

Normal Human Sleep: An Overview

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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 physiological and behavioral processes. Sleep is usually (but not necessarily) accompanied by postural recumbency, 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 may include sleepwalking, sleeptalking, toothgrinding, and other physical activities. Anomalies involving sleep processes also include intrusions of the sleep processes—sleep itself, dream imagery, or muscle weakness—into wakefulness.

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

NREM (pronounced non-REM) sleep is conventionally subdivided into four stages, which are relatively precisely, although somewhat arbitrarily, 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 fragmented mental activity. A shorthand definition of NREM 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 generally is not divided into stages, although tonic and phasic types of REM sleep are often distinguished for certain research purposes. The tonic versus phasic distinction is based on short-lived events that tend to occur in clusters separated by

episodes of relative quiescence. In cats, REM sleep phasic activity is epitomized by bursts of pontogeniculo-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 100, 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). 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 motoneurons via

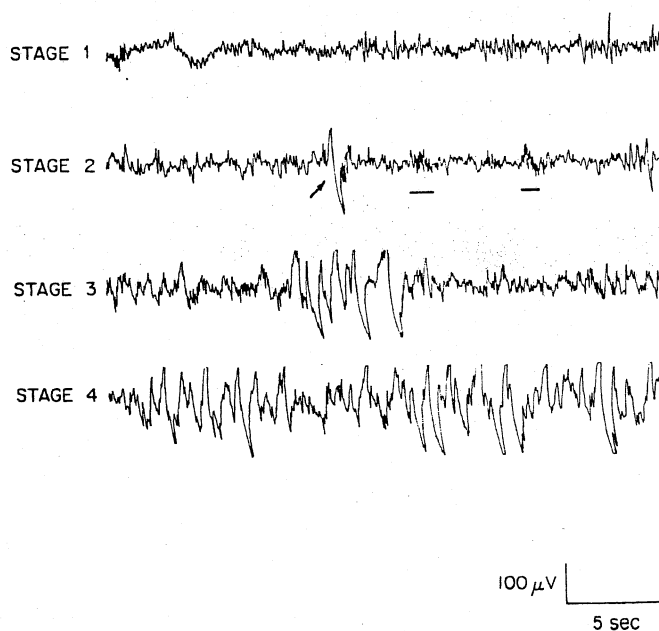


Figure 2-1. The stages of NREM sleep. The four EEG tracings depicted here are from a 19-year-old female volunteer. Each tracing was recorded from a referential lead (C3/A2) recorded on a Grass Instruments Co. Model 7D polygraph with a paper speed of 10 mm/sec, time constant of 0.3 sec, and $\frac{1}{2}$ -amplitude high-frequency setting of 30 Hz. On the second tracing, the arrow indicates a K complex, and the underlining shows two sleep spindles.

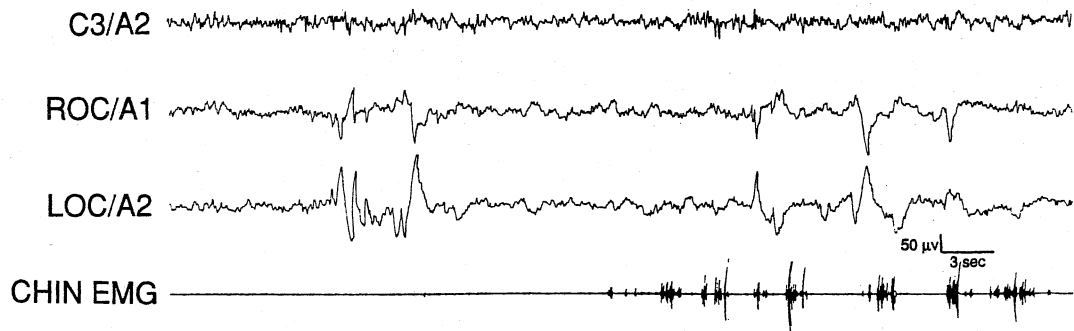


Figure 2-2. Phasic events in human REM sleep. On the left side is a burst of several rapid eye movements (out-of-phase deflections in ROC/A1 and LOC/A2). On the right side, there are additional rapid eye movements as well as twitches on the EMG lead. The interval between eye movement bursts and twitches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

brainstem mechanisms mediates suppression of postural motor tonus in REM sleep. A shorthand definition of *REM sleep*, therefore, is a highly activated brain in a paralyzed body.

