Rechtschaffen, A. and Siegel, J.M. Sleep and Dreaming. In: Principles of Neuroscience. Fourth Edition, Edited by E. R. Kandel, J.H. Schwartz and T.M. Jessel, 936-947, McGraw-Hill, New York, 2000.

Allan Rechtschaffen

Jerome Siegel

Sleep and Dreaming

Why do we spend so much time sleeping? What are the neural and chemical mechanisms that produce this state? What makes us dream? These are some of the central issues that confront the study of sleep.

The age-old, common-sense explanation of sleep is that it results from reduced brain activity, induced by fatigue. Until 1950 scientists working on sleep thought that the awake state was maintained by active sensory stimulation and that accordingly, the brain fell asleep when, with fatigue, sensory stimulation decreased. In the late 1940's and early 1950's, a series of startling discoveries disproved this notion. First, Giuseppe Moruzzi and Horace Magoun found that severing the ascending sensory pathways of cats did not interfere with either sleep or wakefulness. By contrast, lesions of the reticular formation that did not interfere with the ascending sensory pathways resulted in a behavioral stupor and a continuous EEG pattern resembling sleep. Moruzzi and Magoun concluded that although reticular activity could be increased by collaterals from the specific sensory systems, the forebrain is kept awake not by direct input from sensory pathways, but by tonic activity in pathways from the reticular formation to the cortex, According to this view, sleep results from the reduction in activity in the reticular formation, wakefulness by the return of activity.

For the next decade this passive view of sleep dominated sleep research. Then in the late 1950s Moruzzi and his colleagues reported that transecting the brain stem at the pontine level greatly *reduced* sleep in the forebrain of cats. This result suggested that the rostral reticular formation contains neurons whose activity contributes to wakefulness, and that this activity was normally inhibited by neurons in the caudal reticular formation.

Another major impetus to our present understanding of sleep research came from Nathaniel Kleitman and two of his graduate students, Eugene Aserinsky and William Dement, who discovered that sleep was not a single process but that there were two distinctly different kinds of sleep: rapid eye movement (REM) sleep and non-REM sleep, and that these phases alternate cyclically in a highly structured pattern throughout the

night. Together with the Moruzzi findings, these results displaced the old idea that sleep was simply a state of reduced activity that occurred by default when activation subsided. Rather, sleep is an actively induced, highly organized brain state.

In this chapter we first describe the rhythmic occurrence of sleep, the major stages of sleep, and the neural mechanisms underlying these stages. In the next chapter we shall consider the disorders of sleep.

Sleep Is Expressed As a Circadian Rhythm

Like many behavioral activities such as feeding and foraging, and many homeostatic regulatory mechanisms such as the release of corticosteroids and the regulation of body temperature, sleep and wakefulness have a periodicity of about 24 hours. These circadian rhythms are endogenous, i.e., they can persist in the absence of environmental time cues. Nevertheless, the phases of the rhythms are normally maintained in adaptive relationship to the environment by their response to external cues called zeitgebers (time givers). Sunlight is a powerful zeitgeber which can be linked to active or inactive phases of the circadian rhythms. Thus, most adult humans sleep at night, whereas nocturnal animals such as rats and mice sleep mostly when it is light.

One major internal clock or pacemaker of circadian rhythms is the suprachiasmatic nucleus of the anterior hypothalamus. Lesions of the suprachiasmatic nucleus dampen the circadian rhythm of sleep as they dampen other circadian rhythms, and these rhythms can be restored by transplanting a fetal suprachiasmatic nucleus. Entrainment of rhythms to light is mediated partly through a retinohypothalamic tract to the suprachiasmatic nucleus..

The circadian pacemaker neurons can be reset, albeit with considerable discomfort. Familiar examples of resetting are recovery from jet-lag and the readjustment required of people who work at night. Not all the discomfort involved in resetting results from the disturbance in the sleep/wake cycle, however, since many other physiological mechanisms regulated by circadian rhythms are also disturbed.

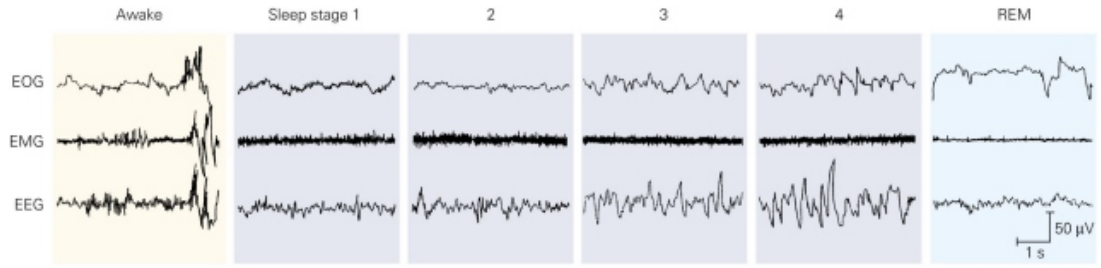
Even though the distribution of sleep and wakefulness within a day is normally under the influence of circadian regulators, sleep does not simply result from troughs in circadian activity cycles. Whereas normal rats sleep primarily during light periods, rats with lesions of the suprachiasmatic nucleus show the same amount of sleep in light and in dark periods. Nevertheless, the lesioned animals sleep the same *total* amount of time per 24 hours as do control rats. Thus, the suprachiasmatic nucleus is not required for sleep. Furthermore, when rats with lesions of the suprachiasmatic nucleus are experimentally sleep deprived, they subsequently show rebounds of increased sleep as normal rats do.

Total sleep time normally remains fairly stable from day to day, even under a wide variety of conditions. Thus, variations in the amounts of activity and of sensory stimulation have only modest effects on total sleep time, which is not appreciably affected by exercise, eventful or routine days, prolonged bed rest, profound sensory deprivation, or increased visual stimulation. Changes in total sleep time are typically not as great as day to day variations in food intake, physical or mental work, and mood. The only pre-sleep manipulation that reliably and substantially influences sleep in most animals is prior sleep loss.

Sleep Is Organized in Cycles of Non-REM and REM Stages

Sleep is defined behaviorally by four criteria: (1) reduced motor activity, (2) decreased response to stimulation, (3) stereotypic postures (for example, lying down with eyes closed in humans), and (4) relatively easy reversibility (distinguishing it from coma, hibernation and estivation). Sleep and its REM and non-REM stages can be conveniently monitored by electrical recordings. Muscle activity is assessed by electromyography (EMG), eye movements are recorded by electrooculography (EOG), and the collective activity of cortical neurons is monitored by electroencephalography (EEG). Humans usually fall asleep by entering non-REM, which is identified primarily by its EEG characteristics. The REM sleep phase is characterized not only by rapid eye movements, but also by essentially complete inhibition of skeletal muscle tone (atonia), and, in some animals, EEG patterns similar to those obtained during wakefulness. Most dreams are thought to occur during this phase of sleep.

