase was actually greater after sleep fragmentation.[94] These findings of similar impacts on hormones, respiratory parameters, psychomotor performance, and objective sleepiness after similar periods of sleep deprivation and sleep fragmentation indicate that there is much in common between the high-frequency sleep fragmentation and total sleep deprivation. Clearly, the restorative function of sleep is impaired by high rates of sleep fragmentation. However, as indicated by Figure 5-2, the impact of periodic sleep fragmentation decreases rapidly as the intervals between arousals increase, and this may imply that normal restoration during sleep requires periods of consolidated sleep of 10 to 20 minutes.[94] Recovery sleep following high rates of sleep fragmentation is characterized by rebounds of SWS and REM sleep like that seen after total sleep deprivation. In addition, recovery sleep after sleep fragmentation and sleep deprivation is notable for decreased arousals.[98]

A broad range of physiologic indices have been examined as possible measures of sleep fragmentation.[94] A number of respiratory, cardiac, and alternative EEG measures have been examined, with the general conclusion that most of these physiologic measures, including traditional arousals, are moderately correlated with daytime sleepiness. However, much empirical work needs to be done to determine the extent to which these other physiologic measures are simply correlates of EEG arousals rather than new measures of sleep continuity. A physiologic event more specific than the EEG arousal remains to be identified.

New animal models of sleep fragmentation in rats have revealed decreases in hippocampal neurogenesis and increases in basal forebrain adenosine to levels found after similar amounts of total sleep deprivation.[99]

Sleep Disorders and Fragmentation

The earliest study of sleep fragmentation in dogs documented impaired arousal responses to hypercapnia and hypoxia during sleep.[100] Further studies following dogs with experimentally produced apnea or sleep fragmentation for periods of more than 4 months showed that both the sleep fragmentation procedure and the experimentally produced apnea produced increased time to arousal as well as greater oxygen desaturation, greater peak inspiratory pressure, and greater surges in blood pressure in response to airway occlusion. It was concluded that the sleep fragmentation alone was responsible for the sleepiness symptoms associated with sleep apnea, and "the changes in the acute responses to airway occlusion resulting from OSA (obstructive sleep apnea) are primarily the result of the associated sleep fragmentation."[63, p. 1609]

Other clinical studies have documented that the number of brief arousals is significantly correlated with the magnitude of daytime sleepiness in groups of patients.[94] Traditional sleep-stage rebounds (see Recovery Sleep, next) are seen when the pathology is corrected. After effective treatment of sleep apnea and the corresponding decrease in frequency of arousals during sleep, alertness was improved as measured by either MSLT or reduction in traffic accidents.[101] There are many other instances of sleep fragmentation as a component in both medical illnesses (such as fibrositis, intensive-care-unit syndrome, chronic movement disorders, and chronic pain disorders) and life requirements (infant care, medical residents). Some of these impositions may not produce the critical number of arousals required for significant decrements in the apnea patients and in sleep fragmentation studies. However, most of these situations are a combination of chronic partial sleep loss and chronic sleep fragmentation.

RECOVERY SLEEP

Sleep is all that is required to reverse the effects of sleep deprivation in almost all circumstances. The EEG characteristics of recovery sleep depend on the amount of prior wakefulness and the circadian time. These effects have been successfully modeled (see Chapter 37).

Performance Effects

Several efforts have been made to assess recovery of performance after sleep deprivation. It is commonly reported that recovery from periods of sleep loss of up to 10 days and nights is rapid and can occur within 1 to 3 nights. Several studies have reported recovery of performance after a single night (usually 8 hours) of sleep following anywhere from 40 to 110 hours of continuous wakefulness.[5] Such experiments suggest that an equal amount of sleep is not required to recover from sleep lost. However, sleep deprivation itself was typically the main concern of these studies and, therefore, recovery was given minimal attention.