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 pathological sleep. For example, the abnormal entry into sleep via REM is 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 for many years, primarily because there is not one single measure that is 100% clear-cut 100% of the time. For example, a change in EEG pattern is not always associated with whether a person perceives sleep; yet even when individuals may 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 100.

Electromyograph

Electromyograph (EMG) levels may show a gradual diminution as sleep approaches, but there is rarely a discrete change that can be pinpointed as sleep onset. Furthermore, the waking level of the EMG, particularly if the individual is relaxed, can be entirely indistinguishable from that of unequivocal sleep (Fig. 2-3).

Electro-Oculogram

As sleep approaches, the electro-oculogram (EOG) shows slow, often asynchronous eye movements (see Fig. 2-3) that generally 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, individuals will report that they are 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 sec [cps]) activity, particularly in the occipital region, to a relatively low-voltage, mixed-frequency pattern (stage 1 sleep). This EEG change generally 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

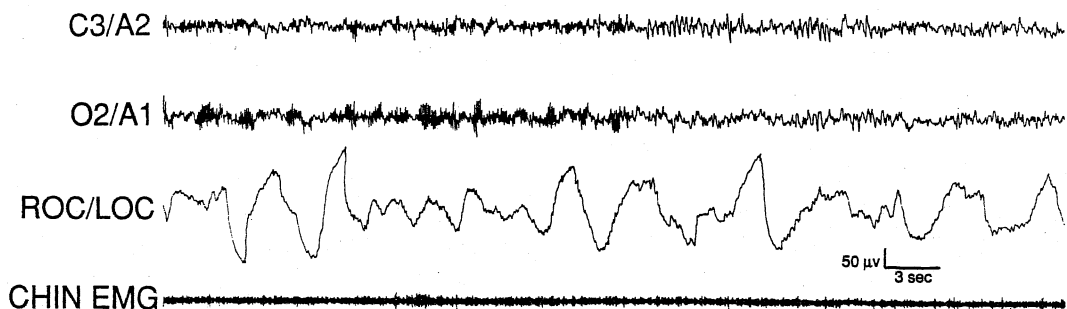


Figure 2-3. The transition from wakefulness to stage 1 sleep. The most marked change is visible on the two EEG channels (C3/A2 and O2/A1), where a clear pattern of rhythmic alpha activity (8 cps) changes to a relatively low-voltage, mixed-frequency pattern at about the middle of the figure. The level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

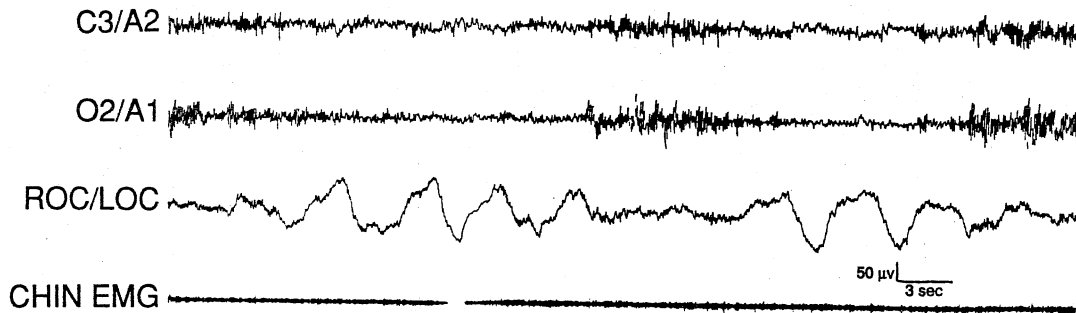


Figure 2-4. A common wake-to-sleep transition pattern. Note that the EEG pattern changes from wake (rhythmic alpha) to stage 1 (relatively low-voltage, mixed-frequency) sleep twice during this attempt to fall asleep.

patterns—the K complex or sleep spindle (i.e., stage 2 sleep)—to acknowledge sleep onset. Even these stage 2 patterns, however, are not unequivocally associated with perceived sleep.² A further complication is that sleep onset frequently does not occur all at once, but 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 wrote many years ago,

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.^{3(p35)}

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 may 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 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 de-

pressed in different sequence and to different degrees in different subjects and on different occasions.”^{3(p35)}

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.

