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PREFACE

There are complex physiologic mechanisms that underly the interaction of sleep and epilepsy and have been recognized since antiquity. Certain epileptic seizures tend to occur predominantly during sleep such as in supplementary sensorimotor area epilepsy or benign focal epilepsy of childhood. Paroxysmal events of sleep may represent manifestations of the parasomnias or may be epileptic seizures restricted to sleep. Sleep disorders in epileptic patients may be secondary to seizures, due to the anti-epileptic drugs they are treated with or may represent a co-existent primary sleep disorder.

This book is based on a symposium of the Clinical Physiologic Core Relationships of Epilepsy and Sleep, which was held in Cleveland June 22, 1998. The book provides a comprehensive and systematic review of the relationships of epilepsy and sleep, as well as of the parasomnias and cataplexy which may masquerade as epilepsy. Our sincere thanks to the authors who have made this text possible.

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1

RELATIONSHIP OF EPILEPSY AND SLEEP

OVERVIEW

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INTRODUCTION

There is a very close relationship between epilepsy and sleep that has been recognized since antiquity. Both Hippocrates and Aristotle observed the occurrence of epileptic seizures during sleep (Passouant, 1984). However, the relationship was not studied until the end of the nineteenth century when Gowers investigated the relationship of grand mal epilepsy to the sleep–wake cycle (Gowers, 1885). Langdon-Down and Brain (1929) investigated the time of occurrence of nocturnal seizures, finding that there were two peaks, approximately 2 h after bedtime and between 4 and 5 A.M., and that daytime seizures occurred predominantly in the first hour after awakening. The effect of epilepsy on sleep was first mentioned by Fere (1890), in the form of difficulty falling asleep and impairing sleep efficiency. All these conclusions were based on clinical observations alone.

After the discovery of the human electroencephalogram (EEG) by Berger (1929), the EEG was incorporated into subsequent studies of the relationship of epilepsy and sleep. The first observation of the relationship of interictal epileptiform activity (IEA) and sleep was reported by Gibbs and Gibbs (1947). They observed an increase in the IEA in sleep compared with the frequency of the discharges recorded in the waking state. In this chapter, an overview of the relationship of epilepsy and sleep will be discussed from the following points of view:

1. Effect of sleep on epilepsy
2. Effect of epilepsy on sleep
3. Effect of antiepileptic drugs on sleep
4. Use of sleep and sleep deprivation in the evaluation of epilepsy

EFFECT OF SLEEP ON EPILEPSY

Cognizant of the intimate relationship that exists between sleep and epilepsy, many authors have classified seizures based on the time of occurrence of seizures with regard to the sleep–wake cycle, with three resultant groups: sleep epilepsy, waking epilepsy, and diffuse epilepsy with seizures occurring in both sleep and waking states (Gowers, 1885; Langdon-Down, 1929; Janz, 1962). In the earlier studies based on clinical observation, it was found that approximately 40–45% of the patients experienced predominantly daytime seizures, 20% expe-

TABLE 1.1 Proportion of Patients with Diurnal, Nocturnal, and Diffuse Epilepsy in Early Clinical Observational Studies

Author	No. of patients	Diurnal epilepsy (%)	Nocturnal epilepsy (%)	Diffuse epilepsy (%)
Gowers, 1865	84	42	21	37
Langdon-Down and Brain, 1929	66	43	24	33
Patry, 1931	750	45	19	36

rienced exclusively nocturnal seizures, and approximately 30% experienced seizures both during the daytime and nighttime hours (Table 1.1). All three studies included in Table 1.1 show very close conformity in the three subgroups of patients. It soon became clear, however, that different seizure types are affected differently by the sleep–wake cycle.

EFFECT OF SLEEP ON GENERALIZED TONIC–CLONIC SEIZURES

Janz performed systematic studies of the relationship of seizures to sleep and waking states and classified his patients into waking epilepsies, sleep epilepsies, and diffuse epilepsies (Janz, 1962, 1969). Table 1.2 demonstrates the association of generalized tonic–clonic seizures in regard to the sleep–wake schedule. In the outpatient studies of Janz (1962, 1969), a large proportion of patients (44%) with primary generalized epilepsy had their seizures restricted to sleep. In the series of Billiard (1982), which includes a smaller number of patients, the proportion of patients with sleep epilepsy is considerably smaller. However, in his group of patients, Billiard included patients with both primary generalized epilepsy and patients with partial epilepsy with secondary generalized motor seizures. This may account for the difference in the number of patients with sleep epilepsy.

TABLE 1.2 Association of Generalized Tonic–Clonic Seizures in Regard to Sleep/Awake Schedule

Author	No. of patients	Waking epilepsy (%)	Sleep epilepsy (%)	Diffuse epilepsy (%)
Janz, 1962	2110	34	45	21
Janz, 1969	2925	33	44	23
Billiard, 1982	314	53	15	32

PRIMARY GENERALIZED TONIC–CLONIC EPILEPSY

Gowers (1885) first noted that patients with generalized tonic–clonic seizures appear to have their seizures in two peaks during sleep, the first two hours after sleep onset and then toward the end of sleep. In the study of Janz (1962), the two peaks of sleep-related seizures were noted to occur between 9 and 11 P.M. and then between 3 and 5 A.M. In various studies, it was documented that generalized tonic–clonic seizures occur from nonrapid eye movement (NREM) sleep (Passouant *et al.*, 1975; Besset, 1982; Billiard, 1987). Patients with sleep-related epilepsy usually continue having their seizures restricted to sleep in the majority of instances, but 20% of these patients may take on a diffuse pattern (Janz, 1962).

Generalized IEA usually increases in NREM sleep (Billiard, 1982; Montplaisier, 1985). In the majority of patients the epileptiform discharges are most prominent at sleep onset and during the first part of the night. However, in some patients the discharges are most prominent in NREM sleep occurring during the last part of the night. In waking or diffuse epilepsy, the IEA may occur at anytime. But in pure sleep epilepsy the epileptiform discharges have been noted restricted to REM sleep or on awakening in 9% of the patients and restricted to NREM sleep in 41% of the patients (Janz, 1962). The morphology of the interictal activity also is affected by sleep. During NREM sleep, generalized bursts of spike–wave complexes become fragmented, polyspikes may appear, and discharges may occur in a focal (regional) distribution or lateralized to one hemisphere (Niedermeyer, 1965; Broughton, 1984).

JUVENILE MYOCLONIC EPILEPSY

In this syndrome, myoclonic and generalized tonic–clonic seizures occur characteristically in the morning in the first one to two hours after awakening. Seizures may also occur on awakening from a nap but are rare at other times during the day (Dinner, 1987). Sleep deprivation and alcohol appear to be an extremely important precipitant for seizures in this syndrome.

The characteristic EEG abnormality in juvenile myoclonic epilepsy consists of spike–wave complexes at 4–6 Hz in a generalized distribution, as well as polyspikes. The discharges increase markedly at sleep onset and on awakening but are virtually absent in NREM and REM sleep and while the patient is awake.

ABSENCE EPILEPSY

Clinical absence seizures are only detectable in the waking state and are often precipitated by photic stimulation or hyperventilation. They are associated with the presence of 3-Hz spike–wave complexes in a generalized distribution (Fig. 1.1A). The activation of the IEA is most marked in the first sleep cycle (Sato *et al.*, 1973). Some investigators have found marked activation of the epileptiform

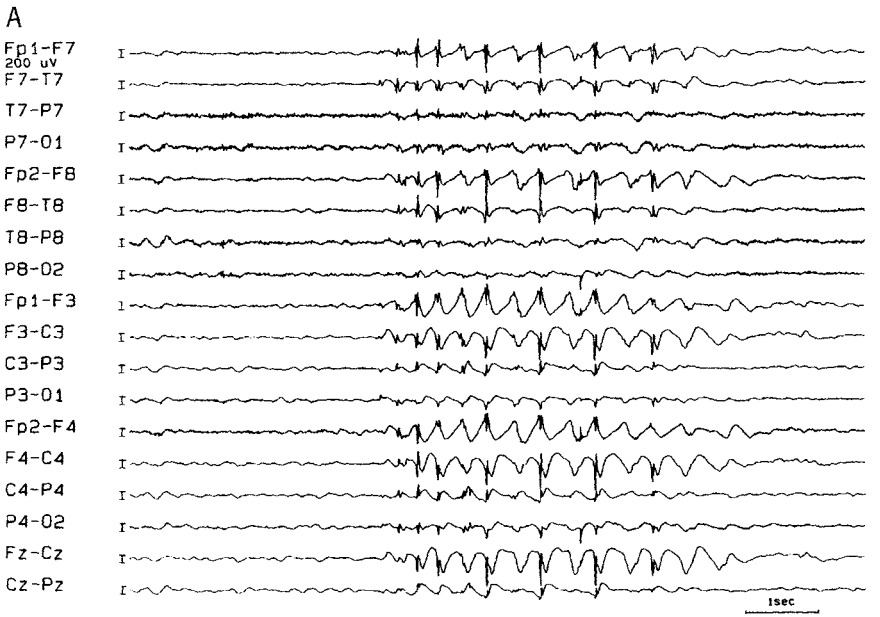

FIGURE 1.1A Bursts of generalized spike-and-wave complexes at approximately 3 Hz in the awake EEG of a 9-year-old girl with absence seizures.

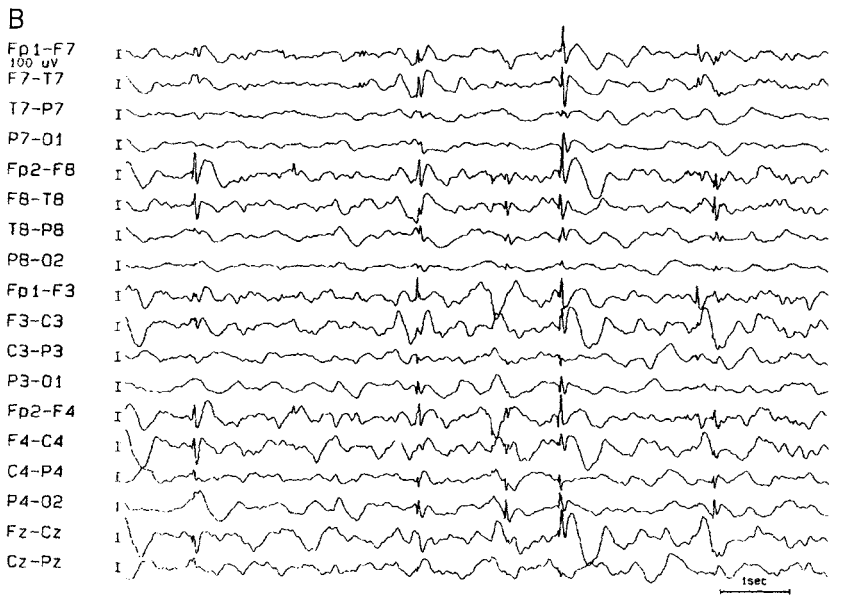

FIGURE 1.1B The EEG tracing of the same girl in NREM sleep, demonstrating focal spikes in the right and left frontal regions as well as single bursts of generalized spikes.

activity in light NREM sleep, stages 1 and 2 (Ross *et al.*, 1966; Daly, 1973; Sato *et al.*, 1973). Other investigators have found a marked activation occurring during deep NREM sleep, stages 3–4 (Ross, 1966; Sato *et al.*, 1973). During stage 1 NREM sleep, the bursts of generalized spike–wave complexes become shorter in duration but maintain a well-defined morphology. During stage 2 NREM sleep, the bursts may appear more irregular and less well defined and become intermixed with polyspikes. Focal spikes may be seen occurring independently in the left and right frontal regions (Fig. 1.1B). The discharges may also recur in a semiperiodic fashion. In deep NREM sleep, stages 3–4, there may be a further decline in the rhythmicity of the spike–wave complexes with a decrease in the repetition rate to between .5 and 2 Hz. In addition, single generalized spikes and polyspikes tend to appear. In REM sleep the bursts of generalized 3-Hz spike–wave complexes are similar to those seen in the wake state but their duration is decreased (Ross, 1966; Sato, 1973).

LENNOX–GASTAUT SYNDROME

This syndrome refers to patients with intractable seizures, mental retardation, and the presence of generalized slow spike–wave complexes occurring at a frequency of 2.5 Hz or less (Fig. 1.2). The intractable seizures include generalized tonic–clonic, tonic, atonic, myoclonic, and atypical absence seizures. The

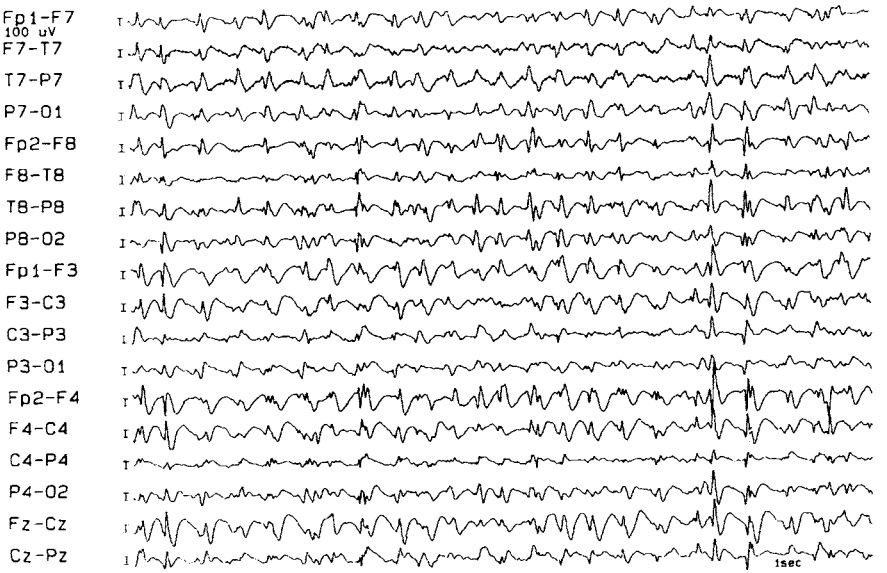

FIGURE 1.2 The EEG tracing in NREM sleep of a 13-year-old girl with Lennox-Gastaut syndrome, demonstrating generalized slow spike–wave complexes at 2–2.5 Hz.

quantity of the bursts of spike–wave complexes increases in NREM sleep. Their morphology may be altered with the polyspikes becoming more prominent. There may be runs of generalized polyspikes and rhythmic bursts of 10–20-Hz fast activity. Periods of electrodecremental activity may alternate with bursts of polyspikes resembling a burst suppression-like pattern may appear.

WEST SYNDROME

This syndrome describes the triad of infantile spasms, psychomotor retardation, and hypsarhythmia on the EEG (Fig. 1.3A). The infantile spasms tend to occur infrequently during sleep (Kellaway *et al.*, 1979; Gomez and Klass, 1983). Only 2–5% of the spasms occurred during sleep in the Kellaway series. The EEG abnormalities may be increased in NREM sleep and the hypsarhythmia pattern may become more apparent during sleep. Occasionally the hypsarhythmia pattern may be seen only during sleep (Jeavons and Bower, 1961). In some patients, bursts of spike and slow waves alternate with periods of generalized suppression of the EEG activity in a semiperiodic fashion, giving rise to a burst suppression-like pattern (Fig. 1.3B) (Passouant *et al.*, 1975). During REM sleep, there is a marked attenuation or disappearance of the hypsarhythmia pattern (Jeavons and Bower, 1961).

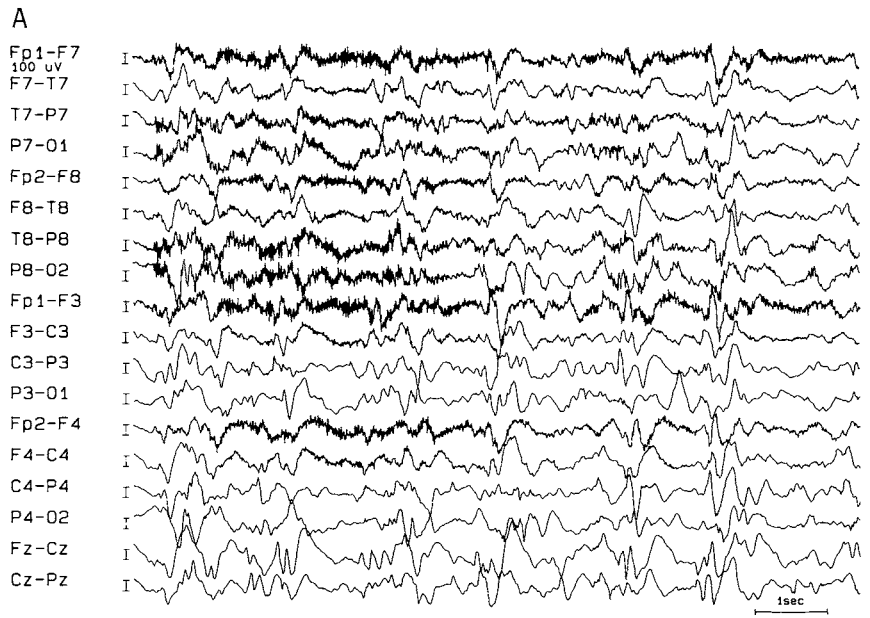

FIGURE 1.3A The awake EEG tracing of a 6-month-old boy with infantile spasms showing hypsarhythmia.

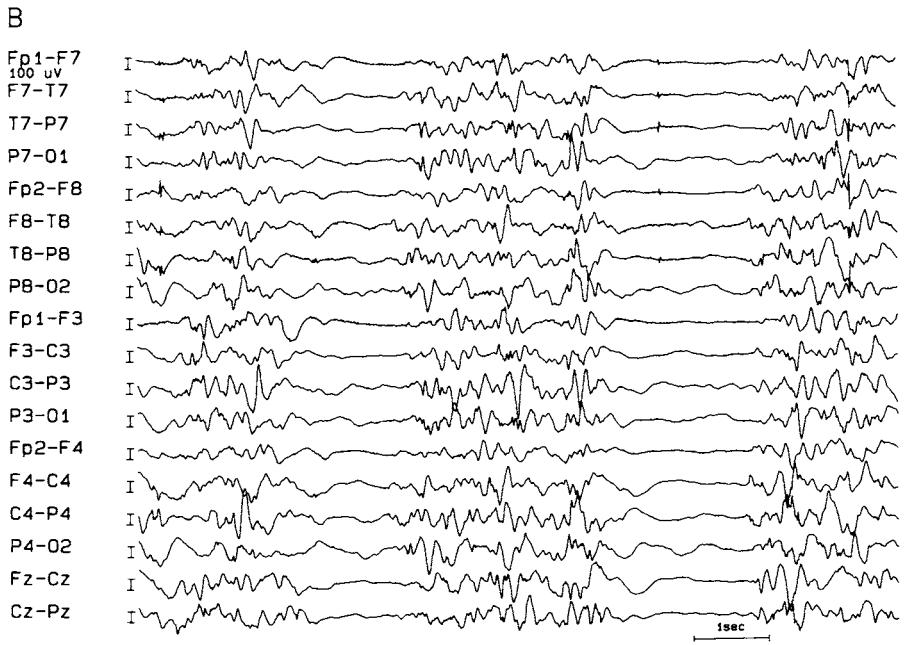

FIGURE 1.3B The sleep tracing of the same 6-month-old boy demonstrating the discharges recurring in a more periodic fashion, alternating with periods of relative suppression, simulating a burst–suppression type of pattern.

TEMPORAL LOBE EPILEPSY

In Billiard's (1982) study of 127 patients, 9.4% had sleep-related complex partial seizures. In a study of 50 patients with sleep-related complex partial seizures, Cadilhac (1982) found that 32 patients had seizures in NREM sleep, 8 in REM sleep, and 10 in both states. However, in a study of 10 patients with a diagnosis of mesial temporal lobe epilepsy, Montplaisier (1985) found that none of these patients had seizures in NREM sleep. In a study of 15 patients with temporal lobe epilepsy, only 7 of the 67 seizures (10.9%) occurred in sleep (Crespel *et al.*, 1998). All the seizures occurred during stage 2 NREM sleep, except for one seizure that occurred from stage 3–4 NREM sleep. Quigg and colleagues (1998) studied the time of day when seizures occurred in patients with mesial temporal lobe epilepsy and found the majority of seizures happened during the waking hours with a peak incidence at 3 P.M.

In terms of the presence of the IEA, most studies of temporal lobe epilepsy have found that there is an increase in interictal epileptiform discharges in NREM sleep with a decrease in REM sleep. There appears to be a maximal peak in the rate of spikes occurring in stage 2 or stage 3–4 NREM sleep (Lieb *et al.*, 1980; Rowan, 1982; Rossi, 1984). In patients with temporal lobe epilepsy, spikes were found in 53% in stage 1, 95% in stage 2, 98% in stage 3, and in all

patients in whom stage 4 was recorded (Sammaritano *et al.*, 1991). The spike frequency was highest in the deepest stage of sleep (3 or 4). The spike frequency was greatest in NREM sleep in 85% of patients and in REM in 12.5% of patients. In addition, the extent of the distribution of the electrical field of the unilateral foci was studied as a function of the sleep state. It was found that the extent of the electrical field increased in more than 75% of the spikes in NREM sleep compared with the wake state. In the patient's EEG demonstrated in Figs. 1.4A and 1.4B, unilateral focal sharp waves were seen in the left posterior temporal region while awake (Fig. 1.4A), and bilateral posterior temporal sharp waves occurred during sleep (Fig. 1.4B). In REM sleep, Sammaritano (1991) reported a restriction of the electrical field of the epileptiform activity. In 53% of the group of patients studied, spike foci that were not seen in the awake state were activated in NREM sleep. In contrast to this in REM sleep, 42.5% of patients showed disappearance of foci observed. Depth electrode recording studies have also shown maximal spiking rates in NREM sleep and decrease in REM sleep (Lieb *et al.*, 1980). Restriction of the field of distribution of the interictal discharges during REM sleep observed by Sammaritano was previously reported by Montplaisier (1985). In the study of Malow and colleagues (1997), they determined log delta power (LDP) that was computed by the fast Fourier transform and then used this as an indicator of the depth of sleep. They studied eight pa-

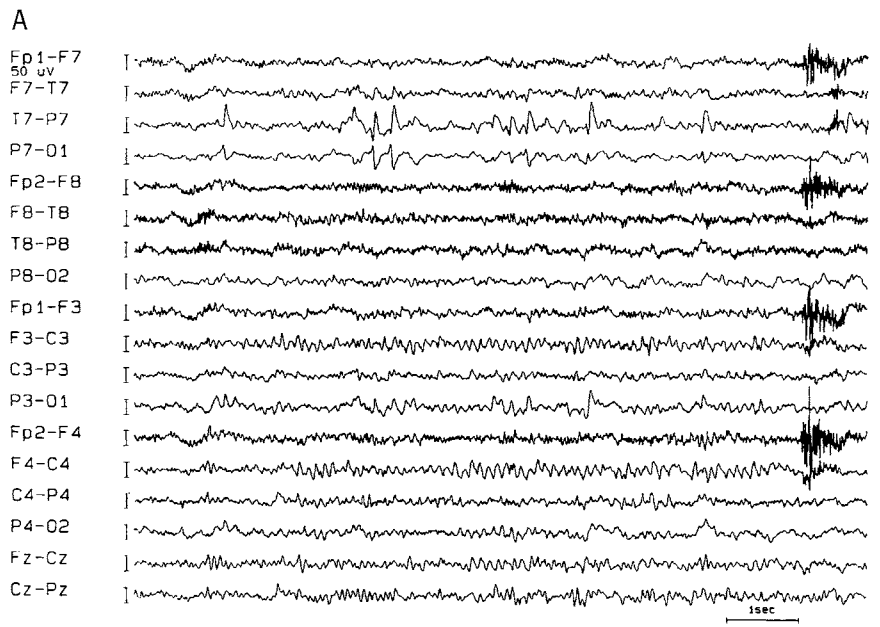

FIGURE 1.4A The waking EEG of a 9-year-old boy with complex partial seizures, showing sharp waves in the left posterior temporal region.

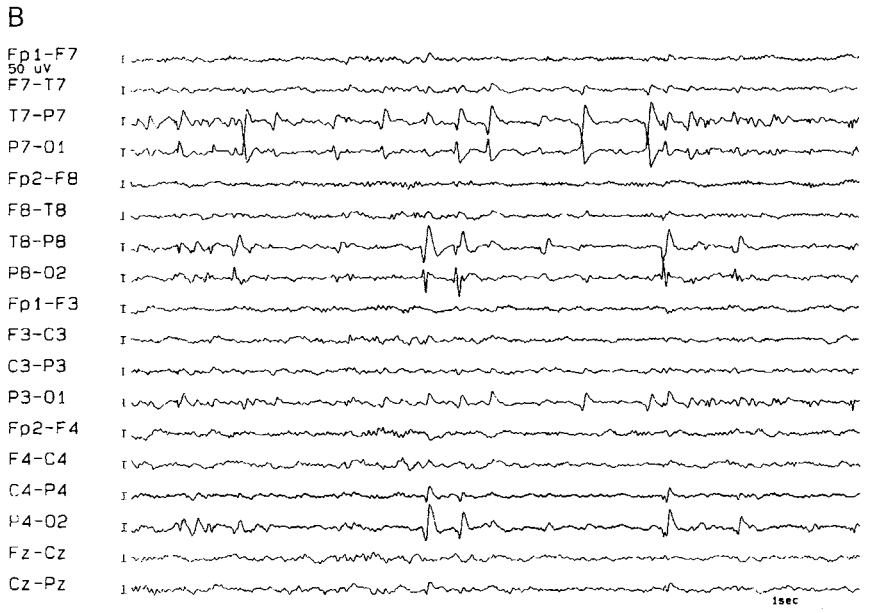

FIGURE 1.4B The EEG tracing in NREM sleep of the same boy, demonstrating sharp waves bilaterally in the left and right posterior temporal regions.

tients with focal epilepsy and found that during NREM sleep there was a direct relationship of IEA and LDP with increased spikes during deep sleep (high LDP). They also found that spikes were more likely to occur on the ascending limb of the LDP and with a more rapid increase in the LDP.

FRONTAL LOBE EPILEPSY

Seizures originating from the frontal lobe show a tendency to occur preferentially during sleep. They also tend to have prominent motor manifestations and are likely to be recognized by the patient or family and friends. There are three major clinical seizure types that characterize seizures originating from the frontal lobe: focal clonic seizures, asymmetrical tonic seizures, and complex motor seizures.

Focal clonic seizures are characterized by unilateral clonic activity frequently not associated with alteration of consciousness. The classic example is in the case of benign focal epilepsy of childhood with seizures originating from the sylvian region with involvement of the primary motor cortex.

Asymmetric tonic seizures are usually due to activation of the supplementary sensorimotor area (SSMA, area 6), located on the mesial aspect of the superior frontal gyrus with extension onto the dorsal convexity. The seizures are charac-

terized by bilateral proximal asymmetric tonic activity of the extremities and trunk and not infrequently consciousness may be preserved. The seizures are usually brief in duration and at times recur in clusters. They demonstrate a propensity to occur in sleep. We reviewed our experience at the Cleveland Clinic Foundation of recording patients with bitateral asymmetric tonic seizures due to activation of the SSMA and found that 65% of the seizures were recorded from sleep. Almost all these seizures were recorded from NREM sleep (Anand and Dinner, 1997). Complex motor seizures may also originate from the frontal lobe. The automatisms in these seizures are frequently very prominent proximally leading to "violent" movements (hypermotor seizures) (Williamson *et al.*, 1985). In patients with frontal lobe epilepsy in the study by Crespel *et al.* (1998), patients with complex partial seizures and asymmetric tonic seizures were included. In this group, 61% of 108 seizures were recorded from sleep. This was in comparison with only 10.9% of their patients with temporal lobe epilepsy experiencing seizures from sleep.

BENIGN FOCAL EPILEPSY OF CHILDHOOD

This syndrome is the most common epileptic syndrome in children, accounting for 15–25% of childhood epilepsy (Lerman and Kivity, 1975). These seizures are unilateral focal clonic seizures involving the face and arm which frequently evolve into generalized tonic–clonic seizures. The generalized tonic–clonic seizure is the more common type. Seizures tend to occur during sleep. They have been reported to occur only in sleep in 51–80% of cases in various series (Beaussart, 1972; Gregory and Wong, 1984). The characteristic IEA consists of the benign focal epileptiform discharge of childhood, which is typically distributed in the centrotemporal region but may occur in any region. It may be unifocal, bifocal, or multifocal in distribution. The discharges have a stereotyped morphology. What is most characteristic is the marked activation by sleep (Gibbs *et al.*, 1954; Nayrac and Beaussart, 1957; Lerman and Kivity-Ephraim, 1974). In some reports, the sharp waves appear only during sleep, 2.5–35% (Lombroso, 1967; Lerman and Kivity-Ephraim, 1974; Lüders *et al.*, 1987).

AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) has been described as a distinct clinical syndrome by Scheffer *et al.* (1994). They described the brief motor seizures, hyperkinetic or tonic in nature, occurring in clusters during sleep. The seizures usually began in childhood with a mean age of onset of 11.7 years and persisted throughout life (Scheffer *et al.*, 1995). The disorder demonstrated an autosomal dominant inheritance pattern. The interictal EEG demonstrated epileptiform discharges in only 6 of 37 individuals (Scheffer *et al.*, 1995).

ELECTRICAL STATUS EPILEPTICUS OF SLEEP

Electrical status epilepticus of sleep (ESES) refers to the occurrence of continuous epileptiform activity for at least 85% of slow-wave sleep. This syndrome is also known as epilepsy with continuous spike waves during slow-wave sleep. The syndrome was first described by Patry (1971). The EEG is characterized by generalized spike–wave complexes at 2–2.5 Hz. There is a marked attenuation of the pattern during REM sleep and in the wake EEG. The condition almost always occurs in patients with a prior history of epilepsy. With the onset of ESES, there is an associated decline in cognitive function with improvement once the ESES has resolved (Jayakar and Seshia, 1991). Seizures may manifest as nocturnal focal motor or generalized tonic–clonic seizures, or as atypical absence or myoclonic seizures.

LANDAU–KLEFFNER SYNDROME

This syndrome was first described by Landau and Kleffner (1957), and refers to previously normal children having language difficulties associated with interictal epileptiform discharges in the centrotemporal regions during sleep. At sometime during the course of this syndrome, there is dramatic activation of the IEA during sleep, occurring for >85% of slow-wave sleep similar to electrical status epilepticus of sleep (ESES) (Tassinari *et al.*, 1992). The occurrence of seizures is relatively rare. There is usually remission of the seizures and epileptiform discharges by the age of 15 years.

EFFECT OF EPILEPSY ON SLEEP

Sleep disturbances are well recognized in patients with epilepsy. The changes reported in the literature with regard to the effect of epilepsy on sleep architecture include an increase of sleep onset latency, an increase in the wake time after sleep onset (WASO), increased instability of sleep stages, increased stage 1 and 2 NREM sleep (light sleep), a decrease in sleep spindle density, and a decrease in REM sleep. With regard to the pathophysiology of the sleep disturbances in these patients, one needs to consider the following mechanisms: (1) the epilepsy itself may be associated with a sleep disturbance due to a mechanism intrinsic to the disease itself without the effect of the associated seizures, (2) the effect of seizures on sleep, and (3) the effect of antiepileptic drugs (AEDs) on the sleep architecture.

EFFECT OF EPILEPSY

To investigate the effect of the epilepsy on sleep architecture, patients have been studied with polysomnography on nights when they are not having seizures. Patients with primary generalized epilepsy and patients with focal epilepsy were evaluated in terms of total sleep time, proportion of NREM and

REM sleep, wakefulness, number of awakenings >2 min, and awakenings <2 min. An increase in the WASO, awakenings <2 min and >2 min were found (Touchon, 1991). In this study, the patients were on their AEDs, which were kept constant. One of the pathophysiologic mechanisms that have been implicated in the pathophysiology of epilepsy is an aberrant GABA release. Deficient GABA or an increase in acetylcholine and norepinephrine could be responsible for the frequent stage shifts that are observed in the epileptic patients. Touchon (1991) also reported that the sleep abnormalities were more marked in temporal lobe epilepsy than in generalized epilepsy. In feline temporal lobe epilepsy in amygdala kindled kittens, chronic sleep disturbances were produced in these kittens as opposed to kindled adult cats, present one year after kindling (Shouse, 1994). She found REM related arousals, increased number of awakenings, decreased REM sleep, and decreased slow-wave sleep.

EFFECT OF SEIZURES

There is a well-documented effect of nocturnal seizures on sleep. Patients have been studied in terms of their sleep architecture on nights with and without nocturnal seizures, and found to have an increase in WASO, a decrease in REM sleep, and a decrease in sleep efficiency. These effects are found with both focal and generalized seizures (Touchon, 1991). However, in the patients with temporal lobe epilepsy, he found that a significant decrease in REM sleep occurred only in the patients with multiple nocturnal seizures and not if only a single seizure occurred. In the patients with temporal lobe epilepsy, in addition to the effect of nocturnal seizures on REM sleep, a decrease in slow-wave sleep (stages 3 and 4 NREM) has been reported (Sammaritano, 1996; Castro, 1997). In addition, daytime seizures may also have an effect on sleep architecture on nights following seizures. A significant decrease in the percentage of REM sleep as well as a prolongation of the REM latency (time from sleep onset to onset of the first REM period) has been demonstrated in patients with temporal lobe epilepsy (Bazil, 1997). Hoeppner *et al.* (1984) reported sleep complaints in epileptics based on a self-reported sleep questionaire. In their study, they evaluated patients in three groups; simple partial seizures, complex partial seizures, and generalized seizures, and compared this with a fourth group of controls without seizures. They found that the patients with the most frequent seizures irrespective of the type were those who had the most sleep disturbances. In patients with an associated severe diffuse encephalopathy with their seizure disorder, there was a marked disturbance of the EEG background such that the sleep architecture could not be defined by polysomnography (Besset, 1982; Declerck, 1982).

MICROARCHITECTURE OF SLEEP AND EPILEPSY

Terzano *et al.* (1985) introduced a new methodology to study the microarchitecture of NREM sleep. Each stage of NREM sleep is divided into periods of transient fluctuations of arousal referred to as cyclic alternating pattern (CAP).

This CAP is then superimposed on a relatively homogeneous background of EEG activity, lasting for more than 60 s in duration, referred to as non-CAP. The CAP consisted of two phases, CPAP-A, which is characterized by a paroxysm of phasic activity, representing a state of greater arousal, and alternates with a second phase, CAP-B, which consists of a return to the background EEG activity and represents a state of lesser arousal. These two phases alternate during CAP, which then alternates with the NCAP state. The amount of sleep time in CAP was expressed as a percentage of the total sleep time, defined as the CAP rate. This represented the amount of relative arousal defined by the microarchitecture. Studies in relation to both primary generalized epilepsy and focal epilepsy report an increase in the CAP rate compared with normal controls. In addition, epileptiform discharges appear to be activated in the CAP-A phase (Gigli *et al.*, 1992). Focal motor seizures occurring in NREM sleep have been reported to arise predominantly from the CAP-A phase, 41 of 43 seizures in a study by Terzano *et al.* (1991).

EFFECT OF ANTIEPILEPTIC DRUGS ON SLEEP

In terms of the effects of the AEDs on sleep, one may think of their short-term (acute) as well as their long-term (chronic) effects. This discussion will consider only the long-term effects of the AEDs (Table 1.3).

Most of the AEDs result in a normalization of the sleep architecture. The medications result in a shortening of the latency to sleep onset, with a decrease in the number of awakenings or arousals and a decrease in the amount of time awake after sleep onset. There is usually a resultant improvement in the sleep ef-

TABLE 1.3 Long-Term Effects of the Antiepileptic Drugs

	SL	AW/AR	WASO	S1S2	SWS	REM
PHT	↓			↑	↓	NC
PB	↓	↓		↑	NC	↓
CBZ	↓		↓		↑	NC
VPA		↑	↑		↑	↓
CZP	↓	↓	↓	↓1 ↑2	↓	↓
ESM		↑		↑	↓	↑
GBP		↓			↑	↑

PHT, phenytoin; PB, phenobarbital; CBZ, carbamazepine; VPA, valproic acid; CZP, clonazepam; ESM, ethosuximide; GBP, gabapentin.

↓, Decrease; ↑, Increase; NC, no change; SL, sleep latency; AW/AR, awakenings/arousal; WASO, wake time after sleep onset; S1, stage 1; S2, stage 2; SWS, slow-wave sleep.

ficiency (the total sleep time expressed as a percentage of the time spent in bed). In addition, there is a decrease in the shifting of sleep stages, resulting in an improved sleep stability. This improvement occurs together with the control of the seizures and probably occurs as a result of the improved seizure control. However, this also poses the question that the improvement in the sleep architecture may be independent and in fact may play a role in the therapeutic benefit of the AEDs. In regard to the effect on the independent states of NREM and REM sleep, as one can see in the table, some of the AEDs result in an increase, others a decrease, and some may have no effect (Wolf, 1985; Wolf, 1987; Declerck, 1991; Gann, 1994; Placidi, 1997).

USE OF SLEEP AND SLEEP DEPRIVATION IN THE EVALUATION OF EPILEPSY

Sleep is an extremely valuable physiological activating technique that is used in routine EEG. It should be used routinely in the EEG recordings in the evaluation of patients for epilepsy, especially when the IEA is not recorded during the waking state. Sleep was first demonstrated to be important in the activation of epileptiform discharges by Gibbs and Gibbs (1947). In their study, only 19% of 174 patients demonstrated the presence of IEA awake, but 63% demonstrated discharges in the sleep state. In subsequent studies, sleep was found to be necessary to define IEA in 26.7–63.8% of patients in various reports (Silverman, 1956; White *et al.*, 1962; Mattson *et al.*, 1965; Niedermeyer and Rocca, 1972; Dinner *et al.*, 1984). Medication is frequently used to induce sleep in the EEG laboratory.

Chloral hydrate is frequently the medication used, because it has a low potential for side effects. In addition, patients are frequently asked to deprive themselves of sleep and only obtain 3–4 h of sleep on the evening prior to their routine EEG recording. Sleep deprivation acts to promote sleep in the daytime routine EEG recording, but in addition may act as an independent activator for IEA that may be found in the waking EEG recording (Degen and Degen, 1991). In the routine EEG recording, which lasts 20–30 min, there is frequently only a short period of sleep that is recorded. In the routine EEG laboratory, a prolonged daytime EEG recording occupying two routine EEG slots is an extremely useful technique to obtain a good amount of sleep recording in the daytime EEG, which may prove to be extremely beneficial in yielding IEA in a patient with suspected epilepsy.

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2

ELECTROPHYSIOLOGY OF SLEEP

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INTRODUCTION

Understanding basic electrophysiological mechanisms of sleep, as well as the role of the various structures participating in the genesis of sleep activities, is an essential step in investigating the causes and treatment of epilepsy, because

it has been shown that spike–wave (SW) and other forms of seizures occur prevalently during sleep. One may wonder whether epileptic seizures develop from sleep oscillations or are triggered by independent causes and only appear superimposed over sleep activities. The initial observation that incidence of SW seizures increases during sleep in humans (Gibbs and Gibbs, 1947; Kellaway, 1950; Niedermeyer, 1965; Penry *et al.*, 1971), monkeys (Steriade, 1974), and cats (Guberman and Gloor, 1974) suggests that sleep promotes epileptic behavior. To disclose the precipitating sleep factors, we start by presenting the structures playing a role during sleep. Then we summarize the cellular mechanisms underlying the stereotyped sleep patterns.

Data mainly are derived from *in vivo* intraneuronal, intraglial, and field potential [electroencephalogram (EEG)] recordings performed on anesthetized cats. The extrapolation from anesthesia to sleep is based on extracellular and EEG recordings in chronically implanted, naturally sleeping cats and on EEG recordings in humans. The assessment of synchrony (coherence) of oscillatory phenomena relies on multisite recordings, especially on double intracellular recordings.

OSCILLATORY NATURE OF THE ELECTROENCEPHALOGRAM

From the first EEG recordings of Berger (1929), it became obvious that brain electrical activity displays an oscillatory behavior. Ever since, a great deal of research effort has been devoted to revealing the sources of these activities (for reviews, see Elul, 1972; Rappelsberger *et al.*, 1982; Barlow, 1993). The traditional agreement is that neuronal activities are modulated by a series of intrinsic membrane conductances (Llinás, 1988). Further, these intracellularly occurring events generate currents in the extracellular medium that summate algebraically and linearly (see Hubbard *et al.*, 1969) and together with synaptic potentials (Purpura, 1959) contribute, to the genesis of the EEG. Active dendritic responses may also contribute to EEG potentials (see Pedley and Traub, 1990). Although the contribution of glial activities to the shape of slow EEG components has long been suspected (Elul, 1972), it has only recently been demonstrated (see Fig. 6 in Amzica and Steriade, 1998a).

In this chapter, we place emphasis on a clear distinction between oscillations and waves. From the spectral point of view, there is no reliable border between the two, both contributing to the power spectrum. However, from the electrophysiological point of view, waves and oscillations may reflect different phenomena. In its most general form, an oscillation is a variation of a parameter (e.g., current, or voltage) between two extreme values. Some applications introduce the additional requirement of regularity of the variation. However, most biological phenomena resulting from large population interactions, such as the EEG, are rarely associated with clocklike rhythmicity. Because regularity is practically unachievable, its quantification through autocorrelation and/or power spectral functions remains a necessary requirement.

Furthermore, a relative regular oscillation at the cellular level may appear less regular at the EEG level, due to lack of synchronizing synaptic linkages or to competing activities. It is also possible that the dynamic recruitment of neuronal populations by an oscillation can be translated in variations of the amplitude of the recorded field potentials. This brings us to use a very loose definition of oscillations, in which the alternation between two states is essential, while the regularity and the extreme values play a subsidiary role. At the limit of the definition is the wave, as a stereotyped and time-limited variation of a parameter leading to a well-defined shape. Thus, rhythmic waves may build up oscillations.

BRAIN STRUCTURES INVOLVED IN SLEEP OSCILLATIONS

The corticothalamic system is the main structure generating sleep oscillations and is modulated by the brain stem and basal forebrain during various states of vigilance (see Steriade and McCarley, 1990).

A detailed description of the corticothalamic network is beyond the purpose of this chapter. For that, the reader is directed to the monograph by Steriade *et al.* (1997). Briefly, the corticothalamic circuit is made of the cortex, the dorsal thalamic nuclei, and the reticular (RE) nucleus of the thalamus (Fig. 2.1A). Cortical neurons send glutamatergic projections to the thalamus, to both thalamocortical and RE cells. Reticular neurons send γ-aminobutyric acid (GABA) ergic axons to both thalamocortical and local inhibitory elements. In turn, thalamocortical neurons project back to the cortex and to the RE nucleus of the thalamus through glutamatergic axons. The network is therefore made of several intricate loops whose interactions lead to complex balances of the output. For instance, a corticothalamic projection directly excites thalamocortical neurons, but at the same time inhibits them via RE GABAergic axons directly contacting thalamocortical cells and creates a disinhibitory effect through the same RE GABAergic axons contacting local inhibitory elements of the dorsal thalamus. The activity of these loops belonging to the corticothalamic system is modulated, during various behavioral states, by ascending activating structures.

Sleep oscillations are suppressed on arousal due to the influence of ascending cholinergic, glutamatergic, and monoaminergic activating systems. Moruzzi and Magoun (1949) have demonstrated that electrical stimulation of brain stem reticular formation yields to an activated pattern of the EEG. The prevalent origin of arousal systems in the rostral reticular formation was also indicated by earlier transection experiments. Bremer's (1935) *cerveau isolé* (collicular-transected) cats are comatose and characterized by continuous EEG spindling. By contrast, the midpontine pretrigeminal preparation realized by Moruzzi and colleagues (Batini *et al.*, 1958), by means of a transection only a few millimeters behind the collicular cut, displays persistent EEG and ocular signs of alertness. The obvious conclusion was that a small sector at the mesopontine junction, between the

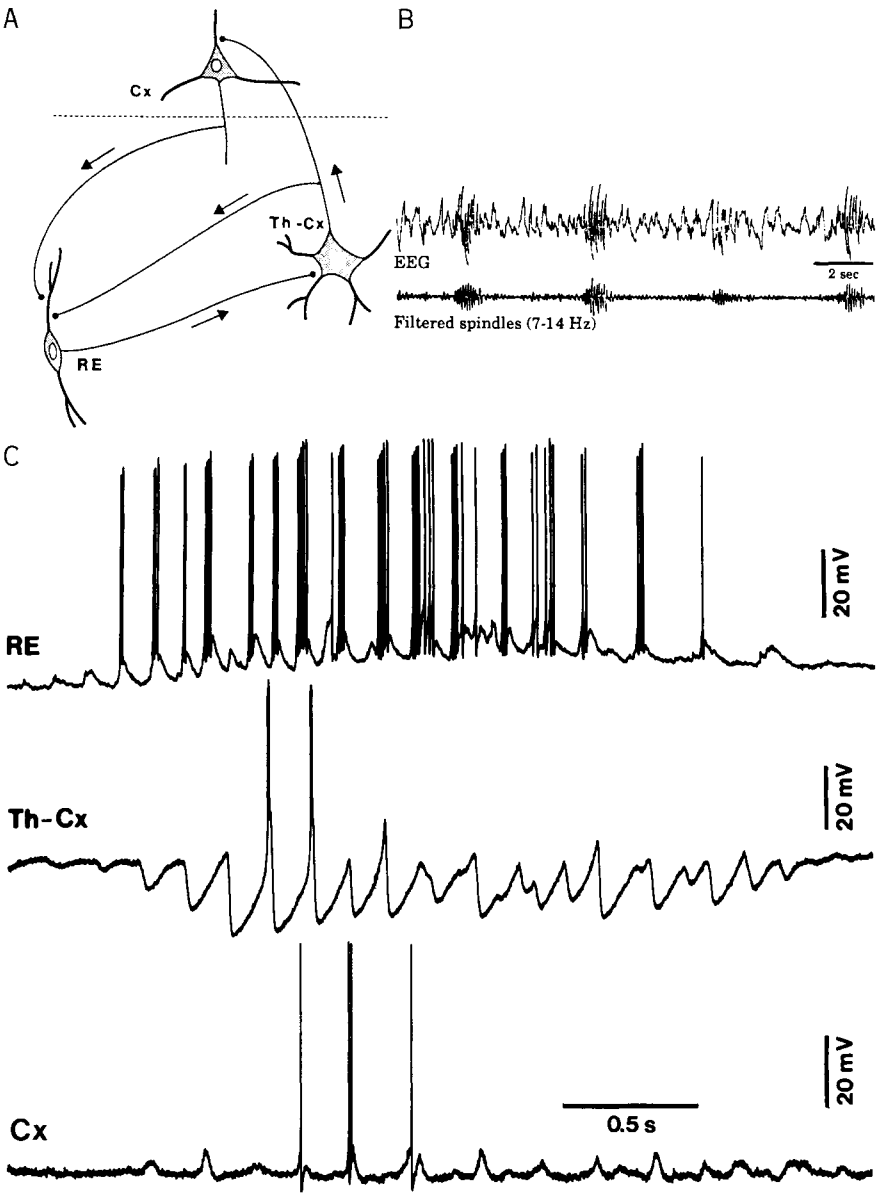

FIGURE 2.1 Thalamic generation of spindles. (A) Circuit between thalamic reticular (RE), thalamocortical (Th-Cx), and neocortical (Cx) cells. (B) Field potentials recorded from the thalamic centrolateral intralaminar nucleus in an unanesthetized cat, with isolated forebrain (*cerveau isolé*). (C) Cellular bases of spindles, intracellular recordings in cats under barbiturate anesthesia; and one spindle sequence, as indicated in the (B) field potential recording. In the RE cell, spindles are superimposed on a slowly growing and decaying depolarization. In the thalamocortical cell, spindles are characterized by rhythmic IPSPs that occasionally de-inactivate low-threshold spike bursts. In the neocortical cell, bursts of thalamocortical cells trigger EPSPs and action potentials within the frequency range of spindles. (Modified from Steriade *et al.*, 1997.)

levels of collicular and midpontine transections, contains the neurons involved in the ascending activation of the thalamus and the cortex. Two groups of cholinergic [pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT)] nuclei have been identified by using choline acetyltransferase (ChAT) immunohistochemistry. The projections to the thalamus of brain stem cholinergic cells were demonstrated by combining the retrograde HRP transport with ChAT labeling (see reviews by Wainer and Mesulam, 1990; Steriade and McCarley, 1990). In addition to cholinergic nuclei, the same restricted brain stem territory at the mesopontine junction contains the norepinephrine (NE)-containing cells of the locus coeruleus and the serotonin [5-hydroxytryptamine (5-HT)]-containing cells of the dorsal raphe nucleus. These monoaminergic aggregates have much less dense thalamic projections, but their axons directly innervate the cerebral cortex (for review, see Saper, 1987).