Non-REM Sleep. When awake, humans and several other vertebrates show low- voltage (10-30μV), fast (16-25 Hz) EEG activity. When relaxed, humans also show sinusoidal alpha activity of about 20-40 μV and 10 Hz. Passage from wakefulness to non-REM sleep is characterized by progressively slower frequencies and higher voltage activities in the EEG. Non-REM sleep comprises four stages (Figure 47-1).



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 47.01

Figure 47-1. Criteria of the EEG stages of human sleep. Stage 1 is characterized by slight slowing of the EEG; Stage 2 by high amplitude K complexes and spindles (low amplitude clusters). Slow, high amplitude delta waves characterize Stages 3 and 4. Eye movements and loss of muscle tone, in conjunction with a Stage 1 EEG characterize REM sleep. Abbreviations: **L EOG and R EOG,** left and right electrooculogram; **EMG,** electromyogram. The higher voltage activity in the EOG tracings during Stages 3 and 4 reflect high-amplitude EEG activity in prefrontal areas rather than eye movements. (Adopted from A. Rechtschaffen and A. Kales (1968) *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*, by permission).

Stage 1: This stage lasts only several minutes and is the transition from wakefulness to the onset of sleep. During this stage, the sleeper shows slow, rolling eye movements and low voltage, mixed-frequency EEG activity. In this stage and throughout the non-REM phase there is some activity of skeletal muscle but no rapid eye movements.

Stage 2: Bursts of 12-14 Hz sinusoidal waves called sleep spindles and high-voltage biphasic waves called K complexes occur episodically against a background of continuing low-voltage EEG activity.

Stage 3: High-amplitude, slow (0.5-2 Hz) delta waves appear in the EEG.

Stage 4: Slow-wave activity increases and dominates the EEG record. Stages 3 and 4 in humans are sometimes called slow- wave sleep. In some animal species, all of non-REM sleep is called slow wave sleep.

Overall, neuronal activity is at a low level during these phases. This is reflected in metabolic rate and brain temperature, which are at their lowest during non-REM sleep. Thus, sympathetic outflow is decreased as heart rate and blood pressure decline. The pupils are constricted as parasympathetic activity increases and then dominates during the non-REM phase.

REM Sleep Is An Active Form of Sleep. In the REM phase the EEG reverts to a low-voltage pattern similar to stage 1 non-REM sleep. Because the EEG during REM sleep closely resembles that of wakefulness in some animals, this phase has also been called paradoxical sleep. Indeed, during REM sleep the discharge patterns of most neurons resemble those during active wakefulness, and certain neurons — those in the pons, in the lateral geniculate nucleus, and in the occipital cortex — even fire in more intense bursts than normally seen during wakefulness. These bursts generate high-voltage spike potentials, the ponto-geniculo-occipital or *PGO spikes*, named for the structures in which the spikes appear most prominently (the pons, lateral geniculate nucleus, and occipital cortex). PGO spikes are one of the phasic (short-lasting) events of REM sleep that include bursts of eye movements and cardio-respiratory irregularity. PGO-like waves can be evoked in alert waking by abrupt stimuli, similar to those that elicit startle, suggesting that the spontaneous PGO spikes of REM sleep may be generated by internal activation of the neural circuit for the startle response.

Consistent with the overall increase in neural activity during REM sleep, brain temperature and metabolic rate are high, equal to or greater than during the waking state. Surprisingly, however, almost all muscle tone is lost (atonia); small, phasic twitches do occur and the skeletal muscles controlling the movements of the eyes, middle ear ossicles, and diaphragm do not become atonic. In REM sleep the pupils are at their most constricted (miosis), reflecting the high ratio of parasympathetic to sympathetic output to the pupil. Penile erections regularly occur during REM sleep. Finally, this sleep stage is also characterized by a reduction in homeostatic mechanisms. Respiration is relatively unresponsive to changes in blood CO_2, and response to heat and cold are absent or greatly reduced. As a result, body temperature drifts toward ambient temperatures.

These observations make it clear that sleep cannot be easily placed in a continuum from light to deep. Each phase is behaviorally complex, with its own configuration of differentially-activated physiological

mechanisms. By some criteria REM sleep might be considered lighter than non-REM. e.g., humans are easier to awaken from REM than from non-REM stages 3 and 4. By other criteria non-REM might be considered lighter than REM sleep, e.g., muscle tone, spinal reflexes, and body temperature regulation are maintained during non-REM, but are reduced during REM.

Non-REM and REM phases alternate cyclically during sleep. Human adults usually begin sleep by progressing from stage 1 through stage 4 of non-REM sleep. This progression is intermittently interrupted by body movements and partial arousals (Figure 47-2). After about 70 to 80 minutes the sleeper usually returns briefly to stage 3 or stage 2 and then enters the first REM phase of the night, which lasts about 5 to 10 minutes. The length of the cycle from the start of non-REM sleep to the end of the first REM phase is about 90-110 minutes. Typically, this Non-REM-REM cycle is repeated 4 to 6 times a night. In successive cycles the duration of stages 3 and 4 decreases while the length of REM phases increases. In young adults REM phases constitute 20-25% of total sleep time; stages 3 and 4 non-REM about 15-20%; and stage 1 non-REM about 5%. The largest amount of sleep time, 50 to 60%, is spent in stage 2 non-REM sleep.

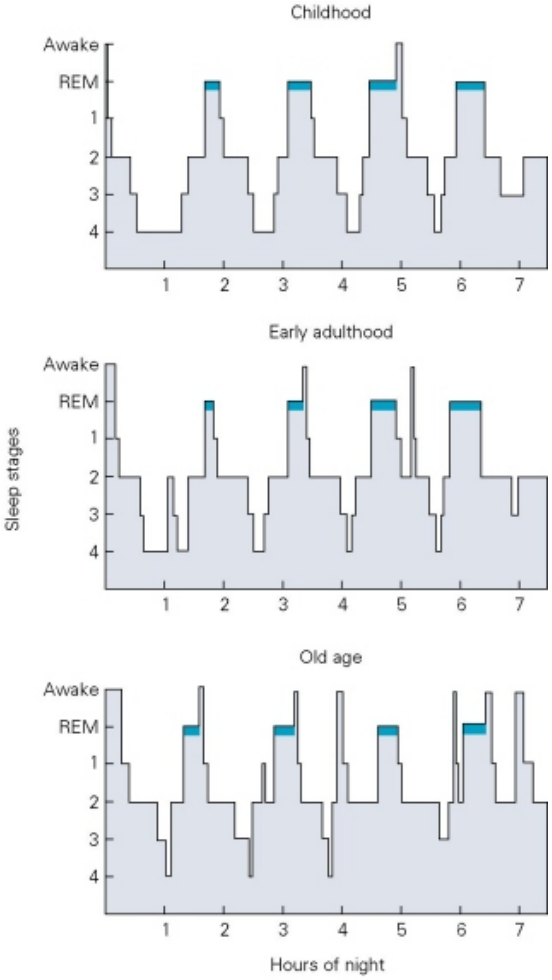


Figure 47-2. Schematic representation of the cycling of human sleep stages at different times of life, with childhood broadly defined to include early adolescence, and old age including the period from the mid-50's to the early 70's. From *Roche Seminars on Aging: Aging in Sleep*, Zepelin, 1982, by permission).

Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 47.02

Non-REM Sleep Is Regulated by Interacting Hypnogenic and Arousal Mechanisms

The work of Moruzzi and Magoun demonstrated that electrical stimulation of the midbrain strongly promotes waking. Conversely, damage to the midbrain reticular formation produces a comatose state followed by a long-term reduction in waking. The midbrain in turn is normally inhibited by systems in the medulla. Disconnecting the inhibitory region by transection of the brainstem just behind the midbrain (the "midpontine-pretrigeminal" transection) produces an animal whose forebrain spends most of its time "awake."

In front of the midbrain lies the posterior hypothalamus. Stimulation of the posterior hypothalamus produces arousal resembling that produced by midbrain stimulation. This arousal is partially mediated by

histaminergic cells that form connections with cells in the brainstem and forebrain. Destruction or chemical inhibition of histaminergic and adjacent neurons in the posterior hypothalamus produces sleep. Blockade of histaminergic outputs by ingestion of antihistaminergic drugs also promotes sleep.

The anterior hypothalamus and adjacent basal forebrain region have the most potent sleep-promoting effects seen in the brain. Electrical stimulation of this region rapidly induces sleep; lesions produce a permanent insomnia. A type of neuron found only in this region, the Non-REM-on neuron (Figure 47-3 #2), is likely to be responsible for these effects. These cells, thought to use GABA as their transmitter, are maximally active in non-REM sleep and are inactive in both waking and REM sleep. Many Non-REM-on cells are activated by heat and thus may mediate the somnogenic effects of elevated temperature. At a more fundamental level, the finding that many Non-REM-on cells are thermosensitive suggests a functional link between sleep and thermoregulatory processes.

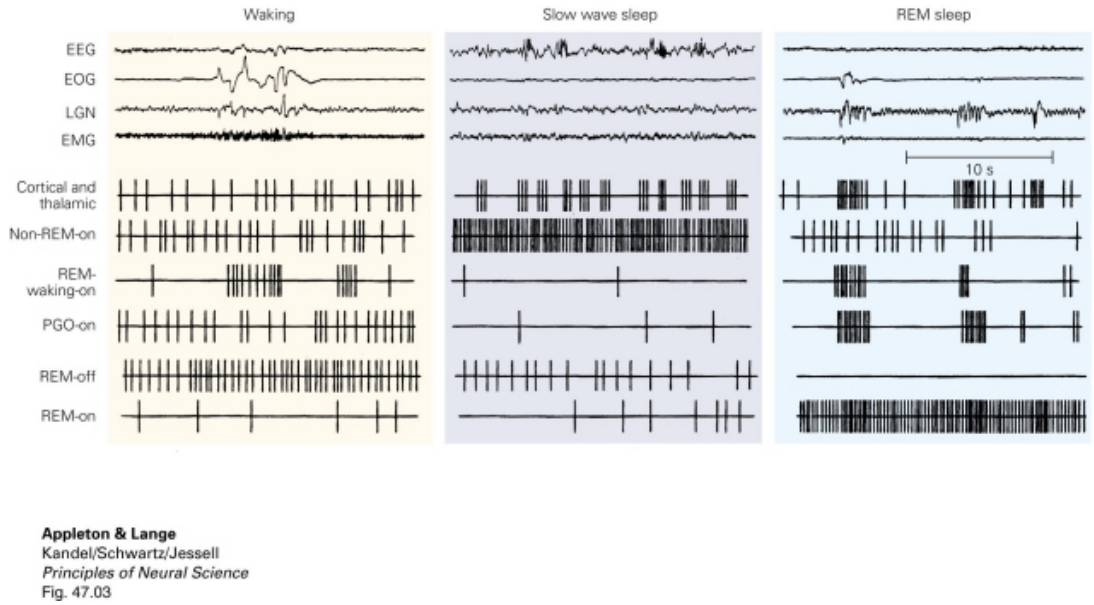


Figure 47-3. This figure illustrates the pattern of neuronal activity of key cell groups across the sleep cycle. A representative 20-second sample of activity is drawn for each state. The traces at the top illustrate the typical sleep pattern of cats. **EEG**, sensorimotor EEG; **EOG**, eye movement; **LGN**, lateral geniculate electrode showing **PGO** (ponto-geniculo-occipital) spike activity during REM sleep; **EMG**, dorsal neck electromyogram. Each vertical line represents an action potential.

1. *Cortical and thalamic cells.* Small rate change across states. At higher speed, SWS activity bursts could be seen to be synchronized with individual waves of the EEG (spindle and slow waves) in the cortex and thalamus.

2. *Non-REM-on Cells.* These cells, located in the anterior hypothalamus and basal forebrain region, participate in the generation of Non-REM sleep.

3. *REM-waking-on cells.* These cells, which form the majority of brain stem reticular neurons, are active in both waking and REM sleep. Many excite motor neurons. Others mediate EEG activation.

4. *PGO-On Cells*. These pontine cells fire in high-frequency bursts prior to PGO waves recorded in the lateral geniculate nucleus.

5. *REM-Off Cells.* Brain stem noradrenergic, adrenergic, and serotonergic cells, and forebrain histaminergic cells have this discharge pattern. Most skeletal motor neurons have a similar pattern.

6. *REM-On Cells*. These cells are maximally active in REM sleep. REM sleep-on cells, using a number of different transmitters are involved in the generation of various aspects of REM sleep.

The non-REM sleep EEG is characterized by "spindles" and slow waves, as described above. These waves result from the synchronized occurrence of excitatory and inhibitory postsynaptic potentials in cortical neurons. The spindle waves that characterize the non-REM-sleep EEG are generated by interactions between thalamocortical neurons and the nucleus reticularis, a nucleus that forms a shell around the thalamus.