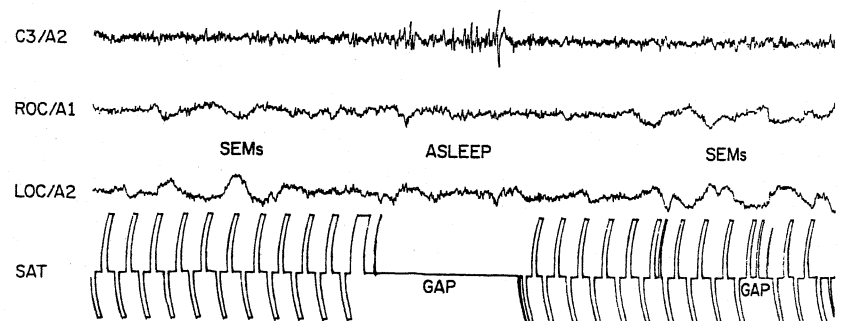
Visual Response

In the second example, a bright light is placed in front of the subject’s eyes. The individual 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 this example, a series of tones is 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 prox-

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 EEG (C3/A2) pattern changes to stage 1 sleep, the behavior stops, returning when the EEG pattern reverts to wakefulness. 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.)



imity 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 requires the resumption of a waking EEG pattern.

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.⁷ 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.

1. A person tends to have a lower arousal threshold for his or her own name versus someone else's name.⁸ 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.
2. Williams and his colleagues⁹ 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.

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 individual will generally report the mental experience as one of losing a direct train of thought and of experiencing vague and fragmentary imagery, usually visual.¹⁰ 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 pathological events, although they tend to occur more frequently 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 move-

ment 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, may become partially opened under unusual circumstances.

Memory

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 may close the gate between short-term and long-term memory stores. This phenomenon is best described by the following experiment.¹¹ During a presleep testing session, word pairs were presented to volunteers over a loudspeaker at 1-min intervals. The subjects were then awakened either 30 sec or 10 min after the onset of sleep (defined as EEG stage 1) and asked to recall those words presented before sleep onset. As illustrated in Figure 2-6, the 30-sec condition was associated with a consistent level of recall from the entire 10 min before sleep onset. (Primacy and recency effects are apparent, although not large.) In the 10-min condition, however, recall paralleled that in the 30-sec group for only the 10 to 4 min before sleep onset and then fell abruptly from that point until sleep onset.

In the 30-sec condition, therefore, both longer term (4 to 10 min) and shorter term (0 to 3 min) memory stores remained accessible. In the 10-min condition, by contrast, words that were in longer term stores (4 to 10 min) before sleep onset were accessible, whereas words that were still in shorter term (0 to 3 min) stores at sleep onset were no longer accessible, that is, 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 min, memory is lost for the few minutes before sleep. The following experiences represent a few familiar examples of this phenomenon:

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

Patients suffering from syndromes of excessive sleepiness may experience similar memory problems in the daytime if sleep becomes intrusive.

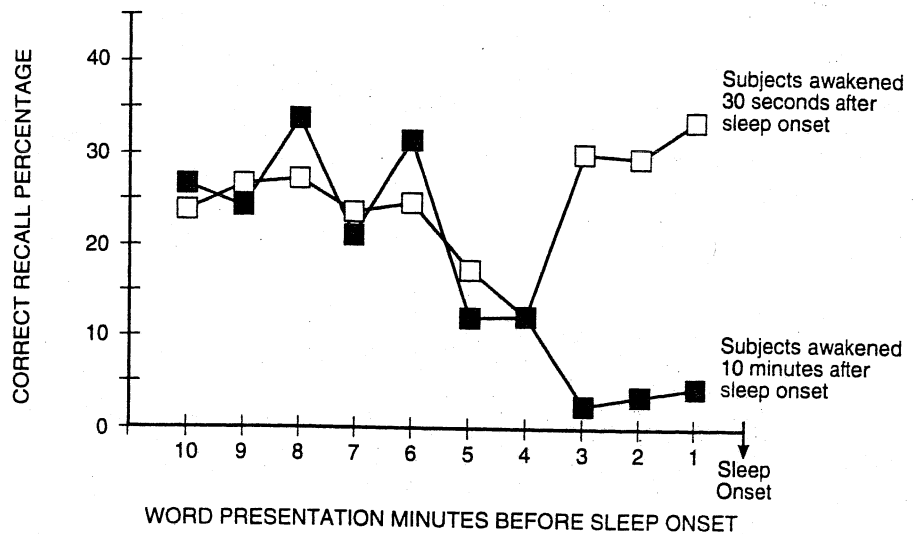


Figure 2-6. Memory is impaired by sleep, as shown by the study results illustrated in this graph. See text for explanation.