The brain stem cholinergic action provokes fast (20–40 Hz) rhythms on the cortical EEG (Steriade *et al.*, 1991b). The brain stem cholinergic actions abolish thalamically generated spindles (Hu *et al.*, 1989) and delta oscillations (Steriade *et al.*, 1991a). Cortical neurons are depolarized due to the glutamate release, mainly by thalamocortical fibers, but also by corticocortical axons once the activation started; and/or to the reduction of K^+ conductances by acetylcholine, NE, and other neuromodulators (see Nicoll *et al.*, 1990; McCormick, 1992).

At the opposite pole, reduced activity of brain stem neurons creates the necessary condition for sleep onset. Indeed, neurons in the midbrain reticular formation and mesopontine cholinergic nuclei diminish their firing rate before the onset of sleep (Steriade *et al.*, 1982), therefore removing the excitatory drive from thalamocortical and cortical elements and allowing the membrane potential (V_m) to reach more hyperpolarized levels. As the V_m of thalamocortical cells is hyperpolarized, synaptic responsiveness diminishes and the transfer of sensory information is interrupted.

SLEEP OSCILLATIONS

The three types of oscillations (spindles, delta, and slow) described in the following sections have distinct generating mechanisms; this is the reason that they are described in sequence. A subsequent section describes their coalescence in an intact brain.

SPINDLES

Sleep spindles are made of the association of two distinct rhythms: (1) waxing and waning waves at 7–14 Hz within sequences lasting for 1–2 s; and (2) periodic recurrence of spindle sequences with a slow rhythmicity of about 0.2–0.5 Hz (Fig. 2.1B). These rhythms accompany sleep onset (mostly stage 2),

although their presence in deeper sleep stages 3 and 4 has been well documented (Niedermeyer, 1999).

Spindles are generated within the thalamus, but their shape and synchronization are influenced by the cerebral cortex. Morison and Bassett (1945) were the first to demonstrate that spindles survive in the thalamus of cats after total decortication and high brain stem transections. Most of the more recent knowledge about the electrophysiology of sleep spindles is derived from *in vivo* experiments on cat and *in vitro* experiments on ferret slices. These studies show the high resemblance between the shape and the incidence of spindles in humans and in previously mentioned species. *In vivo* studies have pointed to the RE nucleus of the thalamus as the pacemaker of spindle oscillations (Steriade *et al.*, 1985, 1987). The term *pacemaker* implies three conditions: the induction of a given phenomenon in a target structure by triggering the pacemaker, the absence of the phenomenon after lesion of the pacemaker, and the presence of the phenomenon in the isolated pacemaker. This is indeed what has been observed for spindles: they disappear from the dorsal thalamus after its disconnection from the RE nucleus (Steriade *et al.*, 1985) and are preserved in the isolated rostral sector of the RE complex deafferented from thalamic inputs (Steriade *et al.*, 1987).

Further demonstrations came from studies in which recordings were performed in thalamic structures devoid of RE inputs. In cat, anterior thalamic nuclei and the lateral habenular complex do not receive inputs from RE neurons (Steriade *et al.*, 1984; Velayos *et al.*, 1989). As a consequence, spindles are absent from the anterior thalamic nuclei (Paré *et al.*, 1987) and from the habenular neurons (Wilcox *et al.*, 1988). Computational studies modeling RE networks (Wang and Rinzel, 1993; Destexhe *et al.*, 1994; Golomb *et al.*, 1994) further supported the hypothesis that spindles are generated in clusters of RE neurons.

Based on their GABA-ergic nature, it was conventionally thought that RE neurons belong to a homogeneous type. Anatomical studies, however, have revealed two classes of neurons: one with and another without axonal collaterals within the RE nucleus (Spreafico *et al.*, 1988, 1991). Electrophysiological data also indicate different types of RE neurons (Llinás and Geijo-Barrientos, 1988; Contreras *et al.*, 1992; Brunton and Charpak, 1997). These features, together with the relative division of the RE into sensory sectors (see Steriade *et al.*, 1997), influence the more or less synchronous emergence of spindles at the cortical level.

Spindles are synchronized at the very site of their genesis, the RE nucleus. This phenomenon relies on the intrareticular connection of neurons through axonal projections, and also through GABA-releasing dendrodendritic contacts (Deschênes *et al.*, 1985; Yen *et al.*, 1985). However, because the RE nucleus does not project to the cortex, the cortical expression of a spindle sequence must rely on intermediate relay stations in the dorsal thalamus. Thalamocortical cells respond to each burst of spikes from the RE with an inhibitory postsynaptic potential (IPSP) and a rebound low-threshold calcium spike, occasionally crowned by a burst of action

potentials (Fig. 2.1C; see also Bal and McCormick, 1996; Timofeev *et al.*, 1996). In an intact brain, these bursts of action potentials are transferred to the cortex, but are also fed back to the RE nucleus, where they contribute to the reinforcing of the spindle waves (Mulle *et al.*, 1986; Shosaku *et al.*, 1989; Buzsáki, 1991; von Krosigk *et al.*, 1993; Contreras and Steriade, 1995). In fact, the waxing of the envelope at the onset of the spindle is due to the progressive entraining of thalamocortical neurons in the oscillating process. The maximum amplitude of the spindle envelope corresponds to the synchronous activity of the largest recruited neural population. The waning phase of a spindle is associated with progressive desynchronization of neurons due to the intervention of network operations and cellular intrinsic properties capable of diminishing the probability of cells to fire spike bursts. The point should be stressed that in the absence of cross talk between dorsal thalamic nuclei (Jones, 1985) and although dorsal thalamic–reticular loops may assist in starting and developing spindles, the synchronization of the whole thalamus during spindling is possible only by invoking widespread projections of the RE neurons to the dorsal thalamus and corticothalamic projections.

DELTA OSCILLATIONS

Walter (1936) assigned the term delta waves to particular types of slow waves recorded in the EEG of humans and used this term to describe pathological potentials due to cerebral tumors. The initial Greek term was associated with frequency bands instead of phenomena generating specific electrographic patterns. The IFSECN (1974) states that delta waves are waves with a duration of more than $\frac{1}{4}$ s. This implies that the frequency band for delta waves is between 0 and 4 Hz. However, ranges such as 0.1–3.5 Hz (Niedermeyer, 1999), 0.5–4 Hz (Kellaway *et al.*, 1966), 0.5–5 Hz (Gibbs and Gibbs, 1951), and 1–4 Hz (Ursin, 1968) are often found in the literature. Moreover, using only spectral limitations for the definition of delta waves may lead to some confusion and to definite dismissal of underlying physiological mechanisms. Therefore, in the case of delta activities, the distinction between waves and oscillations (see earlier) is critical.

There have been various studies aiming at disclosing the relation between cellular activities and EEG (Creutzfeldt *et al.*, 1966) and the sources of delta activities (Kellaway *et al.*, 1966; Rappelsberger *et al.*, 1982). We believe that the 0–4-Hz range reflects more than one phenomenon and that definitions based exclusively on frequency bands may conceal the underlying mechanisms.

Earlier results in which delta oscillations survived in isolated cortex (Frost *et al.*, 1966; Kellaway *et al.*, 1966) or in athalamic cats (Villablanca and Salinas-Zeballos, 1972; Villablanca, 1974) pointed toward a cortical origin of these activities. Moreover, Ball *et al.* (1977) showed that delta waves arise between cortical layers 2 to 3 and 5, and that cortical neurons showed a high probability of discharge during the positive phase of the surface waves.

A major breakthrough was caused by the discovery that thalamocortical neurons are also able to generate a clocklike, intrinsic oscillation in the same delta

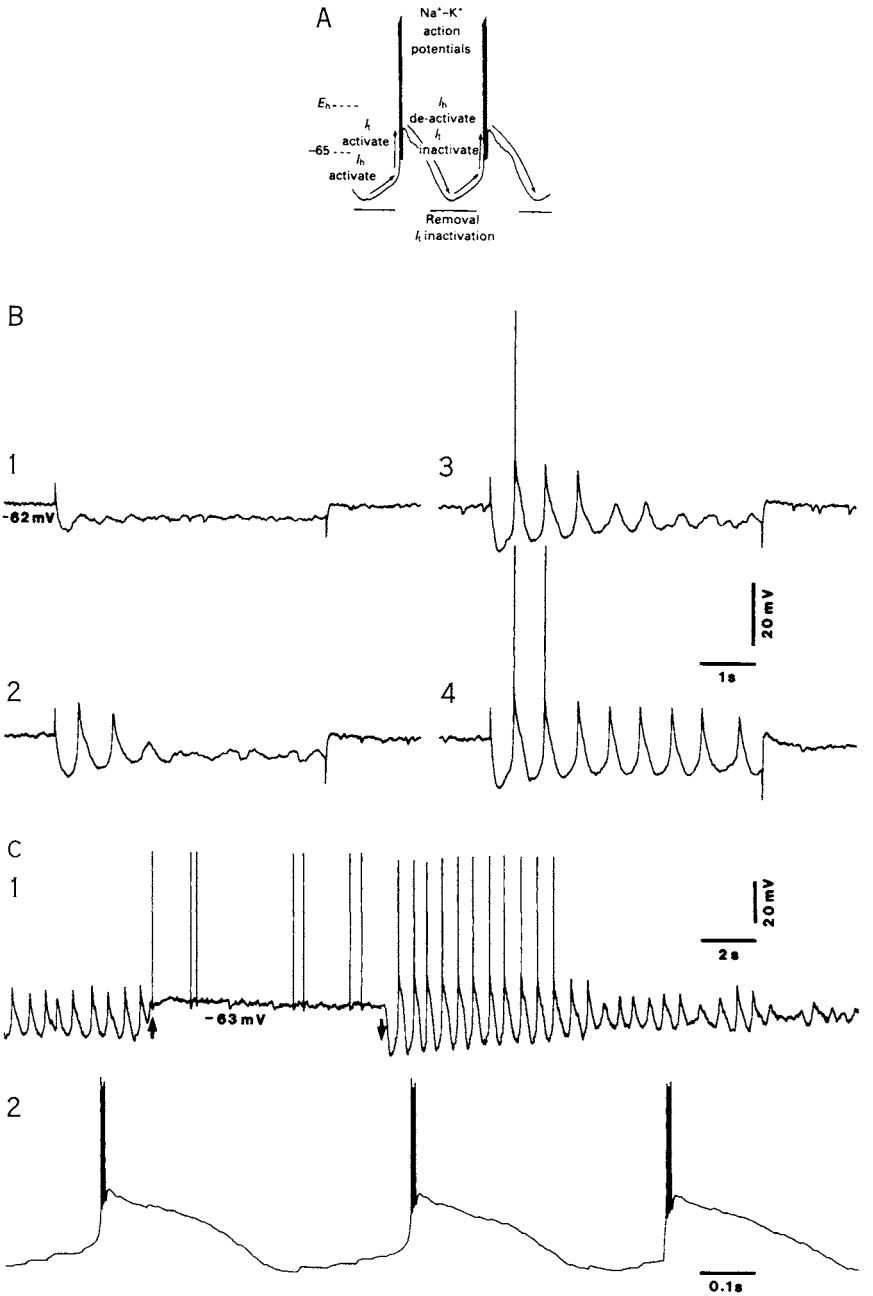

FIGURE 2.2 Delta oscillations in thalamocortical cells result from the interplay between two intrinsic currents, I_h and I_t. (A) Proposed model for interaction between these intrinsic currents. Activation of the low-threshold calcium current (I_t) depolarizes the membrane toward threshold for a burst of sodium- and potassium-dependent, fast-action potentials. The depolarization inactivates the

range. This oscillation was initially described *in vitro* in lateral geniculate (LG) neurons of rodents (McCormick and Pape, 1990; Leresche *et al.*, 1991), and *in vivo* in motor, sensory, association, and intralaminar thalamic nuclei of cats (Steriade *et al.*, 1991b; Curró Dossi *et al.*, 1992). This oscillation is generated as the result of an interplay between two currents of thalamocortical cells: the low-threshold transient Ca^{2+} current (I_t) and the hyperpolarization-activated cation current (I_h) (Fig. 2.2A) (McCormick and Pape, 1990; Soltesz *et al.*, 1991).

Regardless of the functional system they belong to, thalamocortical neurons appear to share similar basic electrophysiological properties (Deschênes *et al.*, 1984; Jahnsen and Llinás, 1984a, 1984b; Roy *et al.*, 1984; Paré *et al.*, 1987). They characteristically fire tonically at relatively depolarized membrane potentials, while stereotyped high-frequency bursts of action potentials may be induced by brisk depolarizing steps from more hyperpolarized levels. This bimodal pattern of activity underlies the differences that exist between the discharge pattern of thalamic neurons in wake or rapid eye movement (REM) sleep and resting sleep states. Also, it is responsible for the functional gating effect exerted at the thalamic level on the afferent information flow as a function of the state of vigilance.

This clocklike delta oscillation of thalamocortical neurons is mainly intrinsic because it appears in neurons disconnected from extrinsic connections and its development does not depend on the particular location of a cell in the surrounding network. The oscillation lasts as long as the membrane potential is kept in the range where the two currents may act and interact optimally (i.e., between −68 and −90 mV, Curró Dossi *et al.*, 1992). This voltage range may be achieved artificially by intracellular current injection (Fig. 2.2B) or by deafferentation (e.g., decortication, Fig. 2.2C), or naturally, during sleep with the withdrawal of excitatory inputs arising in brain stem activating cholinergic and monoaminergic nuclei (see Steriade and McCarley, 1990). Therefore, the presence of the mentioned intrinsic properties constitutes a necessary, still not sufficient, condition for development of oscillations. The hyperpolarization of neurons, as another necessary factor (a network-dependent one), must occur to allow clocklike delta oscillations.

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portion of I_h that was active immediately before the calcium spike. Repolarization of the membrane due to I_t inactivation is followed by a hyperpolarizing overshoot, due to the reduced depolarizing effect of I_h. The hyperpolarization in turn de-inactivates I_t and activates I_h, which depolarizes the membrane toward threshold for another calcium spike. (B) Delta oscillation of cat ventrolateral thalamocortical cell triggered by hyperpolarizing current pulses (0.7 nA in *1*, 1 nA in *2*, 1.1 nA in *3*, and 1.2 nA in *4*). Note increasing number of cycles at a frequency of 1.6 Hz. (C) Lateroposterior (LP) thalamocortical cell after decortication of areas projecting to LP nucleus. The cell oscillated spontaneously at 1.7 Hz. A 0.5-nA depolarizing current (*between arrows*) prevented the oscillation, and its removal set the cell back in the oscillatory mode. Three cycles after removal of depolarizing current in 1 are expanded in *2* to show high-frequency bursts crowning the low-threshold calcium spike. [(A) modified from McCormick and Pape, 1990; (B) and (C) modified from Steriade *et al.*, 1991b.]

It is also known that intrinsic delta oscillations are incompatible with spindle oscillations in single thalamocortical neurons (Nuñez *et al.*, 1992). It is suggested that the disruption of the former oscillation is due to an increase in membrane conductance by opening Cl^- channels through $GABA_A$ receptors during the occurrence of the latter.

The disclosure of the mechanisms responsible for the thalamic clocklike delta oscillation raised several questions about its significance and contribution to the homogeneous EEG delta rhythm observed during sleep. The issue is particularly critical because this oscillation, generated at the cellular level, must benefit from a synchronizing mechanism to become a population phenomenon and thereafter to be transferred from its very origin, the thalamus, toward the cerebral cortex. The synchronizing device should meet two requirements: (1) to be able to reset several independent oscillators and (2) to provide a mechanism that should prevent periodically the dampening of the oscillation.

The first synchronizing tool that comes to mind is a net of reciprocal synaptic linkages between thalamocortical neurons. It is, however, generally accepted that the presence of recurrent collaterals in dorsal thalamic nuclei is rather the exception than the rule, hence preventing any direct cross talk between dorsal thalamic elements (Jones, 1985). Another synchronizing structure could be the RE nucleus. To elucidate the role of RE neurons in the synchronization of thalamic delta oscillations, we addressed two questions: (1) Do RE neurons themselves generate an oscillation in the delta range? If they do, taking into account their projection to thalamic nuclei, which in turn project toward the cortex, they would be in a strategic position to send synchronized delta oscillations toward the cortex. (2) If they do not, are they able to integrate the delta oscillation sent from more or less isolated thalamocortical elements and to convey it back in a synchronized manner? The results from the visual sector of the RE (the perigeniculate) nucleus suggest that two types of delta rhythmicity exist, that they result from intrinsic and network properties of visual thalamic neurons, and that perigeniculate cells may synchronize—through backward connections—the activity of dorsal lateral geniculate cells during deep stages of resting sleep (Amzica *et al.*, 1992).

At this point, the role of the cortex in the reception and synchronization of the thalamically generated clocklike delta remains to be clarified. It is known that cortical and thalamic relay neurons are reciprocally linked through excitatory synapses (Gilbert and Kelly, 1975; Wise and Jones, 1977) that render their communication quite rapid. In addition, the cortex was known to generate waves within delta rhythmicity even without the assistance of the thalamus (see earlier). This led us to investigate the oscillatory behavior of cortical neurons.

SLOW CORTICAL OSCILLATIONS AND DELTA WAVES

The pivotal rhythmic event of sleep is played by a slow oscillation with a frequency of less than 1 Hz (mainly 0.5–0.9 Hz) generated within the cortical

network (Steriade *et al.*, 1993c,d). At the neuronal level, this oscillation is made of an alternating pattern during which the membrane potential fluctuates between a depolarized and a hyperpolarized level (Fig. 2.3). Each of these two phases of the slow oscillation lasts for about 0.5–0.6 s. The depolarizing phase is made of synaptic potentials (excitatory and inhibitory), thus revealing a period with enhanced activity of the network (Steriade *et al.*, 1993c,d). In contrast, the hyperpolarized phase of the slow oscillation is mainly due to network disfacilitation (Contreras *et al.*, 1996). Multisite recordings of the slow activity have assessed its synchronous behavior at the scale of the whole corticothalamic network (Amzica and Steriade, 1995a; Contreras and Steriade, 1995) and have emphasized the role of intracortical synaptic linkages in the synchronization and spread of the slow oscillation (Amzica and Steriade, 1995b). The slow oscillation is disrupted by the activation of cholinergic and adrenergic systems (Steriade *et al.*, 1993a).

The slow oscillation has been recorded in cats under various anesthetics such as urethane, a mixture of ketamine and xylazine, and nitrous oxide; in unanesthetized cats with high brain stem transections (cerveau isolé) (Steriade *et al.*, 1993c,d, 1994; Amzica and Steriade, 1995a); in humans anesthetized with halothane (Christopher Sheib, personal communication); and, importantly, in naturally sleeping cats (Steriade *et al.*, 1996; Amzica and Steriade, 1998b) and humans (Steriade *et al.*, 1993c; Achermann and Borbély, 1997; Amzica and Steriade, 1997). Explicit comparisons between anesthesia and natural sleep on the one hand (Steriade *et al.*, 1996; Amzica and Steriade, 1998b) and between cats and humans on the other hand (Amzica and Steriade, 1997) were made.

Double neuron–glia impalements show that the slow oscillation is equally expressed in glia (Amzica and Steriade, 1998a). The neuronal depolarizing phase is associated with a more sluggish glial depolarization, while the hyperpolarized segment corresponds to a slow repolarization of the glial membrane (Fig. 2.4). The shape of these intraglial potentials is supposed to reflect the uptake of extracellular potassium. The precise timing of these components suggests that the neuron–glia dialogue may control the pacing of the slow oscillation and that its dysfunction may entrain pathological behavior (see later).

Another consequence of the coherent nature of the slow oscillation is its reflection in the EEG. The depolarizing segment corresponds to a depth-negative wave (reversed at the cortical surface), while the subsequent hyperpolarization is associated with a domelike depth-positive potential (negative at the surface). Given the shape of these field potentials, it has been proposed that each cycle of the slow oscillation represents a K-complex (KC) (Amzica and Steriade, 1997, 1998b). This finding elucidated, 60 years after its description (Loomis *et al.*, 1937), the cellular bases of the KC, placed its site of genesis at the level of the cortex, and disclosed the rhythmic nature of KCs during sleep. Often, and depending on the depth of sleep, a KC may be followed by a spindle (Niedermeyer, 1999). This association is explained by the fact that KCs are transferred to the RE nucleus, where they may trigger a spindle (see later).

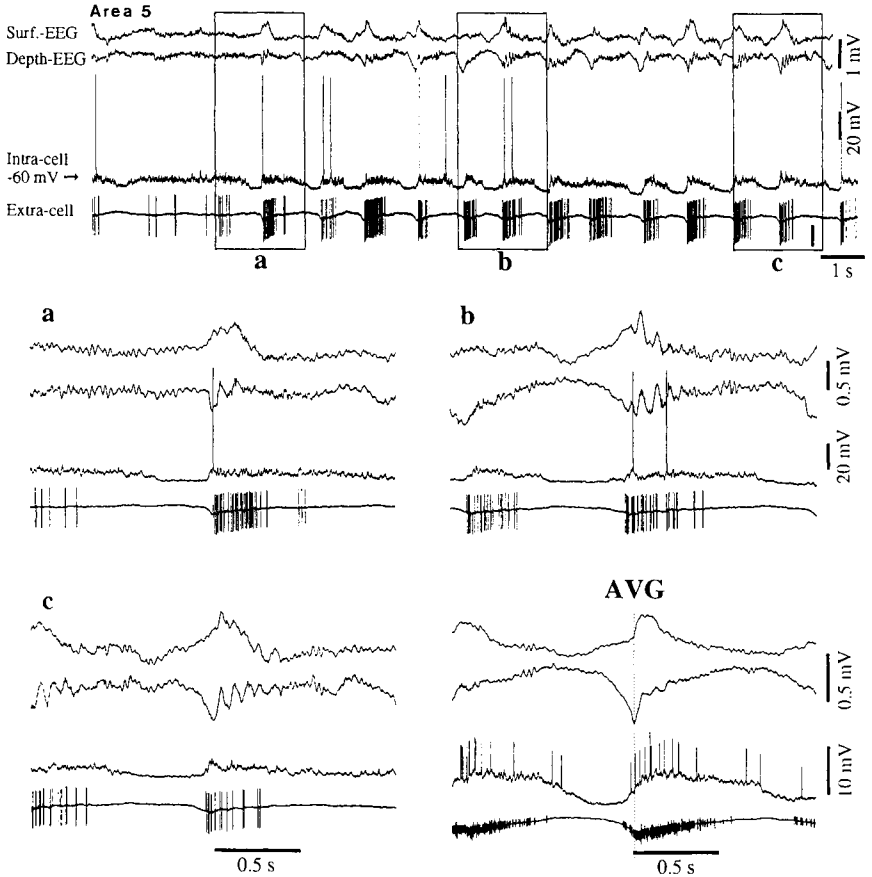

FIGURE 2.3 Rhythmic K-complexes (KCs; around 0.9 Hz) under ketamine and xylazine anesthesia; recordings from association suprasylvian cortex (area 5). The depicted period contains a short epoch of activated EEG (*left*) followed by the recovery of the slow oscillation. The intra- and the extracellular activities are accompanied by the EEG recordings in the surface and in the depth of the cortex. The KCs display a potential reversal between the surface and the depth. The rhythmic negative peaks in the depth reflect cellular excitation (see depolarization of the membrane potential in the intracellular recording and tonic firing in the extracellular recording) and are followed by spindles and/or by fast activities in the 40-Hz range. These negative peaks are preceded by a slow, depth-positive wave associated with neuronal silence. The evolution from the activated epoch (*left*) to the deep anesthesia is paralleled by a progressive propensity of the KCs to drive spindles. The first KC (detail a) elicits an abortive spindle with only two cycles. As anesthesia recovers deeper states, spindles are better developed (details b and c), as one would expect from a process achieved under higher synchrony. The average of 25 KCs centered on the depth-negative peak (AVG) further emphasizes the potential reversal of the KC occurring between the cortical surface and depth, and the relation between cellular activities and field potentials. (Modified from Amzica and Steriade, 1998b.)

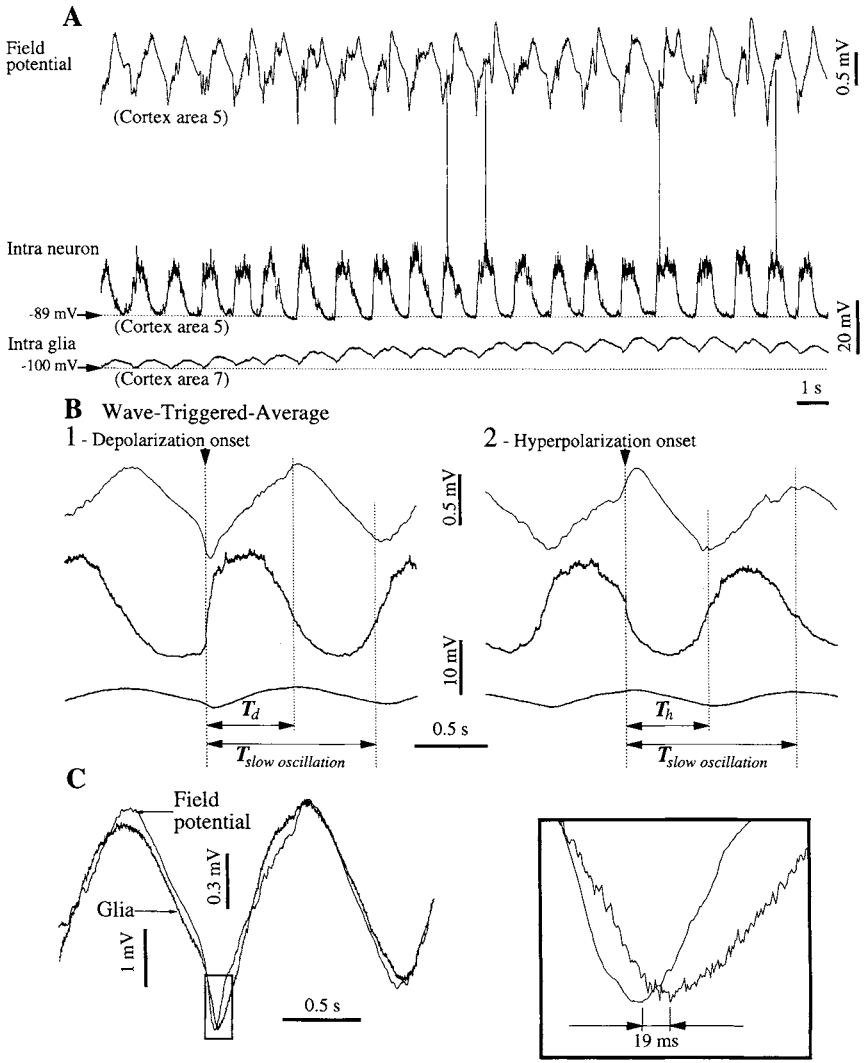

FIGURE 2.4 Dual neuron–glia intracellular recording. (A) Spontaneous slow oscillation. The depth field potential (positivity up) is recorded close to the neuron. (B) Averaged activities (n = 20) at the onset of depolarizing (1) and hyperpolarizing (2) segments. The wave-triggered averages for panel 1 were calculated as follows: for each cycle of the slow oscillation in the neuron, the steepest rising slope at the onset of the depolarizing phase was detected, and equal windows around that point (1 s before and 1.5 s after) were extracted from all channels. All windows belonging to a given channel were finally averaged. Panel 2 was generated in a similar way, but the detection criterion was the steepest negative slope at the offset of the depolarizing phase in the neuron. Note close time relations between EEG, neuron, and glia as well as the voltage relations between neuron and glia. (C) Glia-field potential resemblance. Averaged traces from (B1) were superimposed and artificially amplified to overlap. The area in the square is expanded at right. In spite of the resemblance, there are also differences in the time domain pleading for propagating mechanisms. (Modified from Amzica and Steriade, 1998a.)

Moreover, it was proposed that the KC belongs, through its shape, to the delta waves and contributes to the power spectrum of delta frequency bands (Amzica and Steriade, 1997). Thus, the shape of the KC contains delta waves, whereas its periodic recurrence emerges from the slow (<1 Hz) oscillation.

In addition to the spontaneous KCs, some KCs may be elicited by stimulating sensory pathways. This does not mean, however, that all spontaneous KCs are in fact triggered by sensory stimuli. The state of sleep develops in rather sensory-free environments and it would be hard to believe that this would generate rhythmic stimuli to account for the slow oscillation of the KCs. Therefore, the evoked KCs are the exception rather than the rule. *The wide majority of KCs that permeate our sleep stem from the slow (<1 Hz) cortical oscillation.*

The KC has been repeatedly considered an arousing reaction during sleep (e.g., see Niiyama *et al.*, 1996; Halasz, 1998). It was indeed shown that the depolarizing phase of the slow oscillation, underlying the peaky wave of the KC, displays fast activities (20–50 Hz) similar to those present during activated states (Steriade *et al.*, 1996). In our opinion, however, this is not enough to make the KC an arousing reaction, because the KC is part of the slow cortical oscillation generated only during slow wave sleep (Steriade *et al.*, 1993c; Amzica and Steriade, 1997, 1998a,b) and because the slow oscillation—KCs included—is abolished by the action of cholinergic- and adrenergic-activating systems (Steriade *et al.*, 1993a). In addition, one must bear in mind that during resting sleep the thalamus achieves the functional disconnection of the cerebral cortex from the sensory environment (Steriade *et al.*, 1997), thus preventing ascending stimuli to exert or trigger efficient arousing responses. A further objection to interpreting the KC as an arousing reaction is related to the fact that KCs, as precursors of ictal spikes during SW seizures (Steriade *et al.*, 1998), become rather associated with an impaired state of consciousness.

INTERACTIONS BETWEEN SLEEP OSCILLATIONS IN INTACT BRAINS

The complex electrographic pattern of slow wave sleep results from the coalescence of the slow oscillation, the cortical delta waves, and the thalamically generated clocklike delta oscillation and spindles. The weight of each of these major components is dynamically modulated during sleep by synaptic coupling, local circuit configurations, and general behavioral state of the network.

The slow oscillation is transmitted to other subcortical structures, mainly to the thalamus, where it triggers locally generated sleep oscillations such as spindles and intrinsic clocklike delta oscillations (Fig. 2.5). The synchronous and periodic input exerted by the slow cortical oscillation on the thalamus favors the synchronization of spindles and intrinsic clocklike delta oscillations at the thalamic level and their emergence in the cortex. Thus, the dynamic structure of sleep

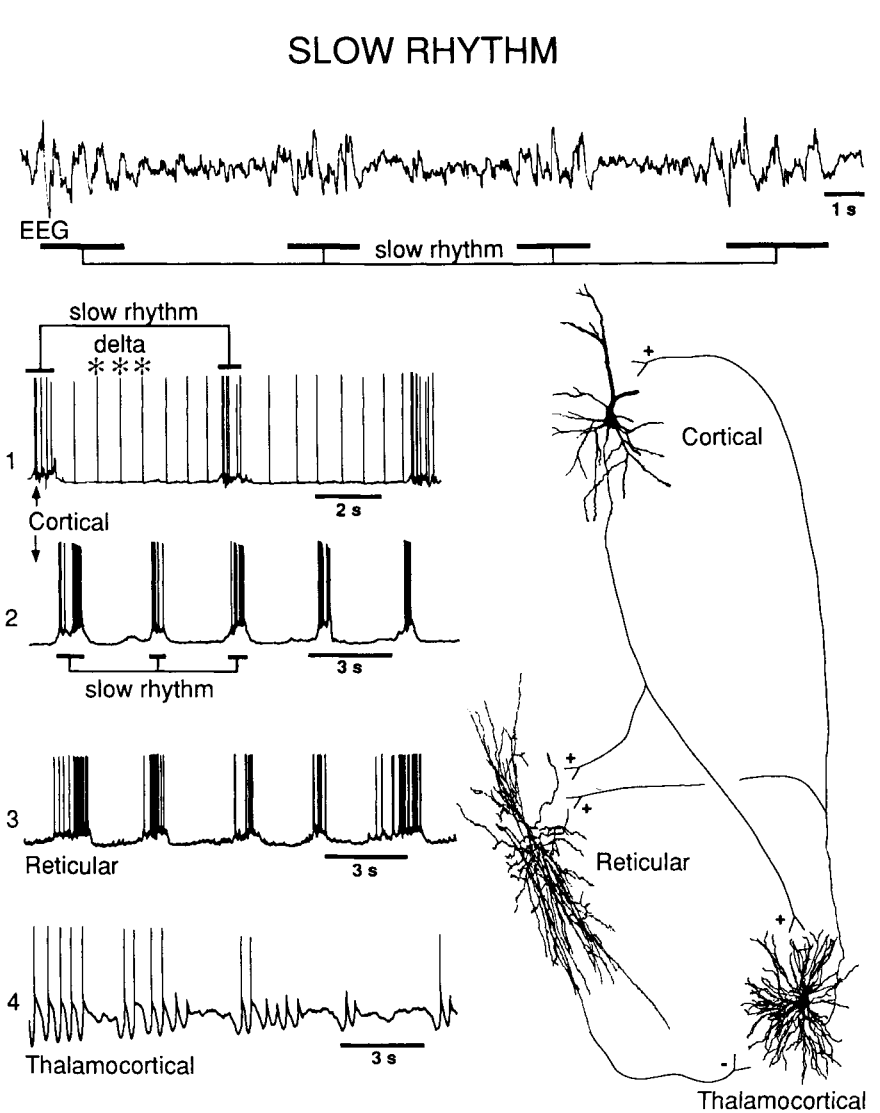

FIGURE 2.5 The slow cortical oscillation and its reflection in thalamic neurons; intracellular recordings of four neurons in anesthetized cats. *From top to bottom*: two pyramidal cortical cells (1 and 2), one thalamic RE cell (3) and one thalamocortical cell (4). Intracellularly stained cortical and thalamic neurons are illustrated at right. Neuron 1 from cortical association area 5 displayed the slow rhythm (≈ 0.2 Hz); between the slow depolarizing events, clocklike action potentials (*asterisks*) recurred at the delta (1.6 Hz) frequency, arising probably in thalamocortical cells. Cortical cell 2 exhibited the slow rhythm at 0.3 Hz. Thalamic RE neuron 3 oscillated at 0.3 Hz, the same frequency as slowly oscillating cortical cells. Thalamocortical cell 4, from the ventrolateral nucleus, oscillated within the delta frequency (2.5 Hz); the oscillation tended to dampen and was periodically revived, within the frequency range of the slow rhythm (0.2–0.3 Hz). (Modified from Steriade *et al.*, 1993b,c,d.)

EEG may derive from the following sequence of interactions within the corticothalamic network.

At sleep onset, neurons in the midbrain reticular formation and mesopontine cholinergic nuclei diminish their firing rate (Steriade *et al.*, 1982, 1990), therefore removing a steady excitatory drive from cortical and thalamocortical elements and allowing the membrane potential to reach more hyperpolarized levels. As thalamocortical cells hyperpolarize, synaptic responsiveness diminishes and the transfer of sensory information is interrupted. There is a first voltage range (between −60 and −65 mV), probably corresponding to drowsiness, where incoming excitatory postsynaptic potentials (EPSPs) may not reach the firing threshold and thus the sensory flow is blocked. During this stage, the EEG displays decreased amplitude, and no sleep oscillations are present. This stage probably provides the necessary mental rest that allows further progression toward sleep. It also keeps the possibility for preserved awareness if powerful sensory messages (materialized by summated EPSPs) pass through to the cortex.

Toward the end of drowsiness, vertex potentials (biparietal humps; see Gibbs and Gibbs, 1951) are noticed in the EEG. They very much resemble the KCs; as previously suggested (IFSECN, 1974), vertex potentials could be incipient KCs, and thus part of the same general pattern as the slow oscillation, with the proviso that at this stage the slow oscillation is not yet fully developed.

Further hyperpolarization of the thalamocortical cells (V_m more negative than −65 mV) is detrimental to sensory flow due to the de-inactivation of low-threshold Ca^{2+} spikes. They generate high-frequency burst discharges that do not reflect the temporal code of incoming impulses and have a refractory period of about 170 ms (Deschênes *et al.*, 1984; Jahnsen and Llinás, 1984a). At the same time, thalamic RE cells become hyperpolarized too, de-inactivation of low-threshold Ca^{2+} spikes is achieved, and hence spindle sequences appear in the RE nucleus—followed by interactions with thalamocortical cells.

At the same time, cortical neurons begin to be deprived of the usual sensory bombardment and of the activating action of generalized neuromodulatory systems. The cortex acts as a partially deafferented structure. The slow cortical oscillation (<1 Hz) begins to organize in small territories, thereafter recruiting larger ones through coupling mechanisms. This statement is indirectly supported by the moderate levels of correlation of EEG waves during early stages of sleep and by its increase as sleep progresses. The EEG shows mainly sporadic KCs followed by spindles (Niedermeyer, 1999). As sleep deepens, the slow cortical oscillation becomes more synchronized over larger surfaces, and thalamocortical cells are more hyperpolarized, but still in the bursting mode. The incidence of thalamically generated spindles increases and more of them may be triggered by the onset of the depolarizing phase of the slow cortical oscillation (Contreras and Steriade, 1995). The EEG therefore reflects a higher incidence of slow waves mixed with spindles.

As the brain continues to plunge into sleep, the deafferentation of the cortex from the sensory world becomes complete and the intracortical connections fulfill their synchronizing task with more efficiency. The slow oscillation is now fully

developed at the cortical level and is reflected in the thalamic RE and relay nuclei (Steriade *et al.*, 1993b). This state probably corresponds to stage 3 of human sleep. Thalamocortical neurons reach, through further hyperpolarization, the voltage range in which the interplay between I_h and I_t currents may take place generating the intrinsic delta oscillation (McCormick and Pape, 1990; Leresche *et al.*, 1991; Steriade *et al.*, 1991b; Curró Dossi *et al.*, 1992). In deafferented thalamic preparations, the clocklike thalamic delta may persist for long periods of time, but in intact brains, it undergoes the modulatory influence of the slow cortical oscillation (see Fig. 2.5). In this case, the sequence of low-threshold spikes recurring at delta frequencies in relay cells starts with the rebound following an inhibition (latency of ≈300 ms) induced by the RE nucleus (see Fig. 6 in Amzica and Steriade, 1995b). Due to the lack of intranuclear collaterals, there is little chance for intrinsic delta oscillations generated in individual relay neurons to synchronize and to be returned as such to the cortex. At best, the first rebound burst may accidentally occur at similar latencies in independent neurons and, being conveyed to the cortex, would produce a depth-negative indentation following the higher negative peak associated to the depolarizing onset of a slow cycle in cortical neurons. The consecutive delta cycles in thalamocortical neurons should be affected by increased jittering due to individual differences and should not be reflected as synchronized waves at the cortical level. The EEG pattern of this period is dominated by high-amplitude slow waves in the frequency range of the slow oscillation (<1 Hz), superimposed by spindles or few recurrent delta waves.

As sleep attains its deepest electrophysiological expression (stage 4), relay cells are so hyperpolarized that direct corticothalamic volley can trigger a delta sequence, hence in a more synchronized manner. Curró Dossi *et al.* (1992) suggested that delta oscillations of higher frequency and reduced temporal jitter are obtained at more negative membrane potentials (see Fig. 3 in that article). Under these circumstances, more synchronized delta cycles from the thalamus may reach the cortex and be reflected in the EEG. Its polymorphic aspect and its possible overlapping with the following cycle of the slow oscillation would make it difficult to separate the components of the slow cortical oscillation from those of the thalamic delta. We submit that this is the pattern of polymorphic delta waves representative of slow wave sleep. Therefore, the growing complexity of corticothalamic activities requires a more specific language (slow oscillation, thalamic clocklike delta, or cortical delta) taking into account the distinct underlying mechanisms. The interpretation of various EEG activities should be based on local field potentials and on their shape in addition to their spectral content.

HOW DO SLEEP OSCILLATIONS DEVELOP INTO SPIKE–WAVE SEIZURES?

The predominant incidence of spike–wave (SW) seizures during resting sleep has been reported in children with absence epilepsy (Sato *et al.*, 1973) and in the Lennox-Gastaut syndrome (Velasco *et al.*, 1995). The site of genesis of SW

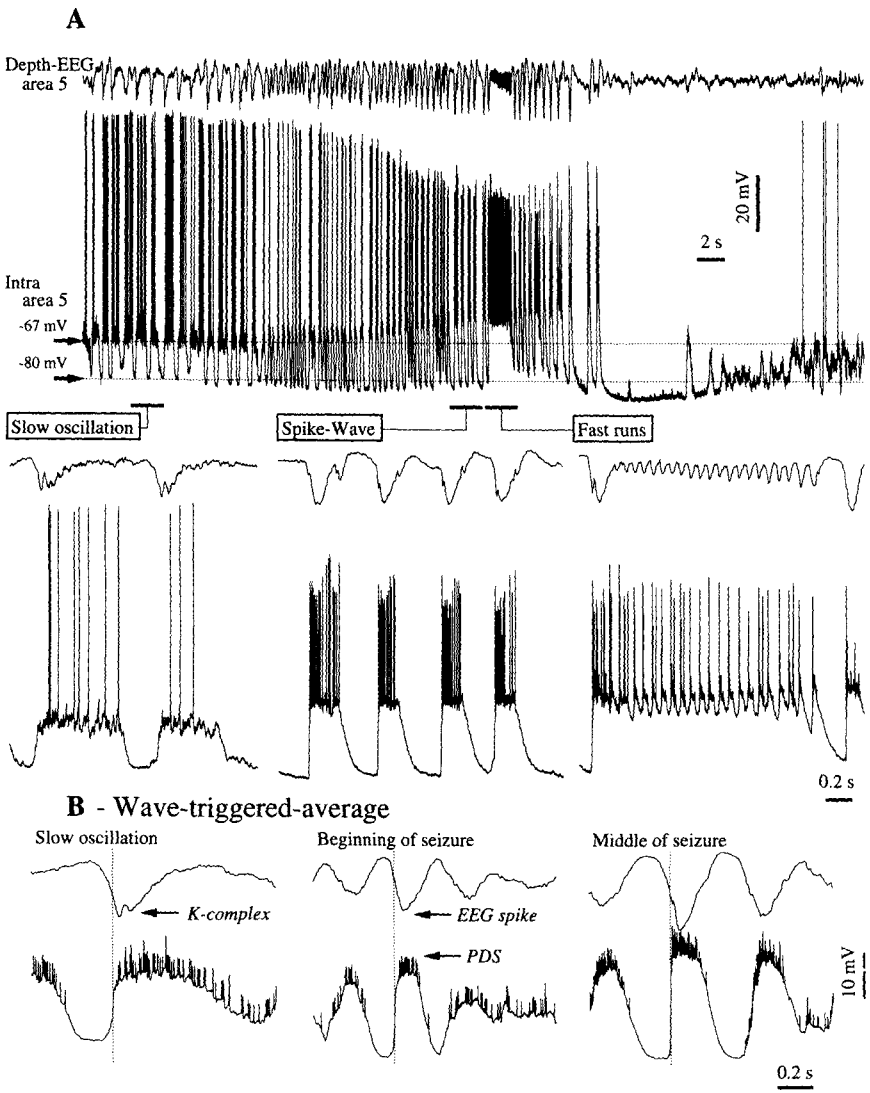

FIGURE 2.6 Spontaneously occurring seizure, developing without discontinuity from slow sleeplike oscillation; intracellular recording from regular-spiking area 5 neuron together with depth–EEG from the vicinity in area 5. This and all following intracellular recordings are from cats under ketamine–xylazine anesthesia. (A) Smooth transition from slow oscillation to complex seizure consisting of SW complexes at ≈2 Hz and fast runs at ≈15 Hz. The seizure lasted for ≈25 s. Epochs of slow oscillation preceding the seizure, SW complexes, and fast runs are indicated and expanded below. Note postictal depression (hyperpolarization) in the intracellularly recorded neuron (≈6 s), associated with suppression of EEG slow oscillation (*compare to left part of the trace*). (B) Wave-triggered averages during the slow oscillation, at the beginning of seizure and during the middle part of the seizure. Averaged activity was triggered by the steepest part of the depolarizing component in cortical neuron (*dotted lines*), during three epochs. The depth-negative field component of the slow oscillation (associated with cell depolarization) is the KC. During the seizure, the depolarizing component reaches the level of a paroxysmal depolarizing shift, associated with an EEG spike. (Modified from Steriade *et al.*, 1998.)

seizures has been hotly debated during the past decades. After Jasper and Droogleever-Fortuyn (1947) suggested the pathogenic role of the thalamus (although the epileptiform activity they had triggered by stimulating the thalamus did not outlast the stimulation), a series of researchers studied the role of various thalamic nuclei in promoting SW seizures. However, a parallel set of investigations, starting with those of Marcus and Watson (1968), emphasized the leading role of the cortex. Intracellular studies in our laboratory have demonstrated that the slow oscillation is the seed for paroxysmal developments such as SW seizures (Steriade and Amzica, 1994; Steriade *et al.*, 1998). They also have emphasized that SW seizures disappear after decortication and survive after thalamectomy (Steriade and Contreras, 1998). Moreover, in a majority of thalamocortical neurons, SW seizures are associated with a tonic hyperpolarization and phasic IPSPs (Steriade and Contreras, 1995; Pinault *et al.*, 1998), which further precludes the active implication of these cells in reinforcing the oscillations.

Thus, SW seizures are generated in the cortex, and they develop as a smooth acceleration of the slow oscillation (Fig. 2.6). This outburst of a SW seizure from the slow oscillation is associated with increased synchrony within cortical networks (Steriade and Amzica, 1994). The mechanisms underlying the transformation of the sleep KC into epileptic paroxysmal depolarizing shifts (PDSs) are not fully understood. A possible implication of glial cells has been emphasized (Fertziger and Ranck, 1970). The increased synchrony of neuronal discharge may generate a supplement of extracellular K^+, which in turn may disturb its normal uptake by glia and, by the same token, increase the neuronal excitability, leading to an avalanche process.

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3

PHYSIOLOGY UNDERLYING RELATIONSHIP OF EPILEPSY AND SLEEP

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INTRODUCTION

The two main sleep states, nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, have different physiological components and contrasting effects on generalized ictal and interictal discharges (IIDs). Epileptiform discharges are likely to propagate during NREM sleep, including its synchronized electroencephalographic (EEG) transients, such as K-com-

plexes and sleep spindles, and its transitional "drowsy" EEG arousal periods. In contrast, REM sleep, with its asynchonous cellular discharge patterns and skeletal motor paralysis, is resistant to propagation of epileptic EEG potentials and to clinical motor accompaniment even though focal IID persists at this time.

The contrasting effects of NREM and REM on IIDs and clinically evident seizures are to some extent nonspecific with respect to epileptic syndrome (Shouse *et al.*, 1996), defined by seizure type, etiology, and clinical course (Commission Report, 1989). On the other hand, clinically evident seizures, particularly generalized tonic–clonic or myoclonic convulsions, occur mainly during NREM sleep, mainly during drowsy wakefulness, or randomly in the sleep–wake cycle depending on epileptic syndrome (e.g., Janz, 1962). Interictal discharges are less likely to propagate and to lead to a clinically evident seizure during intact REM sleep than in any other state regardless of epileptic syndrome (e.g., Sammaritano *et al.*, 1991; Shouse *et al.*, 1989, 1996).

The clinical observations raise three questions that this chapter addresses: (1) Which characteristics of NREM account for the activation of IIDs? (2) Which characteristics of REM sleep suppress them? (3) How do the physiological mechanisms of specific sleep–waking state components interact with epileptic seizure pathology to provoke clinically evident seizures at different times?

METHODS AND RESULTS

To address these questions, we have employed several feline epilepsy models. Most of the findings presented here are based on studies of systemic penicillin epilepsy and/or amygdala(AMY) kindling. Figure 3.1 shows that these models resemble human counterparts with respect to the timing of IIDs and clinically evident seizures in the sleep–wake cycle.

PENICILLIN EPILEPSY

Injection of large dosages of penicillin [300,000–400,000 IU/kg, i.m.; (Fig. 3.1, *top*)] induces seizure manifestations of primary generalized epilepsy, particularly juvenile myoclonic epilepsy (Gloor, 1979). This is the prototypic epilepsy on awakening at least with respect to convulsions (Janz, 1962). Spike–wave and multi-spike–wave complexes with myoclonic jerks accompany sleep EEG transients such as sleep spindles and K-complexes during slow-wave sleep (SWS), the feline equivalent of human NREM, and decline during stable REM sleep. Nearly all generalized tonic–clonic convulsions (GTCs) occur during drowsiness after awakening.