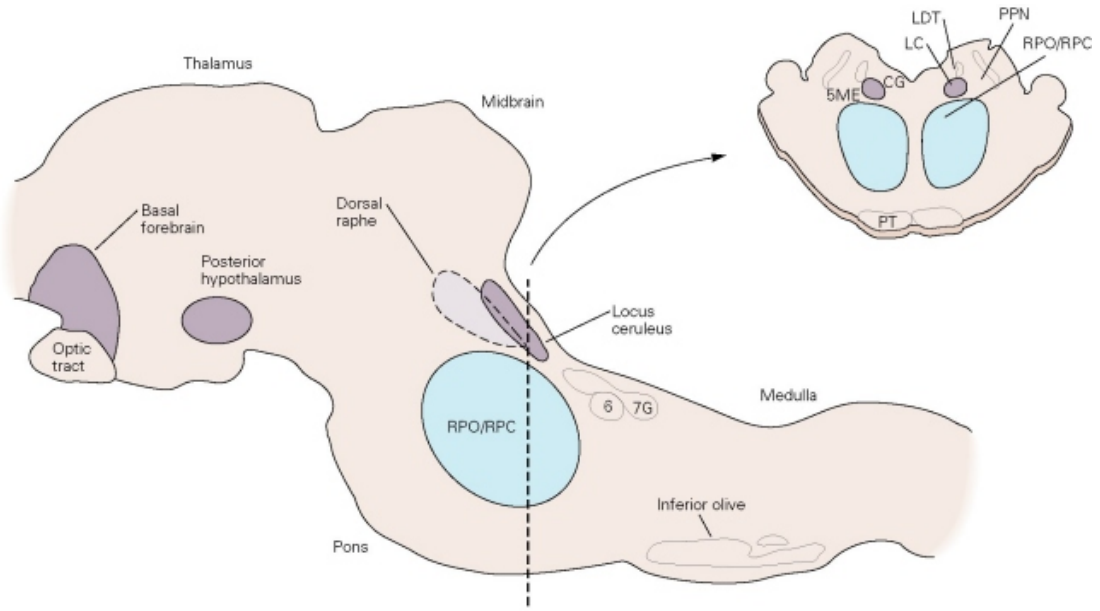
The nucleus reticularis is composed of GABA-ergic neurons capable of generating a novel type of action potential — a low threshold calcium spike. These depolarizing potentials, which are a key event in the sequence of membrane currents generating spindles, occur when calcium is admitted through voltage-sensitive membrane channels that open *only* when the cells are hyperpolarized. During the calcium spike, reticularis cells produce a burst of action potentials. After the calcium spikes, membrane currents return the

cell to the hyperpolarized state, restarting the process. This cycle of calcium influx followed by hyperpolarization results in rhythmic firing. Reticularis neurons release GABA when they fire and thereby hyperpolarize thalamocortical neurons. This hyperpolarization results in a rebound low threshold calcium spike in these thalamocortical cells. The rhythmic firing of thalamocortical cells (figure 47-3 #1) produces synchronized postsynaptic potentials in cortical neurons. It is these potentials that cause the spindle waves seen in the sleep EEG. The rhythmic firing of thalamic and cortical cells occludes the transmission of sensory information through the thalamus and cortex and blocks the irregular impulse flow of information processing, thus preserving sleep.

During REM sleep and waking, these spindle waves are blocked. How does this occur? Cholinergic and adjacent neurons in the midbrain and dorsal pons constitute an important component of the midbrain arousal system. Many of these cells are maximally active during waking and REM sleep. Acetylcholine and other transmitters released by these cells depolarize the GABA-ergic cells in the nucleus reticularis, thus preventing the hyperpolarization that initiates the rhythmic firing of reticularis cells. In the absence of this rhythmic input, asynchronous and higher frequency background activity in thalamic cells projecting to the cortex results in the low-voltage EEG and correlated brain activation characteristic of waking and REM sleep.

Key Mechanisms for the Generation of REM Sleep Are Located at the Junction of the Midbrain and Pons

The neuronal machinery most important for REM sleep resides in the nucleus reticularis pontis oralis which lies in the caudal midbrain and the rostral pons. Bilateral destruction of this nucleus eliminates REM sleep for extended periods (Figure 47-4). Microinjection of the acetylcholine agonist carbachol in the same portion of the pons elicits extended periods of REM sleep. Thus many of the neurons critical for REM sleep are responsive to acetylcholine.



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 47.04

Figure 47-4. Sagittal section showing major regions of the brainstem and forebrain involved in sleep control. The inset is a coronal section through the center of the pontine region critical for triggering REM sleep. Nuclei within the critical area are indicated on the left side of the inset. The circled area in the inset and sagittal section can be stimulated to produce various characteristics of REM sleep. Depending on their exact size and location, bilateral lesions within this region will completely block REM sleep or will block components of REM sleep,. **CG,** Central gray; **IO,** inferior olive; **LC**, locus coeruleus; **PPN** pedunculopontine nucleus; **PT**, pyramidal tract; **RPO/RPC**, nucleus reticularis pontis caudalis/oralis; **5ME**, mesencephalic nucleus of the trigeminal nerve.

The most common cell type in the brain stem has maximal levels of activity in both REM sleep and active waking and minimal rates during non-REM sleep (REM-waking-on cells, Figure 47-3 #3). Some cells with this discharge pattern have projections to motoneurons in the spinal cord and extraocular muscle nuclei. Burst firing in these neurons mediates movement of the head, neck, limbs and eyes during waking, as well as

the rapid eye movements and muscle twitches that occur during REM sleep despite peripheral motor inhibition.

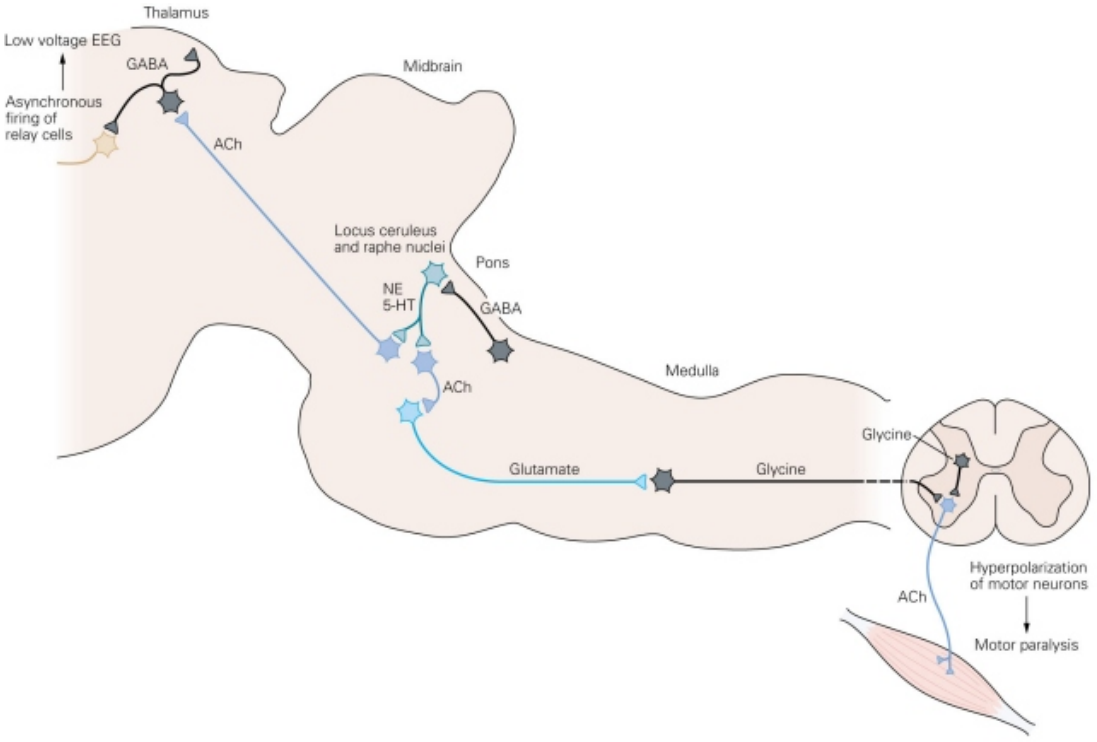
The PGO spikes characteristic of REM sleep originate in a group of cholinergic neurons in the pons. These PGO cells, fire in a burst (Figure 47-3, #4) that initiates the PGO spike in cells in the lateral geniculate nucleus of the thalamus. It is thought that these bursts are due to a low-threshold calcium spike in the pontine PGO related cells, similar to the low threshold calcium spikes involved in the generation of sleep spindles. Destruction of these cells blocks PGO activity, while other aspects of REM sleep continue. Conversely, stimulation of this area produces PGO waves, even in the absence of REM sleep.