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 (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 min or longer thereafter, and NREM sleep and REM sleep alternate through the night, with an approximately 90-min cycle. (See Chapter 100 for a full description of sleep stages.)

First Sleep Cycle

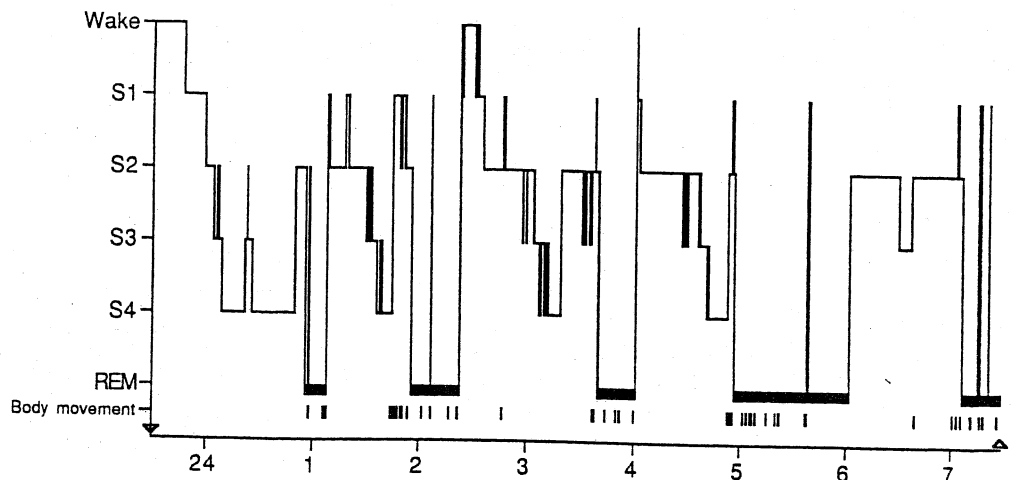
The first cycle of sleep in the normal young adult begins with stage 1 sleep, which generally persists for only a few (1 to 7) minutes at the onset of sleep. Sleep is easily discontinued during stage 1 by, for example, softly calling a person's name, touching the person lightly, quietly closing a door, 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 about 10 to 25 min. 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, there is a gradual appearance of high-voltage slow wave activity in the EEG. Eventually, this activity meets the criteria¹² for stage 3 NREM sleep, that is, high-voltage ($\geq 75\mu\text{V}$) slow (≤ 2 cps) wave 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 is more than 50% of the record—generally lasts

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 EEG, electro-oculogram, and EMG in a normal 19-year-old man. The record was assessed in 30-sec epochs for the various sleep stages.



about 20 to 40 min in the first cycle. An incrementally larger stimulus is generally 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 + 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. There may be a brief (1- or 2-min) episode of stage 3 sleep, followed by perhaps 5 to 10 min 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 min). 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 individual'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 stage 3 + 4, which is also 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 + 4 NREM) in human beings.

NREM-REM Cycle

NREM sleep and REM sleep continue to alternate through the night in cyclical fashion. REM sleep episodes generally become longer across the night. Stages 3 and 4 sleep occupy less time in the second cycle and may 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 min; the average length of the second and later cycles is about 90 to 120 min. Across the night, the average period of the NREM-REM cycle is approximately 90 to 110 min.