One study specifically examined the rate of performance recovery during sleep in young adults, normal older subjects, and insomniacs after 40- and 64-hour sleep loss periods.[27] Participants were awakened from stage 2 sleep for 20-minute test batteries approximately every 2 hours during baseline and recovery nights. Therefore, it was possible to follow the time course of return to baseline performance during recovery sleep in the three groups. In normal young adults, reaction time returned to levels not significantly less than baseline after 4 hours of sleep during recovery sleep following 40 hours of sleep loss. However, reaction time remained significantly slower than baseline in young adults throughout the first night of recovery sleep (including the postsleep morning test) following 64 hours of sleep loss. In contrast, reaction time in both older normal sleeper and insomniac groups was significantly slower than baseline at 5:30 AM but had returned to baseline levels by 8:00 AM after the first recovery night after 64 hours of sleep loss. The young adults not only recovered more slowly from sleep loss on the initial recovery night

Table 5-1 Effects of Sleep Loss on Stages of Recovery Sleep

	SLEEP LOSS: 40 HR						SLEEP LOSS: 64 HR	
	YOUNG ADULTS (SD)	OLDER ADULTS (SD)	DEPRESSED ADULTS	DEMENTED ADULTS	SHORT SLEEPERS	LONG SLEEPERS	OLDER NORMAL SUBJECTS	OLDER INSOMNIAC PATIENTS
Sleep latency	0.38 (0.09)	—	0.22	0.14	—	—	—	—
Wake time	0.44 (0.19)	0.51 (0.11)	—	—	0.13	0.48	—	—
Stage 1	0.42 (0.12)	0.59 (0.14)	0.61	0.68	0.98	0.60	0.56	0.52
Stage 2	0.87 (0.10)	0.95 (0.07)	1.06	1.08	1.38	0.99	1.07	1.20
Stage 3	0.98	1.32 (0.25)	1.14	1.16	—	—	2.36	3.00
Stage 4	2.40	2.06 (0.45)	1.35	1.12	—	—	7.00	5.25
Slow-wave sleep stage	1.53 (0.11)	1.56 (0.23)	1.23	1.15	1.37	1.52	2.56	3.30
REM sleep stage	0.89 (0.13)	1.04 (0.09)	0.84	0.78	1.26	1.03	0.26	0.92
REM sleep latency	1.01 (0.20)	0.77 (0.20)	2.2	2.0	1.13	1.26	0.35	0.96

The values presented in this table are the mean percentages of baseline levels of the indicated sleep stages for the indicated groups during the first sleep recovery night. Where sufficient studies were available, the standard deviation around the mean percentage is also given (SD). For example, on their recovery night after 1 night of sleep loss, young adults have a sleep latency that is 38% ± 9% of their baseline sleep latency. (See text for references.)

but also had some decrease in their reaction times that extended into the second recovery night. This result is consistent with other data showing that older subjects had daytime MSLT values at baseline levels following sleep loss and a single night of recovery sleep, whereas shorter-than-normal latencies continued in young adults.[102]

EEG Effects

A large number of studies have reported consistent effects on sleep EEG when totally sleep deprived individuals are finally allowed to sleep. If undisturbed, young adults typically sleep only 12 to 15 hours, even after 264 hours of sleep loss.[103] If sleep times are held to 8 hours on recovery nights, effects on sleep stages may be seen for 2 or more nights.

The effects of 40 and 64 hours of sleep loss on recovery sleep stages during the initial recovery night are summarized in Table 5-1 for normal young adults,[47,104-107] young adult short sleepers,[108] young adult long sleepers,[108] 60- to 80-year-old normal sleepers,[102,109,110] 60- to 70-year-old chronic insomniacs,[109,111] and 60- to 80-year-old depressed and demented patients.[112,113] The table presents percentage change from baseline data, with an indication of study-to-study variability where the number of studies allowed computation. The table is presented as a summary device so that EEG effects of sleep deprivation can be predicted (roughly by multiplying population baseline values by figures presented in the table), and so that the potential differential effects of sleep deprivation on EEG recovery sleep as a function of group can be more clearly seen. The results of these several studies indicate that recovery sleep EEG changes that occur as a function of sleep deprivation are remarkably consistent across studies and across several experimental groups including men, women, older subjects, and older insomniacs. Significant deviations from population recovery values are seen primarily in REM latency changes in depressed and demented patients, and secondarily in some less robust differences found in small groups of long and short sleepers. These latter findings might be related to differential sleep-stage distributions secondary to long or short sleep times.