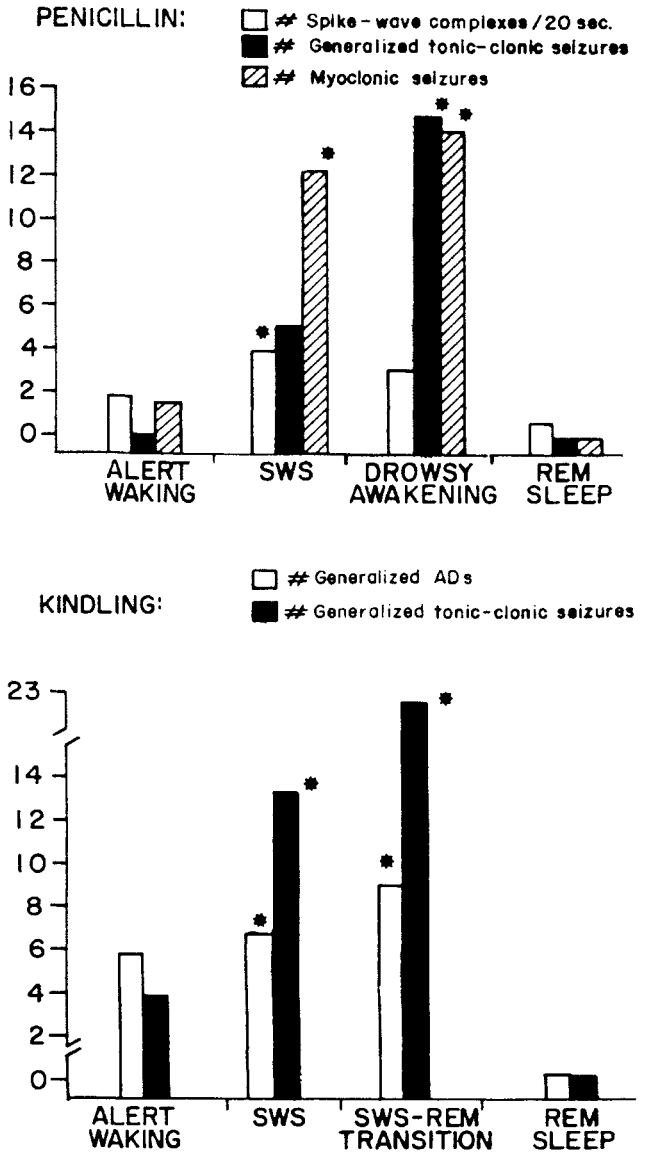

FIGURE 3.1 The incidence of interictal and ictal discharge in penicillin epilepsy (*top*) versus amygdala kindling (*bottom*) in 20 cats ($n = 10$ per model). * = $p < .05-.01$ from alert waking.

AMYGDALA KINDLING

Amygdala kindling (Fig. 3.1, *bottom*) provides a model of a localization-related epilepsy, in this case temporal lobe epilepsy (TLE), which is the prototypic pure sleep epilepsy in humans (Janz, 1962). Repetitive electrical stimulation in

kittens creates a spontaneous sleep epilepsy that persists to adulthood (e.g., Shouse *et al.*, 1990a,b, 1995). EEG seizure discharge propagation and GTCs occur most often in SWS and in the transition into REM. Focal discharge persists in REM unless the animal wakes up.

Figure 3.2 shows a spontaneous GTC, which occurs during the transition from SWS to REM sleep in an adult cat kindled as a kitten. Seizure onset seems associated with a ponto-geniculo-occipital (PGO) wave in the geniculate lead ipsilateral to the kindled AMY. PGO waves are sleep EEG transients that herald the onset of REM sleep (e.g., Siegel, 1994).

Thus, both epilepsy models resemble human counterparts in that generalized seizures occur during NREM sleep or transitional arousal periods characterized by EEG synchronization, often with phasic events that include sleep EEG tran-

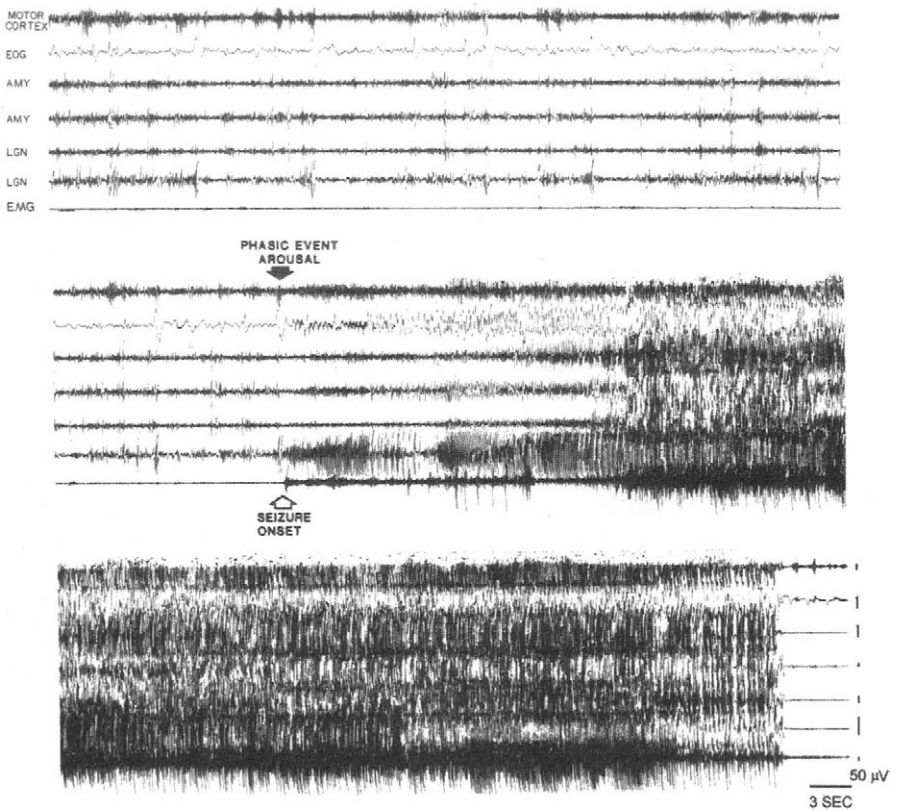

FIGURE 3.2 Continuous 3-min polygraphic recording of a spontaneous convulsion in a kindled cat during a phasic "arousal" event in the transition from slow-wave sleep (SWS) to rapid eye movement sleep (REM). The phasic arousal event correlated with seizure onset is a ponto-geniculo-occipital (PGO) spike. Paper speed is 10 mm. AMY, amygdala; LGN, lateral geniculate nucleus; EOG, electrooculogram; EMG, electromyogram. (From Shouse *et al.*, 1995.)

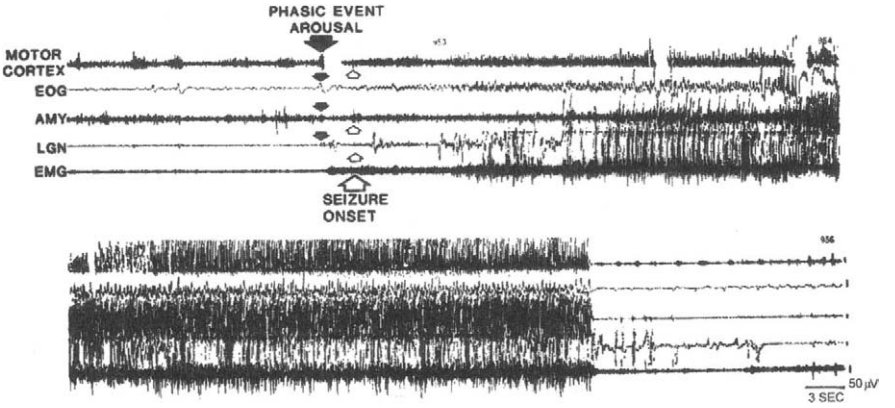

FIGURE 3.3 Continuous 2-min polygraphic recording of an evoked "phasic arousal" event, in this case a high-amplitude sleep spindle, by an accidental loud noise that precedes a convulsion. The spindle in the motor cortex lead (channel 1) was of such high voltage as to displace the pen from the recording. Paper speed is 10 mm. Abbreviations as in Fig. 3.2.

sients such as sleep spindles, K-complexes, and PGO waves. This may involve state or stage shifts as well as cyclic alternating patterns (CAPs) (e.g., Janz, 1962; Stevens *et al.*, 1971, 1972; Halász, 1982; Terzano *et al.*, 1985, 1989, 1992 Gigli *et al.*, 1992). In contrast, EEG seizure discharge propagation is reduced during states characterized by tonic EEG desynchronization, such as alert waking and particularly REM sleep (e.g., Sammaritano *et al.*, 1991). REM sleep is the most antiepileptic state in the sleep–wake cycle for generalized EEG and motor seizure activity, even though phasic events and localized EEG discharge persist in REM.

Phasic events of sleep are thought to reflect aborted arousals related to brain stem processing of intrinsic stimulation and can be provoked by extrinsic stimulation, such as a loud sound (e.g., Morrison, 1979). We verified that exogenous stimulation, including a random loud sound (Fig. 3.3) and photic stimulation (20 per second; Fig. 3.4), not only can evoke phasic events in cats but also can precipitate GTCs in spontaneously epileptic, kindled cats (Shouse *et al.*, 1995). The most vulnerable periods for extrinic stimulus-evoked GTCs are those in which spontaneous seizures most frequently occur, notably in SWS and in the transition into REM (Shouse *et al.*, 1990a,b). The least vulnerable time for evoked seizure activity is REM sleep, even though spontaneous phasic activity and focal EEG seizure discharge persist at this time and may be evoked by photic stimulation. Figure 3.5 shows that the same photic stimulation protocol (20 per second) can elicit epileptiform phasic events that occasionally outlast the stimulus in waking and REM. However, this least frequently occurs in REM sleep, and even then, there is no clinical accompaniment. These findings suggest that phasic activity can provoke epileptiform discharges, but the extent of epileptic EEG dis-

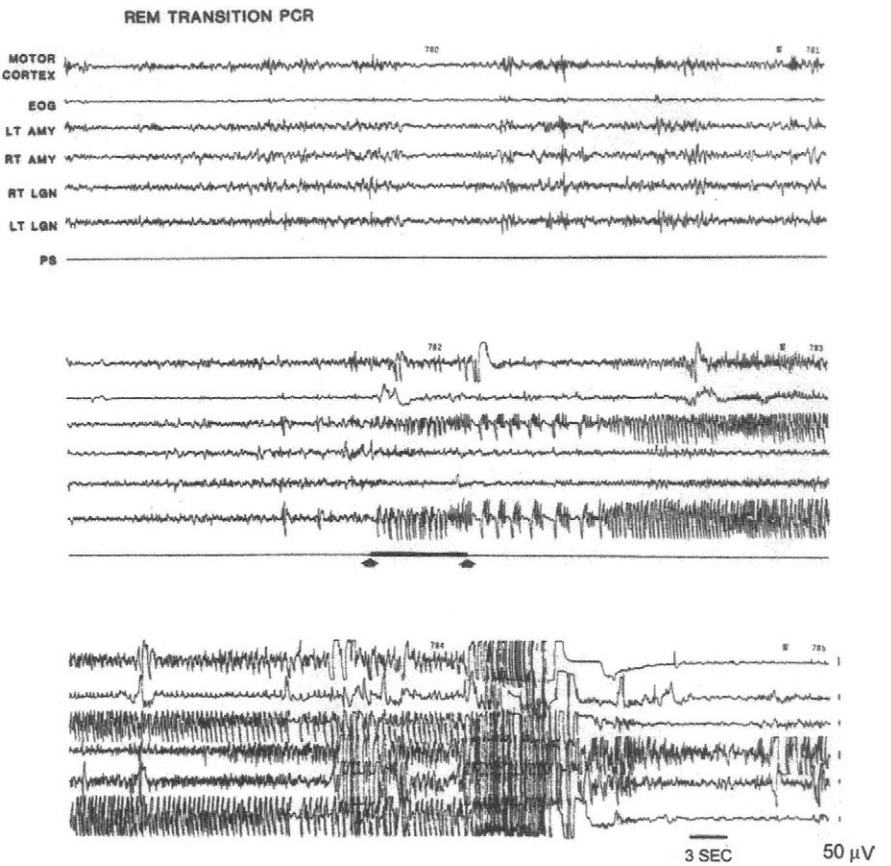

FIGURE 3.4 A REM transition photoconvulsive response (PCR) elicited by 20 per second photic stimulation (PS). PS onset and offset are indicated by arrows. The PS initially evoked epileptiform K-complexes in the kindled AMY and ipsilateral LGN, followed by EEG seizure discharge propagation with clinical accompaniment. Paper speed is 10 mm. Abbreviations as in Fig. 3.2.

charge propagation and clinical motor accompaniment depends on tonic EEG and motor sleep components.

The role of two tonic sleep components (synchronous versus asynchronous background EEG and presence versus absence of tone) was evaluated before and after the experimental manipulations depicted in Fig. 3.6. The top tracing (A) shows normal REM sleep with tonically desynchronized EEG [motor cortex, AMY, and thalamic lateral geniculate nucleus (LGN)], rapid eye movements [electrooculogram] (EOG) channel], PGO waves (LGN channel), and atonia (EMG channel). The middle tracing (B) shows a model of REM sleep without EEG desynchronization induced by systemic administration of atropine. The anticholinergic agent presumably acts by blocking cholinergic cell activity in the

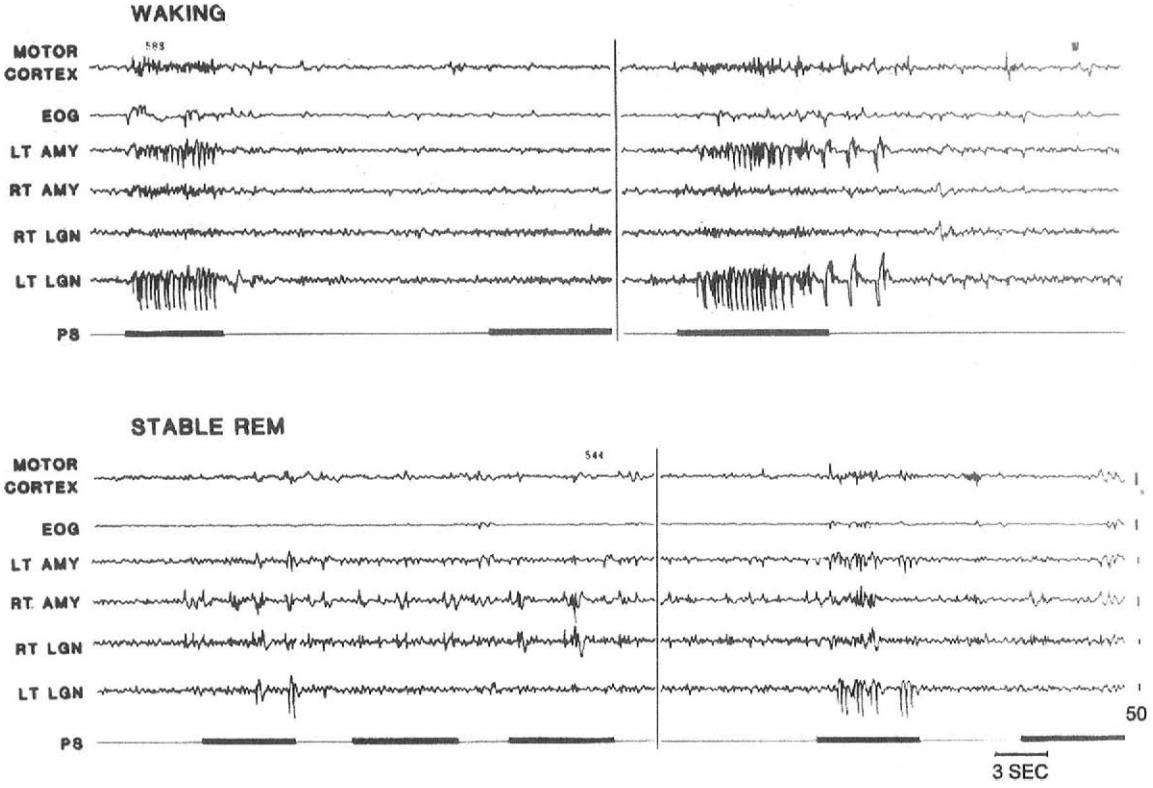

FIGURE 3.5 Photic stimulation, as described in Fig. 3.4, was applied in waking or REM sleep. Localized epileptiform activity resembling phasic arousal events can be seen in the kindled AMY, ipsilateral LGN, and motor cortex. Seizure discharge could outlast the stimulus (*black bars on bottom channel*), as seen in drowsy wakefulness (*top right*). Epileptiform EEG discharge was most difficult to obtain in REM sleep (*bottom panels*), and no clinically evident seizure activity was detected in this state. Paper speed is 10 mm. Abbreviations as in Figs. 3.2–3.4.

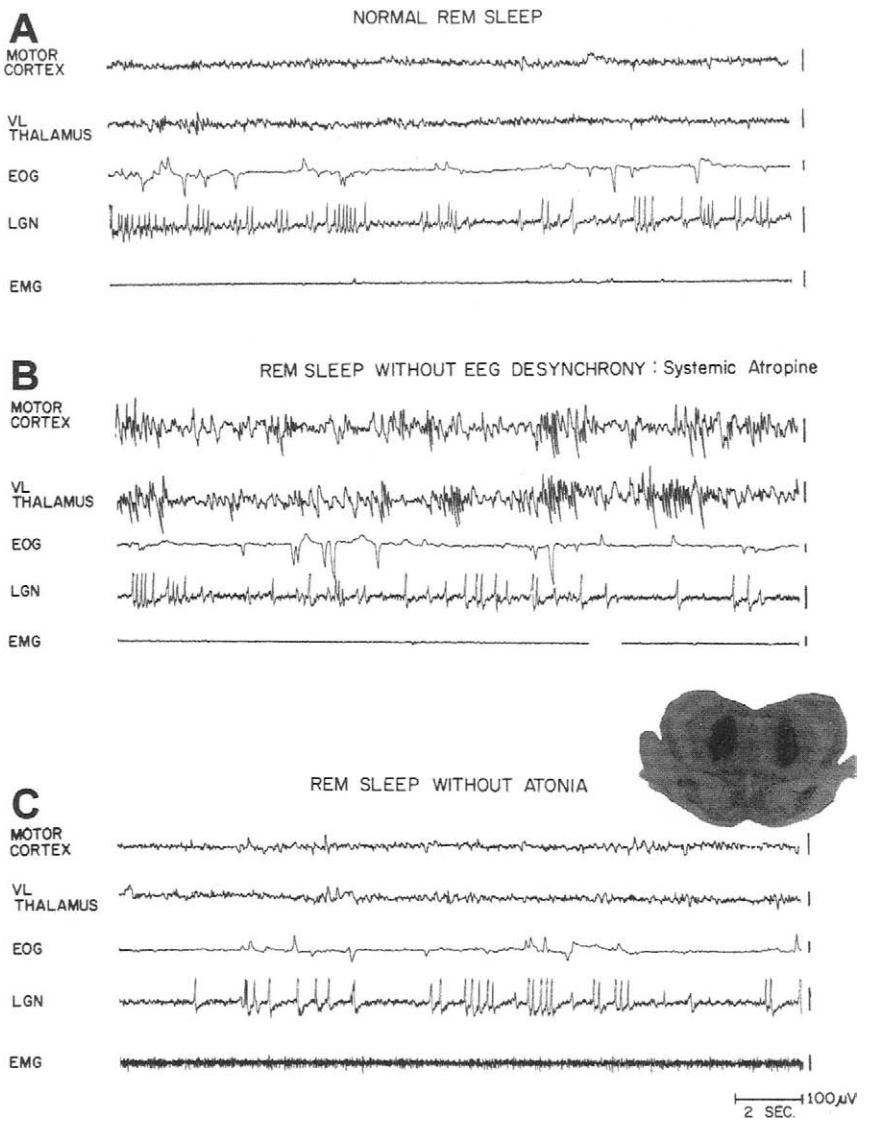

FIGURE 3.6 REM sleep before (A) and after experimental techniques designed to selectively alter either EEG synchronization or atonia. At (B), atropine induces REM sleep without EEG desynchonization. At (C), a medial-lateral pontine lesion induces REM sleep without atonia. Paper speed is 15 mm. Abbreviations as in Fig. 3.2 except addition of ventral lateral (VL) nucleus of thalamus. (From Shouse *et al.*, 1989.)

pedunculopontine tegmentum and nucleus basalis, which are thought to be the critical generators of EEG desynchronization in REM and waking (e.g., Jones, 1994; Siegel, 1994). The result is a NREM-like EEG with sleep spindles, but other phasic and tonic components of REM are intact, including rapid eye movements, PGO waves, and atonia [note electrical silence in electromyographic (EMG) channel]. The third tracing (C) shows REM sleep without atonia created by lesions of the medial lateral pontine tegmentum. This lesion is thought to destroy cholinoceptive and glutaminergic cells proposed to hyperpolarize lower motor neurons during REM sleep (e.g., Chase and Morales, 1994; Siegel, 1994). EEG desynchronization, REMs, and PGO waves are intact, but the cat has tone (note tonic discharge in EMG channel).

Figure 3.7 illustrates the effect of these dissociative sleep manipulations on penicillin epilepsy. The top tracing (A) shows spike-and-wave complexes riding upon sleep spindles in SWS and accompanied by myoclonic twitching (note related discharge in EMG channel). During REM, spike-and-wave activity is rare and occurred without clinical motor accompaniment. The middle tracing (B) shows that atropine does not affect the rate of EEG and motor seizure activity in SWS. However, the REM-sleep EEG is synchronized in cortex and ventral lateral (VL) thalamus, and EEG seizure discharge rate cannot be distinguished from SWS. There is still no clinical motor accompaniment, presumably because lower motor neuron inhibition is intact. The bottom tracing (C) shows seizure activity during REM sleep without atonia. Spike–wave activity is as infrequent as during normal REM; however, when a spike-and-wave complex does occur, there is clinical motor accompaniment, presumably because the animal can now move. Similar results were obtained after these dissociative sleep manipulations in 26 cats undergoing either penicillin epilepsy (n = 10; e.g., Fig. 3.7), electroconvulsive shock (n = 10; e.g., Fig. 3.8), or AMY kindling (n = 6; e.g., Fig. 3.9).

DISCUSSION

We find that the physiological mechanisms of different sleep–waking states are to some extent nonspecific with respect to different epileptic syndromes. This conclusion is consistent with evidence of the widespread cerebral influences of sleep and arousal mechanisms. For example, the hypothalamic and brain stem generators of sleep and arousal have diffuse ascending and descending projections (e.g., McBride and Sutin, 1976; Mugnaini and Oertel, 1985; Jones and Beaudet, 1987; Woolf *et al.*, 1990; Jones, 1994) that give rise to a number of distinguishing physiological characteristics, called components, and that influence the likelihood that an electrographic or clinical seizure can occur.

The most salient state-specific components affecting epilepsy seem to be the degree to which cellular discharge patterns are synchronized and alterations in antigravity muscle tone (Cohen *et al.*, 1970; Gloor, 1979; Recktor *et al.*, 1984,

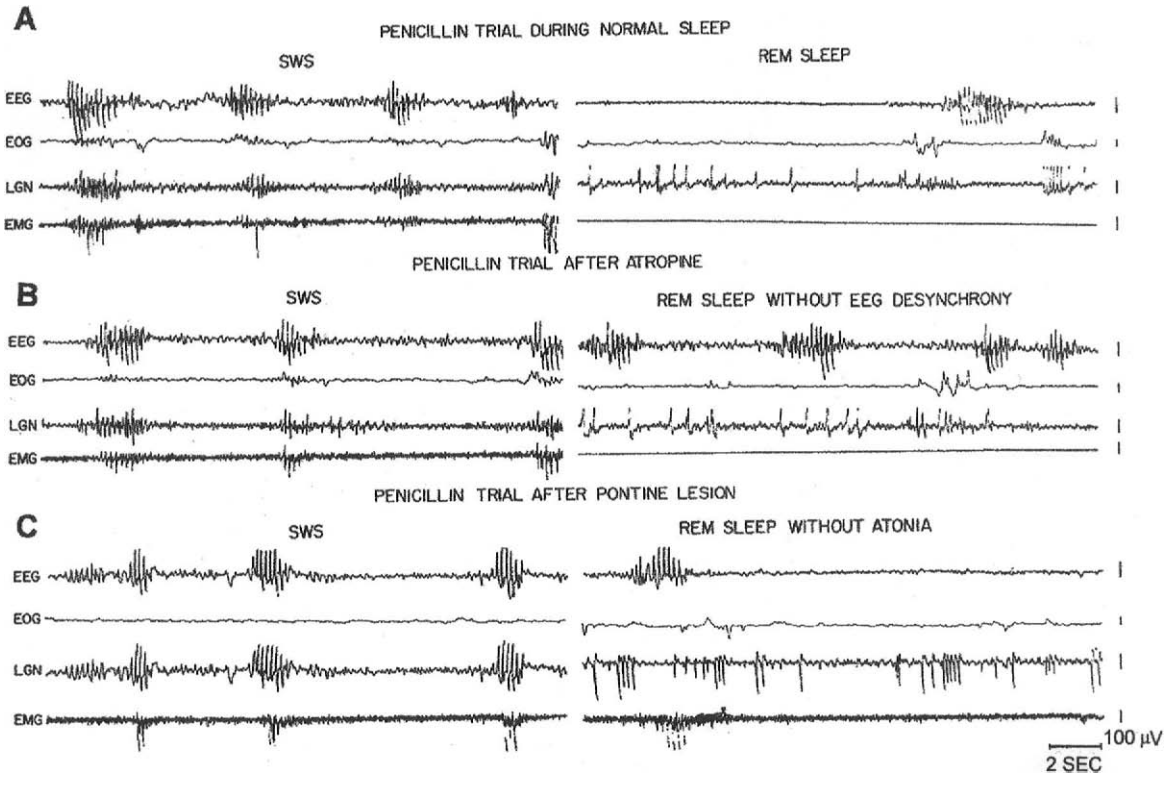

FIGURE 3.7 Penicillin epilepsy during SWS and REM sleep before (A) and after atropine or pontine dissociation techniques. At (B), atropine creates a SWS-like EEG synchrony in REM and selectively increased incidence of EEG seizure susceptibility in REM without clinical motor accompaniment. At (C), pontine lesions that caused REM sleep without atonia selectively increased clinical motor accompaniment. Paper speed is 15 mm. Abbreviations as in Fig. 3.6; the EEG in the top channel for each recording is from motor cortex. (From Shouse *et al.*, 1989.)

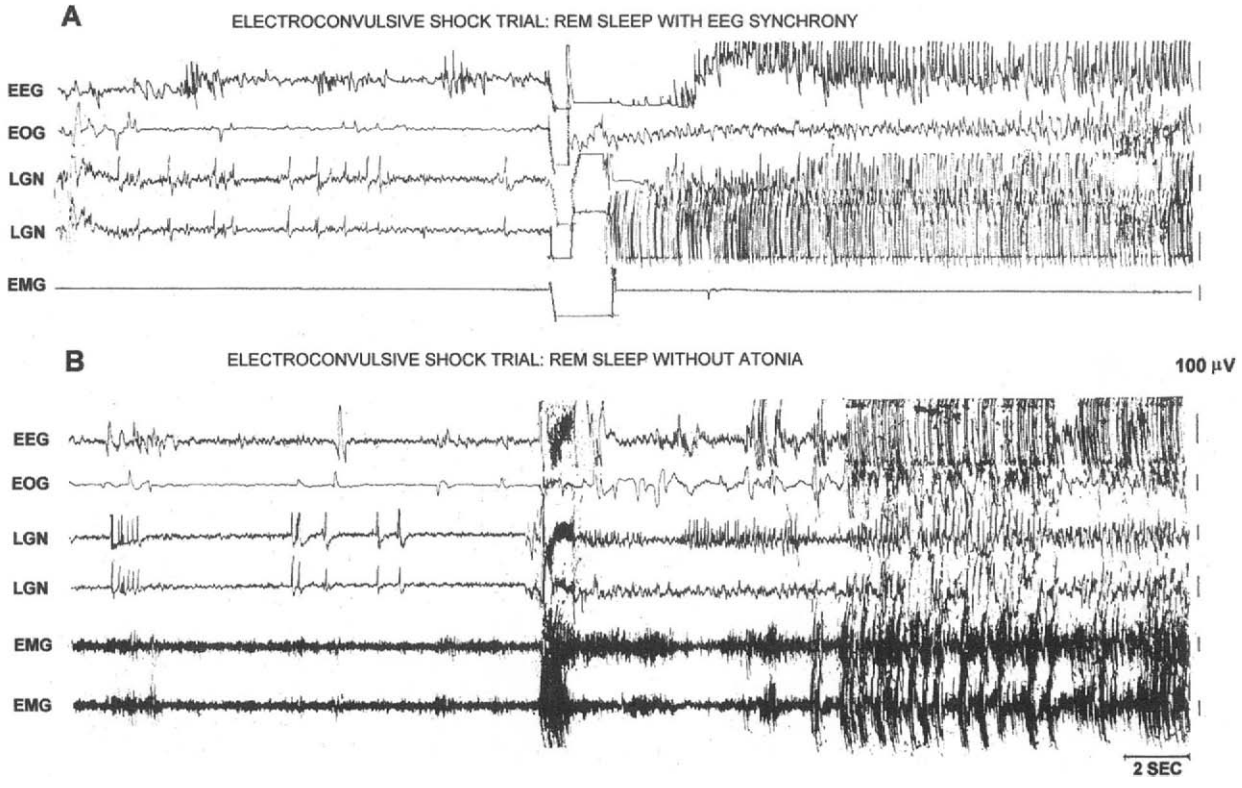

FIGURE 3.8 Electroconvulsive shock trials during atropine-induced REM sleep with synchronized EEG (A) and a medial pontine lesion evoking REM sleep without atonia (B). The atropine model significantly increased EEG discharge propagation, but there was no clinical accompaniment unless the animal awakened. In REM sleep without atonia, EEG seizure discharge was more difficult to obtain, because it required a higher voltage stimulus and still had a longer EEG seizure discharge propagation latency. Stimulus artifact is seen in the middle of the two tracings. Paper speed is 15 mm. Abbreviations as in Figs. 3.6 and 3.7 (From Shouse *et al.*, 1989.)

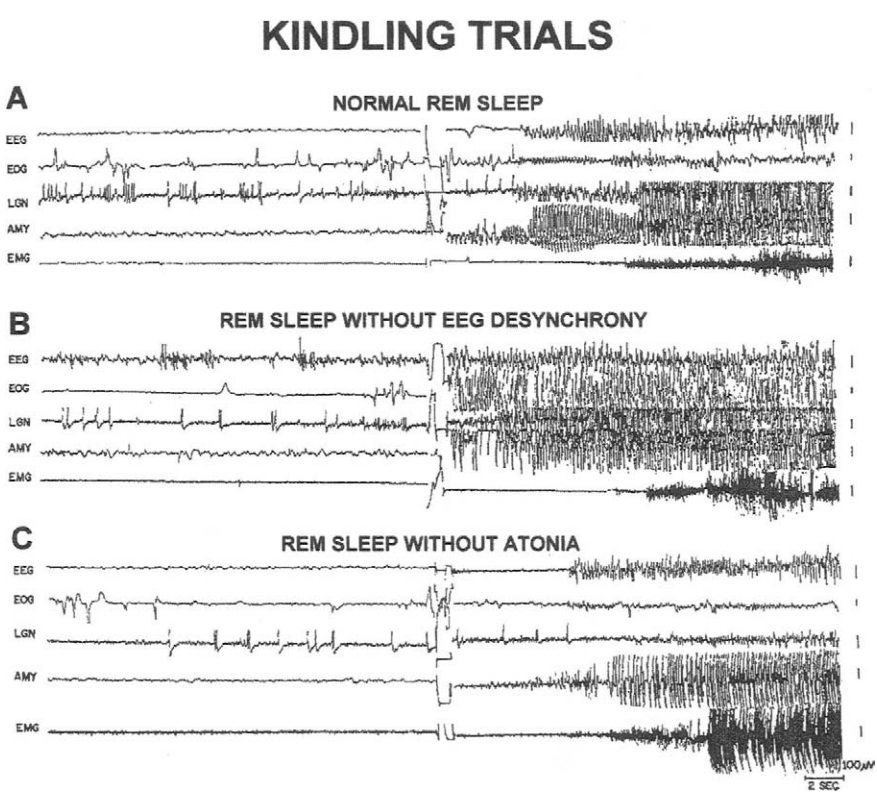

FIGURE 3.9 Evoked kindled seizures during REM sleep before (A) and after atropine (B) or pontine dissociation techniques. At (B), atropine creates a SWS-like EEG synchrony in REM and selectively increased incidence of EEG seizure susceptibility in REM without clinical motor accompaniment. At (C), pontine lesions that caused REM sleep *without* atonia selectively increased clinical motor accompaniment. Paper speed is 15 mm. Abbreviations as in Figs. 3.2–3.7. The EEG in the top channel is from motor cortex. (From Shouse *et al.*, 1990a.)

1987; Gloor and Fariello, 1988; Shouse *et al.*, 1989). NREM and drowsiness differ from alert waking and REM sleep in that EEG activity is synchronized and postural muscle tone is diminished. REM sleep differs from NREM in that EEG activity is desynchronized and differs from waking and NREM in that postural muscle tone is absent. REM sleep has sometimes been called "paradoxical sleep" (Jouvet, 1962) because it is characterized by a "highly active brain in a paralyzed body" (Carskadon and Dement, 1994).

During NREM, virtually every cell in the brain discharges synchronously (e.g., Steriade *et al.*, 1993). This occurs to a lesser extent in drowsiness. Lasting oscillations of rhythmic burst–pause firing patterns result in concerted synaptic actions. Synchronous synaptic effects, whether excitatory or inhibitory, are likely to augment the magnitude and propagation of postsynaptic responses, including epileptic discharges. During REM and alert waking, cells discharge

asynchronously (Siegel, 1994). The divergent synaptic signals associated with asynchronous discharge patterns are less likely to augment the magnitude or propagation of epileptic EEG discharges.

Skeletal muscle tone also varies by sleep or waking state. Antigravity muscle tone is preserved in NREM and waking (Rechtschaffen and Kales, 1968; Carskadon and Dement, 1994), thus permitting seizure-associated movement. Profound lower motor neuron inhibition occurs in REM (Rechtschaffen and Kales, 1968; Carskadon and Dement, 1994; Chase and Morales, 1994; Siegel, 1994), creating virtual paralysis and preventing seizure-related movement.

These conclusions are supported by other experimental and clinical findings indicating that substrates of state-specific components instead of integrity of the state per se can be salient determinants of seizure propagation regardless of epileptic syndrome. Agents that synchronize the EEG, such as cholinergic or noradrenergic antagonists, have proconvulsant effects (e.g., McIntyre *et al.*, 1979; Guberman and Gloor, 1982; Applegate *et al.*, 1986). Conversely, agents that desynchronize the EEG discourage epileptic EEG discharge propagation. Examples are cholinergic and noradrenergic agonists (e.g., Velasco and Velasco, 1982; Recktor *et al.*, 1984, 1987; Corcoran, 1988) as well as β-carbolines such as abnercil (Coenen *et al.*, 1992), which act on central benzodiazepine receptors. Finally, pharmacological manipulations that induce atonia, such as carbachol infusion into the brain stem, also block clinical motor accompaniment (Velasco and Velasco, 1982). Consistent observations have been reported in experimental models of PGE, such as electroconvulsive shock, penicillin epilepsy, and photosensitive epilepsy (Guberman and Gloor, 1982; Recktor *et al.*, 1984; Shouse *et al.*, 1989); in animal models of localization-related epilepsies, such as limbic system kindling and the cortical alumina cream preparation (Velasco and Velasco, 1982; Shouse *et al.*, 1990a); and in clinical literature on symptomatic generalized epilepsies, such as West syndrome also known as infantile spasms (Recktor *et al.*, 1987). Collectively, the findings confirm that cellular discharge patterns and alterations in tone affect electrographic and clinically evident seizure manifestations in diverse epileptic syndromes.

Although the generators of different sleep or arousal states exert some common effects on seizure disorders, the discrete pathways, seizure manifestations, and mechanisms involved also depend on the pathophysiology of the specific seizure disorder. For example, the presumed pathophysiology of PGEs is a diffuse cortical dysfunction that probably reflects age-related genetic penetrance (Niedermeyer, 1987; Delgado-Escueta *et al.*, 1989), often remits spontaneously, and is thus less severe than that seen with a focal or multifocal epileptogenic lesion (e.g., Gloor *et al.*, 1977; Gloor, 1979; Niedermeyer, 1987; Gloor and Fariello, 1988). This concept is illustrated in Fig. 3.10, which is adapted from Gloor (1979). It contrasts surface electrographic and intracellular discharge patterns in cortex associated with normal rhythmic activity (A), PGE (B), and either localization-related or symptomatic-generalized epilepsies (C).

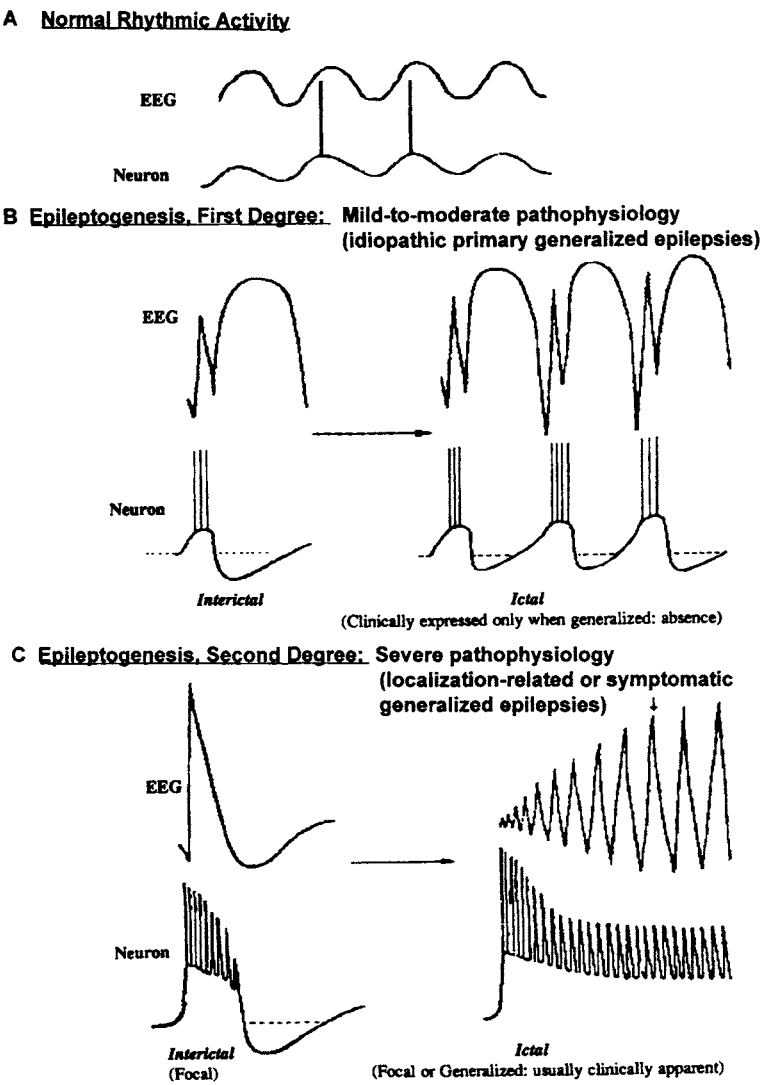

FIGURE 3.10 Diagrammatic representation of the relationship between surface EEG and intracellularly recorded activity. At (A), normal rhythmic background activity. At (B), mild to moderate pathophysiology characterized by abnormal sequencing but not amplitudes of EPSPs and IPSPs [interictal discharge (IID) *on the left*; ictal discharge is *on the right*]. At (C), more serious pathophysiology exemplified by a depolarization shift, which is an abnormally large hyperpolarization followed by intense rebound EPSP sequence (IID: *left;* ictal: *right*). (From Gloor, *Epilepsia* 20:583, 1979, with permission.)

In PGE, the membrane potential of individual cortical cells is within normal range, and intracortical inhibitory mechanisms are intact. Neuronal hyperexcitability is expressed only by populations of cortical neurons entrained to a synchronous burst–pause firing pattern by the thalamocortical volleys that normally evoke spindles and recruiting responses. The sequential alternation of cortical excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) that generate normal rhythmic events persists in PGE but is altered by the increased amplitude of temporally and spatially summed EPSPs and IPSPs. The enhanced excitatory response generates the action potentials underlying the spike component of the spike–wave or polyspike–wave complex and is followed by a longer lasting period of neuronal silence that gives rise to the slow-wave component of the complex (see Fig. 3.10B, *left*). Generalized spike–wave complexes lasting 5–15 s are typically accompanied by a clinically evident absence seizure (see Fig. 3.10B, *right*). Preservation of γ-aminobutyric acid (GABA)-mediated intracortical inhibitory mechanisms is considered critical to the generation of the slow component and terminates the spike train that, if unopposed, could lead to a convulsion.

Both localization-related and symptomatic seizure disorders are thought to result from focal regions of cerebral dysfunction (e.g., Commission Report, 1989). Localization-related and symptomatic epilepsies presumably reflect a more severe pathophysiology than that seen in PGE because individual neurons in the focus exhibit sudden depolarization shifts, which probably represent giant EPSPs (e.g., Gloor and Fariello, 1988). Depolarization shifts are characterized by high-amplitude, long-lasting depolarizations with superimposed and high-frequency action potentials corresponding to spikes and sharp waves in surface recordings. Recurrent GABAergic inhibitory mechanisms are present but impaired (e.g., Ribak *et al.*, 1979; Daly *et al.*, 1981), as evidenced by the absence of rebound inhibition (see Fig. 3.10C, *left*). The intense hyperexcitability of focal epileptic neurons without compensatory inhibition could increase the likelihood of seizure discharge propagation and clinically evident seizures in response to synchronous bursts of excitatory synaptic inputs during NREM sleep (see Fig. 3.10C, *right*).

As suggested earlier, cholinergic and noradrenergic neurons of the ascending reticular activating system are implicated in the propagation of diverse seizure events in NREM and their suppression during REM. However, they can also affect PGE and localization-related epilepsies differently (e.g., Wada and Sato, 1975; Gloor, 1979; McIntyre, 1979; Gloor and Fariello, 1988; Shouse *et al.*, 1990a,b). We propose the following two hypotheses (e.g., Shouse *et al.*, 1996).

PRIMARY GENERALIZED EPILEPSY

Reduced cellular discharge and chemical release in *reticulothalamic* pathways promote IID generation during NREM in primary generalized epilepsies (e.g., Gloor and Testa, 1974; Gloor, 1979; Steriade *et al.*, 1993), probably by en-

hancing the thalamocortical EEG synchronization patterns with which spike–wave and polyspike–wave complexes are associated. Synchronized sleep transients such as sleep spindles and possibly even delta waves are contingent on sequenced hyperpolarizing GABAergic input from the thalamic reticular nucleus to the thalamocortical relay cells (e.g., McCormick, 1992; Steriade *et al.*, 1993; Steriade, 1994). Increased GABA release from thalamic and cortical neurons is considered critical to generation of slow components of these IIDs (e.g., Gloor and Fariello, 1988; von Krosigk *et al.*, 1993).

The peak in GABA release that occurs during NREM, although promoting IIDs, seems to discourage clinically evident seizures such as generalized myoclonic and tonic–clonic convulsions. The moderate levels of reticular activation, chemical release, and synchronous thalamocortical discharge patterns during drowsiness are conducive to generalized epileptic EEG discharge propagation *with clinical accompaniment* (e.g., Gloor and Testa, 1974). In contrast to NREM and drowsiness, extreme activation of ascending brain stem afferents, particularly cholinergic cells, occurs during alert waking and REM sleep (e.g., Jones, 1994; Siegel, 1994), abolishes GABA-mediated synchronous thalamocortical discharge oscillations (Steriade, 1994), and is thought to suppress both ictal and interictal events in PGE (e.g., Guberman and Gloor, 1982; Shouse *et al.*, 1989).

LOCALIZATION-RELATED EPILEPSIES

Reduced electrochemical activity in *reticulolimbic* pathways most parsimoniously explains IID propagation from temporal or frontal lobe foci during NREM sleep (McIntyre *et al.*, 1979; Applegate *et al.*, 1986; Corcoran, 1988; Pelletier and Corcoran, 1993). Effects could be mediated by direct innervation of focal epileptic neurons (e.g., Jones and Beaudet, 1987; Woolf *et al.*, 1990; Jones, 1994). This perspective is supported by microinfusion studies indicating that local application of norepinephrine (NE) receptor antagonists to limbic seizure foci promotes ictal discharge propagation, whereas NE receptor agonists block seizure discharge generalization (Pelletier *et al.*, 1993; Shouse *et al.*, 1994). Epileptic neurons in seizure foci also differ from those in PGE by exhibiting increased excitability without adequate inhibitory mechanisms (e.g., Ribak *et al.*, 1979; Daly *et al.*, 1981). This feature may render focal epileptic cells especially hyperresponsive to synchronous excitatory synaptic inputs, thus increasing propensity to focal epileptic discharge propagation with clinical accompaniment during NREM sleep.

CONCLUSIONS

Collectively, the findings suggest how sleep mechanisms influence epileptic cells, which are considered inherently hyperexcitable and therefore hyperresponsive to afferent input (Gloor, 1979; McNamara, 1994). Specifically, (1) during

NREM, virtually every cell in the brain discharges synchronously. Rhythmic burst–pause firing patterns generate synchronous synaptic actions, which—via spatial and temporal summation—are more likely to augment the magnitude and spread of excitatory and inhibitory postsynaptic responses, including epileptic ones. Effects may be exacerbated by sudden surges of afferent stimulation associated with phasic events. Antigravity muscle tone is preserved, allowing seizure-related movement. (2) During REM, asynchronous cell discharge patterns generate divergent synaptic signals, which—due to reduced spatial and temporal summation–are less likely to augment propagation of postsynaptic epileptic responses. Profound lower motor inhibition during REM blocks clinical motor accompaniment (Shouse *et al.*, 1989, 1996). (3) Severity (organicity) of epileptic syndromes correlates with and may contribute to variability in the dispersion of interictal and particularly ictal seizure manifestations across the sleep–wake cycle.

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4

SLEEP DEPRIVATION AND EPILEPSY

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INTRODUCTION

As far back as the last century, the relationship of seizures to sleep has been noticed. Gowers reported that 21% of epileptics had seizures predominantly during sleep (Gowers, 1885). Even prior to the electroencephalogram (EEG) era, it was observed that seizures occurred at particular times of the day (Langdon-Down and Brain, 1929). In his description of "awakening epilepsies," Janz (1969) mentions that seizures frequently occurred after holidays or on Mondays

and that some individuals, like students and bakers, tended to have more seizures after sleep deprivation (SD).

EFFECT OF SLEEP ON EPILEPTIFORM DISCHARGES

Sleep not only may activate clinical seizures but also may lead to activation of interictal epileptiform discharges (EDs). Gibbs and Gibbs (1947) first pointed out the usefulness of sleep as an activating method for the detection of EDs. They reported that of 174 patients with grand mal seizures only 19% had seizure discharges in wakefulness compared with 63% during sleep. Since then recording of sleep has become an important part of the routine EEG examination. Sleep leads to activation of both focal and generalized spikes in about one-third of all patients (Silverman, 1960; White, 1962; Niedermeyer, 1972). Table 4.1 summarizes data from Shinnar's (1994) study of the yield of the EEG in 347 children with their first unprovoked seizure. Some patients had spike discharges that were only seen during sleep. Thus, obtaining an EEG with adequate sleep in addition to wakefulness improves the chances of detecting such discharges (Shinnar, 1994). Sedated sleep also appears to be similarly effective (Rowan, 1982).

Sleep also alters the morphology of EDs; for example, the typical 3 per second spike and slow-wave complexes of patients with childhood absence epilepsy are replaced by either single spike–wave discharges or polyspike and wave configuration (Fig. 4.2). The hypsarhythmic pattern of infantile spasms is modified during NREM sleep by the appearance of 1–3-s periods of background suppression (Kellaway, 1983). In REM sleep, the EEG may look quite normal (Hrachovy, 1981). Sleep produces marked activation of sharp waves in benign focal epilepsy of childhood (Fig. 4.1). An EEG containing adequate sleep without the typical sharp waves makes it unlikely that the child has this disorder.

TABLE 4.1 Yield of the EEG in 347 Children with Their First Unprovoked Seizure

EEG finding	Awake (%)	Sleep (%)	Awake + Sleep (%)	No.
Normal	31	21	48	186
Abnormal	47	9	44	135
Focal spikes	39	9	52	77
General spikes	64	4	32	28
Focal slow	52	5	43	21
Photoconvulsive	50	17	33	6

Modified from Shinnar, 1994, with permission.