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 tends to be greatest in the last one third of the night. Brief episodes of wakefulness tend to intrude later in the night, generally near REM sleep transitions, and 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 and can be gauged by the oscillation of body temperature.^{13, 14} The preferential distribution of SWS toward the beginning of a sleep episode is not thought to be mediated by circadian processes but is linked to the initiation of

sleep, the length of prior wakefulness, and the time course of sleep per se.¹⁵

Length of Sleep

The length of nocturnal sleep is dependent 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 h a night on weekday nights and slightly longer, 8.5 h, 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,¹⁶ 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. 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 is dependent 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 individual who is living on a conventional sleep-wake schedule and who is without sleep complaints:

1. Sleep is entered through NREM.
2. NREM sleep and REM sleep alternate with a period near 90 min.
3. SWS predominates in the first third of the night and is linked to the initiation of sleep.
4. REM sleep predominates in the last third of the night and is linked to the circadian rhythm of body temperature.
5. Wakefulness within sleep usually accounts for less than 5% of the night.
6. Stage 1 sleep generally constitutes about 2 to 5% of sleep.
7. Stage 2 sleep generally constitutes about 45 to 55% of sleep.
8. Stage 3 sleep generally constitutes about 3 to 8% of sleep.
9. Stage 4 sleep generally constitutes about 10 to 15% of sleep.
10. NREM sleep, therefore, is usually 75 to 80% of sleep.
11. 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. The

most marked age-related differences in sleep from the patterns described earlier are found in newborn infants. For the 1st year of life, the transition from wake to sleep is often accomplished through REM sleep (called *active sleep* in newborns). The cyclical alternation of NREM-REM sleep is present from birth but has a period of about 50 to 60 min in the newborn compared with about 90 min 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,¹⁷ a 123-dB tone failed to produce any sign of arousal in a group of children whose mean age was 10 years. There is a similar, although less profound, qualitative difference between SWS occurring in the first and later cycles of the night in a given individual. The quantitative change in SWS may best be seen across adolescence, when SWS decreases by nearly 40% during the 2nd decade, even when length of nocturnal sleep remains constant.¹⁸ Feinberg¹⁹ hypothesized that the age-related decline in nocturnal SWS may parallel loss of cortical synaptic density (Fig. 2-8). By age 60 years, SWS may no longer be present, particularly in men. Women appear to maintain SWS later into life than men do.

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 functioning²⁰ and declines markedly in the case of organic brain dysfunctions of the elderly.²¹

Arousals during sleep increase markedly with age, both extended awakenings, of which the individual is aware and can report, and brief and probably unremembered arousals.²² The latter type of transient arousals may occur with no known correlate but are frequently associated with occult sleep disturbances, such as periodic movements during sleep (PMS) and sleep-related respiratory irregularities, which also become more prevalent in later life.^{23, 24}

Perhaps the most notable finding regarding sleep in the elderly is the profound increase in interindividual variability,²⁵ which thus precludes generalizations such as those made for young adults.

Prior Sleep History

An individual who has experienced sleep loss on one or more nights will show 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.