On the first recovery night after total sleep loss, there is a large increase in SWS over baseline amounts.[70,111] As would be expected, wake time and stage 1 sleep are usually reduced. Stage 2 and REM sleep may both be decreased on the first recovery night after 64 hours of sleep loss,[27,47] at least in young adults, as a function of increased SWS. In older normal sleepers and insomniacs, there is less absolute increase in SWS than in young adults on the first recovery night, although the percentage increase in SWS may be as great. Because there is less SWS rebound, there may be no change (geriatric normals) or even an increase in stage 2.[27,113] Normal older individuals had a decrease in REM latency during recovery sleep[102,109,113] rather than the increased REM latency common in young adults. It was found that REM latency in the older population was positively correlated with baseline SWS amounts[109,113] and that sleep-onset REM periods occurred in about 20% of those carefully screened normal subjects.[109,113] These REM changes were interpreted to be the result of decreased pressure for SWS in older humans. The REM latency findings did not apply to older depressed or demented individuals. REM rebound effects appear to be related to the amount of lost SWS, so that REM rebound is more likely on an early recovery night when there is less SWS loss as a function of either a shorter period of sleep loss or age.

On the second recovery night after total sleep loss, SWS amounts approached normal values, and an increase in REM sleep was found in young adults.[47] Total sleep time was still elevated. By the third recovery night, all sleep EEG values approached baseline. In situations where REM rebounds on the first sleep-recovery night, sleep EEG values may normalize by the second recovery night.

Exceptions to these general rules may include older insomniacs, who have increased total sleep for at least 3 nights after 64 hours of sleep loss[27] and individuals who have had significant selective REM deprivation.

Relationship between EEG and Psychomotor Performance Recovery Effects

The increase in SWS during recovery from sleep loss leads to the speculation that SWS is implicated in the sleep recovery process. Unfortunately, human studies designed to test this hypothesis directly by experimentally varying the amount of SWS during the recovery sleep period or during a sleep fragmentation period have not implicated any sleep stages as central in the recovery process.[114] However, these studies were not designed to look for more subtle effects that might have occurred in the initial recovery night.

Studies have also examined recovery of alertness and performance after total sleep deprivation for 1 or 2 nights. An early study that examined performance recovery in the sleep period found recovery of response speed to baseline levels after 1 night of recovery sleep following 40 hours of sleep loss and recovery to baseline levels during the second night of recovery sleep following 64 hours of sleep loss.[115] More recent studies with larger groups of subjects have reported that simple response speed had recovered to baseline levels after 1 night of recovery sleep following 64 hours of sleep loss in one study[116] but did not recover to baseline levels even after 5 recovery nights in a second study.[117] MSLT was still significantly shorter after 1 night of recovery sleep following both 1 and 2 nights of total sleep loss.[116,117] One study reported recovery for the MSLT after a second night of recovery sleep following 64 hours of sleep loss,[116] but the second study did not.[117]

CONCLUSIONS

The physiologic and behavioral effects of sleep loss in humans are consistent and well defined. There is a physiologic imperative to sleep in man and other mammals, and the drive to sleep can be as strong as the drive to breathe. Future work should (1) examine in more detail the physiologic microstructure of the sleep process and its relationship to sleep restoration, (2) reconcile response differences among species, (3) examine differences in response to sleep deprivation in normal and depressed humans, and (4) further explore the interaction of the sleep and the arousal systems, (5) examine impact in specific occupations.[118]

❖ Clinical Pearl

The impact of sleep deprivation on performance and physiology has been examined in thousands of studies for over a hundred years. These findings might not seem directly relevant in a clinical sense, but it should be remembered that the clinical diagnosis of insufficient sleep syndrome is based on sleep deprivation. Sleepiness symptoms secondary to sleep apnea and periodic limb movements (sleep fragmentation) also evolve from sleep deprivation.

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