Serotonergic neurons of the raphe nuclei, a group of cells that lie along the midline of the brainstem, have a REM-off discharge pattern (Figure 47-3 #5). These cells have an important role in regulating the discharge of the cholinergic cells responsible for PGO spikes. During waking serotonin blocks the burst firing mode of PGO cells by hyperpolarizing them. In the transition from Non-REM to REM sleep the cessation of activity in serotonergic cells allows the PGO cells to begin discharging in bursts, generating PGO waves.

Noradrenergic neurons in the locus coeruleus and histaminergic neurons in the posterior hypothalamus have a REM-off discharge pattern similar to that of the serotonergic cells in the raphe nuclei. Cessation of activity in serotonergic, noradrenergic, and histaminergic cells during REM sleep may contribute to changes in autonomic tone, EEG, and other state-specific changes in neuronal activity. Cessation of activity in the noradrenergic cells of the locus coeruleus and serotonergic cells of the raphe during REM sleep is due to the release of GABA onto these cells by populations of GABAergic REM-on neurons (Figures 47-3 #6 and 47-5). The location and driving force behind the activity of these GABAergic cells remains to be determined. It is likely that further analysis of the conditions altering the excitability of REM-on and REM-off cells will provide important clues to the functional role of REM sleep.

Muscle tone is at its lowest level in REM sleep. This reduction in muscle tone is actively induced by the release of glycine onto the motoneurons (Figure 47-5). The circuitry mediating this suppression of muscle tone resides in the brain stem. Michel Jouvet discovered that a small lesion within a portion of the pontine region critical for REM sleep released motor activity in REM sleep. Cats with this lesion have normal non-REM sleep episodes. When they enter REM sleep, they raise their heads, walk, and engage in a variety of vigorous motor activities. A similar syndrome can be produced by lesions of the medial medulla. The suppression of muscle tone in REM sleep is mediated by interconnections between several types of REM-on neurons (Figure 47-5). Abnormal activity in the brain stem neurons responsible for suppressing muscle tone suppression during REM sleep is believed to contribute to cataplexy, one of the primary symptoms of narcolepsy, REM sleep behavior disorder, and sleep apnea (all of which are discussed in Chapter 48).

Figure 47-5 presents a model of the locations and some of the hypothesized connections of the cells responsible for the generation of atonia and of the EEG changes of REM sleep and waking.



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 47.05

Figure 47-5. This sagittal section of the cat brain stem shows a simplified model of hypothesized connections between key neuronal groups involved in REM sleep control. As discussed in the text, other transmitter groups and receptors are also involved.

A system triggering muscle atonia is activated in REM sleep leading to the discharge of GABAergic neurons, the inhibition of noradrenergic and serotonergic neurons and the activation of cholinergic neurons in the pons. These cholinergic neurons excite pontine neurons that use glutamate as their transmitter. The glutamatergic neurons project to the medulla, where they terminate on interneurons that release glycine onto motor neurons. This release of glycine hyperpolarizes motor neurons leading to the motor paralysis of REM sleep.

A pontine system with ascending connections contributes to the production of an activated EEG in REM sleep. Some cholinergic cells and adjacent non-cholinergic cells activated during REM sleep project to GABA-ergic cells in the thalamus. Release of acetylcholine and other transmitters blocks the burst firing mode of these GABAergic neurons and contributes to the change from a non-REM sleep EEG to one of REM sleep.

The waking EEG is also maintained by depolarization of the thalamic GABAergic neurons. During waking, in addition to the rostrally projecting cholinergic neurons active in REM sleep, rostrally projecting serotonergic, noradrenergic and histaminergic neurons are active and contribute to the creation of the waking EEG.

ACH, acetylcholine; **NE**, norepinephrine; **5HT**, serotonin.

The third class of cells in the nucleus reticularis pontis oralis are referred to as REM-on cells (Figure 47-2). These cells show little or no activity in waking and nonREM sleep but have high levels of activity in REM sleep. Although there are relatively few of these cells, they play the key role in REM sleep control. One subtype of these cells is GABA-ergic and is responsible for the inhibition of activity in serotonergic and noradrenergic cells during REM sleep. Another subtype of REM sleep-on cell is responsible for the loss of muscle tone in REM sleep.

Muscle tone is lost during REM sleep because motoneurons are actively inhibited.

Melatonin stimulates wakefulness when given to rats during the daytime and has a powerful hypnotic effect in birds. Human studies have not shown a consistent hypnotic effect, although recent studies have indicated that it can facilitate sleep onset in old people who are melatonin deficient and may be of value in treating jet lag. It remains unclear if it is effective as a treatment for insomnia, despite its popular promotion as a safe, natural sleeping pill.

Several Endogenous Substances Affect Sleep

For nearly a century, sleep researchers have searched for substances that accumulate with waking and are metabolized in sleep. An understanding of how soluble substances might determine sleepiness would provide an important insight into sleep function, as well as allowing the development of potent "natural" sleeping pills. However, no substance is yet widely accepted as being the driving force for sleep. Among

those substances that have been identified as having hypnogenic properties are muramyl peptides (a chemical related to substances found in bacterial cell walls), interleukin-1 (a cytokine that may mediate the effects of muramyl peptides as well as immune responses), delta sleep-inducing peptide (a substance isolated from the blood of sleeping rabbits), and a long-chain fatty acid primary amide, cis-9,10-octadecenoamide.