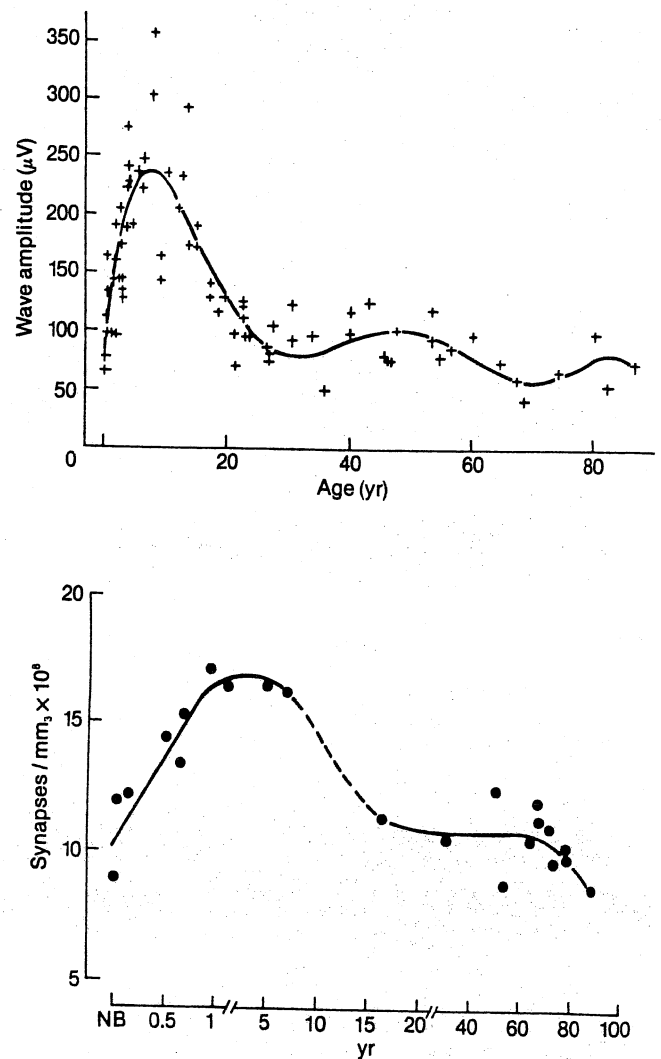


Figure 2-8. These graphs illustrate age-related changes in human EEG amplitude and in cortical synaptic density. Although relatively few data points were used to produce the lower curve, Feinberg¹⁹ suggested that the decline in EEG amplitude during adolescence, which is most remarkable during sleep, is causally linked to a "programmed" thinning of synaptic density in the cortex. (Reprinted from *Journal of Psychiatric Research*, vol. 17, Feinberg J, Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence?, 319-334, Copyright 1983, with permission from Elsevier Science.)

REM sleep tends to show a rebound on the 2nd 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 an individual is differentially deprived of REM or SWS—either operationally by being awakened each time the sleep pattern occurs, or pharmacologically (see later)—a preferential rebound of that stage of sleep occurs when natural sleep is resumed. This phenomenon has particular relevance in a clinical setting, in which abrupt withdrawal from a therapeutic regimen may result in misleading diagnostic findings (e.g., sleep-onset REM periods [SOREMs] as a result of a REM sleep rebound) or could conceiv-