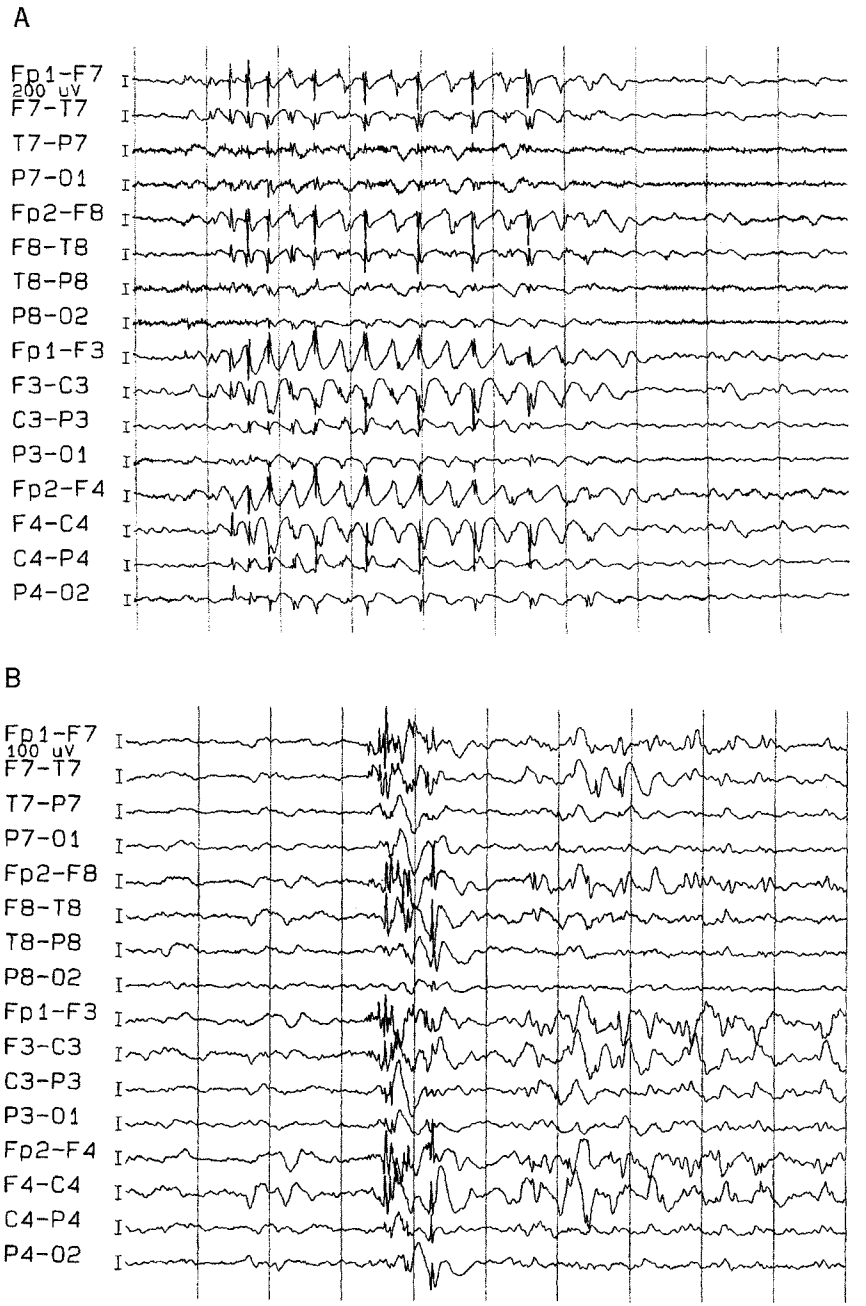


FIGURE 4.1 In this EEG of a child with childhood absence epilepsy, the typical 3 per second spike–wave complexes in wakefulness (A) are replaced by polyspike and wave discharges during NREM stage 2 sleep (B).

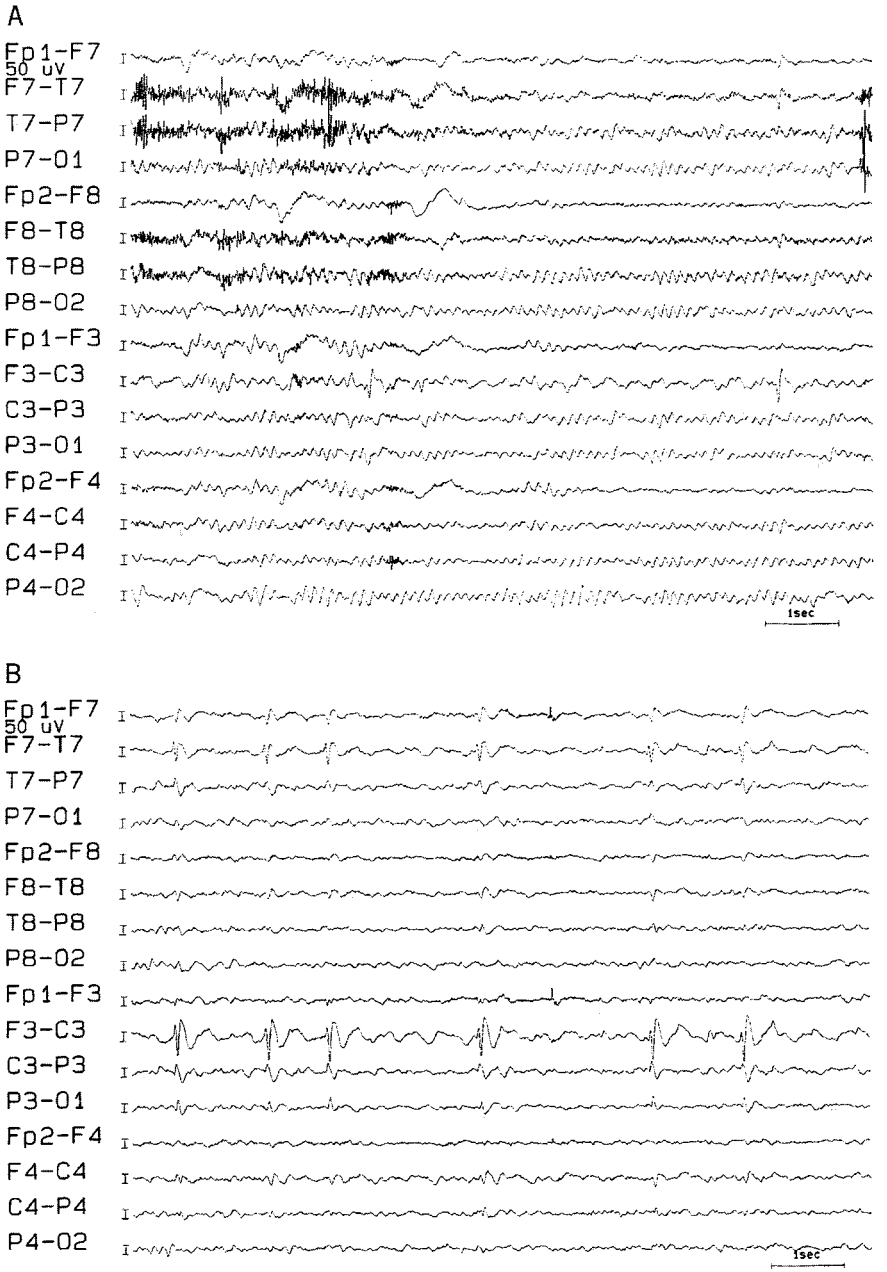


FIGURE 4.2 An isolated sharp wave is seen in the left centrotemporal region in this 10-year-old boy with benign focal epilepsy of childhood (A). During sleep (B), note the marked increase in the frequency of sharp waves that occur in long runs.

Children with symptomatic generalized epilepsy and multifocal independent spike discharges show bilateral synchrony between frontal and temporal sharp wave foci that often occur with a repetition of 1.5–2.5 Hz (Kotagal, 1995). Children with Lennox-Gastaut syndrome often exhibit long runs of slow spike–wave complexes during sleep. The most pronounced activation by sleep occurs in some children manifesting with continuous spikes and waves during slow sleep (CSWS) (formerly known as electrical status in slow-wave sleep or ESES) (Patry, 1971). The spike–wave discharges become nearly continuous, and by definition should occupy >85% of slow-wave sleep. These children usually present with intellectual and behavioral regression; some patients also have seizures. A subset of children with CSWS have Landau-Kleffner syndrome in which loss of acquired language is the main feature (Landau and Kleffner, 1957; Paquier, 1992). Figure 4.3 shows the influence of sleep stages on the EEG of a child with Landau-Kleffner syndrome and response to therapy.

ACTIVATING EFFECT OF SLEEP DEPRIVATION ON EPILEPTIFORM DISCHARGES ON THE ELECTROENCEPHALOGRAM

Rodin *et al.* (1962) reported high-voltage paroxysmal activity on the EEG in 16 normal subjects following 120 h of SD, concluding that "prolonged loss of sleep is associated with increased cerebral irritability which may result in epileptic-like manifestations in certain predisposed individuals." In two publications Bennett (1963) and Bennett *et al.* (1964) reported five pilots with no prior seizure history who suffered a single convulsion after SD. Although they had experienced concurrent physical and mental stress, lack of sleep was the common factor in all. EEGs were normal in four of five subjects, but one subject showed left temporal spikes after 30 h of SD (Bennett, 1963; Bennett *et al.*, 1964). Bennett also reported the effects of 24–72 h of SD in 118 healthy air crew personnel ages 18–32 years. No EEG abnormalities were reported following SD (Bennett *et al.*, 1969). Gunderson and Dunn (1973) also reported an increased incidence of seizures in Army soldiers returning to the United States from the far east. Following these reports, SD soon became established as an activating method to elicit epileptiform activity in EEGs. This activation method has a very low false positive rate between 1.2 and 2.2% (Bennett, 1963; Bennett *et al.*, 1964; Geller, 1969; Welch and Stevens, 1971).

A number of conditions have to be kept in mind when examining various studies on SD and activating effects. First, subject selection is important. Whereas some looked only at healthy individuals (Bennett, 1963; Bennett *et al.*, 1969), others looked at possible or known epileptics who may or may not have shown EDs on their non-SD EEGs. A second factor involves the conditions under which SD was carried out and how strictly these were enforced. Another is the duration of the non-SD and SD recordings and whether roughly equal

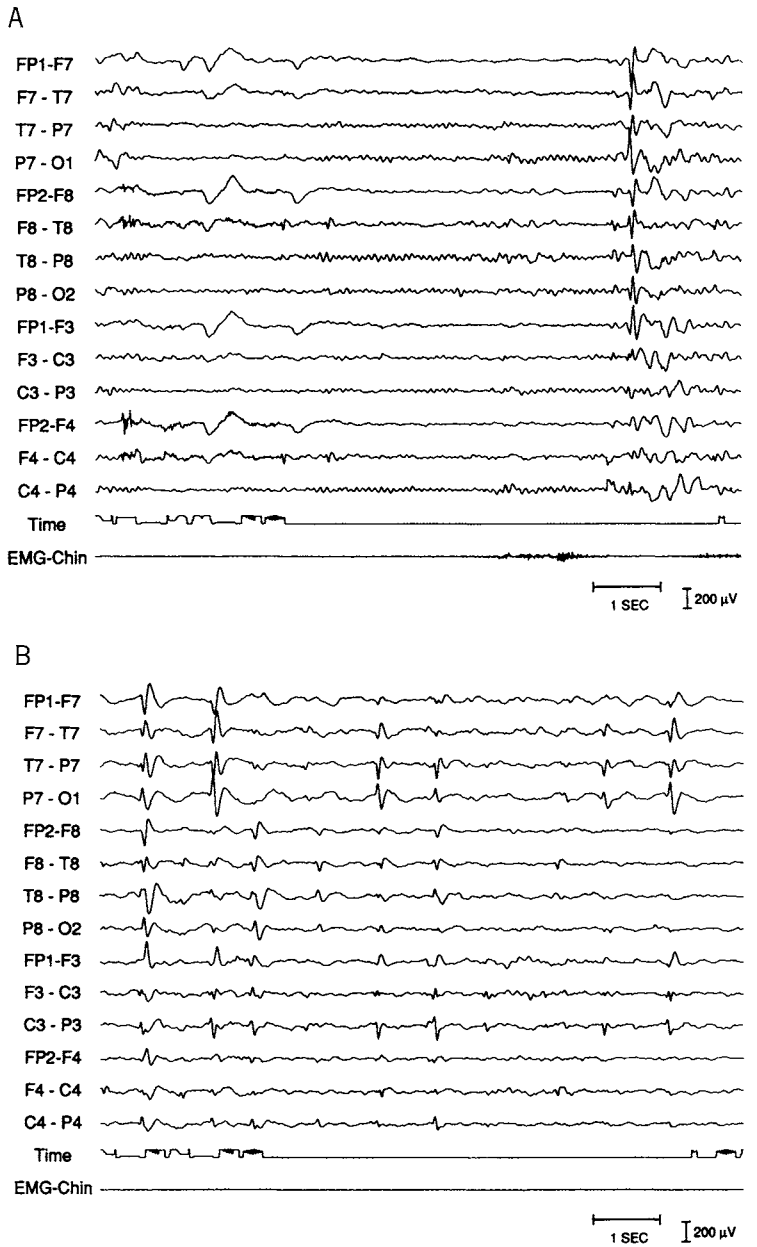
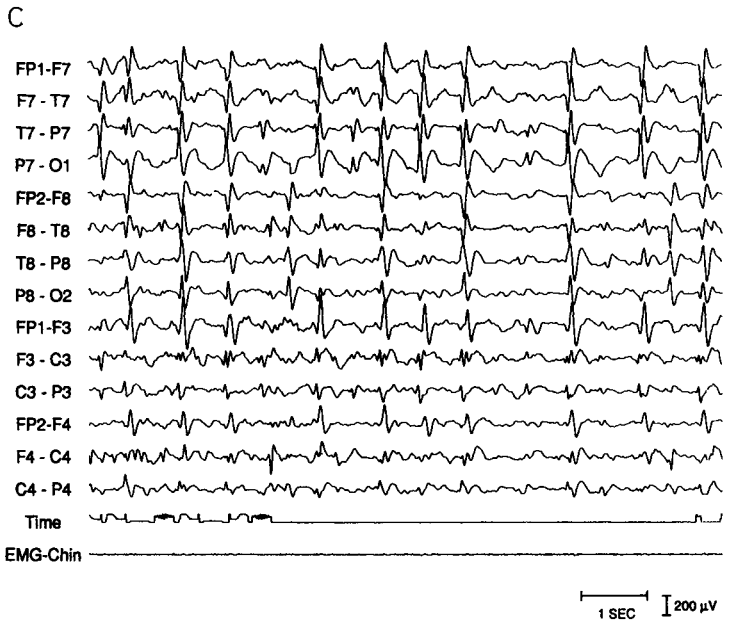


FIGURE 4.3 Segments of the EEG from a 6-year-old boy with Landau-Kleffner syndrome. During wakefulness (A), occasional sharp waves are seen in the temporal regions bilaterally. These increase somewhat during NREM stage 2 sleep (B); however, they become nearly continuous during slow-wave sleep (C). Following treatment with a benzodiazepine, the spikes disappeared completely—this was associated with clinical improvement seen in the boy's speech and behavior (D).



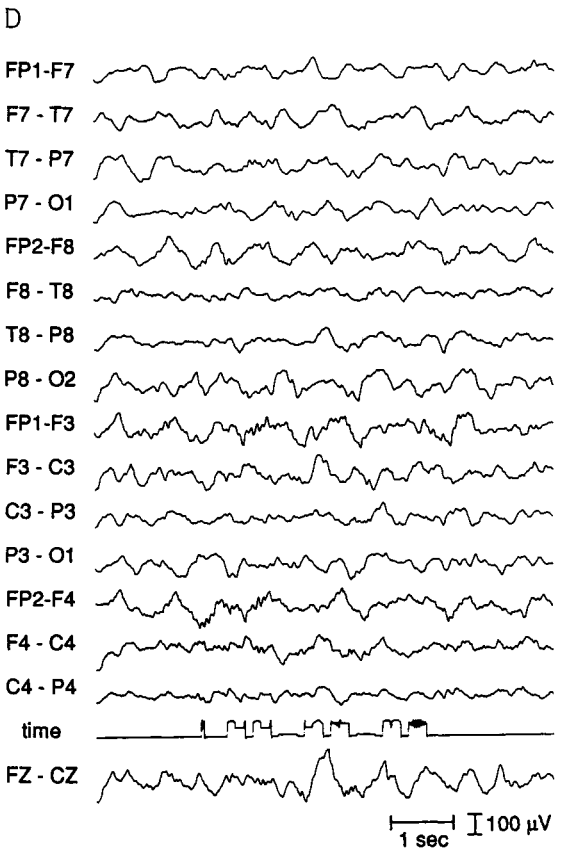


FIGURE 4.3 *(Continued)*

amounts of sleep were obtained. It has been estimated that simply repeating the EEG at another point in time may increase the yield by 20% (Salinsky *et al.*, 1987; Pratt, 1968; Fountain *et al.*, 1998).

Studies comparing sleep deprived EEG with drug-induced sleep EEGs have reported conflicting findings, some finding greater activation of ED with drug-induced sleep (Degen and Degen, 1981, 1983, 1991; Veldhuisen, 1983; Degen *et al.*, 1987). Others (Sherwin and Hooge, 1973; Rumpl *et al.*, 1977; Rowan *et al.*, 1982; Aguglia *et al.*, 1994) found greater activation with sleep-deprived EEGs. Rowan examined EEGs of 43 successive patients over 11 months who had EEGs done both with sedated sleep and with sleep-deprived EEGs; 41 of 43 also had routine awake recordings. Of 20 patients with a final diagnosis of epilepsy, 25% of routine awake EEGs, 50% of EEGs with sedated sleep, and 80% of sleep-deprived EEGs showed epileptiform activity (Rowan *et al.*, 1982). However, Degen found no difference in activation of ED between sedated sleep and sleep after SD (Degen *et al.*, 1987). Degen also failed to find significant activation of ED in patients with complex absence (Degen and Degen, 1983) as well as a selected group of patients with complex partial seizures (Degen and Degen, 1981). This was probably due to already high rates of EDs. Another study reported by Fountain *et al.* (1998) found activation of ED in 15 of 29 (52%) of patients whose routine EEGs contained wakefulness and stage 2 NREM sleep did not show ED. Even accounting for a 20% yield due to sampling, there was a marked activation of ED by SD. Carpay *et al.* (1997) reported on 552 children with new onset seizures of whom 243 (44%) had ED; only 20% of children fell asleep during the routine EEG. Then 177 patients underwent sleep-deprived EEGs and 81% had sleep recorded. Another 61 patients (36%) had ED, half of them only during sleep. Thus, SD increased the yield by 11% in this group (Carpay *et al.*, 1997). Klingler (1991) looked at spike counts before SD, SD awake, and SD asleep; the total count of spike–wave discharges were 407, 852, and 641–these differences were statistically significant. Klingler (1991) concluded that SD has "a genuine activating influence on the EEG and does not act merely by way of sleep induction." Degen noted that children ages below 10 showed 10% more activation than 11–20-year olds who in turn showed more activation than patients >30 years old (Degen, 1980). El-Ad *et al.* (1994) addressed the issue of whether it is necessary to record sleep from subjects who have been sleep deprived. Whereas 9% of the subjects showed spikes after SD only in wakefulness versus 40% who had spikes only during sleep, 51% had spikes in both wakefulness and sleep (El-Ad, 1994).

EFFECT OF SLEEP DEPRIVATION ON SEIZURES

There is widespread agreement that SD does induce clinical seizures in persons with no prior history or only a remote history of seizures (Rodin *et al.*, 1962; Bennett, 1963; Bennett *et al.*, 1964). The risk of having a seizure appears to be

greatest within 48 h after SD (Aird, 1983; Rodin, 1991). In many cases associated factors like physical and emotional stress, fatigue, and alcohol use are also present. David (1955) studied seizure frequency in relation to the duration and timing of night sleep in 100 patients with awakening epilepsy. He found that seizures occurred in 65% due to SD, and in 15% from altered rhythmicity or depth of sleep, and in 18% both factors were present (David, 1955). Rajna and Veres (1993) examined seizure diaries of patients with temporal lobe epilepsy who recorded whether they slept the usual number of hours or less than usual, or were sleep deprived. The highest numbers of seizures were precipitated by SD; a smaller though not significant increase of seizures also occurred if the patients slept longer than usual (Rajna and Veres, 1993). By combining data from several studies (Bechinger, 1973; Rumpl *et al.*, 1977; Degen, 1980; Tartara *et al.*, 1980), Ellingson *et al.* (1984) calculated that clinical seizures occurred after SD in 19 of 788 or 2.4% of otherwise healthy subjects without a previous history of seizures.

The value of SD in provoking seizures is put to use routinely in epilepsy monitoring units everywhere. At our institution, we generally allow young children <12 to sleep 6 h, whereas adolescents and adults might be allowed to sleep 4 h or to be totally sleep deprived; it is, of course, necessary to ensure that the patient does not nap during the day. Patients awaiting injection of the isotope for ictal single photon emission computed tomography (SPECT) are instructed to stay up until the prepared isotope is available at the bedside in the morning and then are allowed to fall asleep. Patients often have a seizure as they become drowsy and fall asleep and then the isotope for ictal SPECT can be injected.

SD may also affect seizure semiology; typically patients are more likely to have prolonged or more intense seizures that might display focal clonic movements, version or secondary generalization that may serve to clarify the epileptic nature of events (Benbadis *et al.*, 1995). In many patients, we have found SD helpful in allowing us to lateralize the onset of the seizure for presurgical evaluation.

Seizure control in patients with epilepsy who also have sleep apnea may improve after treatment with continuous positive airway pressure (CPAP), positional treatment, or tracheostomy, highlighting the clinical importance of treating associated disorders that cause sleep disruption and resulting SD (Devinsky, 1994; Vaughn *et al.*, 1996; Britton *et al.*, 1997).

EFFECT OF SEIZURES ON NOCTURNAL SLEEP AND DAYTIME FUNCTION

Frequent nocturnal seizures disrupt sleep continuity and can result in daytime sleepiness and increased seizures in the daytime. This is usually seen in children with symptomatic generalized epilepsy (Lennox-Gastaut syndrome) who often have many nocturnal tonic seizures (Erba and Ferber, 1983). Optimizing their medical therapy may result in improved daytime alertness.

EXPERIMENTAL DATA

Although the cellular basis of sleep in activating spikes and seizures has been studied (see Chap. 3) very little information exists concerning the mechanism by which SD affects EDs or epileptic seizures. In epileptic rats, Drinkenburg *et al.* (1995) found an increase of spike–wave discharges during the first 4 h of SD, following which spike counts returned to normal, paralleling a return of REM sleep. Marrosu *et al.* (1996) investigated the effects of SD in patients with primary generalized epilepsy by administering naloxone to see if it would block the activation of ED due to SD. However, naloxone did not modify this activation; it was concluded that nonopiod mechanisms are probably involved in patients with generalized epilepsy. However, naloxone administration in patients with localization-related epilepsy resulted in significant increase in ED after SD (Molaie and Cruz, 1988; Molaie and Kadzielawa, 1989).

SUMMARY

SD is a powerful activating agent both for EDs as well as clinical seizures. However, the cellular basis of this effect has not been elucidated but may possibly involve modulation of cortical excitability by deeper brain structures such as the thalamus and brain stem reticular formation. It is of considerable usefulness in epilepsy monitoring units for precipitating epileptic seizures; for elucidating the epileptic nature of paroxysmal events; and for obtaining special procedures like ictal SPECT, postictal magnetic resonance spectroscopy (MRS), or postictal diffusion weighted magnetic resonance imaging (MRI) scans. In the outpatient EEG laboratory, SD is useful in activating spikes not previously seen both in wakefulness and in sleep following SD and appears superior to EEGs obtained during sedated sleep. From the standpoint of management, obtaining adequate sleep improves seizure control and may sometimes obviate the need for antiepileptic medication if the patient has had rare seizures occurring only after SD.

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5

GENERALIZED EPILEPSY AND SLEEP

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INTRODUCTION

There are several relationships between generalized epilepsy and sleep, both clinically and electroencephalographically. It has been known since the days of Aristotle (Aristoteles, 1924) that epileptic seizures may occur exclusively during sleep. Several authors observed that epileptic seizures may show a tendency to occur during sleep or waking periods and recognized the relation to the sleep–wake cycle (Gowers, 1885; Langdon-Down and Brain, 1929; Patry, 1931; Hopkins, 1933; Magnussen, 1936; Griffiths and Fox, 1938; Janz, 1953). It was

later recognized that epileptiform discharges occur more frequently during non-rapid eye movement (NREM) sleep than in rapid eye movement (REM) sleep and waking periods (Gibbs and Gibbs, 1947; Gloor *et al.*, 1958; Shouse *et al.*, 1996). Arousals and transition periods between sleep stages were considered to facilitate epileptiform discharges (Terzano *et al.*, 1989; Halász, 1991; Gigli *et al.*, 1992). In this chapter, we discuss clinical and electroencephalographic (EEG) relations between generalized epilepsy and sleep and the effects of antiepileptic drugs on the sleep of patients with generalized epilepsy.

RELATIONS OF EPILEPTIC SEIZURES TO SLEEP–WAKE CYCLE

Langdon-Down and Brain (1929) were the first to subdivide epilepsy patients according to the occurrence of their seizures. They described (1) a "diurnal type," that seizure occurred predominantly during the day with a maximum following morning awakening and two smaller peaks in the afternoon; (2) a "nocturnal type," that seizures occurred during the night with maxima shortly after falling asleep and in the early morning hours; and (3) a group without any discernible pattern, the "diffuse type" (Langdon-Down and Brain, 1929). Relations of epileptic seizures to the sleep–wake cycle were evident from the observation that the times at which the seizures occurred changed when the sleep regimen was altered (Gowers, 1885; Marchand, 1931). Generalized tonic–clonic seizures show a clearer relation to the sleep–wake cycle than "minor seizures" show (Janz, 1962). However, myoclonic seizures tend to occur predominantly in the early morning hours shortly after awakening from night sleep in patients with juvenile myoclonic epilepsy (Janz and Christian, 1957; Gigli *et al.*, 1992). Based on the patients' recollections of their seizures and the patients' histories Janz (1962) classified epilepsies according to the time of occurrence of the "grand mal" seizures. He coined the term "awakening" epilepsy for patients, whose generalized tonic–clonic seizures predominantly occur in the first 2 h after awakening (Janz, 1962). A second peak was described in the afternoon (Feierabend) (Janz, 1962). Janz (1953) reported that in 45% of his 2110 patients with grand mal epilepsies, seizures happened predominantly during sleep: in 34% they occurred in the first 2 h after awakening from night sleep, and in 21%, no relation to the sleep–waking cycle was found. During the course of the epilepsy, the pattern may change, such as fewer patients having an awakening predominance (31%) and more patients showing a diffuse pattern (26%) (Janz, 1974). The awakening type seemed to be associated with idiopathic generalized epilepsy (Janz, 1962). Half of Janz's patients with hereditary idiopathic epilepsy belonged to the awakening group, whereas most patients with epilepsy secondary to brain tumors (53%) had a diffuse pattern of seizure occurrence and only 8% showed an awakening pattern (Janz, 1962). Of the 2110 patients 1059 also had "minor attacks" (Janz, 1962). The minor seizures in patients with epilepsy on awakening comprised predominantly absence seizures (94%),

myoclonic seizures (96%), and less frequently psychomotor seizures (16%) or jacksonian seizures (9%) (Janz, 1962). A major bias of the study of Janz (1962) is the observation that the recollection of epileptic seizures is unreliable (Blum *et al.*, 1996). Patients, their caregivers, and families are usually not able to accurately report on the seizure frequency and seizure occurrence, which could be demonstrated in an epilepsy monitoring unit using video recordings of seizures (Blum *et al.*, 1996). A considerable number of seizures, particularly minor seizures pass unnoticed (Blum *et al.*, 1996). The etiologic diagnoses are subject to uncertainties in the study of Janz (1962) because at that time no modern imaging studies were available. Few more current studies have dealt with the relation of the occurrence of generalized tonic–clonic seizures to the sleep–wake cycle (Billiard, 1982; Touchon *et al.*, 1982). The distribution of generalized tonic–clonic seizures was as follows in 77 of 141 patients with generalized epilepsy, in whom generalized tonic–clonic attacks were observed (Billiard, 1982): (1) 16.8% have had seizures after awakening, (2) 36.3% have had seizures during waking hours of the day, (3) 28.5% have had seizures during night sleep, and (4) 18.1% have had seizures both during night sleep and during waking periods of the day. Morning and nocturnal awakenings accounted for 36 of 51 seizures in 33 patients with juvenile myoclonic epilepsy, whereas the evening relaxation period ($n = 6$), sleep onset ($n = 3$), and sleep ($n = 6$) were less frequently associated with seizures (Touchon *et al.*, 1982).

SLEEP PATTERN OF PATIENTS WITH GENERALIZED EPILEPSY

Janz (1953, 1974) described that patients with awakening epilepsy and patients with sleep epilepsy had distinct sleep patterns and sleep habits. According to Janz (1953, 1974) patients with generalized epilepsy like to stay up late in the evening and often have difficulty falling asleep. Their sleep appeared to be disrupted. In the morning, they felt drowsy and unrefreshed, and preferred to get up late if they could (Janz, 1953, 1974). A different pattern was reported to occur in patients with focal epilepsy, who would fall easily into deep sleep and awake refreshed early in the morning (Janz, 1974). Early polygraphic studies seemed to support this concept (Christian, 1961; Jovanovic, 1967). The sleep EEG recordings were discontinuous in the study of Christian (1961), which does not allow interpretation of the sleep structure. Other investigators found no differences in the sleep patterns of patients with awakening and sleep epilepsy (Maxion *et al.*, 1973). Other polygraphic sleep studies in patients with idiophatic generalized epilepsy found normal sleep patterns unless seizures occurred during the night (Sato *et al.*, 1973; Tassinari *et al.*, 1974; Passouant *et al.*, 1975). These studies were performed either with patients on chronic antiepileptic medication or with patients for whom the drugs (usually phenobarbital and phenytoin) were discontinued a few days prior to the sleep investigations. Thus, chronic drug effects or rebound effects after discontinuation, which may influence the results, cannot be excluded.

Only one study (Röder-Wanner *et al.*, 1985) investigated the night sleep of unmedicated epilepsy patients. Adaptation nights to the sleep lab were also included in this study (Röder-Wanner *et al.*, 1985) to avoid "first night" effects (Agnew *et al.*, 1966). Photosensitive patients with generalized epilepsy had significantly more slow-wave sleep (sleep stages 3 and 4) and less light sleep (sleep stages 1 and 2) than the other patients with generalized epilepsy (Röder-Wanner *et al.*, 1985). No differences of global or structural sleep parameters were found between patients with generalized epilepsy ($n = 19$) and focal epilepsy ($n = 21$) as long as photosensitive patients with generalized epilepsy were excluded from the comparison (Röder-Wanner *et al.*, 1985). Likewise, no differences existed between patients with awakening epilepsy ($n = 12$) and patients with sleep epilepsy ($n = 12$) (Röder-Wanner *et al.*, 1985). Thus, the systematic polysomnographic evaluation of unmedicated patients with generalized epilepsy (Röder-Wanner *et al.*, 1985) did not reveal distinct sleep patterns in patients with awakening and sleep epilepsy hypothesized by Janz (1953) based on unstructured interviews.

RELATION OF EPILEPTIFORM DISCHARGES TO THE SLEEP–WAKE CYCLE AND SLEEP STAGES IN GENERALIZED EPILEPSY

The circadian sleep–wake cycle significantly influences the occurrence of epileptiform discharges (Shouse *et al.*, 1996). During non-REM sleep, generalized epileptiform discharges are more frequent than during waking and REM sleep (Gibbs and Gibbs, 1947; Gloor *et al.*, 1958; Billiard *et al.*, 1987). This observation is the rationale for performing sleep EEGs in patients, for whom the diagnosis of epilepsy is not established or the epilepsy syndrome is unclear and the waking EEG is unrevealing. Generalized epileptiform discharges increase gradually with deepening of NREM sleep (Ross *et al.*, 1966; Sato *et al.*, 1973). In patients with absence epilepsy the lowest discharge rates were found during REM sleep (Sato *et al.*, 1973). Because deep sleep stages are most pronounced during the first sleep cycle, it is not surprising that the highest rate of interictal epileptiform discharges were found during the first sleep cycle (Sato *et al.*, 1973). The morphology of generalized spike–wave complexes is more irregular during NREM sleep and is similar in waking and REM sleep (Ross *et al.*, 1966; Sato *et al.*, 1973; Tassinari *et al.*, 1974).

The hypothesis of Patry (1931) that transitional states between wake and sleep and vice versa may be epileptogenic in selected patients, was supported by polygraphic studies. Several authors demonstrated the facilitating effects of transitional states of sleep such as sleep onset, changes between sleep stages, and arousals on the occurrence of epileptiform discharges in patients with generalized (absence) epilepsy (Tassinari *et al.*, 1974; Passouant *et al.*, 1975; Halász, 1991). Niedermeyer (1982) emphasized that an abnormal paroxysmal response

to arousal and the influx of upward traveling stimuli seem to be the most important epileptogenic mechanisms in primary generalized epilepsy. The concept of the cyclic alternating pattern (CAP), which is based on these observations, provides a new approach and supports the idea that transitional cyclic sleep patterns activate epileptiform discharges (Terzano *et al.*, 1989).

SLEEP DEPRIVATION

Sleep deprivation is one of the most potent precipitators of epileptic seizures and epileptiform discharges in patients with generalized epilepsy. Janz (1957) reported that sleep deprivation and/or excessive alcohol consumption precipitated the first seizure in 28 of 47 patients with juvenile myoclonic epilepsy. Sleep deprivation also facilitates epileptiform discharges in patients with generalized epilepsy (Janz and Christian, 1957; Pratt *et al.*, 1968; Bechinger *et al.*, 1973). However, there is some debate as to whether sleep deprivation has a genuine activating effect on epileptiform discharges or acts by way of sleep induction (Degen and Degen, 1983). Direct comparison of drug-induced sleep EEG and EEG after sleep deprivation in patients with normal or borderline waking EEG revealed epileptic discharge activation in 44% after sleep deprivation versus 14% during drug-induced sleep (Rowan *et al.*, 1982). Another study compared the rate of epileptiform discharges of waking EEGs after sleep deprivation with sleep EEG after sleep deprivation and concluded that sleep deprivation had an independent activating effect because the waking EEGs after sleep deprivation showed more epileptiform discharges than the sleep EEGs after sleep deprivation (Klingler *et al.*, 1991).

EFFECTS OF ANTIEPILEPTIC DRUGS ON SLEEP

Many antiepileptic drugs exert some effects on sleep (some are also hypnotics). It was hypothesized that some of their antiepileptic effects may be mediated through an influence on sleep (Janz, 1974). Most studies evaluated short-term effects of the drugs often with healthy volunteers or patients with psychiatric disorders. The sleep studies of patients on chronic treatment were compared with what was considered normal sleep (Wolf *et al.*, 1985). One study compared the therapeutic effects of phenobarbital and phenytoin on the sleep of epileptic patients (generalized epilepsy, $n = 19$; focal epilepsy, $n = 18$; unclassified epilepsy, $n = 3$) intraindividually with their unmedicated baseline sleep, which is the best way to evaluate drug effects (Wolf *et al.*, 1984). Phenobarbital statistically significantly reduced the sleep onset latency from 11 to 5.6 min and the percentage of REM sleep from 18.5 to 14.5%. The number of periods of waking and movement time after sleep onset was reduced from 19.7 to 11.3

($p < .01$), and sleep stage 2 was increased from 43.7 to 47.9% [according to Rechtschaffen and Kales (1968)] (Wolf *et al.*, 1984). Sleep stage 4 was increased in the first sleep cycle only (from 25.4 to 45.1 min and REM sleep started later in each sleep cycle (Wolf *et al.*, 1984). Thus, the usual sleep pattern with maximal deep sleep at the beginning and maximal REM sleep during the second half of the night was accentuated by phenobarbital as deep sleep became still longer early in the night, and REM sleep was further postponed (Wolf *et al.*, 1984). The comparison of the patients with generalized and focal epilepsies revealed the following differences: whereas in patients with generalized epilepsy sleep stages 1–3 were decreased, stages 2–4 of focal patients were increased (Wolf *et al.*, 1984). Phenobarbital reduced the number of REM interruptions only in the patients with generalized epilepsy (including the patients with awakening epilepsy), which is an interesting finding with respect to the observation that transitions between sleep stages seem to provoke seizure discharges in these patients (Passouant *et al.*, 1975; Billiard, 1982; Halász, 1991).

The effects of phenytoin on the sleep of epileptic patients as derived from intraindividual comparison to unmedicated baseline sleep were as follows (Wolf *et al.*, 1984): patients fell asleep more rapidly (5.2 versus 11 min), deep sleep was increased (from 25.9 to 34.2%), and light sleep was decreased (stage 1 from 7.9 to 5.5% and stage 2 from 43.7 to 39.3%). These effects were more pronounced in the second part of the night (third to fifth sleep cycle). Unlike with phenobarbital, the amount and the interruptions of REM sleep remained unchanged with phenytoin. The usual sleep structure seemed to be leveled by phenytoin (Wolf *et al.*, 1984). The comparison of patients with generalized and focal epilepsy revealed only minor insignificant differences. The long-term study (at least 6 months) of phenytoin showed that, as mentioned earlier, the increase of deep sleep and the decrease of light sleep returned to baseline values and only the reduced sleep latency was lasting (Röder-Wanner *et al.*, 1987).

Ethosuximide showed increased light sleep (stage 1) and decreased deep sleep (stages 3 and 4) as compared with unmedicated baseline in patients with generalized epilepsy (Wolf *et al.*, 1985). REM sleep was prolonged in the first sleep cycle (Wolf *et al.*, 1985). Valproic acid led to an increase of light sleep stage 1, but no deep sleep changes occurred; as with ethosuximide, the first sleep cycle was prolonged (Wolf *et al.*, 1985). The effects of valproic acid and ethosuximide on the first sleep cycle may be related to the fact that these drugs were evaluated in patients with generalized epilepsy and these patients showed similar influences of phenytoin and phenobarbital on the first sleep cycle (Wolf *et al.*, 1985).

In summary, there are several effects of antiepileptic drugs on the sleep of patients with generalized epilepsy. However, most drug effects on sleep are nonspecific or temporary. Based on our present knowledge about the sleep of patients with generalized epilepsy, it appears that the antiepileptic effect of the drugs is only little, if at all, related to drug effects on sleep.

SUMMARY

Generalized epilepsy and sleep are related in several respects. Epileptic seizures occur predominantly in the first hours after awakening from night sleep or daytime naps in patients with generalized epilepsy such as juvenile myoclonic epilepsy. Sleep deprivation precipitates epileptic seizures.

Electroencephalogram (EEG) studies demonstrated that there is a tendency toward higher discharge rates of generalized epileptiform discharges during NREM sleep than in REM sleep and waking. Arousal and transitions between sleep than in REM sleep and waking. Arousal and transitions between sleep stages seem to facilitate generalized epileptiform discharges.

Very little information is available on the sleep of unmedicated epilepsy patients. Unmedicated patients with generalized epilepsy, who were photosensitive, show significantly more deep sleep than the nonphotosensitive patients with generalized epilepsy (34 versus 27%). No significant difference was found between generalized and focal epilepsy as long as photosensitive patients with generalized epilepsy were excluded.

Antiepileptic drugs have different effects on the sleep of patients with generalized epilepsy. However, there were only minor differences, particularly in the first REM cycle, between patients with generalized epilepsy as compared with patients with focal epilepsy.

In summary, conventional sleep analysis reveals no differences of sleep structure in unmedicated patients with generalized epilepsy as compared with patients with focal epilepsy (if photosensitive patients with generalized epilepsy were excluded). The analysis of sleep microstructure using the cyclic alternating pattern (CAP) may provide a more sophisticated approach to analyze the relation of sleep and generalized epilepsy.

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6

FOCAL EPILEPSY AND SLEEP

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INTRODUCTION

Many authors have chosen to describe sleep–epilepsy interactions as reciprocal relationships between the effects of sleep on epilepsy and the effects of epilepsy on sleep (Montplaisir *et al.*, 1985; Sammaritano *et. al.*, 1991). To understand these interactions between sleep and epilepsy, one must consider the timing of seizures during the 24-h sleep–wake cycle, that is, whether seizures

occur during the day (diurnal), during the night (nocturnal), or during the day and night (random). These seizure categories and their distribution, described by Janz (1962) and later adopted by Billiard (1982), became the first comprehensive efforts to study the timing of generalized seizures within the 24-h sleep–wake period. Janz reported that 45% of patients with generalized tonic–clonic seizures had seizures predominantly during sleep. Both Janz and Billiard defined three categories, including the "pure" sleep epilepsies, the "day" epilepsies, and the "diffuse" epilepsies, the latter occurring randomly throughout the sleep–wake cycle. Other authors, in both human and animal studies, have also demonstrated this cyclic variation in seizures (Lieb *et al.*, 1980).

This conceptual understanding of seizure timing also applies to the study of interictal discharges and their distribution during the 24-h sleep–wake cycle, that is, their occurrence during wakefulness, nonrapid eye movement (NREM) sleep, or rapid eye movement (REM) sleep. Numerous authors have shown that NREM sleep allows the propagation of interictal discharges and that REM sleep shows a suppression or focalization of interictal discharges (Lieb *et al.*, 1980; Rowan *et al.*, 1982; Rossi *et al.*, 1984; Montplaisir *et al.*, 1987). In addition, studies show that interictal discharges disrupt sleep (Elder *et al.*, 1997). These sleep-related events may be modulated or exhibit fluctuations depending on factors such as antiepileptic drugs (AED), sleep deprivation, and spontaneous sleep abnormalities. Reports show that the AEDs can directly suppress interictal discharges, instead of merely preventing the onset of seizures. The seizure type and etiology determine whether seizures occur predominantly during NREM sleep (as opposed to wakefulness) or randomly during the sleep–wake cycle (Shouse *et al.*, 1995). Sleep deprivation precipitates clinical seizures and activates both focal and generalized interictal discharges (Degen and Degen, 1991). Although the circadian sleep–wake cycle influences the expression or suppression of seizures, the mechanisms underlying the interactions between sleep, arousal, and seizures remain largely unknown.

Seizure patterns show a longitudinal stability over time, meaning that nocturnal seizures have a tendency to remain nocturnal, and seizures occurring both during the day and during the night also tend to recur within these same states. There are reports showing that frequent seizures entrained to a specific sleep or arousal state usually respond better to medical treatment than those that show a randomized timing (Shouse *et al.*, 1995).

VIDEO ELECTROENCEPHALOGRAPHY POLYSOMNOGRAPHY

Much of what has been learned about the interactions between sleep and epilepsy comes from clinical neurophysiological laboratories using intensive long-term monitoring units for the presurgical assessment of medically refractory epilepsy patients. To study these relationships, it requires using a technique that simultaneously records from two data acquisition systems with quantitative EEG and sleep analysis, that is, (1) recording from at least a 16-channel electroencephalogra-

phy (EEG) system with intensive long-term video epilepsy monitoring, either with extracranial and sphenoidal electrodes or with intracranial electrodes—including combinations of depth electrodes, subdural grids, and subdural strips; and (2) recording of a complete continuous polysomnogram. This is done in combination with visual editing of spikes and with software to analyze spikes per stage of sleep or during interspersed wakefulness (Sammaritano *et al.*, 1991). The sleep stage scoring should be visually verified. These methods may be effectively carried out through one system, only recently made available, that performs all these functions with one software system. This technique, as described, is called video EEG polysomnography, and may be used for both human studies and animal models and for both partial and generalized epilepsy. The video EEG polysomnography must be analyzed keeping in mind some common coincident variables: effects of AEDs or other drugs; seizure-free nights or nights with seizures that are partial, generalized, or with secondary generalization; baseline sleep quality; coexistence of other major sleep disorders; and etiology and severity of the epilepsy.

INTERICTAL SPIKING DURING SLEEP

Sleep causes important modifications of the EEG characteristics of epilepsy. The influence of sleep on interictal spike activity may be measured in terms of spiking rate, emergence of new spiking foci, and change in the electrical field (Sammaritano *et al.*, 1991). Spiking rate is affected by the occurrence of sleep and by the transition from one sleep state to another. NREM sleep has been shown by most authors to activate interictal activity in patients with partial epilepsy, with the maximal spiking rates occurring during the deeper stages (S3 and S4) of sleep, and less frequently, to occur during the lighter stages (S1and S2) of sleep (Rossi *et al.*, 1984; Sammaritano *et al.*, 1991; Scheffer *et al.*, 1995; Malow *et al.*, 1999).

In one study of 40 presurgical medically refractory temporal lobe epilepsy (TLE) patients, maximal spiking rates occurred in stages S3 and S4 in 78%, in S1 and S2 in 7%, and in stage REM in 13% (Sammaritano *et al.*, 1991). Figure 6.1 illustrates the changes in spiking rates as a function of sleep. The rates calculated for 34 patients who had maximal spiking in NREM sleep are divided randomly into two groups for purposes of illustration (Fig. 6.1). These results clearly show that maximal spiking rates occurred in S3 and S4 for the majority of patients studied (31 of 34) and that rates were reduced during REM and wakefulness, often of comparable value. For each patient, when spiking rates during REM sleep are compared with wakefulness, 28% showed values at approximate waking level and 42% showed values below the level of wakefulness. Specific characteristics of the patients who demonstrated a maximal spiking rate in REM sleep (5 of 40) could not be identified (Sammaritano *et al.*, 1991). Only one patient had a maximal spiking rate calculated for the state of wakefulness.

In a second study, by the same group, involving 20 medically refractory TLE patients, similar results were found with maximal spiking rates in stages S3 and S4 in 85% and in stages S1and S2 in 15% (Sammaritano and Sherwin, 2000).

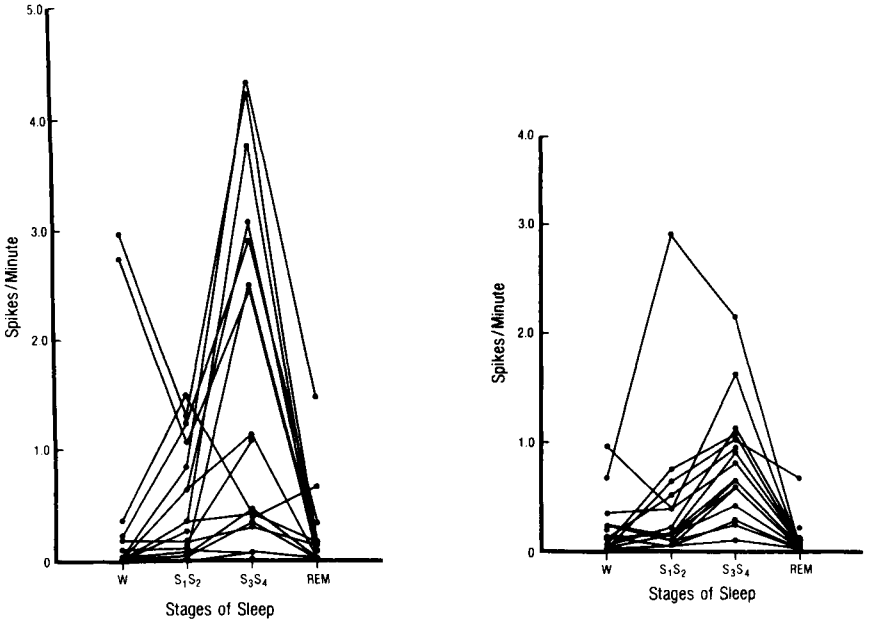

FIGURE 6.1 Changes in spiking rate as a function of wakefulness and sleep stages. Thirty-four patients with maximal spiking rates during NREM sleep divided randomly between two graphs for purposes of illustration. W, wakefulness; S1, S2, average of stages 1 and 2; S3, S4, average of stages 3 and 4; REM, stage REM. (From Sammaritano, M., *et al.*, Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology* **41**:290–297, 1991, reprinted with permission.)

During presurgical assessment of TLE patients, studies have reported both this activation of spiking during NREM sleep and during the recording in NREM sleep of a newly activated independent focus not present in wakefulness (Rossi *et al.*, 1984; Sammaritano *et al.*, 1991). At sleep onset and during NREM sleep, spiking rate has initially increased, and then decreased to the level of wakefulness or below that level in REM sleep. REM sleep and wakefulness have been found to have comparable capacity to elicit interictal spiking (Lieb *et al.*, 1978; Lieb *et al.*, 1980; Montplaisir *et al.*, 1985; Sammaritano *et al.*, 1991). Numerous authors have studied spiking across sleep stages and cerebral areas in an effort to determine the primary area of epileptogenicity or the area from which the clinical seizure originates (Rossi *et al.*, 1984; Montplaisir *et al.*, 1985; Sammaritano *et al.*, 1991). In one report so far, interictal spiking has been shown to disrupt the continuity of sleep (Sammaritano *et al.*, 1995).