Other naturally occurring substances may be sleep factors. Growth hormone and prostaglandin PGD2 increase both REM and non-REM sleep; arginine vasotocin increases non-REM sleep and suppresses REM sleep; insulin increases non-REM sleep. Several substances produce relatively selective increases of REM sleep, including vasoactive intestinal peptide (this may interact with acetylcholine), cholecystokinin and bombesin (both are released in the gut after food ingestion), somatostatin, corticotropin-like intermediate lobe peptide (CLIP), and prolactin. Melatonin stimulates wakefulness when given to rats during the daytime and has a powerful hypnotic effect in birds. Human studies have not shown a consistent hypnotic effect, although one study has shown that it facilitates sleep onset in old people who are melatonin deficient.

Sleep Periods Change Over the Life Span

Daily sleep in humans declines sharply from a peak of 17 to 18 hours at birth to 10 to 12 hours at age 4 and then more gradually to a fairly stable adult duration of 7 to 8.5 hours by age 20. The initial pattern of infancy, consisting of 3 to 4-hour bouts of sleep alternating with brief feedings, is gradually replaced by more continuous sleep. By age 4, sleep becomes consolidated into a single long nocturnal period and sometimes a daytime nap.

In the newborn, REM phases constitute about 50% of sleep, but these REM phases differ from their adult form: atonia is very irregular, and rapid eye movements and muscle twitches occur on a background of low muscle tone and a relatively undifferentiated EEG. This early form of REM sleep is often called active sleep to distinguish it from adult REM sleep. The proportion of time spent in REM sleep declines rapidly until about 4 years of age, when it stabilizes near the young adult level of 20 to 25%. With increasing age, REM declines gradually to 15-20%.

The high-amplitude, slow EEG waves of the non-REM phase are absent at birth. These slow waves appear and their amplitudes greatly increase during the first year of life, reaching a stable, high plateau between 3 to 11 years of age, and then progressively decline during the rest of life. Developmental changes in sleep are accelerated in animals that mature rapidly: for example, in rats a mature sleep pattern is achieved 30 days after birth. Like newborns, many old people show almost no high-amplitude EEG activity (Figure 47-2). The nocturnal sleep of the elderly also tends to be interrupted by many short awakenings.

Phylogenetic Variations in Sleep Relate to Constitutional Differences

All mammals sleep (determined electrophysiologically or behaviorally), but the length and form of sleep (the proportion of non-REM and REM phases) vary greatly. Daily sleep ranges from about 4-5 hours in giraffes and elephants to 18 hours or more in bats, opossums, and giant armadillos. Small mammals generally sleep more than larger mammals. REM sleep as a percentage of total sleep ranges from 10.5% in Guinea pigs and baboons to 25% or more in opossums, hedgehogs, dogs, and giraffes. Mammals born immature tend to have more REM sleep, both in infancy and adulthood, than precocial mammals. The length of the non-REM-REM sleep cycle ranges from 12 minutes or less in shrews, bats, rats, and mice to 30 minutes or longer in humans, pigs, cattle, and elephants. Brain weight is positively correlated with the length of the cycle, independent of the relationship of brain weight to body weight.

Presumably, specific characteristics of sleep have evolved as adaptations to a particular animal's way of life. For example, several marine mammals, in an apparent accommodation to maintaining respiration, show non-REM sleep patterns in only one cerebral hemisphere at a time. If a dolphin is awakened when only one hemisphere sleeps, that hemisphere later shows a sleep rebound while the other does not. Like mammals, birds show non-REM and REM sleep, but their sleep episodes are much shorter, REM period episodes may last only several seconds, muscle atonia during the REM phase is rare, and unihemispheric non-REM sleep is more frequent. Reptiles show several indicators of non-REM, but not of REM sleep. Lower orders show quiescent periods that resemble sleep behaviorally, but it is not clear whether these periods are ancestral to mammalian sleep or whether they are simply species-specific forms of rest.

The phylogenetic differences in sleep suggest that it is largely under genetic control. This idea is supported

by laboratory studies that show significant correlations of sleep time and REM amount in monozygotic but not dizygotic twins. Moreover, hereditability of sleep patterns has been demonstrated within species. Inbred rodent strains show differences in total sleep time, REM sleep, and circadian rhythms, and cross-breeding studies of mice indicate that each of these sleep characteristics are inherited independently.

The Functions of Sleep Are Not Yet Known

It is likely that sleep is functionally important because it has ubiquitously persisted during the evolution of mammals and birds (and perhaps lower forms as well). Its importance is also shown by rebounds of sleep following total sleep deprivation and rebounds of slow wave or REM sleep following selective deprivation of these stages, as well as by functional impairments following sleep loss. All rats chronically deprived of sleep by an automated apparatus died after about 2-3 weeks; REM-deprived rats survived about twice as long. (Unfortunately, a necessary cause of death has not yet been identified.) In spite of these indications of functional importance, there is no widespread agreement on why sleep is important. Several ideas have been advanced, but they have been challenged by contrary evidence or proven to have limited generality.

Conservation of Metabolic Energy. The idea that sleep conserves energy is supported by several studies that have shown increased food intake during sleep deprivation. However, metabolic rate during sleep is reduced from quiet wakefulness by only about 15%; the energy loss of a sleepless night could be compensated by only a handful of food. The idea that sleep enforces rest is supported by the tendency for small mammals, which have high energy demands for thermoregulation and locomotion but low energy reserves, to sleep the most. However, rest is possible during wakefulness. Why suffer a form of rest with impaired vigilance? Furthermore, rest without sleep still leaves us sleepy. Because we feel refreshed after sleep, the theory that sleep is restitutive is intuitively appealing, but sleep-enhanced restitutive processes have not been confirmed.

Cognition. Because humans show little or no physiological impairment after several days of sleep deprivation, but do show impaired intellectual performance, it has been proposed that sleep serves higher mental functions. However, the performance deficit could result from a homeostatic pressure to enter sleep rather than from impaired intellectual capacity. Most of the deficits can be reversed by strong motivation or analeptic drugs.

Thermoregulation. There are strong indications that sleep has thermoregulatory functions. Body and brain temperatures are usually reduced during sleep. Heating the hypothalamus induces sleep in animals, and body heating prior to sleep increases subsequent slow wave sleep in humans. Rats that are chronically deprived of sleep show increases of 10° C or more in preferred ambient temperatures. These facts suggest that sleep has cooling functions. On the other hand, rats deprived of sleep for two weeks show a significant drop in body temperature in spite of a doubling of metabolic rats, suggesting that sleep may also have a role in heat retention.

Neural Maturation and Mental Health. The idea that REM sleep aids neural maturation is strongly supported by the association of REM sleep with immaturity at birth across and within species. But why would REM sleep then persist and rebound following its selective deprivation in adults? Early anecdotal reports of disturbed behavior following REM deprivation suggested that REM sleep is important for mental health, but none of several controlled studies has demonstrated an impairment of mental health during REM deprivation. In fact, severely depressed patients improve following REM deprivation. Some reports have indicated that REM sleep facilitates learning or memory, but effects of REM deprivation on learning and memory have not always been demonstrable or very strong. Clearly, learning can occur without sleep. The fact that REM sleep follows non-REM sleep suggests that REM sleep compensates for the cerebral inactivation or temperature declines of non-REM sleep. However, even when wakefulness (with its cerebral activation and increased temperature) follows selective REM sleep deprivation, rebound increments of REM sleep follow later.