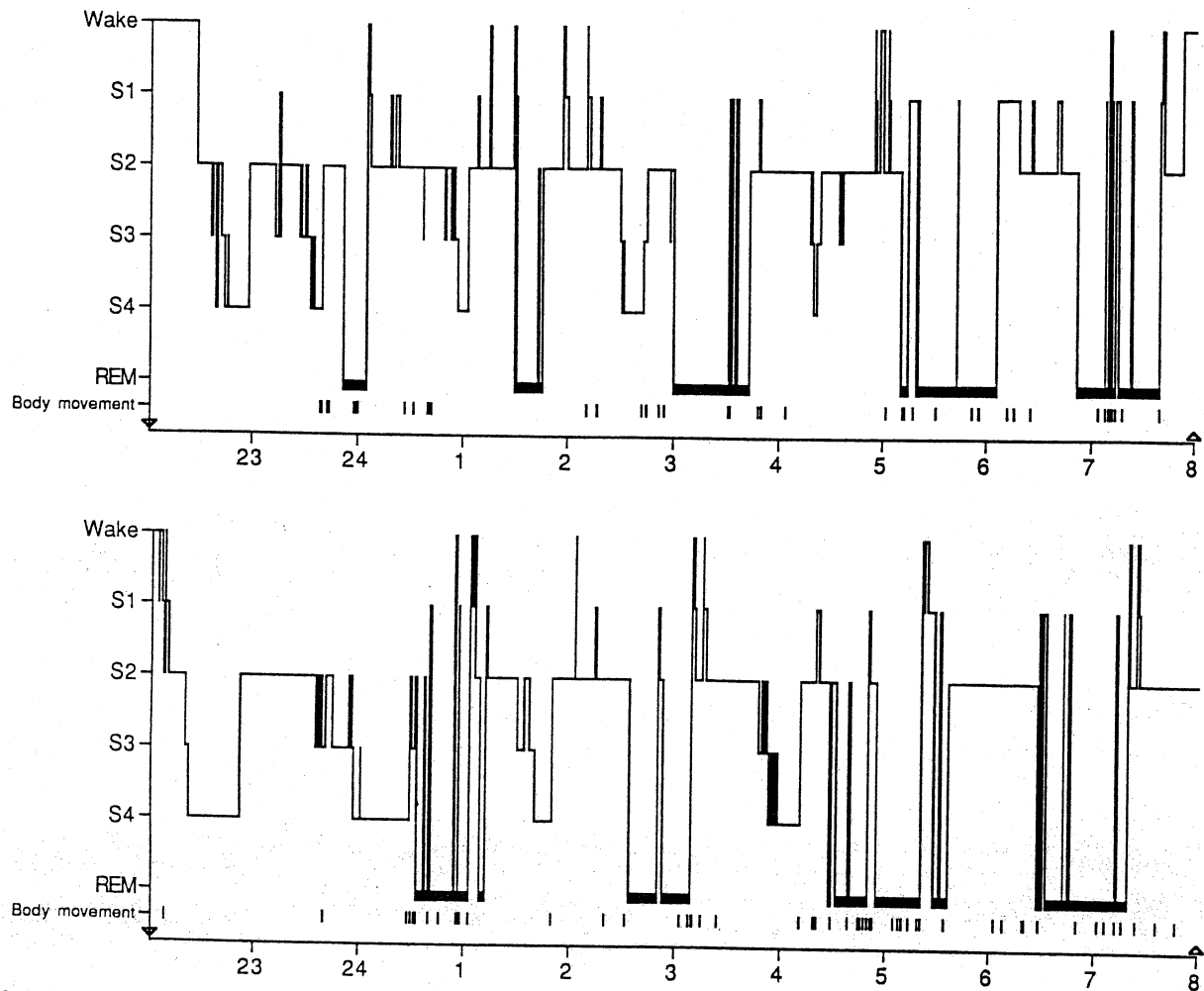


Figure 2-9. The upper histogram shows the baseline sleep pattern of a normal 14-year-old female volunteer. The lower histogram illustrates the sleep pattern in this volunteer for the first recovery night after 38 h without sleep. Note that the amount of stage 4 sleep on the lower graph is greater than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

ably 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 frequently characterized by premature REM sleep, that is, SOREMPs. Such episodes can be associated with hypnagogic hallucinations, sleep paralysis, or an increased incidence of hypnic myoclonia in individuals 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.²⁶ Frequently, this delay takes the form of missing 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 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 body temperature.^{13, 14} 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 may 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 a change resulting from jet travel across a number of time zones. Studies of individuals 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.^{27, 28} In patients whose sleep distribution is examined with reference to the circadian body

temperature phase position, it is clear that sleep onset is likeliest to occur on the falling limb of the temperature cycle, although 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.²⁹

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, if any, ability to thermoregulate during REM sleep; in other words, the control of body temperature is virtually poikilothermic in REM sleep.³⁰ 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 sweating or shivering during sleep in response to ambient temperature extremes occurs in NREM sleep and ceases 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. It is unknown whether changes in sleep stage distribution have any relevance to health, illness, or psychological well-being; 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 frequently used compounds on sleep stage distribution follow:

1. Benzodiazepines tend to suppress SWS and have no consistent effect on REM sleep.
2. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) 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 PMS.
3. 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 MAOI 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 a false-positive diagnosis of narcolepsy.

4. Acute presleep alcohol intake produces REM suppression early in the night, which is often followed by REM sleep rebound in the latter portion of the night as the alcohol is metabolized.
5. 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.³¹

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 in any implications about general health or illness resulting from specific sleep stage alterations. Listed are a number of common sleep stage anomalies associated with sleep disorders:

1. *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 104). If REM sleep occurs abnormally on two 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 latency may occur include infancy, in which sleep-onset REM is normal; sleep reversal or jet lag; acute withdrawal from REM-suppressant compounds; chronic restriction or disruption of sleep; and endogenous depression, in which a shortened latency to REM sleep is thought to be a biological marker of this psychiatric entity.³² Recent reports have indicated a relatively high prevalence of REM onsets in young adults^{32a} and in adolescents with early rise times.^{32b} In the latter, the REM onsets on morning (8:30 and 10:30 AM) naps were related to a delayed circadian phase as indicated by later onset of melatonin secretion.
2. *Sleep apnea syndromes* may be associated with suppression of SWS or REM sleep, secondary to the sleep-related breathing problem. Suppression of SWS occurs most commonly in children with sleep apnea; REM suppression is more common in adults with sleep apnea syndromes. Successful treatment of this sleep disorder, as with nocturnal continuous positive airway pressure (CPAP), produces huge rebounds of SWS or REM sleep (Fig. 2-10).