NREM sleep is associated with an increased propagation of focal and generalized spikes, recorded as an extension of electrical field. REM sleep is associated with a focalization of interictal discharges or a restriction of electrical field (Lieb, 1980; Rossi *et al.*, 1984). In most studies reported, more spiking foci are seen in NREM than in REM sleep, and all REM foci are unilateral (Sammaritano *et al.*, 1991).

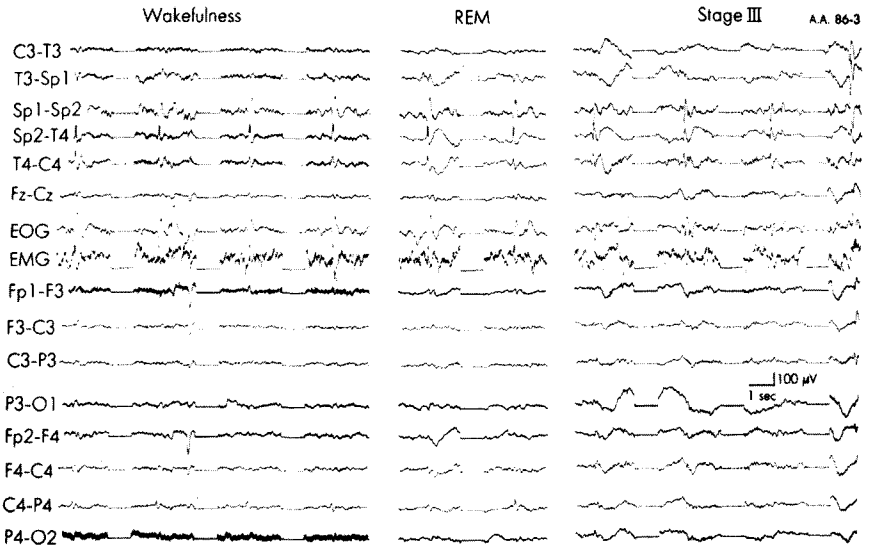

FIGURE 6.2 EEG from scalp and sphenoidal electrodes during wakefulness, sleep stage 3 and REM sleep for this same patient with a temporal lobe focus. Sp1 and Sp2 are the left and right sphenoidal electrodes. Note similarity of spiking fields in wakefulness and REM sleep and bilateral independent temporal spiking in stage 3. There is maximal focalization of spiking during REM sleep. (From Sammaritano, M., *et al.*, Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology* **41**:290–297, 1991, reprinted with permission.)

Epileptogenic spike foci may be recorded as unilateral temporal or bilateral independent temporal, depending on which state is recorded. Figure 6.2 shows an example from a TLE patient with a unilateral focus in wakefulness, bitemporal foci in slow-wave sleep (S3) with an extension of electrical fields, and a similarity of field and foci in wakefulness and REM. During wakefulness, spikes are recorded from the right inferomesial temporal region with phase reversals at Sp2. The electrical field extended to include the right midtemporal region. During slow-wave sleep, spikes are from the right inferomesial and midtemporal areas with a zone of equipotentiality at electrodes Sp2-T4. A new left temporal focus is recorded in slow-wave sleep (S3) that was not present in wakefulness. Also, the right temporal field extends to channels 3, 4, and 5, compared with channels 3 and 4 in wakefulness. During REM sleep, spikes are recorded from the right inferomesial temporal region, showing an identical right temporal focus and electrical field when compared with wakefulness.

REM sleep has the best localizing value for the primary area of epileptogenicity both in TLE (Sammaritano *et al.*, 1991) and in extratemporal lobe epilepsy (ETE) (Sammaritano and Saint-Hilaire, 1988) as seen by success and outcome of surgery. In the smaller series of ETE, all of whom were studied with intracranial electrodes, the maximal REM spiking rate was recorded from the precise site of consistent seizure origin, and the area surrounding this site had a

somewhat lower REM spiking rate (Sammaritano and Saint-Hilaire, 1988). Using REM sleep spiking data can improve the localization of epileptic foci in presurgical epilepsy patients. In certain centers for epilepsy surgery, routine selective use of REM sleep recordings of interictal spikes are done during presurgical assessment and are used as important information for the localization of the epileptogenic zone (Sammaritano *et al.*, 1991, 1995).

MODIFICATION OF SLEEP ARCHITECTURE IN EPILEPSY

Sleep disorders in epilepsy patients include both major sleep disorders diagnosed clinically and those identified by polysomnography (PSG), and the disorganization of sleep found in the majority of epilepsy patients. This disorganized sleep is attributed to effects of AEDs and other drugs, the occurrence of seizures, and the severity of the epilepsy. According to the literature (Baldy-Moulinier, 1982; Montplaisir *et al.*, 1985; Touchon *et al.*, 1991; Sammaritano *et al.*, 1996; Sammaritano and Saint-Hilaire, 1997), sleep architecture in epileptic patients is frequently altered by a decrease in total sleep time, an increase in the number of stage shifts, more frequent awakenings, and a reduction of up to 50% of REM sleep. Less common observations include an increase in NREM S1 and S2 sleep, a reduction in the spindle density, a decrease in NREM S4 sleep, and an increase in sleep onset latency and REM sleep latency. These observations constitute a summary of all current, well-noted sleep disturbances (without selecting for any uniform variables such as seizure type, seizure occurrence, or polytherapy). In severe forms of epilepsy, such as the Lennox-Gastaut syndrome, or in syndromes with generalized tonic–clonic seizures, the sleep is often difficult or even impossible to adequately score in the PSG.

However, in the majority of epileptic patients, the organization of sleep is disturbed, even in the well-controlled patients with TLE. As might be expected, the sleep architecture is more disrupted during nights with partial seizures, than in seizure-free nights. When compared with controls, REM sleep is found to be relatively preserved during the seizure-free nights, but is found to be altered more than other parameters during nights with seizures (Sammaritano and Saint-Hilaire, 1997). The sleep architecture is more disrupted in severe TLE than in comparable severe ETE, when comparing the seizure–free nights (Baldy-Moulinier, 1982; Crespel and Baldy-Moulinier, 1998). Others have substantiated these findings, showing that TLE patients have a nocturnal sleep pattern with a much lower efficiency index when compared with ETE patients (Bazil and Walczak, 1997). Touchon *et al.* (1987) have reported a severe disruption of sleep in TLE, even before the institution of therapy with the AED carbamazepine.

In one series of TLE patients, sleep analysis showed a decrease in the percentage of S4, an increase in the percentage of S3, and prolonged latency to S2

and S3. The REM percentage was statistically significantly decreased. The movement arousals, full awakenings, and stage shifts were increased in TLE patients compared with age-matched controls. Both sleep efficiency and continuity were decreased (Sammaritano *et al.*, 1994).

In contrast to their TLE patients, when these same authors looked at ETE patients, they found normal REM sleep statistics, normal sleep efficiency and continuity, and a percentage of S3–S4 more comparable to normal values. Rates of movement arousals, full awakenings, and stage shifts were also more comparable to controls (Baldy-Moulinier, 1982).

NOCTURNAL SEIZURES AND EPILEPSY

It is not understood why seizures, or even more difficult to understand, why certain seizure types occur preferentially during the night. Why is this mentioned? It follows that if one were to understand the mechanisms by which these seizures interact with sleep and consequently occur during the night, then perhaps one could use this understanding of mechanisms to aim at alternative therapeutic options.

Seizure occurrence is believed to be independently influenced by sleep onset, awakening, sleep deprivation (acute or chronic), and internal circadian rhythms. The frontal and temporal lobe seizures represent the largest group of partial seizure disorders that occur primarily or exclusively during sleep, that is, the "pure sleep epilepsies." Certain authors have shown that frontal lobe seizures occur more frequently during the night than do temporal lobe seizures (Crespel and Baldy-Moulinier, 1998). A study by Basil and Walczak (1997) showed that temporal lobe seizures that did occur during the night showed secondary generalization more frequently than did the frontal lobe seizures attacks.

The proportion of patients who have seizures occurring either exclusively or predominantly during sleep, depending on the study, ranges from 7.5 to 45% (Hayman *et al.*, 1997). Certain epileptic syndromes are defined by their relationship to sleep. Epileptic syndromes associated with sleep-related seizures include the following: benign partial epilepsy with centrotemporal spikes; benign epilepsy of childhood with occipital paroxysms; electrical status epilepticus of sleep with continuous spike–wave discharges and seizures in NREM sleep (associated with Landau-Kleffner syndrome); juvenile myoclonic epilepsy; Lennox-Gastaut; epilepsy with generalized tonic–clonic seizures (GTCS) on awakening; nocturnal TLE (Bernasconi *et al.*, 1998), autosomal dominant frontal lobe epilepsy (Scheffer *et al.*, 1995; Hayman *et al.*, 1997; Picard and Chauvel, 1999; Provini *et al.*, 1999); and paroxysmal nocturnal dystonia. It is important to identify these clinical syndromes diagnostically with neuroimaging and EEG, because certain syndromes can be targeted as having a better prognosis. For example, the nocturnal temporal epilepsy syndrome has been identified, and these patients have been shown to have a better surgical outcome (Bernasconi *et al.*, 1998).

The nighttime ultradian cycle, defined as a cycle occurring within the 24-h sleep–wake cycle, also affects the timing of partial seizures. In a study by Sammaritano and Saint-Hilaire (1997), nocturnal temporal lobe seizures occurred predominantly in NREM sleep, particularly during S2 (52%), S3, and S4 (44%), suggesting an underlying rhythmicity, with 44% of seizures occurring during the first third of the night, as opposed to their random occurrence during the night. In several reported studies, seizures frequently occurred during transitions to and from REM sleep, but not during stable REM sleep (Cadhillac, 1982; Sammaritano and Saint-Hilaire, 1997). Higher rates of sleep spindles per minute are calculated in PSGs of patients when partial seizures occur, than in the PSGs of the same patients when recordings are seizure free. The calculated spindle per minute rates before the first seizure were higher than the spindle per minute rates following the seizure(s), suggesting higher rates or changes in sleep synchronization (Sammaritano and Saint-Hilaire, 1997).

Analysis of sleep microstructure of these same patients with TLE showed that the PSGs containing nocturnal seizures had the following results: each seizure was followed by a full awakening (100%); seizure onset occurred immediately after stage shift to deeper sleep (59%); and seizures occurred close to the onset of REM episodes (28%). These findings held for nights with a single seizure or multiple seizures (Sammaritano and Saint-Hilaire, 1997).

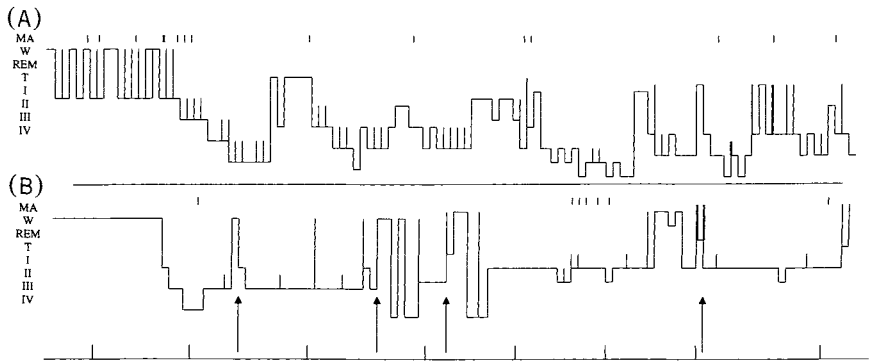

FIGURE 6.3 A comparison of hypnograms and related statistics using Somnis C software (AMISYSE), a semiautomatic method for sleep analysis of polysomnograms, which was validated by manual scoring: (A) Depicts the sleep in a medically refractory temporal lobe epilepsy (TLE) patient during a seizure-free night, with sleep organization being disrupted when compared with an age-matched nonepileptic patient; (B) depicts the sleep of this same patient during a night when four seizures were recorded. (The levels of antiepileptic medications were constant for the two recordings.) A comparison between (B) (four seizures) with (A) (seizure free) shows a greater disruption of sleep in the recording with seizures than in the seizure-free recording. Abbreviations: A, movement arousal; W, wakefulness; REM, rapid eye movement sleep; T, transitional stage; I, stage 1 sleep; II, stage 2 sleep; III, stage 3 sleep; IV, stage 4 sleep; h (hour) or mn (minute) indicates time. Recordings started at 23 h and ended at 7 h. Each line on the *x*-axis divided the hypnogram into intervals of 1 h. Sleep efficiency + total sleep time/final awakening time − lights off time. Sleep continuity = total sleep time/final awakening time − time of sleep onset. (From M. Sammaritano, unpublished observations.)

Figure 6.3A and B shows an example of the effects of seizures on sleep as measured by PSG. Figure 6.3A represents the sleep of a medically refractory TLE patient recorded during a seizure-free night, and Fig. 6.3B represents, in this same patient, a PSG recorded with four clinical seizures. The patient in the seizure-free recording served as his own control for the recording with seizures, to eliminate the well-recognized influence of antiepileptic medications on the PSGs. For each patient the AED levels were measured and kept constant for both the seizure-containing and seizure-free recordings. In Fig. 6.3A, Table 6.1a, the efficiency and continuity of sleep are decreased when compared with normal values, even in this seizure-free recording. The number of shift changes is increased, but the percentage of stages S1, S2, S3, S4, and REM are normal. In Fig. 6.3B, four partial seizures without secondary generalization are recorded all during stage S2 of NREM sleep. Three seizures occurred near the beginning of the night, at times: 01:27; 02:29; and 03:21 h. The fourth seizure occurred during the last third of the night at 06:02. Refer to the arrows indicating the time of onset of seizures in Fig. 6.3B. When Fig. 6.3B, with seizure, is compared with Fig. 6.3A, seizure free, a further disturbance of sleep parameters is illustrated. In Fig. 6.3B, Table 6.1b, the efficiency is markedly decreased to 0.66, compared with 0.85, in Fig. 6.3A, Table 6.1a. In Fig. 6.3B, again compared with Fig. 6.3A, there is a decrease in REM sleep, 3.8 versus 17.4 min; a decrease in sleep stages S1 and S3; and an absent S4. Stage S2 is increased, which helps to understand the decrease in percentage of S3 and the absent S4. In Fig. 6.3B, three out of four seizures oc-

TABLE 6.1 Polysomnographic Sleep Indices in a Medically Refractory Temporal Lobe Epilepsy Patient during a Seizure-Free Night

(a)

				Sleep architecture		
Parameters		Sleep latency		Duration	%TRT	%TST
Recording onset	23 h0	I	13 mn			
Lights off time	23 h0	II	84 mn	I	101 mn	21.6
Final awakening time	7 h0	III	98 mn	II	125 mn	26.8
Total recording time	481 mn	IV	108 mn	III	73 mn	15.66
Time in bed	480 mn	REM	131 mn	IV	38 mn	8.1
Total sleep time	408 mn			REM	71 mn	15.2
Wake during sleep period	72 mn	Indices		T	0 mn	0.0
Number of awakenings	22 mn	Efficiency: 0.85		Number of stage shifts: 103		
Movement arousals	16	Continuity: 0.87				
Minutes not scored	0 mn					

(continues)

TABLE 6.1 *(Continued)* Polysomnographic Sleep Indices in This Same Medically Refractory Temporal Lobe Epilepsy Patient (as in 6.1a) during a Night with Four Partial Seizures

(b)

Parameters		Sleep latency		Sleep architecture: Duration	%TRT	%TST
Recording onset	23 h0	I	93 mn			
Lights off time	23 h0	II	96 mn	I	23 mn	6.4
Final awakening time	7 h0	III	111 mn	II	248 mn	68.9
Total recording time	481 mn	IV	mn	III	31 mn	8.6
Time in bed	480 mn	REM	391 mn	IV		0.0
Total sleep time	317 mn			REM	12 mn	3.3
Wake during sleep period	163 mn	Indices		T	3 mn	0.8
Number of awakenings	12	Efficiency: 0.66		Number of stage shifts: 46		
Movement arousals	10	Continuity: 0.88				
Minutes not scored	27 mn					

curred close to the onset of a REM episode. The unstageable sleep was most likely the postictal slow-wave activity immediately following each seizure. It is important to note that both PSGs are abnormal. The seizure-free PSG recording was more abnormal than the age-matched control PSG, and the PSG with four clinical seizures was more abnormal than the seizure-free recording.

A comparison of sleep efficiency and sleep continuity using these same methods in 10 patients with medically refractory TLE showed a sleep efficiency of 0.88, a continuity of 0.80 in PSGs with seizure(s), a sleep efficiency of 0.92, and a sleep continuity of 0.86 in PSGs that were seizure free (Sammaritano *et al.*, 1994).

The sleep disruption demonstrated in PSGs with multiple seizures recorded can cause the patient to experience poor sleep quality and subsequent sleep deprivation that may easily cause the symptom of excessive daytime sleepiness. It is well accepted that sleep deprivation is a precipitant of seizures (Degen and Degen, 1991). If there were a method to stabilize the disorganized sleep of epileptic patients during seizure and seizure-free nights, then this method might present another treatment option for seizure control.

The answer to the question as to why certain types of seizures are preferentially facilitated by sleep largely remains unknown. Hypotheses proposed to explain the basis for the occurrence of nocturnal seizures that have been summarized by Malow and Plazzi (in press) include: (1) NREM synchronization, (2) arousals and awakenings from sleep, (3) circadian factors and the sleep–wake cycle, and (4) anatomic location.

The first proposal is that NREM sleep is a physiological state of neuronal synchronization, so that the recruitment of a critical mass of neurons needed to initiate and sustain it is more likely to occur during these NREM sleep stages. By means of simultaneous recordings from thalamus, thalamocortical projection neurons, and pyramidal neurons in anesthetized cats, NREM sleep has been described as a state of relative synchronization or hyperpolarization with the thalamocortical neurons. Subsequently, there is a progressive reduction in the spiking rates of brain stem monoaminergic and cholinergic efferents. This synchronization can be seen in the EEG of NREM sleep, which is characterized by sleep spindles and high-amplitude delta waves (Steriade *et al.*, 1993, 1994; Steriade and Contreras, 1998). Evidence supporting this hypothesis of NREM synchronization varying across sleep stages also comes from Gloor's (1979) penicillin model of generalized epilepsy, in which spindle oscillations are transformed into bilaterally synchronous spike–wave complexes (Gloor, 1979). In clinical studies, Sammaritano and Saint-Hilaire (1997) have shown that there is increased spindle production, or synchronization, occurring prior to the onset of a seizure as recorded by PSG in TLE patients. Further support for this role of NREM sleep in activation of seizures comes from the studies of interictal epileptiform discharges that become more frequent in NREM sleep, with a maximal predominance in deep sleep (S3 and S4) in the majority of cases (Sammaritano *et al.*, 1991; Malow *et al.*, 1999).

Arousals and awakenings from sleep may facilitate seizures. Shouse and Sterman (1983) and Shouse (1986, 1987) have recorded synchronous excitatory input from neurons in the posterior hypothalamus of the awake cat, which may facilitate seizures by projecting to the neocortex, and by causing an exacerbation of cortical hyperexcitability. Shouse has also mentioned that the arousal or awakening can either precede or occur at the same time of seizure onset.

Quigg and colleagues (1998) proposed that circadian factors play a more important role than those related to the sleep–wake cycle. In their studies, a comparison was made between the time of seizure occurrence in both rat models of epilepsy and human epilepsy. A peak was found during the day, which was associated with limbic seizure generation in both species. The primary circadian pacemaker, instead of sleep, was found to have more effect on limbic seizures, because both rats and humans showed a definite "in phase" seizure distribution (Quigg *et al.*, 1998).

Certainly, the neuroanatomic substrate is an important factor, because many of the sleep-related epilepsy syndromes are associated with seizures of frontal lobe origin. Crespel and Baldy-Moulinier (1998) compared patients with frontal lobe epilepsy (FLE) and mesial temporal lobe epilepsy and found a significant difference between the two groups. In the frontal lobe group, the majority of seizures occurred during sleep; in the temporal lobe group the majority of seizures occurred in wakefulness. These results suggest a difference in neuronal excitability associated with sleep between temporal and frontal structures. In FLE patients, the architecture is less disorganized when compared with the

patients with TLE (Baldy-Moulinier, 1982; Sammaritano *et al.*, 1996; Crespel and Baldy-Moulinier, 1998). Bazil and Walczak (1997) also found that frontal lobe seizures occurred more often during sleep, and they report a higher risk for secondary generalization when temporal lobe seizures occurred during sleep. This may reflect the more severely disrupted sleep organization seen in TLE patients (Baldy-Moulinier, 1982).

Until more definitive studies are done, all these above postulated mechanisms should be considered when answering the question: Why do certain epileptic seizures and syndromes occur during the night?

EFFECTS OF ANTIEPILEPTIC DRUGS ON SLEEP

Few studies show the effects of anti-epileptic drugs (AEDs) on sleep by means of PSGs. This is especially true of the more recently released AEDs. Very few PSG studies have been done on normal controls before and after drug administration. PSG studies of epilepsy patients usually involve medically refractory groups, with no baseline PSGs (drug free) done, because patients cannot stop all AEDS until drug clearance, due to possible complications of status epilepticus, or recurring generalized or partial seizures. Human subjects are studied while receiving a somewhat reduced amount of medication, aiming for stable AED doses.

There is a longitudinal stability to seizures; for example, seizures that remain nocturnal for 6 months are very likely to remain nocturnal. There is evidence that state-dependent seizures are more responsive to medical treatment than are seizures that occur randomly in the sleep–wake cycle (Shouse and da Silva, 1996). However, reports show that AEDs can reduce seizure frequency and cause the remaining seizures to become randomly dispersed in the sleep–wake cycle. The reason for this is unknown.

The older or "classical" AEDs have found widespread use in conditions other than epilepsy, but the discovery of primary or secondary uses was often through serendipity. With the "newer" AEDs, drug development is usually based on the targeted epileptogenic mechanism. What separates the classical from the newer AEDs in regard to mechanism of action is the number of different γ-aminobutyric acid (GABA) mechanisms found in many of the newer compounds (Sammaritano and Sherwin, 2000). Although phenobarbital and the benzodiazepines have GABA effects, the newer AEDs such as vigabatrin, topiramate, and tiagabine are more specifically aimed at GABA. These latter drugs have the greatest variety of mechanisms implicated in their actions as AEDs. When the number of mechanisms is increased, then the potential exists for the use of these drugs for other indications; and it can be proposed that these newer AEDs might be of therapeutic value in regulating other types of central nervous system (CNS) disturbances.

Studies have shown that some AEDs may improve sleep stability and quality. Janz (1974) looked at the circadian pattern of generalized major motor seizures and called them either sleep-related seizures, seizures on awakening, or diffuse seizures (random). He stated that the AEDs had a stabilizing effect on sleep by correcting the spontaneous sleep abnormalities associated with epilepsy. He found that drugs effective in treating seizures on awakening increased S3 or S4 of NREM sleep, and that drugs used for sleep-related seizures were effective only if they reduced S3 and S4 sleep. Since that time, it has been shown that most AEDs give rise to normalization and stabilization of sleep (Sammaritano and Sherwin, 2000). It is possible that sleep improvement plays a role in the therapeutic effects of these drugs. The beneficial effect may be expressed as the occurrence of more regular cycles of sleep, or as a decrease in time spent awake during the sleep cycle after the use of an AED and may be a consequence of an increased arousal threshold. There is evidence that valproic acid and carbamazepine stabilize and regulate sleep architecture (Findji and Catani, 1982; Declerck and Waquier, 1991). Of the classical AEDs, carbamazepine has the most convincing evidence for the stabilization of sleep in healthy controls, and in epileptic patients, both with acute and with chronic administration (Riemmann, 1993; Gigli *et al.*, 1994; Gigli *et al.*, 1997; Crespel and Baldy-Moulinier, 1998; Sammaritano and Saint-Hilaire, 1998). Touchon (1991) showed in TLE patients that sleep disturbance was worse before carbamazepine therapy than after treatment. There are no well-controlled studies available for the effects of many classical AEDs on sleep, and some of the newer drugs have not yet been studied at all, such as lamotrigine, topiramate, tiagabine, and vigabatrin.

Of the newer compounds, there are two existing PSG studies of gabapentin, one with normal controls and one with epilepsy patients. Rao and Clarenbach (1988) showed that gabapentin in healthy controls increased the S3 and S4 of deep NREM sleep; in epilepsy patients, Placidi and colleagues (1997) found a significant increase in percentage of REM sleep and a reduction in the number of awakenings. In a qualitative analysis of sleep, Ehrenberg *et al.* (1997) found a subjective improvement in nighttime sleep and daytime alertness.

CONCLUSIONS

Sleep and epilepsy have reciprocal influences on each other; that is, there are the effects of sleep on epilepsy and the effects of epilepsy on sleep. The circadian sleep–wake cycle influences sleep–epilepsy interactions. Certain epileptic syndromes occur exclusively during sleep. Although several proposals have been discussed, the mechanisms at this time remain unclear. NREM sleep promotes the diffusion of interictal spiking, and REM sleep causes the focalization of spikes. State-dependent nocturnal seizures usually remain nocturnal over time, and may respond better to anticonvulsant medications than those seizures that occur randomly during the sleep–wake cycle. Maximal interictal spiking rates in

the majority of reports occur during NREM sleep, S3 and S4, in partial epilepsy. The selective recording of interictal spikes during REM sleep aids in the presurgical evaluation of temporal lobe and extratemporal lobe medically refractory epilepsy patients. The sleep architecture is modified in partial epilepsy patients when compared with age-matched controls. Seizure control may improve with the recognition and treatment of the co-incident sleep disorders that may also disrupt sleep architecture in epileptic patients. The TLE patients have a more severe sleep disorganization than the extratemporal lobe group, as has been shown by several authors. Sleep architecture of partial epilepsy patients is more disrupted during nights with seizures than during seizure-free nights. Ultradian cycles affect the timing of partial seizures, suggesting an underlying rhythmicity. There is evidence that the AEDs improve sleep quality, especially for carbamazepine and gabapentin. The stabilization of sleep of epilepsy patients may lead to improved seizure control.

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7

EPILEPSY IN THE NEONATE AND INFANT AND SLEEP

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INTRODUCTION

Associations between sleep and epilepsy have been increasingly appreciated by neurologists caring for patients with seizure disorders (Mahowald and Schenck, 1997). Interrelationships between sleep and epilepsy during childhood and adulthood have also been addressed (Donat and Wright, 1982; Dalla Bernardina *et al.*, 1983; Bourgeois, 1996; Mahowald and Schenck, 1997). Issues related to the diagnosis of epileptic syndromes and an improved understanding of the pathophysiological mechanisms of epileptogenesis are the two areas that comprise these types of studies. Four possible associations have been discussed:

1. The influence of sleep on interictal and ictal events
2. Modifications of sleep organization induced by epileptic seizures and other epileptic processes
3. Specific epileptic syndromes that are expressed during sleep
4. Nocturnal nonepileptic events

There are a number of well-described epileptic syndromes associated with sleep during childhood (i.e., >2 years), such as benign epilepsy with centrotemporal spikes, autosomal dominant nocturnal frontal lobe epilepsy (FLE) and juvenile myoclonic epilepsy. For the younger child, an understanding of sleep organization may help classify seizure states during the neonatal and infancy periods when epileptic syndromes are not as well recognized or described.

Despite our growing understanding of the rapid stages of sleep ontogeny from birth through 1 year of age, associations between sleep and seizure occurrence remain elusive. A review of the literature reveals only anecdotal comments concerning seizures and sleep during this age span, without specific causal reference to sleep–wake transitions.

Therefore, this chapter explores the possible associations between sleep maturation and epilepsy, as it pertains specifically to the neonatal and infancy periods. An ontogenetic approach to sleep maturation in relation to seizure risk during early life is highlighted (Scher, 1996). While the epileptologist should follow a general assumption to link seizure risk to sleep, the neonate and infant may, in fact, have unique physiological relationships between sleep state transitions and seizures. As this review highlights, only a few clearly defined epileptic syndromes have been identified during this age range, despite dramatic modifications during functional brain maturation in sleep architecture, continuity, and cycle length.

This chapter covers the following areas:

1. Discussion of the emergence of a unique but transitory ultradian sleep cycle during the fetal and neonatal periods, which rapidly evolves from a fetal to infant pattern over 12–16 weeks of maturation
2. Development of circadian periodicity (by 3 months of age) before the appearance of nocturnal organization of the sleep cycle

3. Recognition of encephalopathic states including seizures for the neonate or infant, usually in the absence of sleep/state expression
4. Epileptic syndromes during neonatal and infancy periods that are unique from epileptic syndromes in the older child
5. Nonepileptic paroxysmal behaviors that occur during sleep, which may clinically resemble seizures in the neonate or infant

UNIQUE ASPECTS OF THE ULTRADIAN SLEEP RHYTHM OF THE FETUS AND NEONATE

Physiologists have long described the basic rest activity cycle (BRAC), which is expressed in the immature organism both in utero and during extrauterine life. Incorporated in this BRAC is rudimentary state development, whether in the fetus or in the preterm neonate less than 36 weeks postconceptional age (PCA). This sleep state cycle alternates between rapid eye movement (REM) and nonrapid eye movement (NREM) segments, first evident after 30 weeks PCA. Four distinct electroencephalographic (EEG) polygraphic stages are subsequently expressed over successive ultradian (i.e., <24 h) sleep cycles after 36 weeks PCA (Scher, 1996).

Three developmental niches for sleep maturation are recognized in the fetus or preterm neonate. The earliest temporal coincidence among multiple sleep behaviors is evident by the fetus or preterm neonate by 30–32 weeks PCA, although inconsistently expressed across successive sleep cycles. Figure 7.1 il-

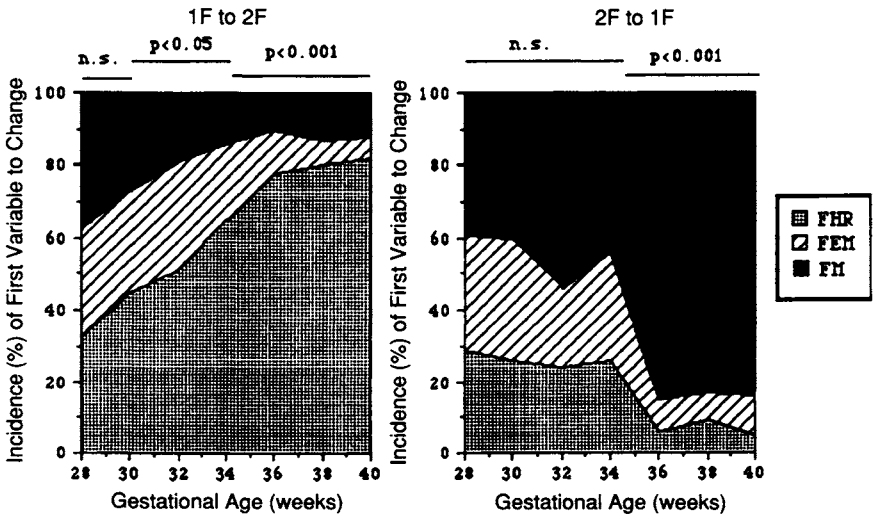

FIGURE 7.1 Distribution of behavioral variables as first variable to change during transitions from quiet to active sleep (i.e., 1F to 2F) and from active to quiet sleep (i.e., 2F to 1F). (From Arduini *et al.*, 1991, Walter de Gruyter & Co. Publishers, reprinted with permission.)

lustrates how coincidence among multiple physiological parameters has a lower significance level before 36 weeks gestation in the fetus. By 36 weeks PCA, the temporal coalescence among multiple sleep behaviors over successive sleep cycles is consistently expressed over time for the individual and is recognizable between different individuals. This allows a higher predictability of state transitions for both the individual child and the population (Arduini *et al.*, 1991). Such a developmental niche is achieved both by the preterm neonate who matures in an extrauterine environment and by the fetus while in utero.

The ultradian sleep-state cycle for the near-term and term neonate (i.e., >36 weeks and <46 weeks PCA) consists of two active (or REM) sleep segments that begin and end for each cycle, in addition to two quiet (NREM) segments interspersed between each REM state. The major NREM segment is discontinuous (i.e., tracé alternant), which is unique over the human life span. Arousals punctuate both active and quiet sleep segments, and may accompany state transitions or apneas within an individual segment.

The third developmental niche for sleep maturation begins after 46 weeks PCA, at which time the fetal/neonatal sleep behaviors evolve into infant sleep state expression. The four-part ultradian sleep cycle of the neonate is no longer expressed; for example, tracé alternant, the quiet sleep segment of the neonate, is replaced by a high-voltage slow segment, which now represents NREM sleep for the infant. No expression of stage 1 or 2 NREM sleep, however, is expressed until after 6 months of age. In summary, the sequence of sleep cycle reorganization of the fetus and neonate and the age-specific temporal occurrence of multiple physiological behaviors occur rapidly over a 12–16 week period of brain development (i.e., 30–46 weeks PCA) and most likely reflect rapid functional maturation of the neuronal systems that subserve motility, REM, and autonomic and cortical behaviors during sleep.

Differences among prenatal, neonatal, and early infancy sleep-state characteristics for architecture, continuity, cycle length, and physiological coalescence are illustrated in Fig. 7.2. As noted earlier, temporal occurrences of multiple behaviors during sleep-state transitions have also been documented in the fetus or neonate of comparable gestational ages. Intrauterine monitoring of the fetal baboon, for example, demonstrates similar maturation of state organization after 36 weeks PCA as noted for the preterm newborn. A shorter cycle length is noted in the less mature fetus. In addition, a diurnal effect showing greater state organization during the waking hours with a peak at 14:00 h is also present even prior to term age in the fetal baboon (Stark *et al.*, 1998).

Preterm neonates, within an extrauterine environment, have similar state reorganization as noted for the fetus at comparable ages of maturity. As described for the prenatal baboon, humans express an increasing duration of state cycling from 8 to 30 min by 36 weeks PCA. As with a fetal primate, there is an increase in active sleep percentage as the child matures closer to term PCA. Similarly, the coincidence among multiple sleep variables, which is first expressed by 30–32 weeks

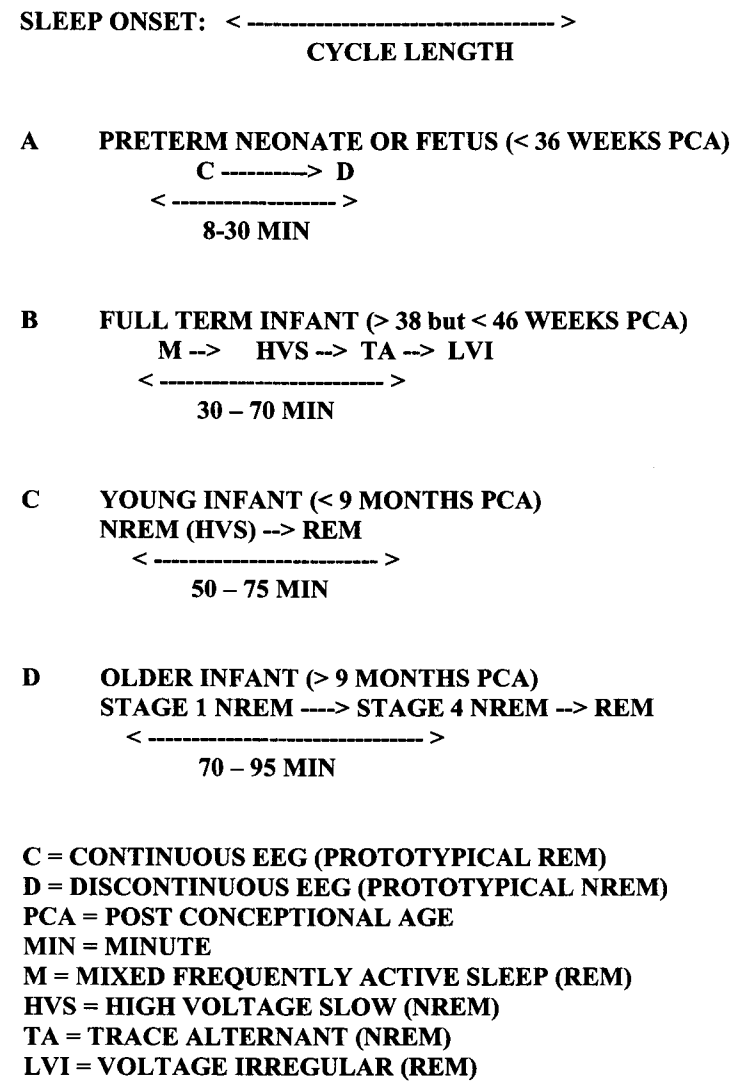

FIGURE 7.2 Differences in sleep onset architecture and cycle length among fetal, neonatal, and infancy sleep cycles.

PCA, coalesces over successive sleep cycles after 36 weeks PCA. A weak diurnal effect is also present in the preterm neonate, like the fetus, as illustrated by a change in spectral power between 9 P.M. and 9 A.M. over a 12-h recording period (Fig. 7.3).

Sleep ontogeny continues after the neonatal period during early infancy, with dramatic changes over the first 2 years of life. By 4–6 weeks of age, tracé alternant quiet sleep pattern disappears. Parasagittal or midline sleep spindles first are expressed after 8–16 weeks of age (Scher, 1996).

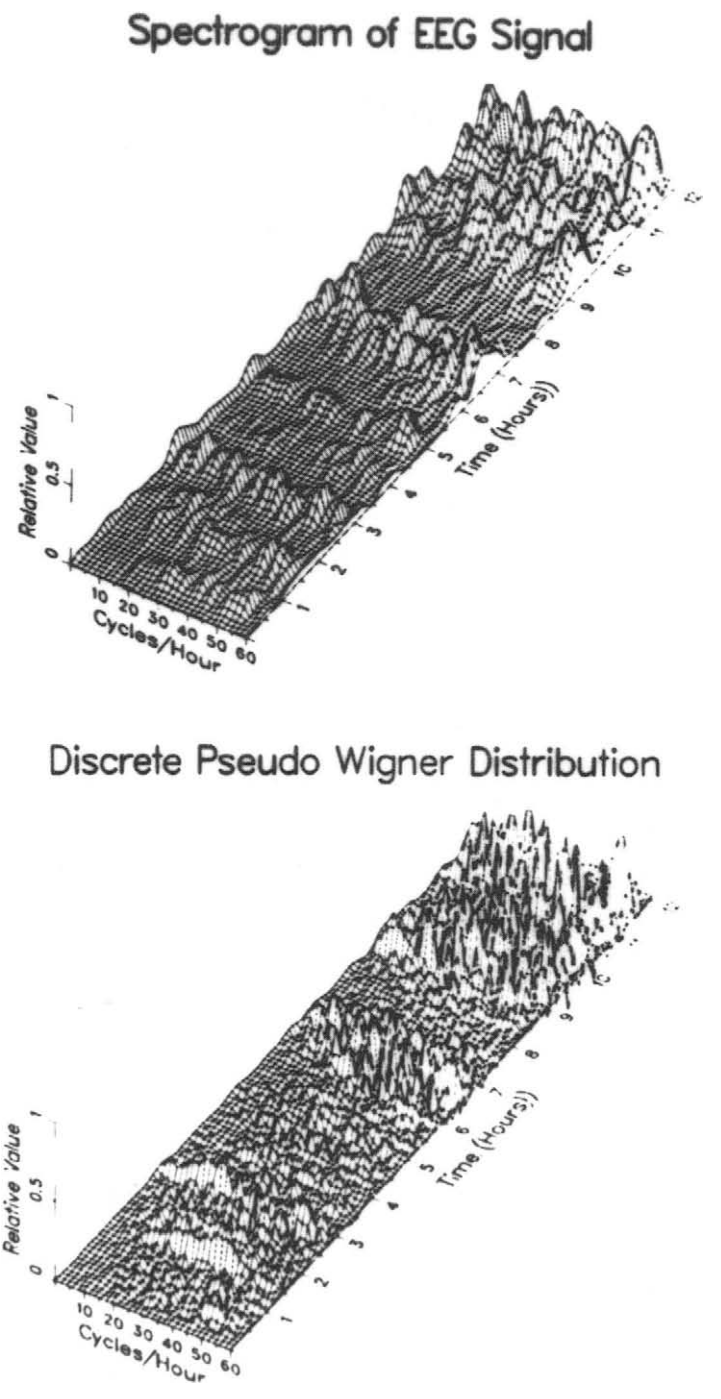

FIGURE 7.3 A 12-h EEG recording, noting changes in spectral EEG power between 9 P.M. and 9 A.M. for a full-term infant. Note the increase in delta power toward the morning hours.

SLEEP REORGANIZATION DURING INFANCY

By using serial home polygraphic studies on 15 normal infants, Louis *et al.* (1997) documented sleep ontogeny over the first 2 years of life. These authors noted several major maturational aspects of sleep organization during infancy (Figs. 7.4A and 7.4B):

1. Circadian periodicity by 3 months of age precedes nocturnal reorganization of the sleep cycle.
2. Diurnal organization of the sleep cycle precedes nocturnal organization of the sleep cycle.
3. Stage 2 non-REM sleep is consistently expressed after 9 months of age.
4. The sleep cycle lengthens to that of an adult (i.e., 75–90 min) over the first year of life.

These major reorganizational changes in sleep occur in the normal child over the first 12 months of life. In addition, decreases in total sleep time over the 24-h day, consolidation of nocturnal sleep time, increasing percentages of quiet sleep, and declining percentages in active sleep also occur during this rapid period of brain maturation. Despite this rapid evolution of sleep architecture, continuity, and spectral power over the first year of life, few examples of sleep and epilepsy relationships can be cited for the neonate and young infant.

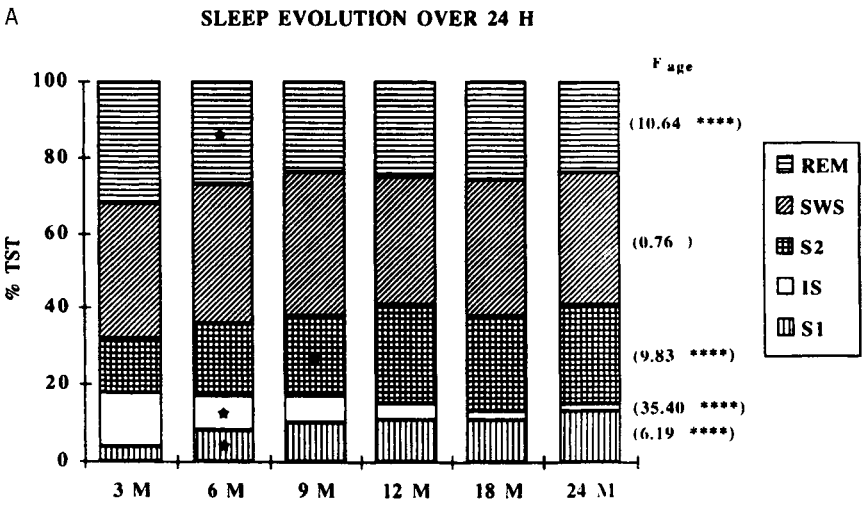

FIGURE 7.4A Appearance of circadian periodicity by 3 months of age preceding reorganization of the architecture of the sleep cycle.

B

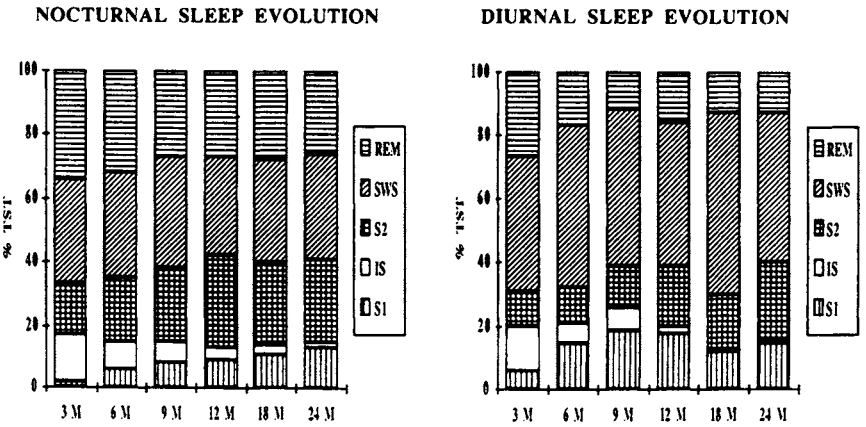

FIGURE 7.4B A diagram illustrating the earlier diurnal organization of the sleep cycle of the infant that precedes nocturnal organization of the sleep cycle. (From Louis *et al.*, *Sleep* **20**(5):330, 1997, reprinted with permission.)

EPILEPTIC SYNDROMES DURING NEONATAL/INFANCY PERIODS

NEONATAL SEIZURES

Neonates with seizures are not primarily associated with epileptic syndromes, with or without sleep activation (Scher, 1997). Newborns largely express seizures as part of transient acute encephalopathic states or severe chronic encephalopathies. Children with brain disorders because of hypoxic ischemic encephalopathy, brain infections, or cerebrovascular disease, for example, present with seizures exclusively during neonatal period, with a risk for epilepsy approximating 20%. Commonly, neonates with seizures also express severe interictal abnormalities, in the absence of sleep-state organization. Less commonly, neonatal seizures may occur after remote brain injury, malformation, or metabolic/genetic disease that originated during the antepartum period. For newborns with different chronic brain disorders, diffuse interictal encephalopathic EEG patterns are generally not as strongly expressed. Alternately, sleep transitions may be more easily identified, but appear dysmature or disorganized. Prolonged video EEG/polygraphic monitoring can more efficiently document neonatal seizures with respect to specific behavioral phenomena during different sleep states. However, as stated earlier, newborns generally express encephalopathic EEG patterns in the absence of organized state transitions. Less commonly, seizures may occur during active or quiet sleep if chronic or remote brain insults occurred, in the absence of an acute brain disorder (Watanabe *et al.*, 1982).

An association between sleep-initiated breathing disorders and seizure control has been recognized in children and older adults (Mahowald and Schenck, 1997). Obstructive sleep apnea in the older patient may result in worsening of

either daytime or nocturnal seizure control. However, such a relationship has not been established for the neonate or infant. While apneas and bradycardias commonly occur in the neonate and infant, these events are rarely clinical expressions of coincident seizure activity, or reflect worsening seizure states. Neonates with recurrent autonomic dysfunction, including desaturations, cardiac dysrhythmias, apneas, or blood pressure alterations (Figs. 7.5A and 7.5B), may be associated with electrographic seizures (Scher, 1997).

BENIGN FAMILIAL NEONATAL (INFANTILE) CONVULSIONS

This rare epileptic syndrome can occur during either neonatal or infancy periods (Berkovic *et al.*, 1994; Bievert *et al.*, 1998). Seizures occur in otherwise healthy infants during preserved sleep transitions. Seizures usually occur within the first several days of life but can begin or recur for several weeks to months in a particular child. Despite a normal clinical examination and normal interictal EEG background patterns, the ictal pattern on the EEG is generally characterized by a sudden suppression of background activity during the tonic phase of the seizure, followed by the emergence of the ictal pattern coincident with the clonic phase of the seizure (Figs. 7.6A and 7.6B).

Molecular genetic studies have isolated the genetic material responsible for benign familial neonatal convulsions to chromosome 20Q and 8Q. Positional cloning has identified a gene that impairs potassium-dependent repolarization; this miscoding of a five-nucleotide sequence leads to a stop codon and the elimination of approximately 300 amino acid sequences. Other forms of benign convulsions have also been described in infants without a family history of neonatal seizures; this suggests that other genetic loci, as yet undiscovered, may be involved.

Sleep organization during which neonatal seizures occur has only been incidently mentioned for this epileptic syndrome. In a study of 20 patients with benign familial neonatal convulsions, all seizures were noted during sleep instead of the awake or transitional sleep segments (Berkovic *et al.*, 1994). However, because the neonate and young infant usually spend a large percentage of each day asleep, no direct causal connection between seizures and sleep onset has been definitely proved.