This abundance of theories suggests that sleep may have many functions, with some correctly identified by the theories presented, or that sleep may serve a single common function that has not yet been identified or widely accepted. Perhaps sleep serves a single, yet unknown cellular function that supports maturational processes in the young, temperature regulation in small animals, and/or higher mental processes in adult humans.

Study of REM and Non-REM Phases Has Increased Our Knowledge About Dreaming

When Kleitman, Aserinsky, and Dement studied the two phases of sleep, REM and non-REM, they also studied the relation of these phases to dreaming. They awakened subjects during REM and non-REM sleep and asked them to describe any dreams they were having. Dreams were far more likely to be recalled when subjects were awakened from REM sleep (74% or more of awakenings) than from non-REM sleep (less than 10% of awakenings). This led many to believe that dreaming occurs exclusively during REM sleep (the non-REM reports were dismissed as recall from earlier REM sleep) and that the physiological basis of dreaming would soon be discovered. This expectation has not been realized. Although REM sleep is the phase from which dreams may be most reliably elicited, REM sleep is not necessary for dreaming. In almost all later studies, the frequency of non-REM dream recall is higher than in the earliest studies; in some studies as high as 70%. Many dream reports are elicited on awakenings from non-REM phases that occur before the first REM phase of the night, indicating that these dream reports do not represent recall from REM periods earlier in the night. In fact, dream reports have also been elicited from subjects at the onset of sleep and from subjects lying quietly awake in a darkened room. Although reports of non-REM dreams tend to be shorter, less vivid, less emotional, and more coherent than reports of REM dreams, there are no qualitative differences between REM and non-REM reports of the same length. Thus, a major difference between REM and non-REM dreams is that the former tend to be longer.

Neither is REM sleep sufficient for dreaming. Dreaming varies with cognitive abilities as well as sleep stages. Despite abundant REM sleep in children, thematically organized dream reports are rare before ages 7 to 9 years, and their appearance is correlated with the development of waking visuospatial skills. Dreaming may be absent in a variety of neurologically damaged patients who nevertheless show REM sleep.

Much of the impetus for modern dream research stemmed from the interest of Freudian psychoanalysis in the interpretation of dream content in psychotherapy. According to Sigmund Freud, dreams are disguised manifestations of strong, unacceptable, unconscious wishes. Modern dream research has provided techniques for identifying when dreams are likely to occur and has therefore facilitated the retrieval of many freshly recalled dreams. But this research has no special procedures for uncovering "hidden meanings" and has therefore contributed little to identifying unconscious determinants of dreams. Neither has modern sleep research had much success in specifying other sources of dream content. Dream content is not greatly influenced by stimuli that are delivered to the sleeper. Even on the relatively infrequent occasions when external stimuli are incorporated into dreams, they usually appear only incidentally in the dream narrative. In one study, subjects had their eyelids taped open and various objects were presented to the subjects during REM sleep. None of the objects appeared in any of the subsequently reported REM dreams. Internal systemic stimulation also does not have a consistent effect on dream content. For example, after 24 hours of fluid restriction, REM dream reports did not have persistent dreams of thirst and only one-third of them contained references to drinking. Although full or partial penile erections occur in 80-95% of REM periods, only 12% of men's dreams contain manifestly sexual content. Moreover, patients with spinal cord transections that preclude genital sensations report dreams with orgasmic imagery. Even immediate pre-sleep experiences do not appear to affect our dreams consistently. For example, viewing violent films does not reliably produce violent dreams, nor do pornographic films increase sexual dreams substantially. Dreaming *per se* does not require stimulus input either before or during sleep, since we normally have several dreams a night under a variety of stimulus conditions.

Although modern dream research has contributed relatively little to uncovering hidden meanings in dreams, the reliable elicitation of detailed dream reports in the laboratory has greatly increased empirical information on the phenomenology and correlates of dreams. Some scholars have proposed that dreams arise from random brain activity, but dreams are not kaleidoscopic jumbles of visual fragments; they are organized thematically and perceptually. Correspondences between REM period duration, length of dream report, and the actual time it took subjects to re-enact a dream experience after they had been awakened negate the old view that dreams occur in an instant. Although threads of specific contents or personal concerns may appear in reports of several discrete dreaming periods during a single night, dreams do not appear as successive chapters in a book, but rather as separate short stories.

Dreams and waking mentation are similar in several respects. Most dreams collected over the course of a whole night are quite ordinary. Dreams have an undeserved reputation for being extremely bizarre because our spontaneous recall of dreams is usually limited to the longer, more exciting dreams that typically occur before morning awakening. In general a person's mood, anxiety, imaginativeness, and expressiveness in dreams are positively correlated with these traits in their waking experience. Except for some decrease in the clarity of background detail and color saturation, visual dream imagery resembles waking visual imagery. Like waking imagery, most dreams are in color; the mystery is why 20-30% of dreams are achromatic.

Perhaps the greatest difference between dreaming and ordinary wakefulness is that we are able to differentiate between real and imagined images only when we are awake. Except for relatively rare lucid dreams during which we know we are dreaming, *all* dream images seem real at the time. In spite of a lifetime of discriminating between dreams and reality, we can make the discrimination only after awakening. Identifying the neural substrates that are responsible for critical self-reflection during wakefulness, and which fail us while dreaming, is a major challenge for sleep and dream research.

An Overall View

The circadian rhythm of sleep is controlled by the suprachiasmatic nucleus of the hypothalamus. Non-REM sleep is generated by neurons in the basal forebrain and medulla interacting with neurons in the midbrain and diencephalon. REM sleep is generated by neurons in the caudal midbrain and pons, interacting with neurons in the medulla and forebrain. Thus, sleep is actively generated by an interplay of several neuronal populations using several different transmitters.

That sleep serves important functions is indicated by its ubiquitous persistence in different environments and across evolution, the rebounds of sleep following sleep loss, and the functional impairments (to the point of death) produced by sleep deprivation. However, no theory of sleep function has yet explained the wealth of data on sleep phenomena so crisply and parsimoniously as to win widespread endorsement by sleep researchers.

The discovery of a relationship between REM sleep and dreaming was a major impetus for modern sleep research. However, we now know that REM sleep is not necessary for dreaming, that dreaming can also occur during non-REM sleep, and that dream-like experiences can be elicited during quiet wakefulness. Neither is REM sleep sufficient for dreaming, since the development and integrity of certain cognitive skills are also necessary. Nevertheless, REM sleep remains the state from which long vivid dreams can be retrieved most reliably. As a result, studies of REM sleep have greatly increased knowledge about the number, temporal characteristics, perceptual features, stimulus determinants, and cognitive properties of dreams. Major unresolved issues are the sources of specific dream contents and an understanding of why we are usually unaware that we are dreaming while the dream is in progress.