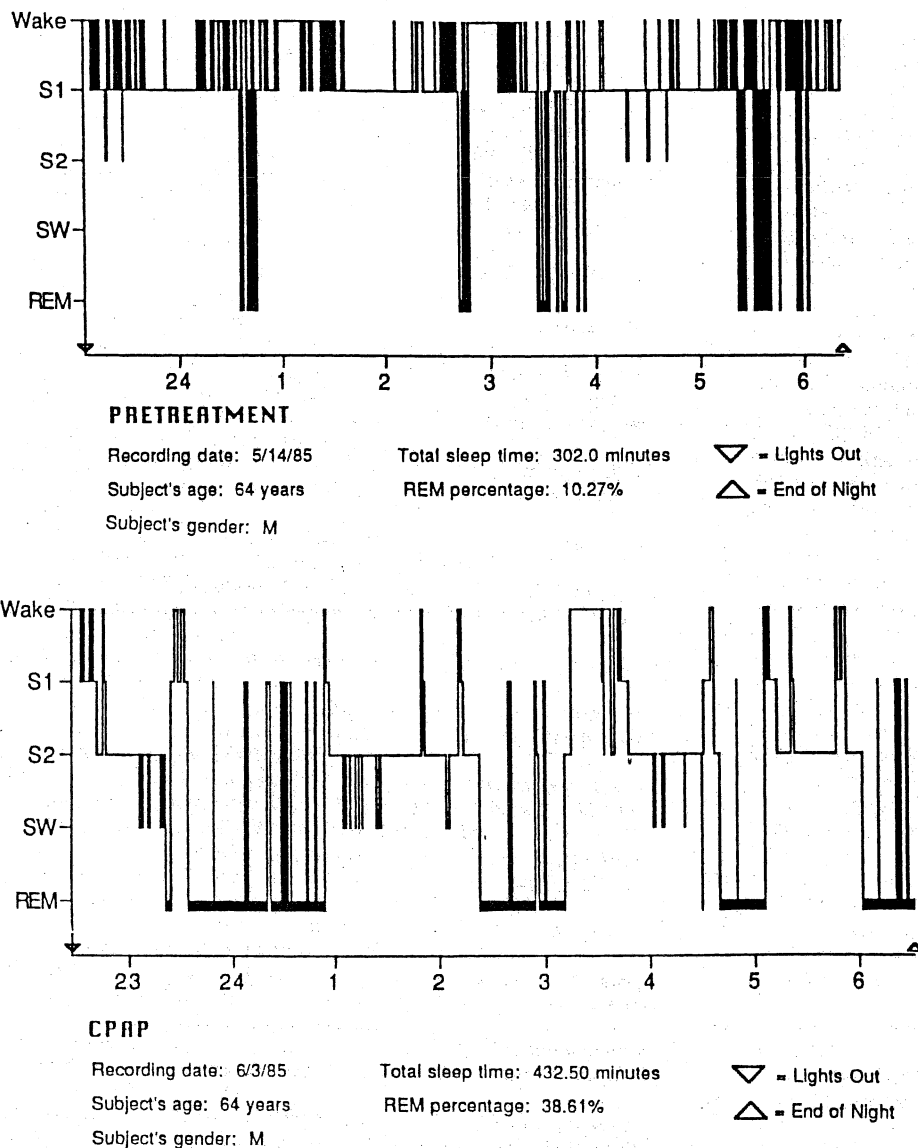


Figure 2-10. These sleep histograms depict the sleep of a 64-year-old male patient with obstructive sleep apnea syndrome. The upper graph shows the sleep pattern before treatment. Note the absence of slow wave (SW) (stage 3 or 4) sleep, the preponderance of stage 1 (S1), and the very frequent disruptions. The lower 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 SW) and more consolidated, and 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, California.)

3. *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. PMS, 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,^{33, 34} juvenile rheumatoid arthritis,³⁵ and Parkinson's disease.³⁶ In upper airway resistance syndrome (UARS),³⁷ EEG arousals are important markers because the respiratory signs of UARS are less obvious than in frank obstructive sleep apnea syndrome (OSAS), and only subtle indicators may be available.³⁸ In specific situations, autonomic changes, such as transient changes of blood pressure,³⁹ may signify arousals; Lofaso and colleagues⁴⁰ 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.

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