BENIGN EPILEPSIES OF INFANCY

Benign myoclonic epilepsy in infancy is a rarely documented clinical syndrome, usually in healthy children between 6 months and 3 years of age (Vigevano *et al.*, 1997; Pachatz *et al.*, 1999). Patients have a normal developmental trajectory, although family members with epilepsy or febrile convulsions have been described. The myoclonic attacks are brief, usually involve the head or arms, and may be augmented during drowsiness; attacks may subsequently subside during sleep. EEG sleep recordings document a temporal

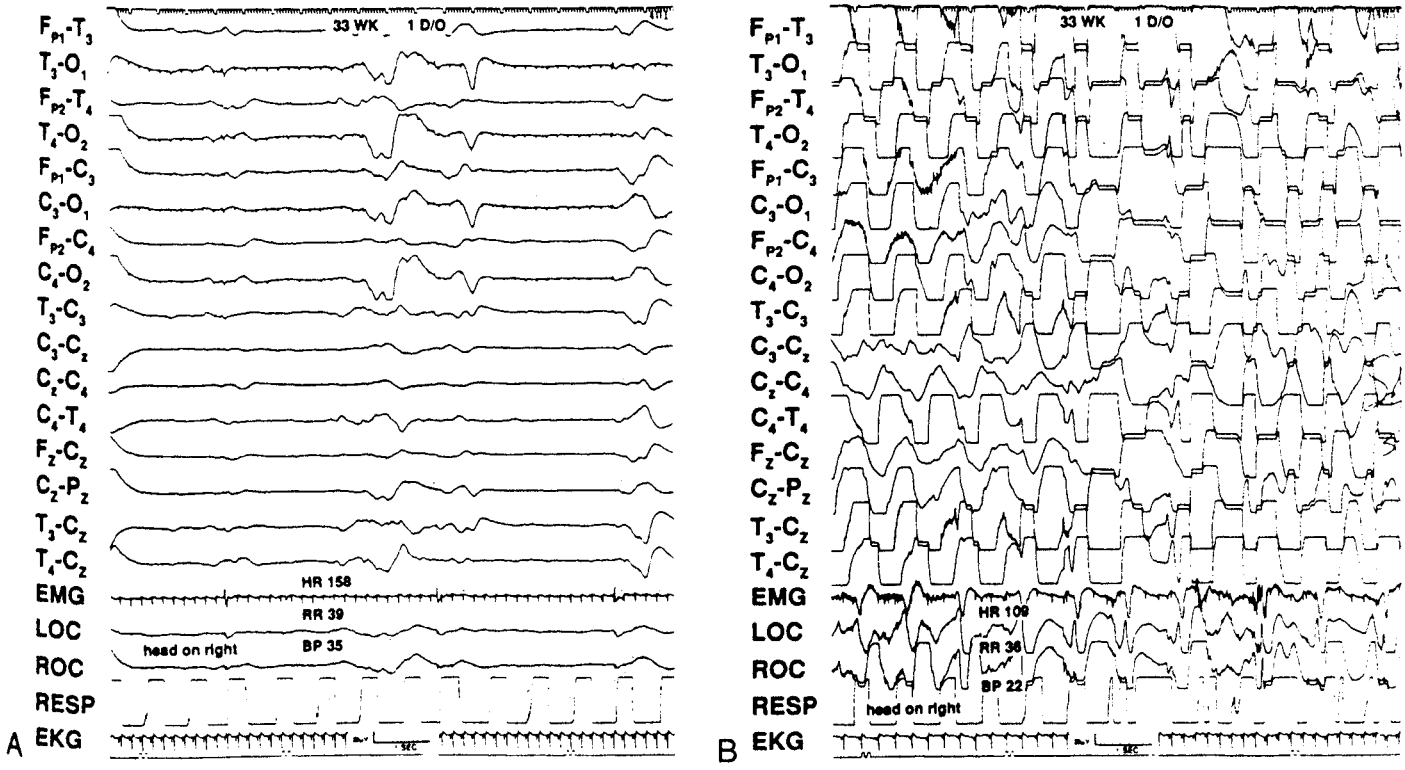

FIGURE 7.5 (A) Segment of an EEG of a preterm infant of 31 weeks at 1 day of age, showing the excessive discontinuous EEG pattern. (B) A burst of high-amplitude slow-activity coincident with electrographic seizure with a sudden change in blood pressure and heart rate. Note the changes in autonomic findings from the interictal to ictal periods. Such seizures are noted in the absence of organized sleep cycling in the encephalopathic preterm or full-term neonate.

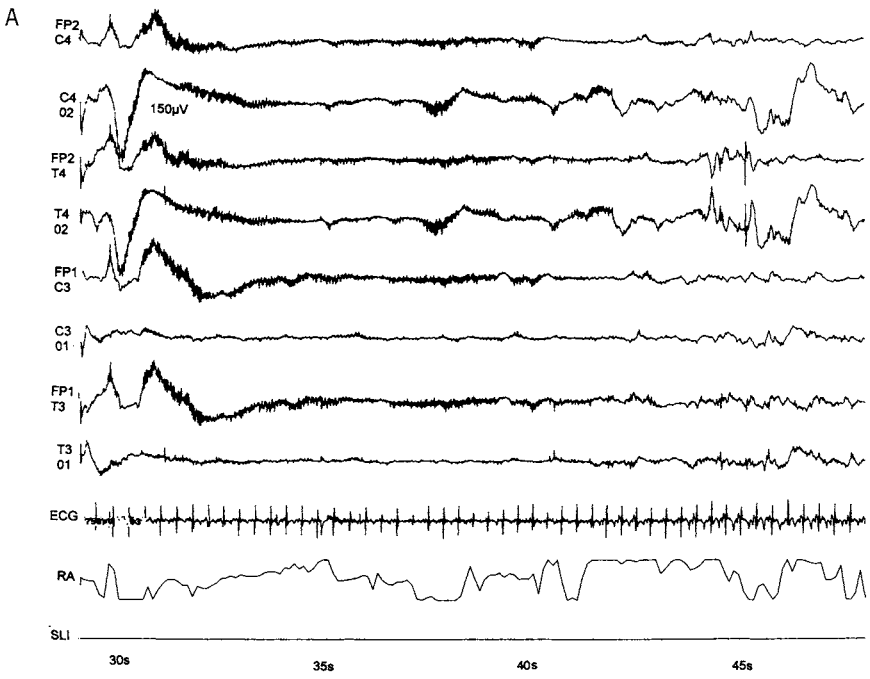

FIGURE 7.6A EEG of a seizure recorded in a full-term infant with benign familial neonatal epilepsy. Note the onset of a seizure with diffuse flattening of the EEG recording during the tonic phase of the seizure. (From Plouin, P., Benign Familial Neonatal Convulsions, In *Epilepsy: A Comprehensive Textbook,* J. Engel and T. A. Pedley, eds., Philadelphia: Lippincott–Raven, 1997, Chapter 24, p. 2250, reprinted with permission.)

relationship between clinical myoclonus and spike or poly spike–wave discharges Fig. 7.7).

This group of children may have either generalized or focal seizures, also mostly during the drowsy period and rarely during NREM or REM sleep segments. Seizure types may also be present during the waking state.

The clinician must be careful to note the neurodevelopment status of these children, because severe myoclonic epilepsy of infancy may also be present in children with significant developmental delay. Several authors have described either spontaneous myoclonic seizures or reflex-induced myoclonic seizures during different stages of sleep; although rigorous sleep studies have not been performed, EEGs of these children usually document persistent myoclonic seizures after sleep onset, unlike the group with benign myoclonic epilepsy who express seizures during the waking–transitional sleep periods. Other epileptic syndromes during childhood are commonly associated with sleep activation, including benign centrotemporal epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and benign partial epilepsy with occipital spike waves. However, children with these syndromes appear during toddler or childhood years.

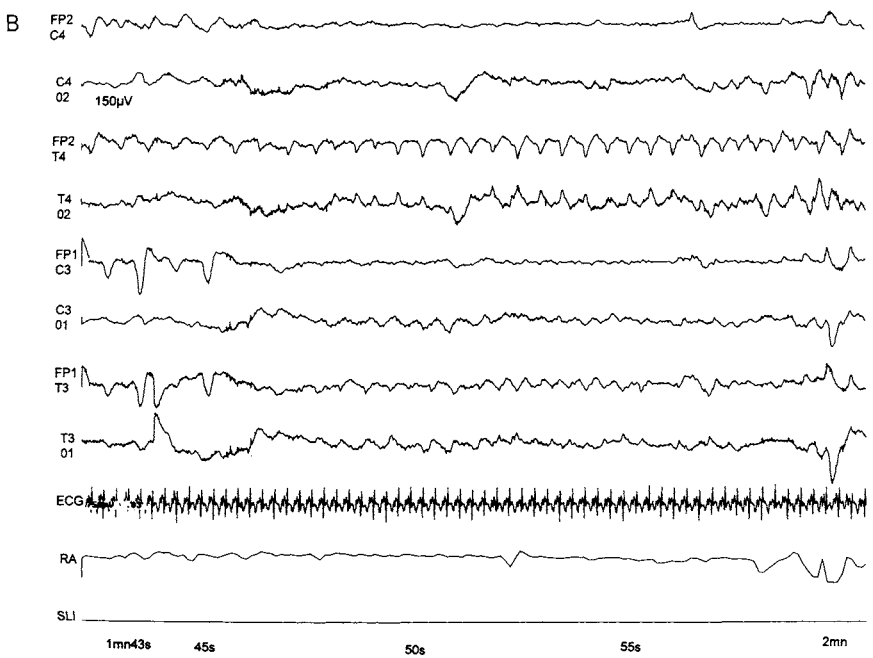

FIGURE 7.6B EEG of a recorded seizure in a full-term neonate with benign familial neonatal epilepsy subsequent to Fig. 7.6A, documenting bitemporal ictal discharges during the clonic phase of the seizure. (From Plouin, P. Benign Familial Neonatal Convulsions, In *Epilepsy: A Comprehensive Textbook,* J. Engel and T. A. Pedley, eds., Philadelphia: Lippincott–Raven, 1997, Chapter 214, p. 2251, reprinted with permission.)

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY

This is an unusual epileptic syndrome associated with a burst suppression pattern on the EEG; such neonates or infants are significantly abnormal on neurological examination. Ohtahara *et al.* (1976) first described children with this early-onset brain disorder with significant suppression burst pattern on these EEGs. Many of these children exhibit severe myoclonic seizures, which may resemble early-onset infantile spasms or West syndrome. Sleep organization is generally not present or is poorly organized.

INFANTILE SPASMS OR WEST SYNDROME

This particular electroclinical syndrome usually occurs with a specific age of onset between 3 months and 1 year, although individuals may present as neonates up to 3 years of life (Dulac, 1998). Specific clinical and electroencephalographic characteristics are relevant to the present discussion of relationship of sleep and epilepsy during early life.

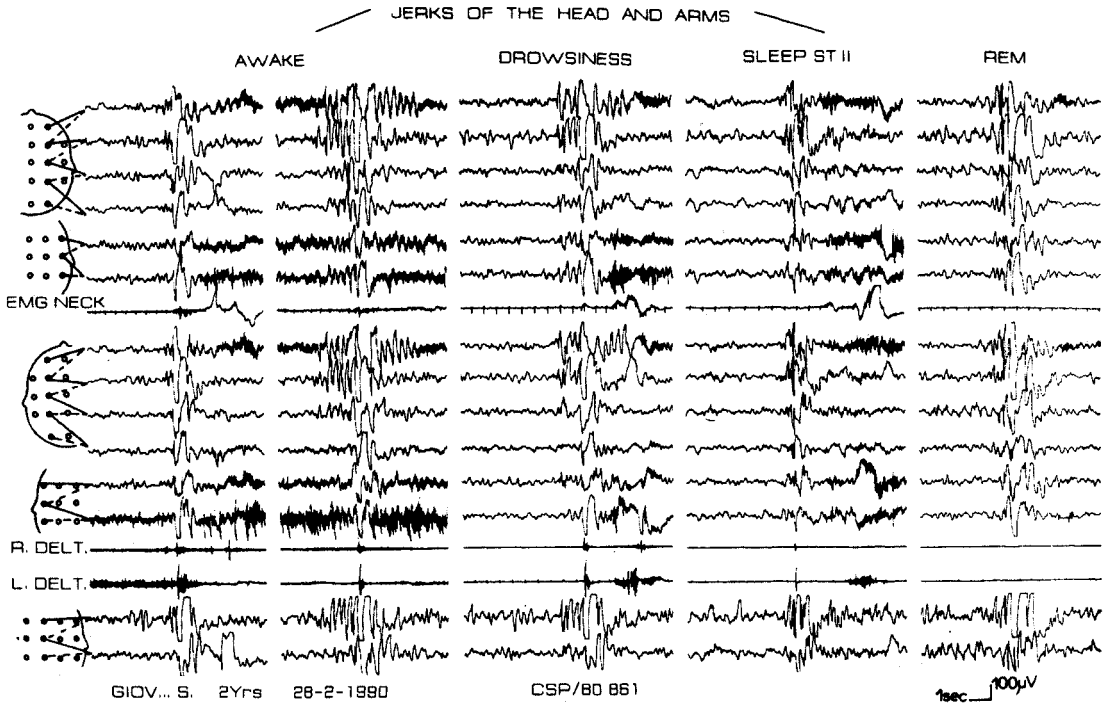

FIGURE 7.7 An example of benign myoclonic epilepsy in infancy in a 2-year-old infant. Myoclonic movements were documented during wakefulness, drowsiness, and sleep accompanied by generalized spike and wave discharges. While generalized discharges with myoclonus can appear during sleep, they usually disappear after the drowsy period. (From Roger J., *et al.*, Less Common Epileptic Syndromes, In *The Treatment of Epilepsy Principles and Practice,* E. Wyllie, ed., Philadelphia: Lea & Febiger, 1997, Chapter 39, p. 586, reprinted with permission.)

Hypsarrhythmia is the interictal EEG pattern for a portion of patients with infantile spasms; high-voltage polymorphic delta activity with multifocal spikes or spike, or sharp wave discharges comprise this pattern. While the pattern is generally seen during the waking state, it may also appear during sleep with certain electrographic modifications. During NREM sleep, the voltage may become greater, with multifocal spike and sharp wave discharges, which occur in a more bisynchronous manner. During sleep, the brief periods of attenuation become more frequent, possibly with a suppression burst pattern (Figs. 7.8A and 7.8B).

Generalized electrodecremental episodes are the most common electrographic accompaniments to clinical infantile spasms. These occur during wakefulness but can also occur during sleep, even in the absence of clinical seizures. Infants with infantile spasms have decreased total sleep time and lower percentage of REM sleep. Following treatment with adrenocorticotrophic hormone (ACTH) or prednisone, an increase in REM percentage has been described. Such observations have led to the consideration that the primary defect underlying this epileptic syndrome may be brain damage sustained during critical periods in early infancy, involving brain stem structures responsible for the regulation of REM sleep. However, etiologies for infantile spasms are diverse, ranging from brain malformations, neurocutaneous syndromes, hypoxic ischemic encephalopathy, and chromosomopathies such as Down's syndrome.

SEVERE EPILEPTIC ENCEPHALOPATHIES

A number of severe epilepsies during early infancy may reflect a static condition of injury, or less commonly, metabolic/degenerative diseases. While the Lennox-Gastaut electroclinical syndrome usually occurs beyond infancy, some patients present as early as 1 year of age. The interictal EEG pattern consists of slow spike or wave discharges that are generalized, maximal over the frontal head regions. These slow spike or wave discharges can be further activated during drowsiness and NREM sleep.

Antiepileptic medications may also have an indirect effect on sleep organization. With antiepileptic medications, a decrease in the number of microarousals associated with seizures may ultimately improve both sleep organization and seizure control. Specific drugs such as phenobarbital may shorten sleep latency, increase the proportion of S2 sleep, decrease the proportion of REM sleep, and decrease the number and duration of arousals. Phenytoin alternatively may shorten sleep latency but has no effect on arousals or REM sleep percentage (Scher, 1996). Most studies, however, have centered on adults; few reports have addressed antiepileptic medication effects on sleep in young infants with seizures.

NONEPILEPTIC BEHAVIORS DURING SLEEP

Nonepileptic disorders during sleep can be mistaken for epilepsy (Herrmann *et al.*, 1993; Scher and Vigevano, 1997; Fusco *et al.*, 1999). Three groups of patients with which potential diagnostic errors can be made have been discussed. First,

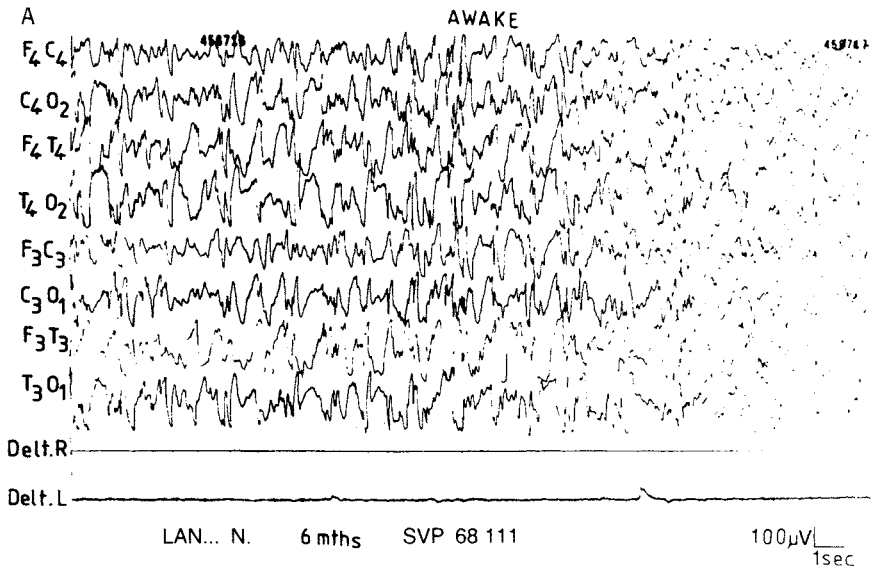

FIGURE 7.8A Example of infantile spasms at 5 months of age, showing an interictal recording with atypical hypsarrhythmia, with continuous and asynchronous spike and wave activity during the waking state. (From Dulac, O., *et al.*, Infantile Spasm and West Syndrome, In *The Treatment of Epilepsy Principles and Practice,* E. Wyllie, ed., Philadelphia: Lea & Febiger, 1993, Chapter 33, p. 469, reprinted with permission.)

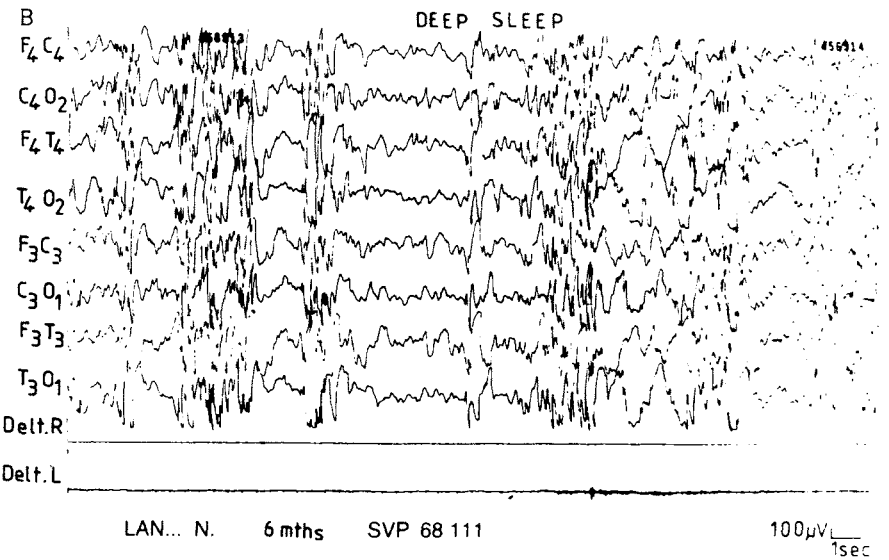

FIGURE 7.8B Same patient as Fig. 7.8A, showing fragmentation of the hypsarrhythmic pattern during sleep. Note the more synchronized irregular, generalized spike and wave discharges. (From Dulac, O., *et al.*, Infantile Spasm and West Syndrome, In *The Treatment of Epilepsy Principles and Practice,* E. Wyllie, ed., Philadelphia: Lea & Febiger, 1993, Chapter 33, p. 469, reprinted with permission.)

adults or children with sleep disorders that are confused as seizures include nightmares, night terrors, and other arousal disorders during NREM sleep. A second diagnostic group includes sleep disorders that could be misdiagnosed as epilepsy during either NREM sleep or REM sleep, such as head-banging, obstructive sleep apnea, automatic behavior disorders, and nocturnal enuresis. A third group represents epileptic disorders that can be mistaken for sleep disorders; nocturnal complex partial seizures of temporal or frontal lobe origin or nonconvulsive status epilepticus may be mistaken for nonepileptic nocturnal hypnogogic paroxysmal dystonia or episodic nonictal nocturnal wanderings.

For the child less than 1 year of age, a number of unique clinical phenomena occur during drowsiness or sleep that can easily be confused with epileptic events as listed in Table 7.1.

The most common sleep phenomenon during infancy that can be confused with seizures is hypnogogic myoclonus or sleep myoclonus (Fig. 7.9). Such movements may be misrepresented as possible seizures, particularly by anxious parents. Parents describe a jerk or start usually during drowsiness or light sleep. It may be problematic, even with home videotaping to document such events. Video EEG/polygraphic monitoring can better document events that are independent to electrographic changes, to distinguish benign neonatal sleep myoclonus from myoclonic epilepsy or infantile spasms. Repetitive nonepileptic sleep starts may also occur in neurologically impaired children, who also may have day or nighttime seizures.

Other phenomena that may be confused with epileptic seizures include shuddering attacks during drowsiness or arousal. Infants with these movements appear tremulous, and involve not only the head but also the upper torso or extremities.

Stimulatory behavior such as head-banging, head-rocking, or masturbation can also occur during drowsiness or arousal, and may mimic clinical seizure

TABLE 7.1 Examples of Nonepileptic Paroxysmal Disorders during Sleep

Unusual movements
Shuddering (during drowsiness or arousal)
Masturbation during drowsiness or arousal
Benign sleep myoclonus
Startle responses
Episodic features of specific disorders
Gastroesophageal reflux during sleep
Respiratory derangements
Apnea
Behavior disorders
Head-banging
Nightmares
Night terrors

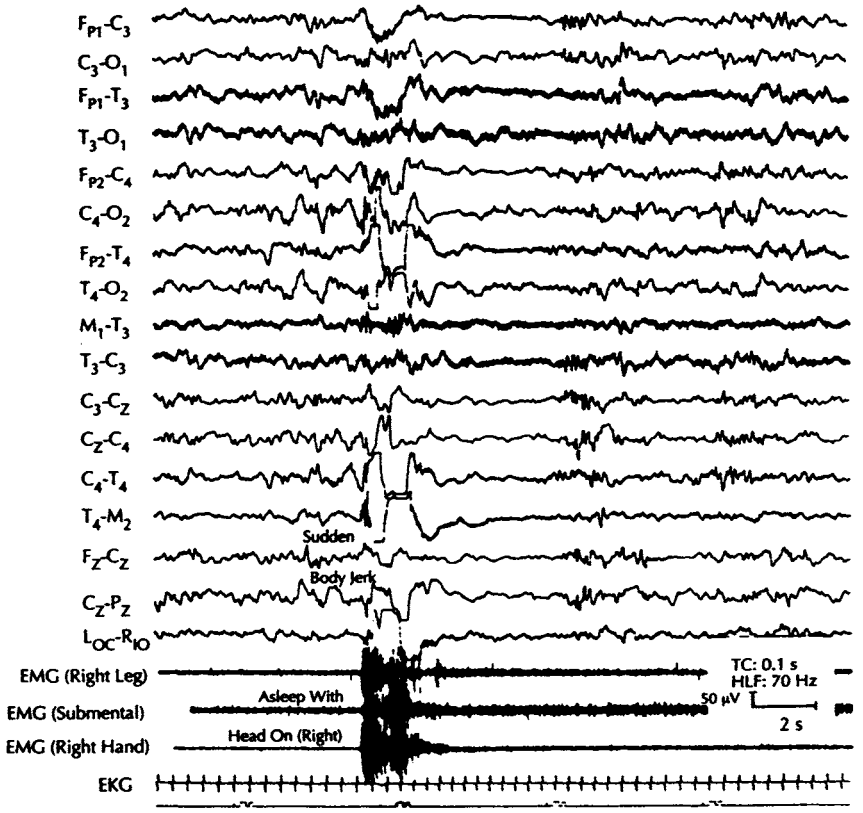

FIGURE 7.9 An example of benign myoclonus of the neonate. Note the prominent myogenic potentials in the absence of electrographic seizures.

activity. Nightmares may occur during REM sleep, and night terrors may occur during NREM sleep in the infant less than a year old. Both of these events superficially resemble seizures. Night terrors tend to occur earlier during the night, shortly after the first NREM period, while nightmares can occur during any REM sleep segment, usually in the early morning hours.

Additional phenomena may also be a source of confusion. Dystonic events during sleep in young infants may represent gastroesophageal reflux (GER). While GER can also occur during the wakeful state, clinical events may occur predominantly or exclusively during sleep; video EEG monitoring with pH probe monitoring can help document this abnormality. While nocturnal paroxysmal dystonia generally does not occur under 2 years of age, dystonic posturing followed by sudden arousal may superficially resemble mesial frontal lobe seizures. Video monitoring may more readily document ictal and interictal electrographic abnormalities in association with such behaviors.

SUMMARY

Many epileptic syndromes affecting the older child are activated during drowsiness, sleep, or arousal from sleep. While there are specific childhood epileptic syndromes that characteristically involve sleep, few epileptic syndromes are described for the child under 1 year of age. Interestingly, this time period from birth through 1 year is rapidly evolving with respect to sleep architecture, continuity, arousal, and cycle length. While the ontogeny of circadian and ultradian organization of sleep and wakefulness is undergoing rapid and tremendous changes, few associations between sleep transitions and seizures have been described. The absence of strong circadian influence until 3 months of age, and little expression of "lighter" stages of NREM (i.e., stage 1 and 2) until after 9 months of age are two examples of maturational characteristics that may limit the expression of seizures during sleep in the neonate or infant.

Aggressive use of EEG/PSG recordings, including simultaneous video documentation, can assist in establishing whether a clinical phenomenon is epileptic or nonepileptic. Further investigations for epileptic syndromes during the neonatal and infancy periods must include both EEG and PSG evaluations. Understanding the effects of antiepileptic medications on sleep also may contribute to more accurate classification of nonepileptic behaviors during sleep.

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8

CYCLIC ALTERNATING PATTERN AND SLEEP

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EPILEPSY AND VIGILANCE STATES

The variations of the arousal level across the 24-h rhythm play an important role in the modulation of epileptic events. The sleep–wake cycle, and particularly the conditions of instability that occur during sleep, affect significantly the appearance of interictal electroencephalography (EEG) discharges and epileptic seizures. This interaction, either in the sense of inhibition or, more frequently, in the direction of activation, relies on the characteristics of the epileptic syndrome (type of attacks, clinical course, and etiology), on the time of the day, and on the structural components of sleep (falling asleep, EEG arousal, nonrapid eye movement (NREM) stages, and rapid eye movement (REM) sleep). In particular, the two neurophysiological states that characterize sleep (NREM and REM) have opposite consequences on interictal abnormalities and on critical manifestations. A pioneering contribution published 60 years ago on the incidence of epileptic attacks over the 24-h period indicated a clear circadian variation (Griffiths and Fox, 1938). During sleep, the number of seizures showed a gradual increase from midnight to dawn. The early morning peak was followed by a sharp reduction until noon. There was a small postmeal peak, while a considerable increase in seizure incidence was found again in the early evening hours.

Other 24-h studies have investigated the influence of the vigilance states on the occurrence of epileptic manifestations, showing that epileptic manifestations are more likely to appear when the level of vigilance is low (relaxation, drowsiness, or sleep) and unstable (arousal fluctuations) and that frequency and morphology of epileptiform EEG patterns may depend on sleep stages. According to most studies, generalized discharges and clinical seizures mostly occur in NREM sleep, which may be globally considered a natural "convulsive agent" (Passouant, 1991). The large majority of EEG paroxysms are found in stage 2 of

sleep, although there are reports of a maximum of discharges during stages 3 and 4. In contrast, there is general agreement on the fact that the number of EEG abnormalities, especially generalized bursts, is lowest during REM sleep (Shouse *et al.*, 1996). These findings clearly indicate that the epileptic event is extremely sensitive to the ongoing arousal condition. Because the vigilance states vary across the diurnal and nocturnal periods and because the changing functional states of the brain seem to have important modulatory effects on most epilepsies, a survey of the basic mechanisms underlying the sleep–wake continuum is outlined.

SLEEP PROPENSITY AND BODY TEMPERATURE RHYTHMS

An important modulation of the sleep–wake rhythm is mediated by the endogenous circadian system. Both human and animal studies have demonstrated that the mammalian circadian oscillator is located in the suprachiasmatic nuclei of the antierior hypothalamus and serves as a topical source for the timing boundaries of sleep and wakefulness in the 24-h cycle. Independent of other factors, the circadian clock potentiates wakefulness at one phase of the diurnal cycle and facilitates sleep at the opposite phase (Fig. 8.1). This autonomous pacemaker determines the sleep propensity in relation to other biological functions and, in particular, to the rhythmicity of deep body temperature. The

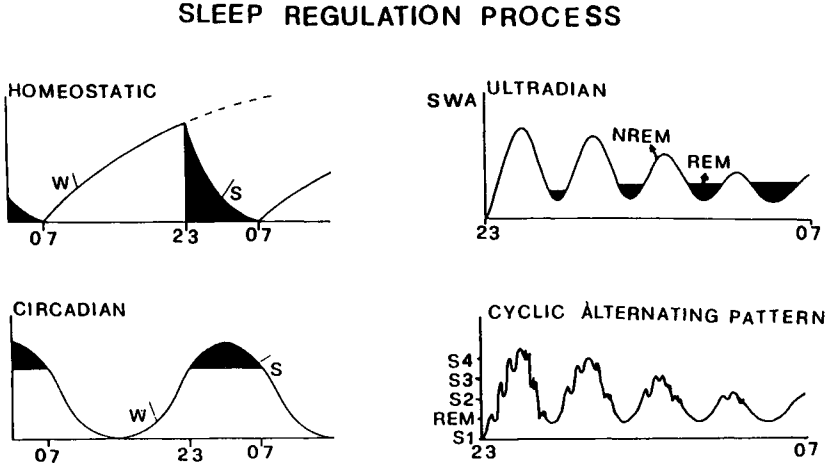

FIGURE 8.1 The four basic mechanisms of sleep regulation. The clock time is reported on the x-axis. In homeostatic and circadian (W, wakefulness; S, sleep). In ultradian (SWA, slow-wave activity). In cyclic alternating pattern (CAP) S1, stage 1; REM, rapid eye movement sleep; S2, stage 2; S3, stage 3; S4, stage 4).

duration of sleep episodes is strongly influenced by the phase of the body temperature rhythm. Decreasing temperature, as occurs in the nocturnal hours, is combined with longer sleep episodes, while increasing temperature, as occurs in the morning hours, is associated with shorter sleep episodes (for a review, see Murphy and Campbell, 1996).

A 12-h-centered regulation of sleep propensity (i.e., a circa-semidian rhythm) was proposed more than 20 years ago (Broughton, 1975). In the last decade, the increasing attention to the circadian rhythm sleep disorders has expanded knowledge on the 24-h sleep propensity function, allowing identification of a total of four phases of sleep propensity (two peaks and two troughs) throughout the day. Laboratory studies (free-running, constant, and ultradian routine) have demonstrated that the timing of peaks and troughs is highly correlated with the thermal curve. In addition to the high sleep propensity during the nocturnal hours (primary sleep gate concomitant to the descending branch of deep body temperature), a less prominent peak of sleep propensity is observed in the midafternoon (secondary sleep gate), about 10 h after the temperature minimum clock time. By contrast, in addition to the trough of sleep propensity in the late morning (ascending branch of deep body temperature), there is a period of low sleep propensity in the early evening (forbidden zones for sleep), about 8 h before the temperature minimum time (Lavie, 1986; Lack and Lushington, 1996).

SLEEP INTENSITY AND SLOW-WAVE SLEEP

The variations of sleep propensity over time not only are affected by the biological clock but also are influenced by the subject's prior sleep–wake history. Extensive studies on sleep deprivation have ascertained an increase of sleep propensity after a certain number of hours of wakefulness. Moreover, there is a positive relationship between the duration of presleep wakefulness and the spectral energy enhancement of slow-wave activities (.5–4 Hz). In effect, sleep stages 3 and 4 are mostly concentrated in the early portions of sleep, while they are practically absent in the final hours. The priority of recuperation of stages 3 and 4 after sleep onset and the progressive decline of deep sleep along the night suggest the involvement of a compensatory mechanism based on the accumulation while awake of some unknown factor, which undergoes a sort of dissipative process during sleep. If we skip a night of sleep, the cumulative evolution continues until the next sleep episode (either nocturnal or diurnal) that is basically characterized by a short sleep latency and by an increased amount of stages 3 and 4, still mostly represented in the early hours of sleep. In short, prolonged wakefulness hastens sleep onset and proportionally potentiates slow-wave activities, regardless of the circadian phase (Dijk *et al.*, 1990). The increased intensity of sleep after prolonged wakefulness indicates that the characteristics of sleep recovery respond to mechanisms of homeostatic regulation (see Fig. 8.1).

The interaction between sleep–wake-dependent and sleep–wake-independent mechanisms has been determined in a number of observations. In the two-process model (Borbely, 1982), sleep regulation is viewed in terms of the interaction of a homeostatic process (S) and a circadian process (C). The displacement of the sleeping hours in inadequate periods in relation to the process C, as occurs in the jet-lag syndrome, in shift work, and in morning recovery after sleep deprivation, alters sleep in the absence of other disturbing factors.

NONRAPID EYE MOVEMENT/RAPID EYE MOVEMENT SLEEP CYCLE

A third mechanism of sleep regulation is the NREM–REM cyclicity characterized by periods of sustained high-voltage, slow-wave synchronized EEG patterns (NREM sleep) that are periodically replaced by sustained periods of low-voltage, fast-wave desynchronized EEG rhythms (REM sleep). The NREM/REM cycle (also referred to as the sleep cycle) is conventionally composed of a descending branch (from light to deep NREM sleep), a trough (the deepest stage of the sleep cycle), and an ascending branch (from the deepest NREM stage to REM sleep). This ultradian rhythmicity of about 90–120 min has been viewed now as an intrinsic phenomenon of sleep, now as an independent manifestation of the basic rest activity cycle (BRAC), expressed in sleep by the NREM and REM alternation and in wakefulness by periodic changes in the vigilance level and in spontaneous motility (Kleitman, 1963).

Experimental investigation has ascertained that the intrinsic alternation between NREM and REM sleep is under the control of an oscillatory process generated by a particular rhythmicity of neurotransmission and by the reciprocal interaction between two neuronal groups with REM-on and REM-off activities. Cholinergic neurons localized preferably in the laterodorsal and peduncular nuclei of the pontine tegmentum promote REM sleep (REM-on cells). In contrast, aminergic neuronal complexes (norepinephrine, epinephrine, and serotonin) localized in the locus ceruleus, in the dorsal nuclei of the raphe, and in the peribrachial region of the pons are very active during the NREM stages and silent during NREM sleep (REM-off cells). The relation between these neuronal assemblies is regulated by the mathematical model of the reciprocal induction defined by Lotka and Volterra (McCarley and Hobson, 1975). Similar to the struggle between preys and predators, their action is always on the move. The slowing of the firing activity of the REM-off cells facilitates the REM-on population that becomes progressively more active and triggers a REM episode. The activity of these cells then declines for the rebound activation of the REM-off cells that block the REM episode and promote a new period of NREM sleep. The nocturnal succession of the NREM/REM cycles originates from this sequence of reciprocally induced effects (see Fig. 8.1). The competitive interaction between these centers appears as an intrinsic chronometric mechanism that

follows an ordinate sequence and that can be quantitatively described by the limit cycle reciprocal interaction model of REM cycle control (McCarley and Massaquoi, 1986).

DYNAMICS OF THALAMIC NEURONS DURING SLEEP

A further pivotal mechanism involved in sleep regulation concerns the transmission of information through the thalamocortical pathways. In particular, the thalamic reticular nucleus (TRN) forms an essential part of the circuits that link the thalamus to the cerebral cortex. The afferent neurons to the TRN from thalamus and cortex, together with those from brain stem and basal forebrain, play a critical role in controlling the firing patterns of thalamocortical relay cells, which can be in either a "tonic" mode or a "burst" mode. In the tonic mode, there is a relatively unmodified, linear information transfer through the thalamic relay from ascending pathways to the cortex. The burst mode has been characteristically seen during sleep or epileptic discharges and has therefore been considered to be a global mechanism that prevents the relay of information to the cortex (Steriade *et al.*, 1994).

The neurophysiological behavior of the TRN has been observed also in other thalamic centers. At the wake–sleep transitions, neurons of various thalamic nuclei quit the tonic firing mode (substrate of the EEG beta waves) to enter the burst or oscillatory mode. During the bursting mode, spindles, K-complexes, and delta bursts become manifest (NREM sleep). When thalamic networks are in the rhythmic bursting mode, they respond to afferent stimulation by producing a stereotyped oscillation, which is characterized by the properties of the neurons involved, but not by the properties of the afferent signal (Steriade *et al.*, 1993). During the tonic firing mode (wakefulness and REM sleep), the transfer ratio has a value of 1.0. When the bursting mode is entered (drowsiness and light NREM sleep), the output reduces and the transfer ratio lowers to .7. This ratio further drops to about .3–.4 when the slow delta waves of deep NREM sleep appear. On awakening, the transfer ratio immediately recovers the 1.0 value (Coenen, 1995; Coenen and Vendrik, 1972).

At variance with this rigid behavior, even in the burst mode, the thalamocortical relay cells can respond to sensory stimuli. Although this transmission is nonlinear, the afferent activity is transmitted to cortex and the signal-to-noise ratio can be even higher than in the tonic mode. That is, in the burst mode, the system is primed to react to changes in input activity instead of transfering this activity reliably to the cortex for analysis. For the latter, the system needs to switch to the tonic mode. In other words, there is a capacity of the thalamic cells, when in the burst mode, to respond to novel activity patterns and then to change to the tonic mode so that the new stimuli can be accurately transferred to the cortex (Guillery *et al.*, 1998).

In light of this, the current view of the function of the thalamus is that it produces state-dependent gating of sensory information flow to the cerebral cortex. Tonic relay cell activity, corresponding to awake, alert behavioral states, allows for faithful information transmission to the cortex. However, rhythmically bursting relay cell firing, which corresponds to sleep states, imposes spindle oscillations on the cortex and produces slow-wave EEG signals. These findings extend the view of the thalamus by replacing the idea of a "gate" with that of a "tunable temporal filter." The thalamic neurons filter the peripheral input while the tuning of the filter varies continuously with the degree of bursting in the neuronal spike train. These variations in the dynamics and the bursting of the relay cells undergo natural fluctuations in arousal and attentiveness (Mukherjee and Kaplan, 1995).

LOW-FREQUENCY (<1 HZ) OSCILLATIONS IN THE HUMAN SLEEP ELECTROENCEPHALOGRAM

Falling asleep is rarely an abrupt process but instead it occurs along a gradual replacement of the faster low-voltage alpha and beta rhythms by the slower high-voltage theta and delta EEG activities. In addition to these tonic changes, the wake–sleep transition is also characterized by the appearance of transient EEG features that allow sleep maintenance through adaptive adjustments of the arousal level to internal or external inputs. In particular, K-complexes, which are physiological markers of NREM sleep but can also be triggered by sensory stimulation, on the one hand serve as momentary arousals (both spontaneous and evoked K-complexes are accompanied by increases of the sympathetic activity); on the other hand, with their ample slow biphasic wave form, reflect sleeplike qualities.

Analysis of K-complex densities (i.e., the number of K-complexes per minute of sleep) has been accomplished and findings indicate densities of one K-complex per minute in stage 2 (Johnson and Karpan, 1968; Johnson *et al.*, 1976; Halász *et al.*, 1985). Further detailed investigation confirmed values of 1.36 ± 0.84 in stage 2, and $1.21 \pm .93$ in stages 3 and 4 (Paiva and Rosa, 1991). However, the K-complex densities have overnight fluctuations according to the distribution within the sleep cycle. Peaks in densities (i.e., when K-complexes can be clustered in sequences) are often observed in connection with stage transitions, independent of the direction of the shift. A study based on spectral analysis revealed that sequences of K-complexes are embedded in a slow oscillation with a period of about 1.5 s (frequency of about .6 Hz). In particular, stage 2 shows a principal peak at .5 Hz surrounded by other lower peaks; whereas in stages 3 and 4, there is a dominant peak at .7 Hz (Amzica and Steriade, 1997).

In addition to this .6–.9-Hz slow oscillation marked by the periodic recurrence of K-complexes, other distinct components below 1 Hz are also present in

the human sleep EEG spectrum. All-night spectral analysis of successive .5-s epochs in NREM human sleep revealed a sharp .23-Hz peak that corresponded to a periodicity of 4 s, and a .047-Hz peak in the low-frequency range that corresponded to a 21–32-s periodicity (Achermann and Borbely, 1997). A 3–5 s periodicity between sleep spindles has been demonstrated in human NREM sleep (Evans and Richardson, 1995), while fluctuations in the 20–35-s range have already been described in human NREM sleep by means of automatic analysis using Hjorth descriptors (Depoortere *et al.*, 1993) and spectral analysis (Ferrillo *et al.*, 1997; Barcaro *et al.*, 1998; Rosa *et al.*, 1999). This rhythm, known to occur in physiological NREM sleep, is referred to as the cyclic alternating pattern (CAP; Terzano *et al.*, 1985, 1988).

CYCLIC ALTERNATING PATTERN AS A MARKER OF SLEEP INSTABILITY

Cyclic alternating pattern (CAP) is a classical EEG feature of periodic activities (Gaches, 1971). It is recognized in the sleep EEG every time this presents an alternating sequence of two stereotyped EEG patterns (Fig. 8.2):

1. The repetitive element, or *phase A*, is identified by a set of phasic events, with a mean duration between 8 and 12 s and occupying about 40% of the entire CAP cycle. The A phase is the expression of a transient activation of the arousal level during sleep. Accordingly, it is associated with an increase of the neurovegetative activities and can be coupled with an enhancement of muscle tone.
2. The recurring interval, or *phase B*, is identified by the recovery of background activities, with a mean duration around 16–20 s and occupying about 60% of the CAP cycle. The B phase of CAP is the expression of a transient deepening of the arousal level during sleep. Accordingly, it is associated with an inhibition of muscle tone and neurovegetative activities (Terzano *et al.*, 1996) that may induce a respiratory event (apnea, hypopnea) or a heart rate blockage. This condition of global inhibition can be contrasted by subwakening stimulation that reactivates immediately an A phase.

In light of this, CAP is the EEG translation of a sustained arousal oscillation between activation (phase A) and inhibition (phase B) that makes sleep as well as muscular and autonomic functions unstable. The complementary pattern, defined as non-CAP (NCAP), consisting of a rhythmic EEG background, with few, randomly distributed arousal-related phasic events, represents, on the contrary, a stable sleep condition associated with regular neurovegetative activities (Fig. 8.2). Intensive though subwakening perturbation delivered during NCAP determines the prompt appearance of a CAP sequence (Terzano and Parrino, 1991).

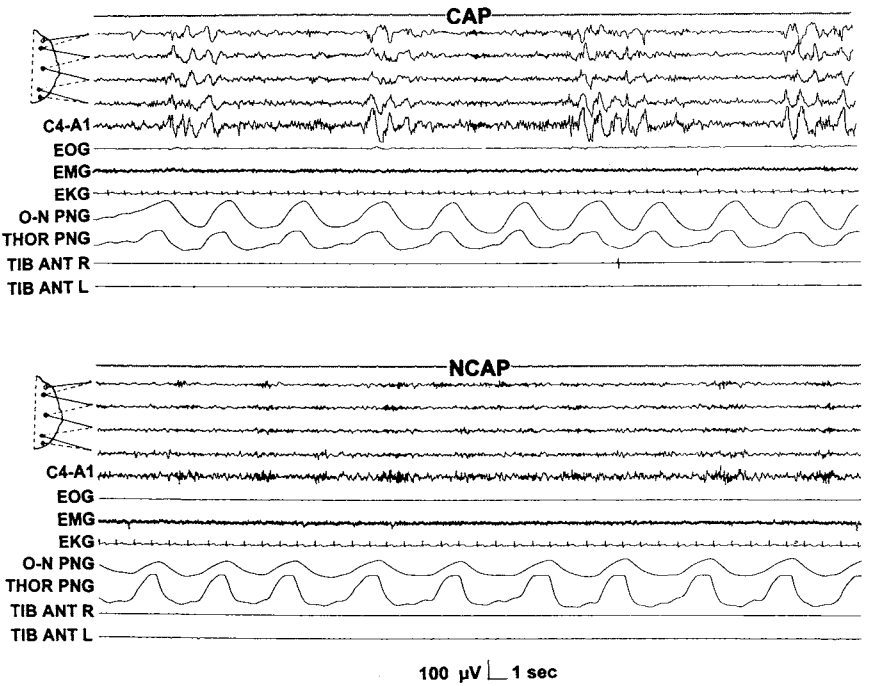

FIGURE 8.2 Microstructural analysis of sleep stage 2 according to the CAP/NCAP framework. *Top*: portion of a cyclic alternating pattern (CAP) sequence identified by separated clusters of arousal-related phasic events against the sleep stage EEG background. Notice that the CAP sequence is not driven by any motor or respiratory disturbance. *Bottom*: period of noncyclic alternating pattern (NCAP), characterized by a sustained homogeneous EEG background. The specimen contains also several recurring sleep spindles. EOG, eye movements. EMG, submental muscle; EKG, heart rate; O-N PNG, oro-nasal flow; THOR PNG, thoracic pneumogram; TIB ANT R, right anterior tibialis muscle; TIB ANT L, left anterior tibialis muscle.

SCORING OF CYCLIC ALTERNATING PATTERN PARAMETERS

CYCLIC ALTERNATING PATTERN AND NONCYCLIC ALTERNATING PATTERN

CAP is organized in sequences of two or more CAP cycles. Each CAP cycle consists of a phase A and a phase B, each lasting between 2 and 60 s. All CAP sequences begin with a phase A and end with a phase B. In NREM sleep, the phase A patterns are composed of the single or clustered arousal-related phasic events peculiar to the single sleep stages:

- Intermittent alpha rhythms and sequences of vertex sharp waves, in stage 1
- Sequences of two or more K-complexes with or without alphalike components and beta rhythms, in stage 2

- Delta bursts that exceed by at least one-third the amplitude of the background activity, in stages 3 and 4
- Transient activation phases (Schieber *et al.*, 1971) or EEG arousals (ASDA, 1992), in all the stages

Sleep spindles are generally excluded from the CAP scoring criteria, especially when they appear at the beginning or at the end of a phase A pattern.

CAP appears as a synchronous and widely diffused EEG activity on both hemispheres with minor differences in morphology and amplitude across the various leads. Bipolar longitudinal montages warrant the most clear cut detection of CAP.

In NREM sleep, the CAP sequences may extend across successive sleep stages and thus the A phases may present different patterns within the same CAP sequence. In REM sleep, due to the lack of EEG synchronization, the A phases consist exclusively of desynchronized patterns (transient activation phases or arousals). Under physiological conditions, the 3–4-min interval between these A phases in REM sleep (Schieber *et al.*, 1971) does not meet the temporal requirements for the scoring of CAP in this sleep stage. The period of sleep between two successive A phases separated by an interval >60 s is scored as NCAP.

Phase A Subtypes

Variations during CAP involve to different degrees muscle tone, heart rate, and respiratory activity, which increase during phase A and decrease during phase B (Lugaresi *et al.*, 1972; Terzano *et al.*, 1985, 1988; Evans, 1992; Terzano and Parrino, 1993). On the basis of the information derived from EEG activities, muscle tone, and neurovegetative responses, three subtypes of A phases (Fig. 8.3) corresponding to different levels of neurophysiological activation can be distinguished.

Subtypes A1

These A phases have synchronized EEG patterns (intermittent alpha rhythm in stage 1; sequences of K-complexes or delta bursts in the other NREM stages), associated with mild or trivial polygraphic variations.

Subtypes A2

These A phases have desynchronized EEG patterns preceded by or mixed with slow high-voltage waves (K-complexes with alpha and beta activities, K-alpha, arousals with slow wave synchronization), linked with a moderate increase of muscle tone and/or cardiorespiratory rate.

Subtypes A3

These A phases have desynchronized EEG patterns alone (transient activation phases or arousals) or exceeding $\frac{2}{3}$ of the phase A length, coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate.