Selected Readings

Anch, M.A., Browman, C.P., Mitler, M.M., and Walsh, J.K. 1988. Sleep: A Scientific Perspective. New Jersey: Prentice Hall.

Antrobus, J.S., and Bertini M. (eds.) 1992. The Neuropsychology of Sleep and Dreaming. New Jersey: Lawrence Erlbaum.

Carskadon, M.A., Rechtschaffen, A., Richardson, G., Roth, T., and Siegel, J. (eds.) 1993. Encyclopedia of Sleep and Dreaming. New York: Macmillan.

Cavallero, C., and Foulkes, D. (eds.) 1993. Dreaming as Cognition. London: Harvester Wheatsheaf.

Horne, J. 1988. Why We Sleep, The Functions of Sleep in Humans and Other Mammals. New York: Oxford University Press.

Klein, D.C., Moore, R.Y., and Reppert, S.M. (eds.) 1991. Suprachiasmatic Nucleus: The Mind's Clock. New York: Oxford University Press.

Kleitman, N. 1963. Sleep and Wakefulness. Chicago: The University of Chicago Press.

Kryger, M.H., Roth,T., and Dement, W.C. (eds.) 1994. Principles and Practice of Sleep Medicine, 2nd ed., Philadelphia: Saunders.

Rechtschaffen, A. 1973. The psychophysiology of mental activity during sleep. In F.J. McGuigan, and R.S. Schoonover (eds.), The psychophysiology of thinking. New York: Academic Press, pp. 153-205.

Rechtschaffen, A. 1978. The single-mindedness and isolation of dreams. Sleep. 1:97-109.

Siegel, J. M. 1994. Brainstem mechanisms generating REM sleep. In M. H. Kryger, T. Roth, and W. C. Dement (eds.), Principles and Practice of Sleep Medicine, 2nd ed. New York: Saunders, pp. 125-144, 1994.

Steriade, M., and McCarley, R.W. 1990. Brainstem Control of Wakefulness and Sleep. New York: Plenum.

Zepelin, H. 1983. A life span perspective on sleep. In A. Mayes (ed.), Sleep Mechanisms and Functions in humans and animals: an evolutionary perspective. Cambridge: University Press.

References

Aserinsky, E., and Kleitman, N. 1953. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Science 118:273-274.

Baghdoyan, H.A., Mallios, J., Duckrow, R.B. and Mash, D.C. 1994. Localization of muscarinic receptor subtypes in brain stem areas regulating sleep, Neuroreport. 5:1631-1634.

Bard, P. and Macht, M.B. 1958. The behavior of chronically decerebrate cats. In G.E.W. Wolstenholme and C.M.O. O'Conner (eds.), Neurological Basis of Behavior. London: Churchill, pp. 55-75.

Chase, M.H and Morales, F.R. 1994. The control of motoneurons during sleep.In , H. Kryger, T. Roth, and W.C. Dement (eds.), Principles and Practices of Sleep Medicine. Philadelphia: W.B. Saunders, 1994, pp 163-177.

Carskadon, M.A., and Dement, W.C. 1994. Normal human sleep: An Overview. In M.H. Kryger, T. Roth, and W.C. Dement (eds.), Principles and Practice of Sleep Medicine. Philadelphia: Saunders, pp. 16-25.

Carskadon, M.A., and Rechtschaffen, A. 1994. Monitoring and staging human sleep. In M.H. Kryger, T. Roth, and W.C. Dement (eds.), Principles and Practice of Sleep Medicine. Philadelphia: Saunders, pp. 943-960.

Dement. W., and Wolpert, E.A. 1958. The relation of eye movements, body motility, and external stimuli to dream content. J. Exper. Psychol. 55,543-553.

Foulkes, D. 1982. Children's Dreams: Longitudinal studies. New York: Wiley-Interscience.

Haimov I; Lavie P; Laudon M; Herer P; Vigder C; Zisapel N. Melatonin replacement therapy of elderly insomniacs. Sleep, 1995 18:598-603.

Hobson, J.A., and McCarley, R.W. 1977. The brain as a dream state generator: an activation- synthesis hypothesis of the dream process. Am. J. Psychiatry 134:1335-1348.

Jones, B.E. 1994. Basic mechanisms of sleep-wake states. In M.H. Kryger, T. Roth, and W.C. Dement (eds.), Principles and Practice of Sleep Medicine. Philadelphia: Saunders, pp. 145-162.

Luebke, J.J., Greene, R.W., Semba, K., Kamondi, A., McCarley, R.W. and Reiner, P.B. 1992. Serotonin hyperpolarizes cholinergic low-threshold burst neurons in the rat laterodorsal tegmental nucleus in vitro. Proc. NAS USA, 89:743-747.

Nitz, D. and Siegel, J.M. Release of GABA, glycine, and glutamate in the locus coeruleus across the sleep/wake cycle. Neuroscience (in press).

Nitz, Douglas and Siegel, J.M., Inhibitory amino acid neurotransmission in the dorsal raphe nucleus during sleep-wake states. Soc. Neurosci. Abstr., 19:1815, 1993.

Pivik, R.T. 1994. The psychophysiology of dreams. In M.H. Kryger, T. Roth, and W.C. Dement (eds.), Principles and Practice of Sleep Medicine. Philadelphia: Saunders, pp. 384-393.

Ralph, M.R., Foster, R.G., Davis, F.C., and Menaker, M. 1990. Transplanted suprachiasmatic nucleus determines circadian period. Science 247: 975-978.

Rechtschaffen, A., and Bergmann, B.M. 1995. Sleep deprivation in the rat by the disk-over-water method. Behavioural Brain Research, 69: 55-63.

Schenkel E. and Siegel, J.M. REM sleep without atonia after lesions of the medial medulla. Neurosci. Lett. 98:159-165, 1989.

Shouse, M.N. and Siegel, J.M 1992. Pontine regulation of REM sleep components in cats: Integrity of the

pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. Brain Res. 571:50-63.

Siegel, J.M., Nienhuis, R., Fahringer, H.M., Paul, R., Shiromani, P., Dement, W.C., Mignot, E., Chiu, C. Neuronal activity in narcolepsy: identification of cataplexy related cells in the medial medulla. Science 262:1315-1318, 1991.

Steriade, M., McCormick, D.A. and Sejnowski, T.J. 1993. Thalamocortical oscillations in the sleeping and aroused brain, Science 262:679-685.

Vogel, G.W. 1978. An alternative view of the neurobiology of dreaming. Am. J. Psychiatry. 135:1531-1535.