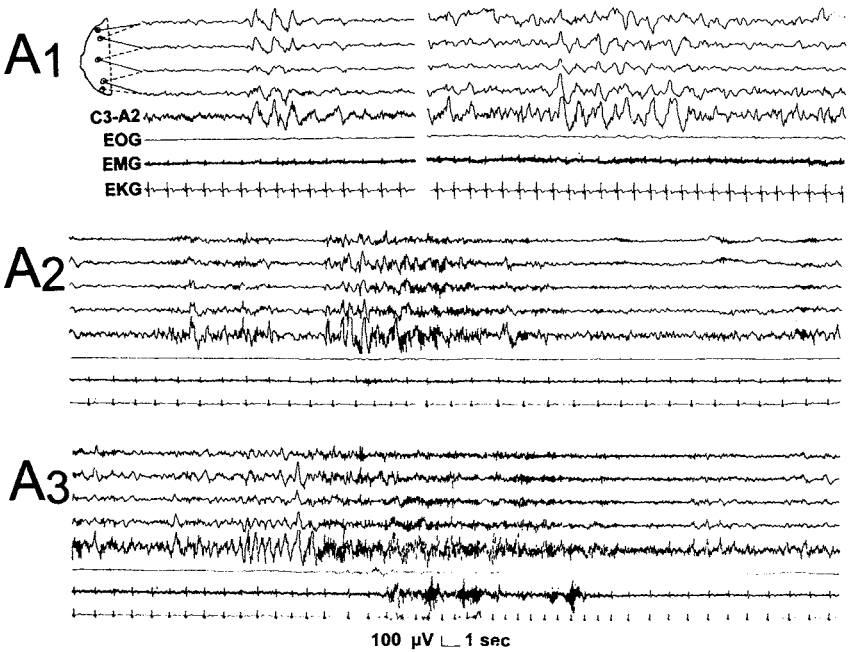

FIGURE 8.3 Specimens of phase A subtypes in NREM sleep. *Top left*, A1 subtype in stage 2: brief cluster of syncronized EEG patterns (sequence of K-complexes). *Top right*, A1 subtype in slow wave sleep: delta burst lasting about 7 s with an amplitude that exceeds the background EEG activities by at least $\frac{1}{3}$. Muscle tone and heart rate show irrelevant modifications. *Middle*, A2 subtype in stage 2: phase A that starts with a dominant EEG synchronization (mainly K-complexes) and continues with a prevailing desynchronized EEG pattern. The synchronized and desynchronized portions of the A2 subtypes are equivalent in duration. Notice the moderate reinforcement of muscle tone and increase of heart rate concomitant to the onset of EEG desynchrony. *Bottom*, A3 subtype in stage 2: phase A introduced by a short EEG synchronization, but occupied extensively by a sustained desynchronized EEG pattern, associated with a robust increase of muscle tone and irregular heart rate acceleration. The A3 phases are characteristically longer than the A1 and A2 subtypes.

The EEG criteria for the identification of subtypes A3 and partially of subtypes A2 show extensive similarities with the ones proposed for arousals by the American Sleep Disorders Association (ASDA, 1992).

In the physiological architecture of sleep, the A1 subtypes prevail in the buildup and maintenance of deep NREM sleep (Ferrillo *et al.*, 1997), while the A2 and A3 subtypes dominate in light sleep that precedes the onset of desynchronized REM sleep (Terzano *et al.*, 2000).

CYCLIC ALTERNATING PATTERN RATE

CAP time is the temporal sum of all CAP sequences. CAP time can be calculated throughout total NREM sleep and within the single NREM stages.

The percentage ratio of CAP time to sleep time is referred to as CAP rate. CAP rate can be measured in NREM sleep (percentage ratio of total CAP time to total NREM sleep time) and in the single NREM stages (percentage ratio of CAP time in a given stage to the total duration of that stage throughout sleep). In human sleep, CAP rate is an index of arousal instability that shows a u-shaped evolution along the life span (teenagers, mean 43.4%; young adults, 31.9%; middle aged, 37.5%; elderly, 55.3%) (Parrino *et al.*, 1998) and correlates with the subjective appreciation of sleep quality (the higher the CAP rate the poorer the sleep quality) (Terzano *et al.*, 1990; Terzano and Parrino, 1992). When the increases of CAP rate are not accompanied by relevant variations of the sleep stages (macrostructure), it means that the flexibility of the microstructure (CAP) protects the stability of the macrostructure. However, because CAP rate is a dynamic parameter that measures the effort of the cerebral centers to maintain a compatible organization of sleep, an excessive enhancement of instability drags a fragmentation of stage sequences, with a drastic curtailment of the deeper ones and an increase of nocturnal awakenings. Thus, the oscillating instability of CAP acts both as a protective mechanism for architectural stability and as a preparatory device for macrostructural alterations.

EFFECTS OF CYCLIC ALTERNATING PATTERN ON EPILEPTIC EVENTS

Across the years, several authors have focused their attention on the dynamic relationship between epileptic paroxysms and EEG phasic events during sleep. In the feline generalized penicillin epilepsy, spike-and-wave discharges are thought to represent a pathological cortical response to afferent thalamocortical volleys, which under normal conditions are involved in sleep spindling (Gloor, 1984). In the feline amygdala-kindled model, which is generally assimilated to human temporal epilepsy (Shouse, 1987), and in WAG/Rij rats, genetic models of human absence epilepsy (Drinkenburg *et al.*, 1991), both interictal and ictal discharges are influenced by rapid shifts of EEG synchrony (Shouse *et al.*, 1995). Even in human epilepsy, the frequent association between spike-and-wave complexes and K-complexes suggests that common basic mechanisms and transmission circuitry may be shared by both epileptic abnormalities and phasic events during sleep.

More than 25 years ago, Niedermeyer introduced the concept of dyshormia (1972), postulating that nocturnal paroxysmal discharges are an abnormal exaggeration of the physiological arousal-related microfluctuations expressed in human NREM sleep by a K-complex. In the following decades, a number of contributions have suggested that vertex sharp waves in stage 1, K-complexes in stage 2, and delta bursts in stages 3 and 4 represent the same arousal-related phenomenon along a continuum from the light to the deep NREM sleep (for

a review, Terzano *et al.*, 1992). The close relation between epileptogenic manifestations and phasic events corroborates the idea of a circular recursive influence between the mechanisms involved in the dynamic organization of sleep and the neurophysiological correlates of epilepsy. In light of this, sleep is a major physiological activator of epileptic manifestations, while the latter represent an important perturbing agent of sleep instability. The arrangement of NREM sleep phasic events into the CAP/NCAP scaffolds not only allows identification of three neurophysiological conditions:

1. Level of transient activation (phase A)
2. Level of inhibition (phase B)
3. Stationary intermediate condition (NCAP)

but also can contribute to shed light on the modulatory factors involved in epileptic phenomena.

PRIMARY GENERALIZED EPILEPSY

In primary generalized epilepsy (PGE; Fig. 8.4), interictal discharges (IIDs) are commonly activated during unstable sleep, with a spike index (SI, number of EEG paroxysms per minute of sleep) significantly higher ($p < .001$) during CAP (SI, 2.9) compared with NCAP (SI, 1.3). The phase A has a significant ($p < .001$) activation influence (SI, 7.4), while phase B exerts a powerful and prolonged inhibitory effect (SI, .3) especially if we consider that its mean duration (16 s) is twice the phase A length (8 s). These data refer to patients with absence seizures or with generalized tonic–clonic attacks (Terzano *et al.*, 1989). Identical CAP-related influences are found in juvenile myoclonic epilepsy, yet in the presence of a lower all-night amount of EEG discharges (Gigli *et al.*, 1992). Regardless of the specific clinical expression, the occurrence of IID in patients with PGE has no remarkable consequences on sleep macrostructure, but produces significant effects on arousal stability (Terzano *et al.*, 1992), because the epileptic patients show higher CAP rate values compared with controls (52.7 versus 34.6%; $p < .003$). Within the epileptic group, the CAP cycles that include at least one IID are significantly longer than those without IID (31.2 versus 25.4 s; $p < .007$). The selective lengthening of CAP cycles (only those with IID) and the increase of CAP rate support the hypothesis that CAP and IID share common anatomic pathways and behave as a concerted pattern that links a regular physiological phenomenon (CAP) to a random pathological event (IID). In the dynamic interplay between EEG spiking and arousal modulation, the CAP sequence (especially its activating swings) triggers the paroxysmal burst, while the latter may in turn promote the generation of a phase A or increase the instability of sleep up to full wakefulness (Fig. 8.5). Though extremely short-lived, the IID is an activating event traveling along the same pathways of normal cerebral communication. The reciprocal support of the two

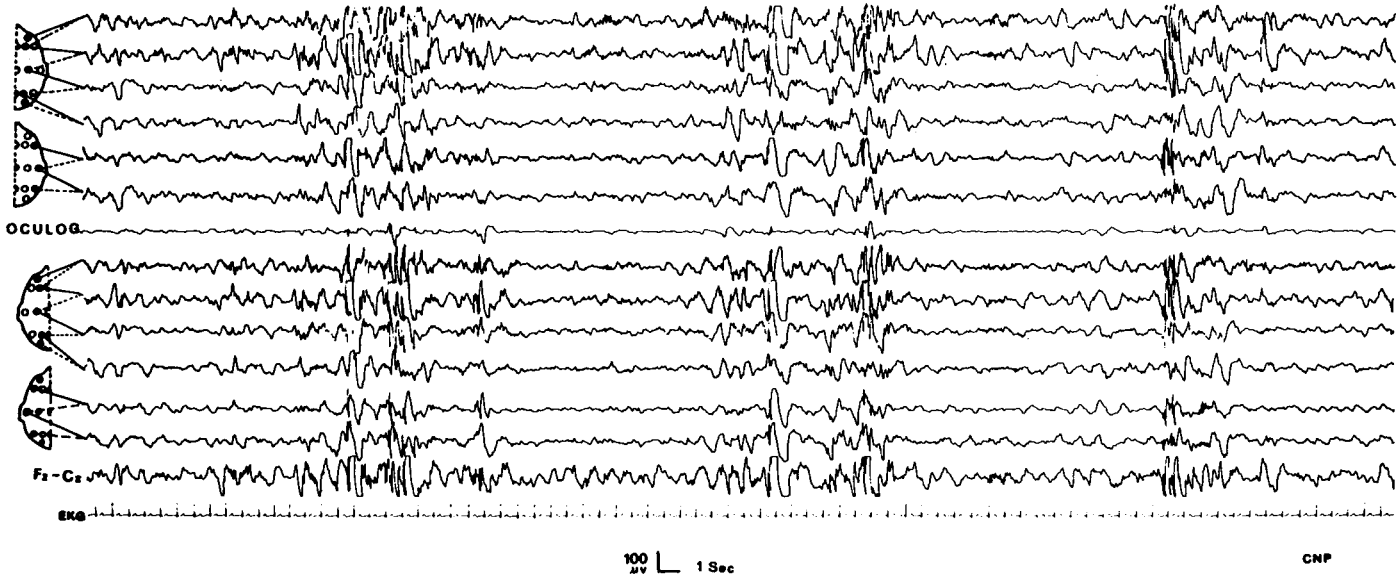

FIGURE 8.4 NREM stage 3. Generalized spike-and-wave complexes modulated by phases A (activation) and B (inhibition) of CAP. OCULOG, eye movements. (From Terzano, M. G., *et al.*, *Epilepsia* **30**(6):772–781, 1989, with permission of Lippincott–Raven Publishers.)

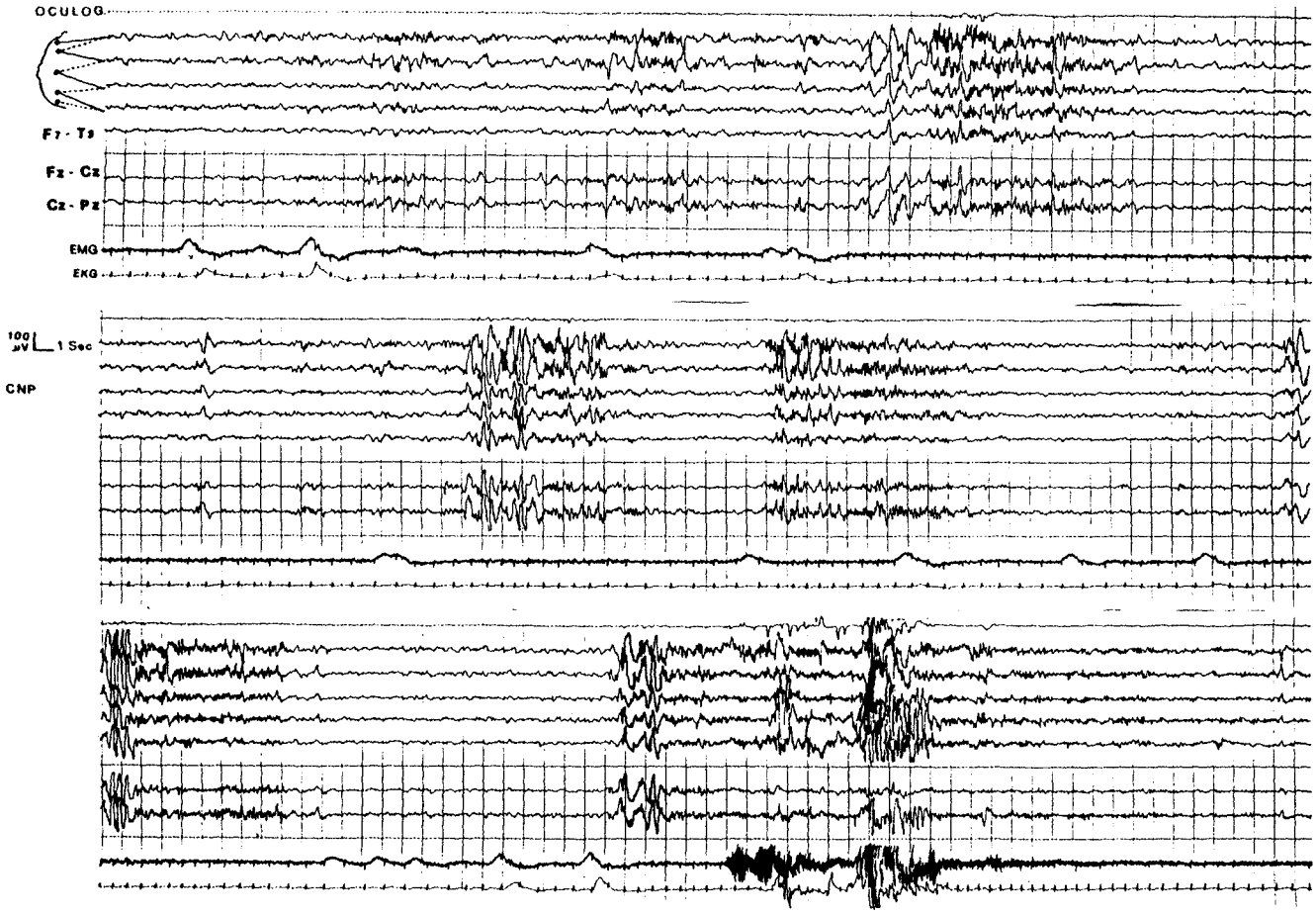

FIGURE 8.5 A cyclic alternating pattern (CAP) sequence originating from a stationary NCAP sleep stage 3 (*top left*) and ending in wakefulness (*bottom right*). The EEG paroxysms introduce some of the A phases and immediately precede the wakefulness trace. Abbreviations as in previous figures. (From Terzano, M. G., *et al.*, *Epilepsia* **33**(2):317–326, 1989, with permission of Lippincott–Raven Publishers.)

activating processes determines the high probability of a simultaneous occurrence of both phenomena. Accordingly, the low amount of arousal-related phasic events that characterizes the NCAP condition makes this an unfavorable background for epileptic discharges.

The quasi-periodic recurrence of generalized discharges just after an EEG waking pattern indicates a condition of unstable vigilance during which the CAP-related mechanisms are still operating. Because arousal activation is higher in wakefulness than in any sleep stage, the epileptic abnormalities can more easily trigger ictal patterns and awakening epileptic manifestations such as myoclonic jerks, clusters of absences, and grand mal seizures (Loiseau, 1964; Niedermeyer, 1991).

LESIONAL EPILEPSY WITH FRONTOTEMPORAL FOCUS

A powerful activating effect of CAP-related events has been described also for interictal epileptic discharges in temporal lobe epilepsy (TLE) with a spike frequency significantly higher ($p < .03$) in phase A (1.71 spikes per minute) than in phase B (.736 spikes per minute). This study also revealed an intermediate activating effect of NCAP (1.18 spikes per minute) between phase A and phase B (Loh *et al.*, 1997).

Patients with focal lesional frontotemporal lobe epilepsy (FTLE; Fig. 8.6) show significant IID differences between CAP and NCAP (SI, 4.9 versus 3.4; $p < .02$), between phase A and phase B (SI, 7.6 versus 3.2; $p < .001$), and between phase A and NCAP (SI, 7.6 versus 3.4; $p < .01$), but not between phase B and NCAP (Terzano *et al.*, 1991b). As occurs for PGE, the presence of focal lesional IID impairs the stability of sleep. In effect, FTLE patients with a mean age of 27 years show a CAP rate of 53% (expected age-matched normal value, 31%). Of secondarily generalized focal lesional bursts, 91% are collected in CAP, but of all the generalized IIDs found in CAP, 96% occur during phase A. Within CAP, the SI of secondary generalized paroxysms is 12.4 in phase A and .7 in phase B ($p < .001$).

BENIGN EPILEPSY WITH ROLANDIC SPIKES

Despite the high-burst frequency during NREM (SI, 15.8), benign epilepsy with rolandic spikes (BERS; Fig. 8.7) are not modulated by the arousal-related mechanisms of CAP (Terzano *et al.*, 1991b). The CAP independence of BERS cannot exclude a possible relation between IID and other microstructural events, in particular, EEG features such as sleep spindles that are generally disjoined from the CAP (especially phase A) patterns. A spectral EEG–polysomnography study in nine patients with BERS actually shows a significant positive correlation ($p < .001$) between interictal epileptic discharges during sleep and sigma (12–16 Hz) activity (Nobili *et al.*, 1999).

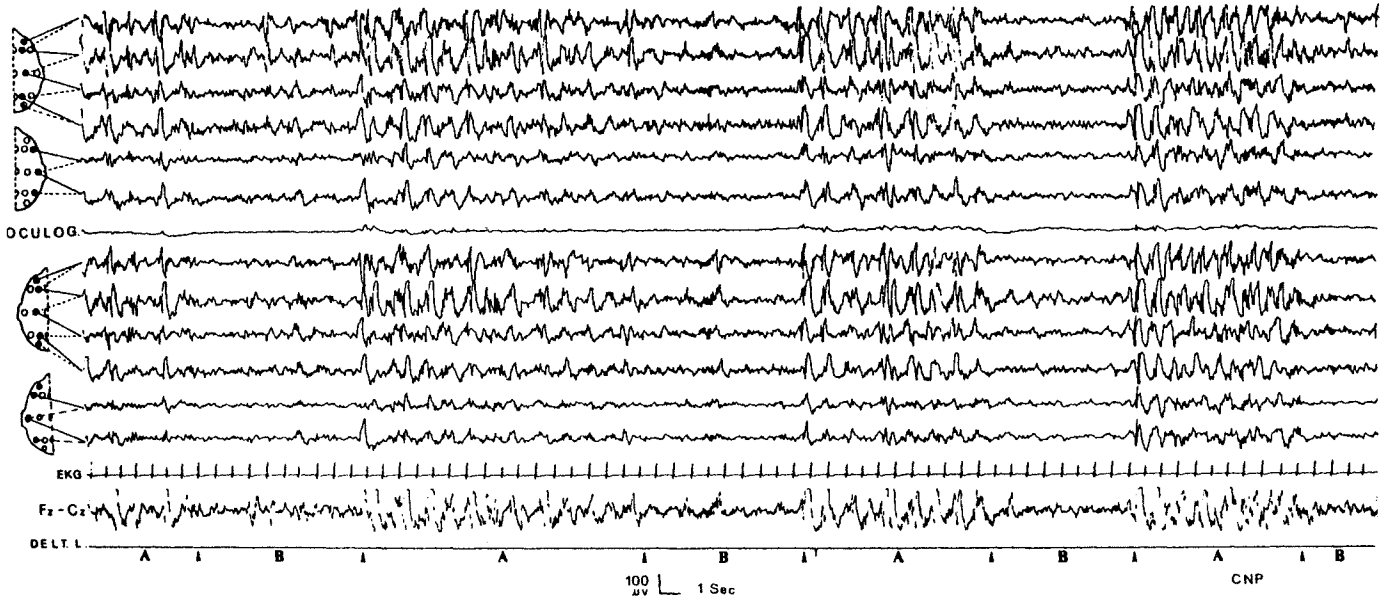

FIGURE 8.6 A cyclic alternating pattern (CAP) in a right frontotemporal epileptic focal lesion during stage 3 sleep becoming secondarily generalized. Notice the triggering role of the A phases on the bilateral expression of EEG discharges. DELT L, left deltoid muscle. Other abbreviations as in previous figures. (From Terzano, M. G., *et al.*, *Epilepsia* **32**(5):616–628, 1991, with permission of Lippincott–Raven Publishers.)

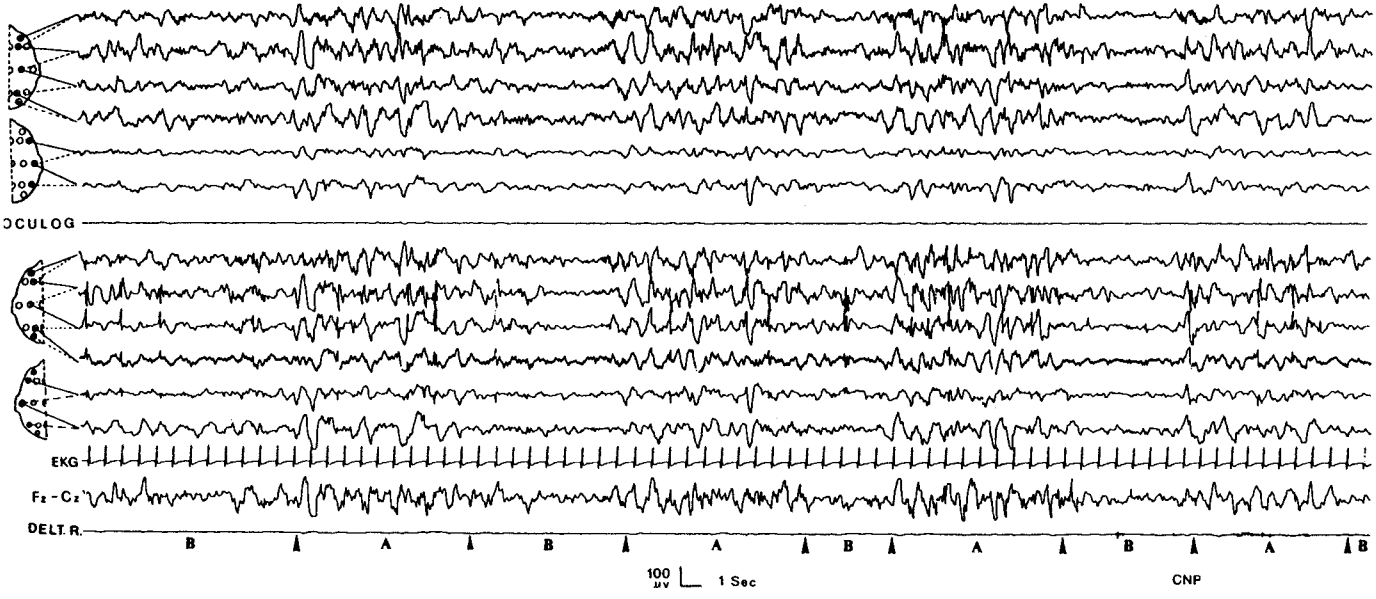

FIGURE 8.7 Spiking activity of a left functional rolandic focus during slow-wave sleep. The EEG bursts occur both in phase A and phase B of the cyclic alternating pattern (CAP). DELT R, right deltoid muscle. Other abbreviations as in previous figures. (From Terzano, M. G., *et al., Epilepsia* **32**(5):616–628, 1991, with permission of Lippincott–Raven Publishers.)

AROUSAL MECHANISMS AND LOCATION OF INTERICTAL FOCI

In PGE and in frontal lobe epilepsy (FLE), the activation of IID is maximal during phase A, whereas these phenomena are sharply inhibited during phase B. However, this rule cannot be extended to all forms of epilepsy because phase A of CAP lacks clear modulatory effects on BERS. What happens during NREM sleep cannot be simply attributed to the presence of an epileptogenic focus, but may depend on more complex factors such as the degree of integration between the epileptogenic focus and the neurophysiological circuits involved in the production of phasic events. Consolidated data indicate that some basic elements of CAP, in particular, K-complexes and delta bursts, are generated in the thalamocortical circuits in which a pivotal role is played by the TRN. The activation of EEG discharges could interfere with the function of these pathways. Hypothetically, in PGE and in FLE, the firing area and these thalamocortical circuits coincide (PGE) or extensively overlap (FLE), and this could explain why in these types of epilepsy the EEG abnormalities are significantly triggered during phase A. In functional epilepsy such as BERS, the focus is probably located in an eccentric cortical area, anyway external to the thalamocortical circuits, and this anatomic position could account for the functional detachment of these EEG abnormalities from the CAP-related mechanisms (Fig. 8.8). Accordingly, CAP rate is increased in the sleep recordings of PGE and FLE without nocturnal ictal manifestations, while it is close to normality in BERS patients.

MODULATORY EFFECTS OF PHASE A SUBTYPES

CAP is a cerebral activity that is independent from the presence of any epileptic activity. CAP is indeed an intrinsic rhythm of the sleeping brain that participates in the buildup, consolidation, and demolition of EEG synchrony. The CAP sequences that accompany the shift from sleep onset or light sleep to deep slow-wave sleep (descending branch of the sleep cycle) consist almost exclusively of repetitive A1 phases (i.e., sequences of K-complexes and delta bursts). In contrast, the CAP sequences associated with the transition from the deeper sleep to the lighter stages that precede REM sleep (ascending branch of the sleep cycle) are mainly composed of phases A2 and A3 that show extensive similarities with the EEG arousals defined according to the American Sleep Disorders Association (ASDA) criteria (1992).

In PGE, ~70% of all the phase A subtypes are A1, ~24% are A2, and ~6% are A3. The equivalent distribution of IIDs throughout the three phase A subtypes (~70% in A1; ~24% in A2; ~6% in A3) clearly indicates that none of the A phase subtypes plays an attractive or repulsive action on PGE paroxysms. However, when the position of PGE interictal abnormalities within each phase A

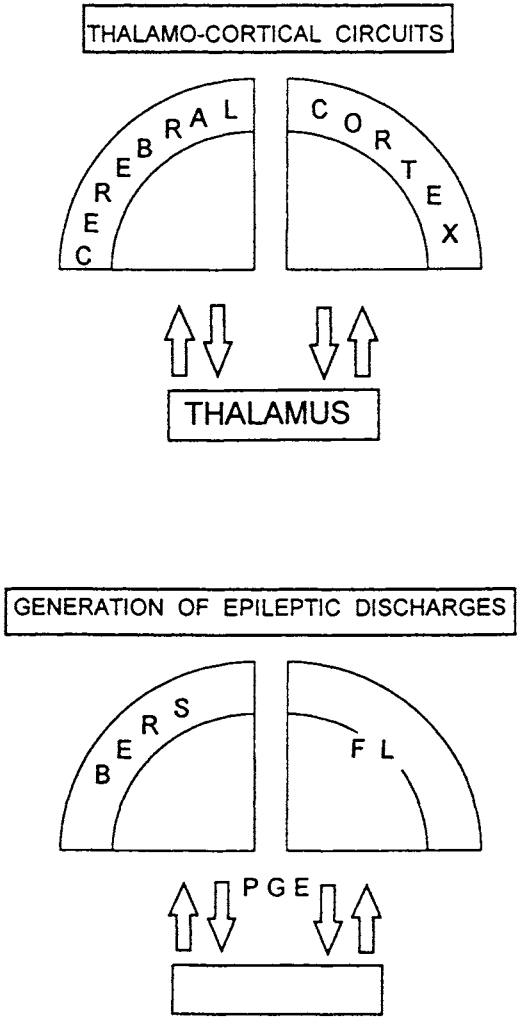

FIGURE 8.8 Schematic representation of the interplay between generators of epileptic discharges and thalamocortical circuits. In primary generalized epilepsy (PGE), the epileptic activity is closely related to the thalamocortical pathways. The focal lesional (FL) spiking involves an intermediate position between the thalamus and the cerebral cortex, while the functional rolandic bursts (BERS) are confined in a far-field cortical position.

subtype is determined, it can be noticed that there is a striking preference for the portions characterized by EEG synchrony. In effect, the EEG paroxysms tend to occur throughout the entire length of subtypes A1 (totally expressed by EEG synchronized patterns), while the IIDs are mostly concentrated in the initial portions of the A2 and in the A3 subtypes that almost invariably start with a K-complex or a delta burst.

The activating power of EEG synchrony is also confirmed by the distribution of IID within the different segments of the sleep cycle. Although the descending branches (prevalence of A1 subtypes) and the ascending branches (prevalence of A2 and A3 subtypes) express equivalent levels of arousal instability (CAP rates: 48 and 44%, respectively), the CAP-related percentages of ID are significantly higher during deepening compared with lightening sleep (67 versus 31%; $p < .03$).

CYCLIC ALTERNATING PATTERN AND NOCTURNAL MOTOR SEIZURES

Although the continuum from subclinical EEG paroxysms to clinical seizures is still incompletely understood, there is, however, general agreement on the assumption that sleep instability facilitates both interictal and ictal phenomena. The close relationship between CAP and spike occurrence actually finds an extensive confirmation in sleep-related seizures. In a study conducted on patients affected by focal epilepsy, 43 of 45 nocturnal partial motor seizures occurred during NREM sleep (Terzano *et al.*, 1991a). Among the NREM seizures, 42 appeared in CAP ($p < .0001$) and always during a phase A (Fig. 8.9). An investigation confirmed that 83% of temporal lobe seizures recorded in stage 2 NREM sleep occurred during CAP with a predominant activating action manifested by phase A (Arunkumar *et al.*, 1997).

In patients with nocturnal paroxysmal dystonia (NPD) characterized by repeated episodes of abnormal stereotyped movements (dystonic–dyskinetic) with duration mostly 10–60 s, motor events are closely related to periods of unstable sleep, as evidenced by the CAP sequences (Fig. 8.10), and occur during an A phase (Sforza *et al.*, 1993; Terzano *et al.*, 1997). NPD recordings are characterized by prolonged and irregular sleep cycles and by significantly higher values of CAP rate compared with normal controls. After effective medication (carbamazepine), sleep showed decreased amounts of CAP rate and a more regular architecture (Terzano *et al.*, 1997).

Confirming that seizure manifestations are strictly connected to fluctuations of arousal (Shouse *et al.*, 1989), these findings also suggest a direct relationship between CAP and motor events. In addition to epileptic manifestations, CAP can trigger other motor activities from physiological body movements to nocturnal myoclonus (Parrino *et al.*, 1996), sleep bruxism (Macaluso *et al.*, 1998), night terrors, and sleepwalking (Zucconi *et al.*, 1995). The definition of clear-cut boundaries between physiological and pathological movement patterns is in progress (Zucconi *et al.*, 1997), while promising results are supplied by the genetic investigation of patients with exclusive nocturnal seizures (Scheffer *et al.*, 1995; Oldani *et al.*, 1998). It is known that the number and distribution of nocturnal movements is a personal characteristic of the sleeper, who is endowed with a given pool of opportunities for the accomplishment of motor episodes

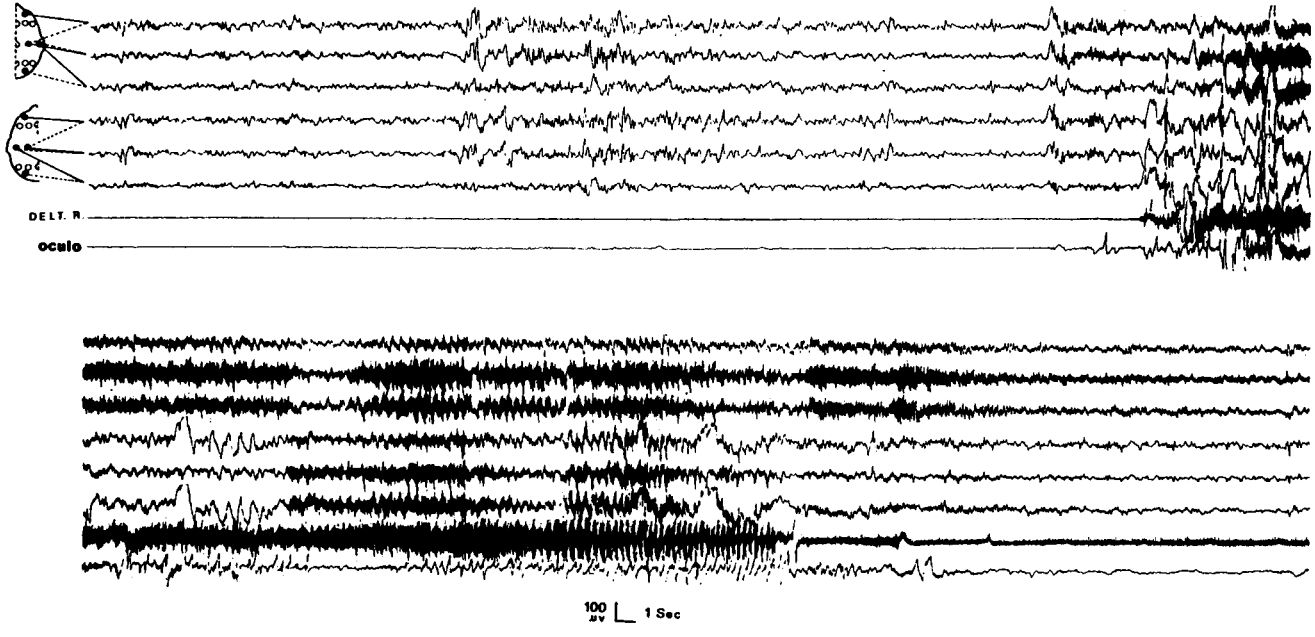

FIGURE 8.9 A nocturnal motor seizure arising from a phase A and heralded by a condition of arousal instability. Abbreviations as in previous figures.

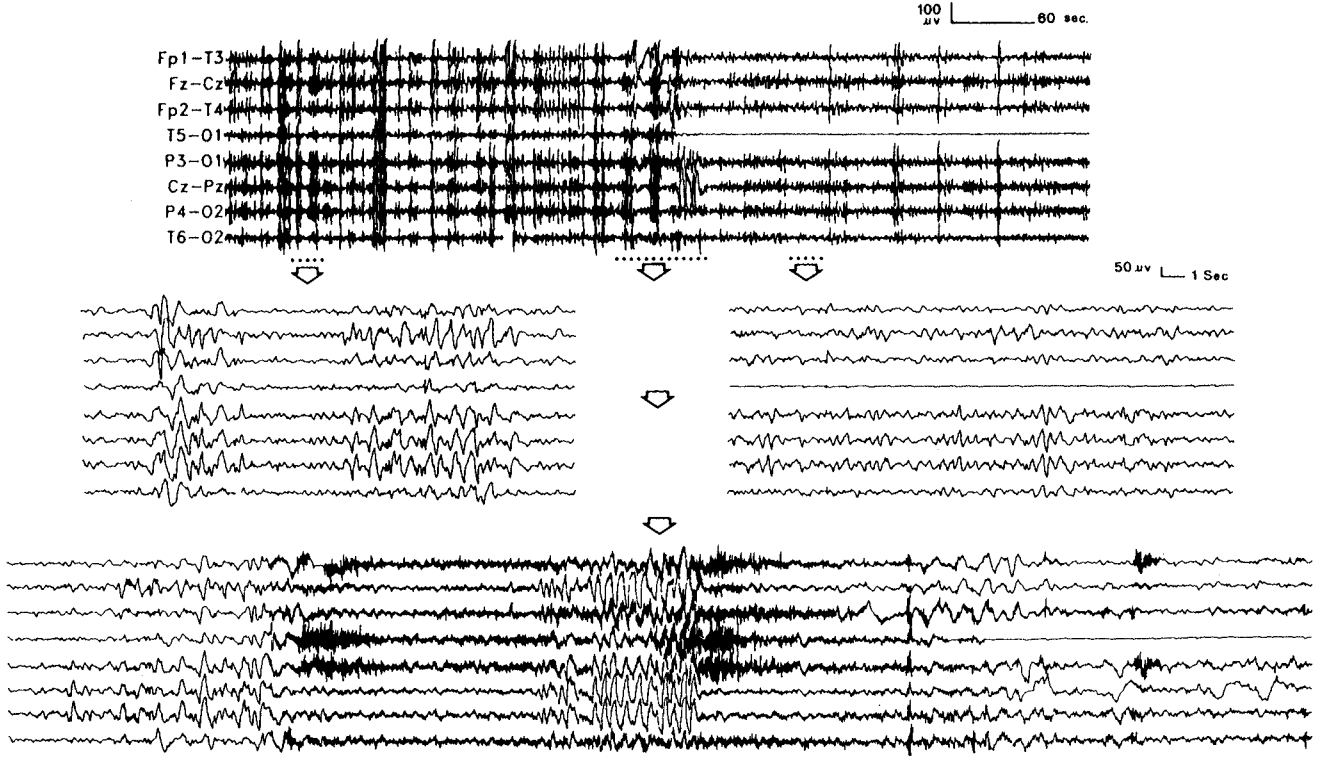

FIGURE 8.10 Nocturnal paroxysmal dystonia. The top strip, recorded at a very low paper speed, shows the EEG trace before, during, and after a major attack. The other three EEG samples (*below*) are enhanced specimens drawn from the top trace and corresponding to the three dotted segments, respectively. The attack is preceded by a slow-wave sleep pattern (*middle-left sample*) dominated by a prolonged CAP sequence, in which aggregates of K-complexes and delta bursts (phase A) are separated by intervals of EEG background activity (phase B). During the attack (*bottom sample*), which takes place within a phase A, EEG synchrony is reduced, while muscle activity appears associated with rhythmic head movement artifacts. The postictal trace (*middle-right sample*) is characterized by a shallower sleep and a transient suppression of CAP. Abbreviations as in previous figures. (From Terzano, M. G., *et al.*, *Epilepsia* **38**(9):1015–1025, 1997, with permission of Lippincott–Raven Publishers.)

during sleep (Muzet *et al.*, 1972, 1974; Naitoh *et al.*, 1973; Loustelan *et al.*, 1981; Muzet, 1988; Terzano *et al.*, 1988). Whether the outcome is a normal or a pathological motor episode depends basically on the type of an eventual lesion, and on the location and extent of neural circuits involved in the behavioral event. In any case, both physiological and abnormal body movements are driven by sleep instability. Arranged in recurring windows of permission (phase A) and deterrence (phase B), CAP operates as a dynamic gate for transient activation and inhibition of motor phenomena (Parrino *et al.*, 1996).

NEUROPHYSIOLOGICAL BASES OF ELECTROENCEPHALOGRAPHIC SYNCHRONY

In the cat, the 3-Hz stimulation of the midline and intralaminar thalamic nuclei under light barbiturate anesthesia (i.e., sleeplike condition) elicits bilateral and synchronous spike-and-wave discharges on the EEG. Conversely, the spontaneous or induced activation of the reticular formation determines the appearance of rapid rhythms on the EEG (i.e., wakelike condition) and the blockage of epileptic sequences (Li *et al.*, 1952; Pollen *et al.*, 1963). These experimental data indicate that the temporal linkages between arousal and epilepsy are conditioned by the dynamic interplay between the cerebral cortex and the deep nuclei. According to the centroencephalic hypothesis, the cerebral cortex is passively submitted to the epileptogenic impact originating in the midline diencephalic and brain stem structures (Penfield and Jasper, 1954). The corticoreticular hypothesis, instead, postulates that the "primum movens" is an overexcited cerebral cortex that only secondarily recruits the corticothalamic and thalamocortical responses (Gloor, 1979; Gloor and Fariello, 1988).

Regardless of the specific theoretical perspectives, arousal and epilepsy appear strictly interconnected as they share extensive cerebral structures and common neurophysiological domains. From the deeper brain stem structures up to the highly complex telencephalic areas, the electrophysiological mechanisms appear organized in interacting hierarchical levels, with several systems for propagation and linked regulatory controls. In the expression of the different rhythms, the nervous circuits harmonize their functional activities by means of resonance processes, which produce graduated levels of synchronization. NREM sleep, which is characterized by prominent epileptic susceptibility, is dominated by EEG synchrony, which is getting neurons to fire together at the same time. By promoting simultaneous synaptic inputs to the neurons and coherent activity in the cellular networks, cortical synchronization amplifies the impact of excitatory information and therefore promotes the onset and propagation of pathological activities. In contrast, the hyperaroused states dominated by EEG desynchrony, which reflects an out-of-phase neuronal communication, determine an inhibitory influence on epileptic phenomena. These general premises are the basis of the greater probabilistic activation of epileptic abnormalities in sleep

compared with wakefulness and in the phases of synchronized sleep (NREM) compared with those dominated by EEG desynchrony (REM). A caricature of paroxysmal activation during NREM sleep and deactivation during REM sleep is supplied by the electric status epilepticus during slow-wave sleep (ESES). From the isolated IID to the extreme ESES pattern, neuronal excitability is strongly regulated by the ongoing arousal state.

COMPREHENSIVE OVERVIEW

Sleep regulation is under the control of four basic mechanisms:

1. Circadian
2. Homeostastic
3. Ultradian
4. Microstructural

Epilepsy susceptibility is variously influenced by these chronobiological factors.

CIRCADIAN

On the basis of their main timing in the 24-h period, Janz (1962) classified epilepsies into: (1) diurnal (i.e., waking and awakening, often in relation with petit mal), (2) nocturnal (i.e., often of the temporal type); (3) diffuse (i.e., of both diurnal and nocturnal character). In spite of its oversimplified arrangement, this classification emphasizes the relation between the level of arousal and the probability of occurrence for epileptic manifestations. Rhythmometric analysis shows a significant opposition between the circadian acrophases of epileptic propensity and vigilance level (Poirel, 1991). The inverse correlation between the level of central activation and the tendency to present ictal or interictal phenomena indicates that the states of hypovigilance and their fluctuations can facilitate the appearance of EEG paroxysms (Touchon, 1982).

A circadian rhythmicity has been described in rats of the WAG/Rj strain (Drinkenburg, 1995), with a significantly higher incidence of spike–wave discharges during the dark period (the active phase of the animal) than during the light period (the major sleep phase of the rat). In contrast, human data show that the maximum number of spike–wave discharges occurs during the sleeping period. However, the discrepancy between animal and human findings is only apparent and it may be explained by the fact that the dark period contains a number of epilepsy-promoting conditions such as higher amounts of superficial slow-wave sleep, more quiet wakefulness and numerous transitions between sleep and wakefulness. In a study conducted on 17 patients with epilepsy monitored continuously for 48 h, there was no evidence of consistent circadian patterns (Martins da Silva *et al.*, 1984), while two types of diurnal profiles, for PGE

and for partial complex seizures, respectively, were identified in a successive study based on ambulatory recordings (Mikol and Monge-Strauss, 1987).

The lack of a general agreement on the circadian distribution of IID is mostly due to the fact that the pattern of EEG activity may be deeply influenced by the increased engagement in physical and mental performances during the diurnal hours. In other words, the genuine distribution of EEG bursts over the 24-h period might be obscured by several maksing factors (Aschoff, 1978). This masking hypothesis can be tested by having patients suffering from epilepsy lie in bed under constant conditions and instructing them to refrain from any type of activity. Then the distribution of EEG paroxysms might reveal a different picture (Drinkenburg, 1995).

Abundant evidence indicates instead that the timing of daytime EEG abnormalities is, of course, dominated by the effects of wake and sleep. Epileptic discharges are actually more prevalent during afternoon naps, or at periods of leisure and relaxation.

HOMEOSTATIC

The investigation of homeostatic aspects in sleep regulation is heavily based on sleep deprivation studies (Borbely, 1994). Partial or total sleep deprivation gives rise to increased slow-wave activities (i.e., stages 3 and 4) during recovery sleep. In contrast, IIDs enhance sleep instability while nocturnal seizures lead to sleep fragmentation. The resultant sleep deprivation increases the probability of further attacks, thereby creating a self-sustained vicious circle (Broughton, 1984).

Sleep deprivation has an overall activating effect on epileptic phenomena. The epileptogenic impact of sleep deprivation can be adequately explained by the high level of EEG synchronization (Dijk *et al.*, 1991) and by the enhanced shifts between different levels of vigilance. Especially during morning recovery, sleep-promoting and arousing mechanisms are in competition and unstable levels of brain synchronization prevail (Parrino *et al.*, 1993). In patients with epilepsy at awakening, paroxysmal discharges are enormously enhanced after a sleep deficit, and they further increase as the period of poor sleep progresses (Jovanovic, 1984). In light of this, recordings during sleep and particularly after sleep deprivation can increase the diagnostic value of EEG analysis for epileptic events.

ULTRADIAN

Overnight investigation has established that, in general, IIDs are activated in NREM sleep relative to wakefulness and deactivated in REM sleep relative to NREM sleep. The latter promotes also secondary generalization of a focal discharge (Gastaut *et al.*, 1965; Gastaut and Broughton, 1972). During NREM

sleep, cerebral electrogenesis tends toward a synchronized functional activity that facilitates the neuronal discharges and the spreading mechanisms of the EEG paroxysmal abnormalities. One report indicates that the onset of a spontaneous absence seizure is characterized by a smooth transition from the <1-Hz slow oscillation of NREM sleep to a gradual accelerating pattern reaching the 2–4-Hz frequency of the seizure (Amzica, 1997).

Physiological desynchronization of cerebral rhythms operating during REM sleep is responsible for an inhibitory action on the occurrence of epileptic discharges and for the more restricted spatial distribution (Rossi *et al.*, 1984; Touchon *et al.*, 1989; Sammaritano *et al.*, 1991). A clocklike ultradian REM-related appearance of seizures every 70–110 min in sleep was postulated (Passouant, 1977), but not confirmed in successive studies. Even the generation of epileptic seizures during REM sleep, as may occur for temporal lobe seizures and petit mal, is linked to the dynamic principle of intensive microfluctuations and arousal shifts within the REM stage (Halász, 1991).

MICROSTRUCTURAL

Spontaneous or evoked arousal shifts followed by a pronounced EEG desynchrony not only fail to evoke but even inhibit the spike-and-wave paroxysm. In contrast, the EEG discharges are strictly associated with arousal responses characterized by EEG synchrony (Halász, 1981). K-complexes, slow high-voltage arousal equivalents of NREM sleep, are actually known to offer a favorable background for IID in patients with generalized synchronous bursts in the waking record (Niedermeyer, 1991). However, the same epilepsy-modulating mechanisms that operate in association with the single K-complex also are working during CAP, in which the arousal events characterized by EEG synchrony (vertex spikes, K-complexes, are slow-wave bursts) represent a predominant feature.

In the attempt to classify sleep-related disorders on the basis of CAP parameters, most epileptic manifestations can be defined as phase A-related pathologies. CAP is a favorable condition for triggering motor seizures (e.g., nocturnal paroxysmal dystoniá) that in most cases arise during a phase A. In PGE and FTLE, the activation of IIDs is maximal during phase A. In PGE, the interictal parosxysms during sleep are equally distributed throughout the phase A subtypes, but EEG discharges mostly occur in close temporal connection with the EEG synchronized portions of the A phase. The latter lacks clear modulatory effects on BERS, which seem to be more sensitive to sleep spindles.

Overall, CAP (sleep instability) and phase A (arousal activation) exert an activating influence on ictal (e.g., motor events of nocturnal paroxysmal dystonia) and interictal phenomena (PGE and focal lesional epilepsy). In contrast, during NCAP and phase B, epileptic propensity remains depressed.

CONCLUSIONS

1. The variations of the arousal level across the 24-h rhythm play an important role in the modulation of epileptic events. The sleep–wake cycle, and particularly the conditions of instability that occur during sleep, affect significantly the appearance of interictal EEG discharges and epileptic seizures. This interaction, either in the sense of inhibition or, more frequently, in the direction of activation, relies on the characteristics of the epileptic syndrome (type of attacks, clinical course, and etiology), on the time of the day, and on the structural components of sleep (falling asleep, EEG arousal, NREM stages, and REM sleep). In particular, the two neurophysiological states that characterize sleep (NREM and REM) have opposite consequences on interictal abnormalities and on critical manifestations.

2. Both in generalized and in focal epilepsy, IIDs are strongly activated by NREM sleep. Similarly, nocturnal attacks are more numerous during NREM, while their occurrence during REM sleep is quite exceptional. Thus, NREM is likely endowed with particular facilitatory properties. A highly fluctuating arousal condition is a favorable background for the appearance of IID and the precipitation of epileptic seizures. Epileptic events appear unlikely when the person is alert and active (either mentally or behaviorally), while they occur preferentially in the presence of arousal reactions (phase A) operating against a background of low and unstable vigilance (CAP).

3. Within the architecture of sleep, the transitional phases that translate a condition of unstable arousal are mainly represented by falling asleep, awakenings from sleep, stage changes, and transition from NREM to REM sleep. The macrostructural parameters based on the concept of stationarity and equivalence of neurophysiological conditions within the single sleep stage, overlook these periods of arousal fluctuations and therefore their support in the diagnostic process is incomplete. The microstructure of sleep, interested in understanding and interpreting physiological EEG patterns shorter than the conventional scoring epochs (20 or 30 s), is a more sensitive procedure for exploring the linkages between the dynamic organization of sleep structure and short-lasting events such as the paroxysmal EEG abnormalities. The analysis of the microstructure based on the CAP parameters offers a dynamic framework for integrating phasic events within the classical structure of sleep (see Fig. 8.1). In particular, the promoting action of the A phases and the inhibitory influence of the B phases also have repercussions on epileptic phenomena.

4. The presence of nocturnal seizures affects the regular profile of sleep architecture. In most cases, the immediate effect of an epileptic attack corresponds to an upward shift toward either an awakening or a more superficial sleep stage. PSG recordings are actually characterized by enhanced sleep fragmentation with a high percentage of wakefulness and light sleep and a decrease in stages 3 and 4 and REM. In addition, marked sleep instability is commonly observed in epileptic patients, even in the absence of nocturnal seizures (Terzano *et al.*, 1992). Overall,

sleep-related attacks mostly affect the macrostructural parameters, whereas nocturnal IID basically have a destabilizing impact on the microstructural patterns.

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9

ELECTRICAL STATUS EPILEPTICUS OF SLEEP

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INTRODUCTION

The history of encephalopathy with electrical status epilepticus during slow sleep dates back to when Patry and co-workers (1971) described a disorder in children in which sleep induced an EEG pattern characterized by apparently "subclinical" spike and waves (SWs) occurring almost continuously during slow sleep and appearing every night for a variable length of time. This entity was originally reported under the title "subclinical status epilepticus induced by sleep in children"; some years later, under the title "encephalopathy related to electrical status epilepticus during slow sleep" (Tassinari *et al.*, 1977b) and "electrical status epilepticus during slow sleep (ESES)" (Tassinari *et al.*, 1977a). Conversely, Morikawa *et al.* (1985) proposed the alternative term "continuous spikes and waves during slow sleep (CSWS)," which was later adopted by the Commission on Classification and Terminology of the International League against Epilepsy (1989).

This commission included epilepsy with CSWS among epilepsies and syndromes undetermined as whether they are focal or generalized, and provided the following definition:

> Epilepsy with continuous spike-waves during slow sleep results from the association of various seizure types, partial or generalized, occurring during sleep, and atypical absences when awake. Tonic seizures do not occur. The characteristic electroencephalography EEG pattern consists of continuous diffuse spike-waves during slow-wave sleep, which is noted after onset of seizures. Duration varies from months to years. Despite the usually benign evolution of seizures, prognosis is guarded, because of the appearance of neuropsychologic[al] disorders.

It has become increasingly evident that the neuropsychological and/or motor impairment is a constant and outstanding feature of the syndrome, likely to be related to the CSWS pattern. Therefore, epilepsy with CSWS is now regarded as a unique epileptic encephalopathy of childhood, combining an epileptic disorder with a distinct neurological regression (Tassinari, 1995). Encephalopathy with ESES (or ESES syndrome) may be defined as an age-related and self-limited disorder of unknown etiology characterized by the following features:

1. Neuropsychological impairment, in the form of global or selective regression of cognitive functions
2. Motor impairment, in the form of ataxia, dyspraxia, dystonia, or unilateral deficit

3. Epilepsy, with focal and apparently generalized seizures (unilateral or bilateral clonic seizures, tonic–clonic seizures, absences, partial motor seizures, and complex partial seizures or epileptic falls); tonic seizures never occurring
4. Typical EEG findings, with the ESES pattern occurring during at least 85% of slow sleep and persisting on three or more records over a period of, at least, 1 month

The clinical and neurophysiological features of this syndrome have been reported mainly by European (Laurette and Arfel, 1976; Tassinari *et al.*, 1977a,b, 1982, 1985, 1992a,b; Dalla Bernardina *et al.*, 1978, 1982, 1989; Billard *et al.*, 1982; Boel and Caesar, 1989; Panayiotopoulos, 1999) and Japanese (Morikawa *et al.*, 1985, 1989, 1992; Yasuhara *et al.*, 1991) scientists. In 1993 a meeting devoted to the ESES syndrome and related disorders was held in Venice, at which 71 new electro-clinical observations were presented (Bureau, 1995b).

CLINICAL AND NEUROPHYSIOLOGICAL FEATURES

CLINICAL FINDINGS

Incidence

Morikawa *et al.* (1989) reported 31 cases out of a population of 12,854 patients, which represents approximately .5% of all childhood epilepsies examined in their center. Bureau (1995a) quoted the existence of 31 cases observed at the Center St. Paul of Marseille between 1968 and 1992. Kramer *et al.* (1998), in a cohort of 440 consecutive pediatric patients with at least two seizures, found that epilepsy with ESES accounted for .2% of all cases. For a variety of methodological reasons, a reliable incidence for this disorder is not available, but ESES syndrome is considered to be rare.

Sex

In the early descriptions of the syndrome, males and females appeared to be equally affected (Tassinari *et al.*, 1985, 1992b; Morikawa *et al.*, 1989). However, studies performed in larger populations have disclosed a male preponderance (63%) (Bureau, 1995b).

Personal Antecedents

Personal antecedents are globally present in about one-third of cases and include encephalopathy, pre- or perinatal problems and congenital hemiparesis.

Familial Antecedents

Familial antecedents of epilepsy (including febrile convulsions) have been mentioned in about 15% of cases. However, there are not precise data on the

type of epilepsy; moreover, EEG studies performed in apparently healthy family members are lacking. In general, genetic factors seem to play a minor role in ESES syndrome.

Epilepsy

Seizures are almost always present and frequently predate the recognition of ESES. The *first seizure* occurs between the age of 2 months (Dalla Bernardina *et al.*, 1989) and 12 years (Bureau, 1995b) (with a peak around 4 and 5 years) and is reported to be frequently nocturnal and to be unilateral in type in almost half of the cases reported, sometimes presenting in the form of unilateral status. In other patients, the first seizure consists of partial motor seizures, absences, "generalized" tonic–clonic seizures, or complex partial seizures. In about 20% of cases, two types of seizures were present at onset. Bureau (1995b) argued that the apparently generalized tonic–clonic seizures were, in fact, a secondary generalization of a hemiclonic seizure not observed clinically from the onset.

At the time of the discovery of ESES, the epileptic seizures frequently change in both severity and frequency. At a given time, the children who had only rare partial motor or generalized seizures, mostly nocturnal, begin to present more or less atypical absences, seizures with falls, and, sometimes, absence status.

Tassinari *et al.* (1985, 1992b) classified the patients into three groups based on the seizure patterns:

1. Group 1 included those patients who only had motor seizures, which were rare and nocturnal throughout their evolution (11%).
2. Group 2 consisted of patients with unilateral partial motor seizures or generalized tonic–clonic seizures mainly occurring during sleep who also had absences (similar to typical absences of childhood absence epilepsy) at the time ESES was detected (44.5%).
3. Group 3 was made up of those patients with rare nocturnal seizures in whom atypical absences, frequently with atonic or tonic components leading to sudden falls, developed at the time of ESES (44.5%).

In the large series assembled during the Venice Colloquium (Bureau, 1995b), it was evident that absences increased from 20% at the time of onset of epilepsy to 48% during ESES; moreover, seizures with falls heralded the appearance of ESES in 23% of cases. Absences were also reported at the time of ESES by Billard *et al.* (1982), Morikawa *et al.* (1985), and Dalla Bernardina *et al.* (1989).

Negative myoclonus was also mentioned as a frequent seizure type during wakefulness, contributing to the development of motor impairment (Dalla Bernardina *et al.*, 1989). Other seizure types, usually partial motor seizures, were described in detail by Morikawa *et al.* (1989).

Despite the wide range of seizure types described in ESES, tonic seizures have never been observed, as has been pointed out by all the authors who performed complete polygraphic sleep studies (Tassinari *et al.*, 1977a, 1985, 1992b;

Billard *et al.*, 1982; Morikawa *et al.*, 1985). Therefore, the absence of tonic seizures is one major characterization of this syndrome.

During ESES, there is an increase in the number of seizure types; from the experience gained during the Venice Colloquium, it can be stated that at the time of the discovery of ESES 60% of cases exhibited several types of seizures (Bureau, 1995b). Frequency of seizures is also markedly increased during ESES. Daily seizures increase from 20% before ESES to 70% at the time of ESES. Epilepsy associated with ESES is considered to be severe.

NEUROPSYCHOLOGICAL DETERIORATION

The majority of patients have normal neuropsychological and motor functions prior to the onset of ESES, as exemplified by 18 of the 29 patients reported by Tassinari *et al.* (1992b), 23 of the 31 cases described by Morikawa *et al.* (1989), and 30 of the 43 patients discussed by Dalla Bernardina *et al.* (1989). The remaining patients have abnormal development prior to the occurrence of ESES.

All cases exhibit further, and often severe, decrease in function during the stage of ESES. The disturbances include a marked impairment of intelligence quotient (IQ), deterioration of language, temporo-spatial disorientation, behavioral changes (reduced attention span, hyperkinesis, aggressiveness, and difficulty in contact), and, rarely, psychotic states (Tassinari *et al.*, 1985, 1992b). IQ was thoroughly investigated in 59 patients assembled during the Venice Colloquium and analytic interpretation of test and single subtest results was carried out (Mira *et al.*, 1995). The data showed that ESES is associated with a disruption of all cognitive functions, but the impairment is sometimes greater in the field of logical–structural intelligence and sometimes in the field of infrastructural intelligence, possibly in relation to a previously different intellectual organization.

Despite the absence of a global decline of cognitive functions, the pattern of psychomotor derangement may differ from patient to patient, and this seems to depend on the predominant localization of the SW discharges. A deterioration of language out of proportion to other abilities has been reported in some cases, showing the predominance of the paroxysmal abnormalities over one or both temporal regions (Patry *et al.*, 1971; Billard *et al.*, 1982; Tassinari *et al.*, 1982, 1985; De Marco, 1988). On the other hand, mental and behavioral deterioration evoking a frontal lobe syndrome has been described in children exhibiting interictal frontal foci or clear-cut anterior predominance of the discharges (Billard *et al.*, 1982; Roulet Perez *et al.*, 1993). Neuropsychological impairment occurs in almost all cases of ESES syndrome, being usually coincidental with the detection of ESES and representing one of the crucial signs of the syndrome.

MOTOR IMPAIRMENT

Motor impairment, in the form of dystonia, dyspraxia, and ataxia (Neville and Boyd, 1995; Neville *et al.*, 1998) or unilateral deficit (Dalla Bernardina *et al.*,

1989), has been emphasized as one of the outstanding disturbances occurring in encephalopathy with ESES.

ELECTROENCEPHALOGRAPHIC FINDINGS

The EEG features of this syndrome may be separated into those before ESES and those during ESES.

Before ESES

In the series reported by Tassinari *et al.* (1985, 1992b), at least one waking EEG was available in each patient after the first clinical manifestation. The background activity was either normal or abnormal. Eleven patients had more or less generalized SWs, sometimes in bursts, clinically with or without an impairment of consciousness with twitching of the eyelids. Thirteen patients had focal interictal spikes, localized over the frontotemporal or centrotemporal regions with or without diffuse abnormalities. In five cases, there were focal or multifocal abnormalities without any generalized discharge. In the same group of patients, sleep recordings were performed in eight cases and showed an increase of the interictal abnormalities, without change in morphology and without alteration of sleep. Morikawa *et al.* (1985) also reported similar findings in waking EEGs before ESES onset.

During ESES

The interictal abnormalities during wakefulness are similar to those before ESES, but are usually more marked. Tassinari *et al.* (1985, 1992b) emphasized the occurrence of diffuse SW at 2–3 Hz, organized in bursts with or without clinical manifestations. Morikawa *et al.* (1989) analyzed the clinical correlates of these diffuse bursts by simultaneous closed-circuit TV–EEG and found out that there were concomitant clinical correlates in only a limited number of patients. More or less prolonged bursts of diffuse slow SW complexes during wakefulness were also reported in 49 of the 73 ESES cases discussed during the Venice Colloquium (Beaumanoir, 1995b). In the same series, a parallel was demonstrated between the diffuse slow SW percentage during wakefulness and the SW index during sleep.

The characteristic feature of this disorder obviously occurs during nonrapid eye movement (NREM) sleep. As soon as the patients fall asleep, continuous bilateral and diffuse slow SWs appear, mainly at 1.5–2 Hz, persisting through all the slow sleep stages (Fig. 9.1). This pattern is generally found between the ages of 4 and 14 years and seems to develop 1 or 2 years after the appearance of seizures. Tassinari *et al.* (1982, 1985, 1992a,b) stressed the importance of the SW index, which was calculated during all night sleep EEG recordings. In the Marseille series, the SW index ranged from 85 to 100% and this parameter was considered an essential feature for the diagnosis of ESES. The same parameter was adopted by Morikawa *et al.* (1985, 1992), Boel and Caesar (1989), Hirsch

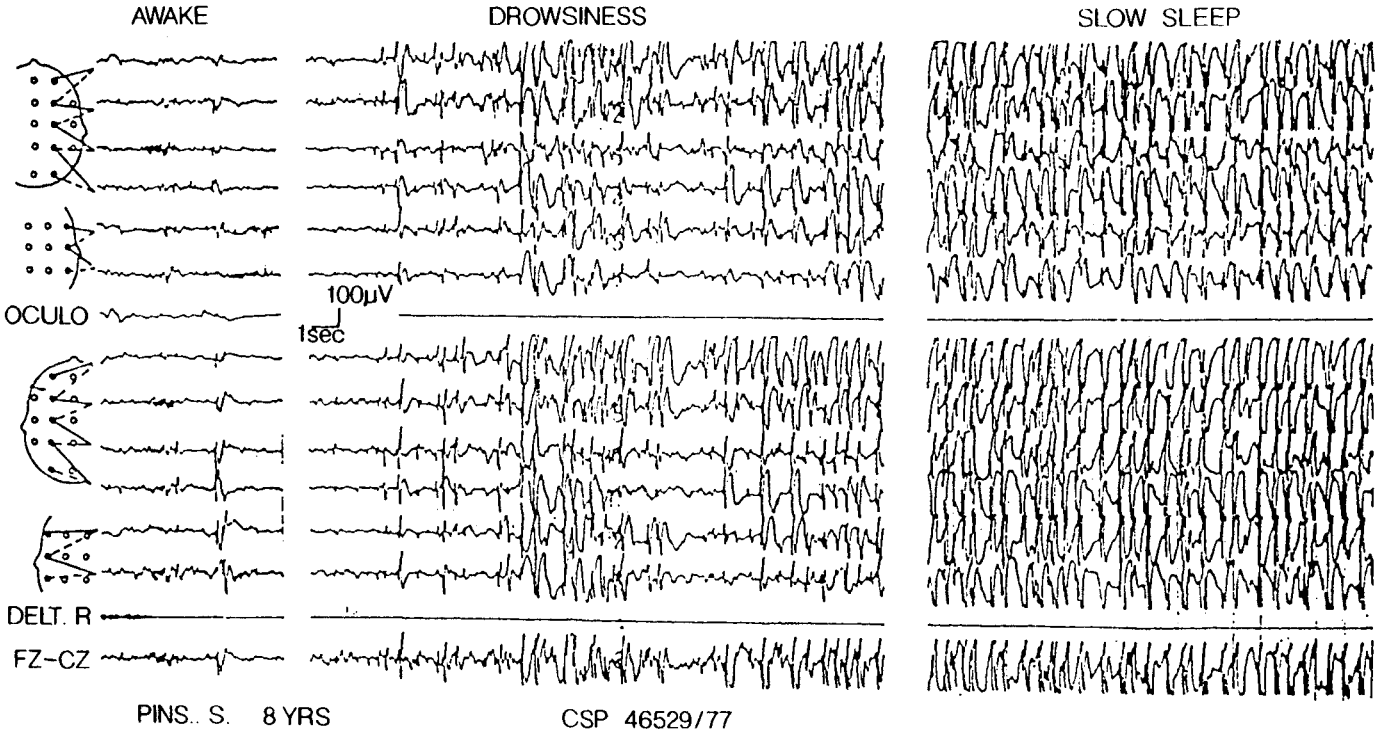

FIGURE 9.1 Awake recording (*left*), showing focal spikes. Drowsiness (*middle*) provokes the appearance of spike and wave discharges, which become continuous during NREM or slow sleep (*right*). (From Tassinari *et al.*, 1985, with permission.)

et al. (1990), Bureau *et al.* (1990), and Yasuhara *et al.* (1991) to define the ESES syndrome. Other authors, however, criticized this view and applied the term "ESES" even if the SW index was under 85%, (Calvet, 1978; Billard *et al.*, 1982). Beaumanoir (1995b) reviewed the sleep EEG data of the new cases labeled as ESES presented during the Venice Colloquium and found that an SW index of at least 85% was reached in 64% of the observations. He separated the patients into two groups according to the SW index and found that 27% of patients belonging to the group with an SW index below 85% did not present a significant drop in their performance scores.

Other relevant features of ESES concern the morphology and distribution of the paroxysms during slow-wave sleep. In the original series (Tassinari *et al.*, 1982, 1985, 1992b; Morikawa *et al.*, 1985), ESES was described as consisting of generalized or "diffuse" slow SWs at 1.5–2 Hz. However, cases displaying slow spikes devoid of the wave component (Michelucci *et al.*, 1987) or sharp waves (Fulgham *et al.*, 1990) have been reported. Moreover, cases with relatively focal, albeit continuous, discharges mainly involving the temporal or frontal regions or markedly asymmetrical SW activity over the two hemispheres have been described (Billard *et al.*, 1982; Morikawa *et al.*, 1985; Michelucci *et al.*, 1987; Veggiotti *et al.*, 1999).

Typically the paroxysmal activity becomes less continuous and the SW index is under 25% in rapid eye movement (REM) sleep; however, the focal discharges, predominantly frontal in location, may become prominent during REM sleep. In general, the EEG patterns during REM sleep are similar to those in the awake record. Finally, ESES disappears as abruptly on awakening as it appears at sleep onset.

PATHOPHYSIOLOGY

Two main issues have been addressed by the scientists involved in this syndrome: (1) the mechanism generating ESES and (2) the mechanism responsible for neuropsychological derangement.

Mechanism Generating ESES

Secondary bilateral synchrony is the mechanism underlying ESES. A number of features support this hypothesis. These include: (1) the principal seizure type that is usually partial motor, (2) the demonstration of EEG foci during both wakefulness and REM sleep, (3) interhemispheric peak latencies determined by computer-assisted analysis (Morikawa *et al.*, 1989), (4) phase reversal of spikes on unilateral frontal regions (Morikawa *et al.*, 1995), (5) coherence and phase analyses (Kobayashi *et al.*, 1990), and (6) evidence of a localized metabolic abnormality by means of positron emission tomography (PET) studies (Hirsch *et al.*, 1995). Additional arguments in favor of secondary bilateral synchrony have been obtained from studies on ESES associated with Landau-Kleffner syndrome (LKS). In this condition, which might well represent a variant of ESES

syndrome, intracranial EEG recordings (Cole *et al.*, 1988; Solomon *et al.*, 1993), EEG spectrum studies (Nakano *et al.*, 1989), and functional cerebral studies with the imaging techniques of PET (Maquet *et al.*, 1990) and single photon emission computed tomography (SPECT) (Mourisden *et al.*, 1993) seem to indicate a dysfunction localized over the temporal areas.

Mechanism Responsible for Neuropsychological Derangement

Since this syndrome was originally described, it has been postulated that ESES could be directly responsible for the appearance of neuropsychological impairment, mental deterioration, and psychiatric disturbances. Following this view, ESES would be a true instance of "status epilepticus" with nonconventional clinical manifestations (i.e., a stable and long-lasting change of mental and cognitive functions). Three main arguments support this hypothesis:

- The existence of a close temporal association between ESES and neurological regression (the latter beginning at the time ESES is discovered and improving after it has disappeared)
- The demonstration of a parallel between the duration of ESES and the final neuropsychological outcome
- The strict association between the pattern of neuropsychological derangement and the location of the interictal focus

The importance of the latter two factors has been clearly demonstrated by Rousselle and Revol (1995), who reviewed 209 observations from the ESES literature. They found that the neuropsychologically normal children (17%) had a relatively short duration of ESES (mean: 6 months) and the preferential focusing of paroxysmal abnormalities concerned cortical areas without any cognitive role. In contrast, the patients with acquired aphasia (16%) and those with global neuropsychological deterioration (67%) had a mainly temporal and frontal epileptogenic focus, respectively; moreover, the ESES duration was about 2 years. Causative factors for motor impairment in the form of dyspraxia, dystonia, ataxia, or unilateral deficit observed in some children during the period of ESES are a predominant involvement of motor areas by continuous SW activity (Tassinari, 1995; Neville *et al.*, 1998; Veggiotti *et al.*, 1999) and the appearance of negative myoclonus during wakefulness (Dalla Bernardina *et al.*, 1989). These results provide evidence that the duration of ESES and its preferential focusing are the main features influencing the degree and pattern of neuropsychological derangement. These above observations also suggest that ESES is a model for prolonged cognitive impairment induced by so-called "interictal paroxysmal activity" (Tassinari, 1995).

In humans, neurophysiological and neuropsychological studies support the view that so-called "interictal paroxysmal activity" may induce prolonged cognitive impairment (Binnie, 1993; Seri *et al.*, 1998). Experimental data also demonstrate that prolonged, even infraclinical, paroxysmal discharges have considerable consequences on metabolism and cerebral biochemistry (Wasterlain *et al.*, 1993).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is concerned mainly with other childhood epileptic syndromes showing a marked activation of the paroxysms during sleep. Tassinari *et al.* (1985, 1992b) have drawn attention to four main syndromes, namely, LKS, Lennox-Gastaut syndrome (LGS), benign epilepsy of childhood with centrotemporal spikes (BECTS), and atypical benign epilepsy.

LANDAU–KLEFFNER SYNDROME

There are several similarities between ESES and LKS and these have been discussed in detail by Tassinari *et al.* (1985). Age of onset, type of epileptic seizures, awake- and sleep-EEG features, type of metabolic dysfunction on PET studies, long-term prognosis, and therapeutic approach are remarkably the same in both conditions. Nevertheless, there are certain differences: (1) a typical ESES pattern was not observed in a number of published LKS cases; and (2) the majority of ESES patients have no evidence of language dysfunction or aphasia. It is now generally accepted that ESES syndrome and LKS are two facets of the same entity, in which the type of neuropsychological dysfunction depends on the preferential focusing (frontal in ESES and temporal in LKS) of SW activity. Furthermore, instances of evolution from LKS to ESES have been described in longitudinal clinical–EEG studies (Giovanardi Rossi *et al.*, 1999).

LENNOX–GASTAUT SYNDROME

The clinical symptomatology of ESES may, at a given moment, evoke the diagnosis of LGS, because of the occurrence of atypical absences, falling seizures, and mental retardation. The differentiation between ESES and Lennox-Gastaut syndrome has been analyzed extensively by Morikawa *et al.* (1985, 1989). Briefly stated, the following points have been emphasized: the SW index is less than 50% in children with LGS and is more than 85% in those with ESES; tonic seizures have never been described in ESES patients, while they are characteristic of the LGS group. Similarly, polyspikes and waves and bursts of fast rhythms, which represent essential features in LGS, are not encountered in ESES.

BENIGN EPILEPSY OF CHILDHOOD WITH CENTROTEMPORAL SPIKES

Five main features Distinguish BECTS from the ESES Syndrome:

1. Sleep may enhance the discharges in BECTS but an SW index greater than 85% was not reported in two large BECTS series studied by means of nocturnal polygraphy (Bureau, 1995a; Ambrosetto, personal communication). At variance with these studies, a true ESES has been described in some cases of BECTS after the introduction of carbamazepine (Caraballo *et al.*, 1989). Dalla Bernardina *et al.* (1989) also described 20

cases of BECTS associated with ESES; in this group, however, 75% of patients also had absences and atonic fits during wakefulness and 90% of cases developed either neuropsychological or motor impairment during the ESES state. These patients may be categorized "atypical BECTS" or they could be more precisely described as examples of "typical" ESES with epilepsy.

2. In ESES, spikes are generally frontocentral in location while those in BECTS are characteristically centrotemporal.
3. Neuropsychological deterioration is the rule in ESES whereas any form of mental or neurological regression is notably absent in BECTS.
4. Familial antecedents of epilepsy are frequent in BECTS and rare in ESES.
5. Organic signs of encephalopathy are relatively common in ESES and are constantly absent in BECTS.

ATYPICAL BENIGN PARTIAL EPILEPSY

As described by Aicardi and Chevrie (1982), the clinical picture of this syndrome is very similar to that of ESES, but there is no intellectual deterioration. However, no information was provided concerning the possible existence of minor behavioral disorders. The sleepEEG revealed an important activation of the abnormalities, but the SW index was not indicated and there was no reference to the duration of this EEG pattern.

LONG-TERM EVOLUTION AND PROGNOSIS

The long-term evolution of this syndrome has been described in detail by Morikawa *et al.* (1985, 1992, 1995), Bureau *et al.* (1990), Tassinri *et al.* (1992b). The data may be "split" into those concerning the EEG features, the epilepsy, and the neuropsychological impairment.

ESES is a self-limited EEG finding and disappears in all cases. Normalization is progressive and is completed within 3 years. In the Marseille series (Bureau *et al.*, 1990; Tassinari *et al.*, 1992b), the average age of apparent end of ESES is 11 years and 1 month. When reexamined some years after the end of ESES, the EEG recordings are always normal during both wakefulness and sleep, with preservation of sleep structure and physiological patterns. However, focal abnormalities during sleep may persist for a variable length of time after the disappearance of ESES (Bureau, 1995a).

It is generally agreed that epilepsy associated with ESES also shows a benign outcome, with disappearance of seizures in all cases. In the Marseille series, complete control of seizures was achieved after a mean period of 12 years (Bureau, 1995a). In the series collected during the Venice Colloquium, the long-term evolution was available in 50 subjects; after the end of ESES, 43 patients were seizurefree and 7 still had some rare or isolated seizures (Bureau, 1995b). The good seizure outcome is independent of the etiology and is also

observed in cases with cortical malformations such as multilobar polymicrogyria (Guerrini *et al.*, 1998).

Despite the invariable normalization of the EEG and the disappearance of seizures, the prognosis of this syndrome must be a guarded one, because of the persistence of neuropsychological impairment. In the Marseille series, an overall improvement was noted in performance and/or behavior after the end of ESES in all patients. However, at the time of the last observation, only 7 of the 15 patients were living normally; of the other 8 subjects, 6 were still institutionalized and 2 were employed, but they were badly adapted in their work and living circumstances (Tassinari *et al.*, 1992b).

A thorough intellectual and cognitive assessment of 33 patients presented during the Venice Colloquium was reevaluated after EEG normalization (Mira *et al.*, 1995). A global improvement in all intellectual areas was found, but this did not lead to complete restoration of functions, particularly in the verbal area and attention. Similar findings were also reported by Billard *et al.* (1982); Morikawa *et al.* (1985, 1992, 1995); Dalla Bernardina *et al.* (1989); and Roulet Perez *et al.* (1993).

TREATMENT

Basically, one should distinguish the treatment for seizures and for ESES:

- Clinical seizures may or may not respond to a variety of drugs including benzodiazepines, sodium valproate, ethosuximide, carbamazepine, and phenytoin. Despite the fact that seizures may be refractory to therapy for months or years, the long-term prognosis is favorable, with disappearance of seizures in all cases. Therefore, seizures do not usually pose a problem of management.
- The electrographic abnormality of ESES is generally refractory to treatment. If one admits some degree of causal relationship between paroxysmal EEG activity and neuropsychological deficits, systematic trials of several drugs should be attempted as for cases of refractory epilepsy. Nevertheless , it is always difficult to justify aggressive therapy on the basis of EEG records alone. In this respect, combined neuropsychological monitoring with serial IQ evaluations could be very helpful in guiding therapy.

Thus far, no controlled study with specific drugs is available in this field. Several authors have reported that benzodiazepines and adrenocorticotrophic hormone (ACTH) may apparently abolish the characteristic SW activity and improve neuropsychological functions (Kellerman, 1978; Billard *et al.*, 1982; Morikawa *et al.*, 1985). However, such effects are frequently self-limited. Intravenous injection of benzodiazepines during slow sleep arrested the ESES for 1 h in two cases reported by Tassinari (1995). Chronic oral treatment with clobazam

(Larrieu *et al.*, 1986), lorazepam (Boel and Caesar, 1989), and clonazepam (Yasuhara *et al.*, 1991), associated with other antiepileptic drugs (usually sodium valproate) seemed to have a long-lasting effect.

At the present time, the combined use of benzodiazepines and sodium valproate is considered to be the most effective treatment. On the other hand, polytherapy should be avoided. A detailed evaluation of antiepileptic regimens in 88 patients reviewed during the Venice Colloquium (Van Lierde, 1995) demonstrated that the reduction in polytherapy coincided with an improvement in the syndrome. It was also suggested that the therapeutic overload and certain drugs could play a role in the maintenance of ESES. In particular, carbamazepine, which may increase the tendency to bisynchronization, can worsen the EEG and clinical epileptic signs, a point that has been emphasized by several authors (Snead and Hosey, 1985; Lerman, 1986; Caraballo *et al.*, 1989).

It is recognized that multiple subpial transection (MST) is a valuable procedure for the treatment of language regression in LKS (Morrell *et al.*, 1995). If one believes that LKS is a variant of ESES syndrome, MST could prove to be also useful in conditions with a more widespread involvement of cognitive functions secondary to ESES. In this respect, improvement of autistic epileptiform regression has been reported in several cases following MSTs of the left neocortex in temporal, parietal, and frontal regions (Nass *et al.*, 1999).

CONCLUSIONS

Encephalopathy with ESES (or ESES syndrome) is an age-dependent and self-limited disorder whose distinctive features include characteristic age of onset (with a peak around 4 to 5 years); heterogeneous seizure types (mostly partial motor or unilateral seizures during sleep and absences or falls while awake); typical EEG pattern (with continuous and diffuse paroxysms occupying at least 85% of slow-wave sleep); invariable neuropsychological regression (consisting of IQ decrease, reduction of language, disturbance of behavior, and psychotic states), and motor impairment (in the form of ataxia, dyspraxia, dystonia, or unilateral deficit). Despite the long-term favorable outcome of epilepsy and ESES, the prognosis is guarded because of the persistence of severe neuropsychological deficits in about one-half of the patients. No specific treatment has been advocated for this syndrome but sodium, valproate, benzodiazepines, and ACTH have been shown to control the seizures and the ESES pattern in many cases; however, the effects are often temporary. On the contrary, drugs augmenting the tendency to bisynchronization, such as carbamazepine, or drug overload can worsen the EEG and contribute to the maintanance of the ESES pattern (Beaumanoir *et al.*, 1995b).

The condition is quite possibly underreported, and the wider use of sleep studies in severe epileptic patients would undoubtedly reveal as yet unsuspected

cases (Jayakar and Seshia, 1991). It is now generally accepted that secondary bilateral synchrony is the mechanism underlying ESES and that the apparently generalized seizures (tonic–clonic, absences) occurring in this condition have, in fact, a focal onset. Therefore, although ESES syndrome (or epilepsy with CSWS) is currently classified among the epilepsies undetermined whether focal or generalized (Commission, 1989), consistent data support the view that this syndrome is to be included in the domain of localization-related epilepsies of cryptogenic or symptomatic nature.

The most intriguing issue is the relationship between ESES and neuropsychological and/or motor derangement. The duration of ESES and the localization of interictal foci seem to play a major role in influencing the degree and type of cognitive dysfunction; moreover, there is a close temporal association between ESES and mental regression. These observations, along with experimental data, have led to the hypothesis that apparently infraclinical epileptic discharges during sleep may disrupt cognitive and/or motor functions.

It has been also postulated that many developmental or acquired defects of language (such as LKS) or behavior (such as autism) in children are a consequence of apparently subclinical spikes interfering with specific cerebral processes (Tauchman and Rapin, 1997; Ballaban-Gil *et al.*, 1998; Goldberg *et al.*, 1998; Lewine *et al.*, 1999). In this perspective the concept of ESES syndrome could be widened to embrace a subset of developmental or acquired regressive disorders of infancy showing marked activation of epileptiform discharges during sleep (Tassinari, 1995; De Negri, 1997).

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10

Acquired Epileptic Aphasia

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INTRODUCTION

Since the first description given by Landau and Kleffner (1957), the clinical significance of the association of language disabilities and a particular sustained centrotemporal epileptic activity with or without partial seizures in Landau-Kleffner syndrome (LKS), has been widely debated. The same happened when Patry *et al.* (1971) described a "subclinical" electrical status during slow sleep in five epileptic children and in another one with language difficulties later defined as encephalopathy with electrical status epilepticus during slow sleep (ESES). In fact, on one side, it was commonly accepted that even a single spike in the motor area was able to evoke a clinical phenomenon like a myoclonic jerk. In contrast, the new concept that a high rate of epileptiform discharges involving apparently "silent" cortical areas could lead to neuropsychological impairment was severely criticized. Moreover, the so-called electrical status epilepticus (lacking of detectable simultaneous clinical signs . . .) whether diffuse (ESES) or focal (LKS) could be observed in nonepileptic children. Only later, several studies demonstrated that both generalized and focal spikes, spike and waves, and even slow waves can influence cognitive functioning including language abilities (Dugas *et al.,* 1976, 1982; Dodrill, 1978, 1992; Aarts *et al.,* 1984; Binnie *et al.,* 1987, 1993; Francione *et al.,* 1997). Despite many common features, over the years LKS and ESES were considered as two separate entities and a number of authors argued about their specificity and nosological boundaries. The syndrome appeared in the first edition of *Epileptic Syndromes in Infancy, Childhood and Adolescence* (Roger *et al.,* 1985) and was included in the International Classification of Epilepsy and Epileptic Syndromes (1989) of ILAE under the name of continuous spike and waves during slow sleep (CSWS) or ESES. On the same occasion, LKS was also recognized among the "epilepsies and syndromes undetermined as to whether they are focal or generalized." The nosology, pathophysiology, electroencephalography, and clinical features of these two peculiar syndromes and their possible relationships were widely discussed during an International Workshop held in Venice on 1993. We are going to draw a picture of the ESES–CSWS and LKS "state of the art."

DEFINITION

LKS is a childhood disorder occurring in previously normal children characterized by the association of loss of language skills with acquired verbal auditory agnosia (Rapin, 1977) and multifocal spikes and spike-and-wave discharges mainly localized over the centrotemporal regions, continuous or subcontinuous during sleep. Epileptic seizures, behavioral disorders, and hyperkinesia are observed in about two-thirds of patients (Beaumanoir, 1985). The epileptic seizures, usually generalized tonic–clonic or partial motor fits, are rare. Their prognosis is favorable, with remission of seizures and electroencephalographic (EEG) abnormalities before the age of 15 years. Deonna and

Roulet (1995) defined the main characteristics of acquired aphasia–epilepsy syndrome (often called Landau-Kleffner syndrome) as an acquired childhood aphasia, paroxysmal EEG abnormalities (mainly bitemporal), a seizure disorder usually "benign" and self-limited, no demonstrable focal brain lesions, and a stabilization of the disease after a variable time. Following the original description of the syndrome given by Landau and Kleffner (1957), the association of language disorders with any kind of EEG abnormality or cases of pervasive developmental delay, mental impairment, and inborn error of metabolism are exclusion criteria. Stressing the necessity to be restrictive with regard to the clinical features, Morrell and co-workers (1995) described LKS patients as showing "a striking discrepancy between verbal and nonverbal IQ scores" with "relatively intact nonlinguistic capacities." If the nonspeech dependent faculties are not normal or psychotic behavior or characteristic signs of autism are present, the diagnosis of LKS is rejected (Morrell, 1995). The discovery that many patients with LKS had an extreme activation of spike-and-waves (SW) discharges during slow sleep raised the hypothesis that this condition was a clinical variant of epilepsy with ESES, as suggested by Tassinari *et al.* (1992, 2000). Instances of transition from LKS to ESES syndrome during long-term clinical and EEG follow-up have been provided by Giovanardi Rossi *et al.* (1999). The preferential focusing of the CSWS pattern over the temporal regions would explain the dysphasic nature of cognitive regression observed in LKS (Rousselle and Revol, 1995).

EPIDEMIOLOGY

Beaumanoir (1992) noted that, whereas only 81 cases were reported during the period 1957–1980, 117 new patients were described in the course of the following 10 years. At the 1993 Venice Colloquium, 31 new cases were presented by participants (Bureau, 1995). In their neuropedriatric service, Dugas *et al.* (1992) saw one new case a year.

The male to female ratio is 2:1 (Beaumanoir, 1992) or 68% (Bureau, 1995). An incidence of neurological disorders and epilepsy has been found in 3% of the cases presented at the Venice Colloquium (Bureau, 1995). However, Beaumanoir (1992) reported that careful investigations revealed a familial history for epilepsy in 12% of the children with seizures and in 5% of the children without epileptic manifestations.

CLINICAL FEATURES

The acquired epileptic aphasia in LKS occurs in previously normal children who have already developed age-appropriate speech. The disorder makes its appearance between 2 and 8 years of age with a peak between 5 and 7 years. LKS manifests in only 5% of the cases after 9 years of age and never after the age of 12 (Bureau, 1995). The first symptom is epilepsy in 60% of cases and

neuropsychological disorders in the remaining cases. According to Bureau (1995), who analyzed the data of 31 patients presented at the Venice Colloquium, LKS never starts with CSWS (Tassinari *et al.,* 1992).

The onset of *aphasia* can be variable, usually subacute, progressive with spontaneous fluctuations, differing in this respect from the aphasic syndromes related to organic brain damage, where the speech disturbance is characterized by an abrupt onset. The fluctuation of language disorder seems usually related to the degree of concomitant EEG abnormality (Landau and Kleffner, 1957; McKinney and McGreal, 1974; Shoumaker *et al.,* 1974; Dulac *et al.,* 1983; Deonna and Roulet, 1991; Lerman *et al.,* 1991). The strongest evidence comes from the dramatic improvement in linguistic function during the epileptic discharge suppression sometimes obtained with corticosteroid therapy. In most cases, the steroid tapering leads to "a recurrence of electrical abnormality followed shortly thereafter by return of the aphasia" (Morrell, 1995).

According to Deonna and Roulet (1995), ". . . the type of aphasia typically seen is a verbal auditory agnosia (Rapin *et al.,* 1977) but probably all types of aphasia can occur" (Chévrie-Muller *et al.,* 1991). Verbal auditory agnosia implies the failure to give a semantic significance to the different sounds. Common first symptoms of LKS are disability in understanding spoken words followed by inarticulation and decreased amount of speech. Spontaneous speech is rapidly reduced: the children can show perseveration, paraphasias, and phonological errors; they tend to use verbal stereotypes—a sort of telegraphic style with jargon speech. "Ultimately, the child may become completely mute and fails to respond even to nonverbal sounds such as the telephone ringing or door knocking, etc." (Morrell, 1995).

Kaga (1999) suggests a "sequential and sometimes clinical language disorder beginning with sensory aphasia followed by auditory agnosia and finally word deafness." Moreover, the primary deficit of the receptive aphasia is an impairment of auditory phonological discrimination instead of a generalized auditory agnosia. The final indifferent attitude of these children toward acoustic messages can lead to a misdiagnosis of acquired deafness (Humphrey *et al.,* 1975; Kale *et al.,* 1995) or autism. As to the time of appearance of aphasia, LKS can present as a global regression in communication, thus being different from developmental dysphasia (Maccario *et al.,* 1982; Deonna and Roulet, 1995).

Hyperkinesia has been reported in about half of the cases of *behavioral and cognitive disturbances.* Disturbances of personality with psychotic characteristics have been described (Dugas *et al.,* 1982; Gordon, 1990; Zivi *et al.,* 1990), as well as a global cognitive regression and impairment of effective development, with aggressiveness and outbursts of rage (White and Sreenivasan, 1987; Roulet *et al.,* 1991). These disturbances can show different degrees of severity, from mild to pronounced (Humphrey *et al.,* 1975) and they seem related to increasing difficulties in communication. Ansink *et al.* (1989) have described the association with a mild form of apraxia. The possibility that continuous paroxysmal EEG activities during sleep, as in ESES or in LKS, could result in an autistic disorder has been

suggested (Rapin, 1995). An unexplainable regression of language has been reported to occur in about one-third of autistic toddlers (Rapin, 1995). Indeed, in a series of 585 children with autistic spectrum disorders, Tuchman and Rapin (1997) observed epilepsy or epileptiform EEGs in a significant minority of children with language regression and in a smaller minority without regression.

Epileptic seizures occur in about 70–80% of LKS (Dugas *et al.,* 1982; Beaumanoir, 1992). The seizures are usually rare, and in one case out of three, the patient suffers from a single seizure or from a unique episode of status epilepticus, most often at the onset of this condition. The peak of occurrence of the epileptic syndrome ranges from 5 to 10 years (Beaumanoir, 1992); if the seizures are recurrent, seizure onset can occur earlier, between 4 and 6 years (Beaumanoir, 1992). Bureau (1995) reported the appearance of the first seizure between 3 and 5 years of age. In 16% of these cases, no seizure was noted before the discovery of ESES. The rare epileptic manifestations are often nocturnal and can be clinically heterogeneous: generalized tonic–clonic (being the first seizure type in 35% of the patients by Bureau, 1995), simple partial motor, atypical absence, and unilateral seizure, with an episode of unilateral status in 6% of the cases (Bureau, 1995). Reports of complex partial seizures are rare, whereas tonic seizures have never been observed (Dulac *et al.,* 1983). In his series of patients with LKS, Morrell (1995) reported the occurrence of subtle seizures, often missed by the family, characterized by minor motor manifestations (such as isolated clonic deviation of the eyes, blinking) and subjective manifestations ("roaring" in the ears, "sounds like a lion") accompanied by covering of the ears with the hands and associated with paroxysmal EEG activity.

Although Dulac *et al.* (1983) reported that myoclonic–astatic fits can occur rarely, Bureau (1995) stated that falling seizures have never been described in LKS and this could be a useful point in differentiating LKS from epilepsy with ESES. Antiepileptic drugs easily control the seizures without any improvement in language skills. Over time seizures disappear and these children are not epileptic as adults. In all described cases of LKS, *no evidence of associated focal brain lesions* was documented. Some cases have been reported presenting with an acquired epileptic aphasia and a focal brain lesion (Otero *et al.,* 1989; Perniola *et al.,* 1993; Solomon *et al.,* 1993). They seem to represent examples of symptomatic focal epilepsies causing aphasic seizures with a persistent language disorder.

NEUROPHYSIOLOGICAL CHARACTERISTICS

Waking background activity is usually normal; in one or two cases, some dysrhythmia has been reported, due perhaps to antiepileptic treatment. Epileptic activities are represented by high amplitude, repetitive spikes, and spike-and-waves, the topography of which can vary over time in the same patient. These multiple foci can be constantly and simultaneously evident (Fig. 10.1), or they can manifest themselves only at certain periods during the course of the syndrome.

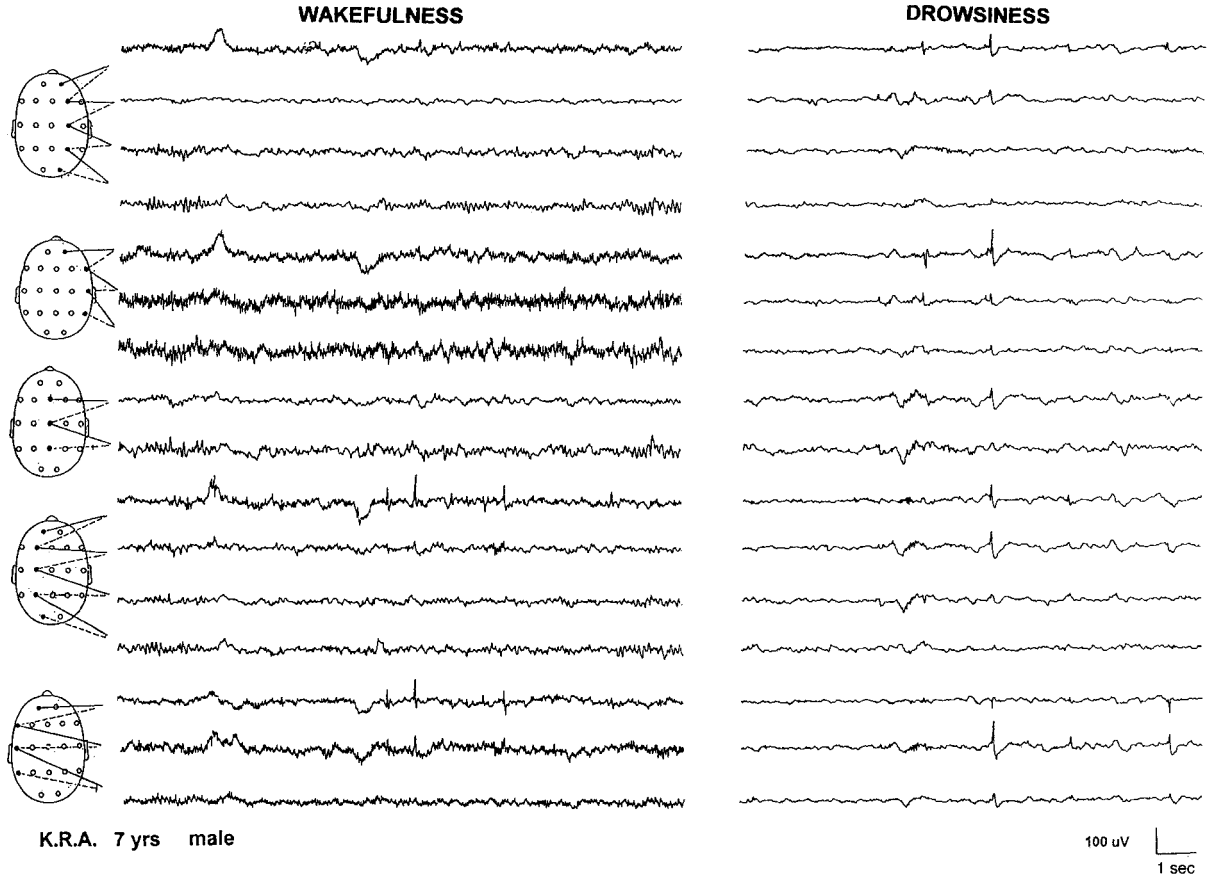

FIGURE 10.1 EEG recording in a 7-year-old male child with LKS and ESES. This child started to suffer, at the age of 5 years, from rare partial seizures characterized by clonic jerks on the left side of the face, with occasional secondary generalization. At the same age a regression of language skills and behavioral disorders appeared. At the age of 6 years, a sleep EEG recording showed continuous paroxysmal activities compatible with ESES. *Left panel*: an awake EEG demonstrated normal background activity and sporadic left frontotemporal spikes. *Right panel*: during drowsiness, left frontotemporal spikes appear diffuse and are seen controlaterally, and independent right frontotemporal spikes appeared.

Unilateral discharges are more common early in the course of the disorder. The foci are usually located in the temporal regions (>50% of the cases) or in the parieto-occipital regions (in about 30% of the patients). Generalized spike-and-wave discharges have also been observed (Hirsch *et al.*, 1990). From a morphological point of view, the paroxysmal abnormalities present some resemblance to "rolandic" spikes of benign epilepsy with centrotemporal spikes (BECTS). Beaumanoir (1992) reported that in 90% of the cases, a focus was already present at the time of the first EEG with a peak of appearance between 3 and 5 years. After the age of 15 years, the spikes disappear. Paroxysmal abnormalities do not seem to be affected by hyperventilation or intermittent photic stimulation.

Sleep, particularly sleep onset, has a remarkable activating effect on epileptic abnormalities (Rodriguez and Niedermeyer, 1982). However, in a given night, the discharges can be focal or unilateral. Unilateral subclinical seizures can be detected alternately in one or the other hemisphere. A nap recording can be as effective as an overnight sleep recording in showing the increment and the topography of the paroxysmal abnormalities (Hirsch *et al.*, 1990). At some time during the course of LKS, the sleep EEG presents a pattern of continuous, bilateral spike-and-waves, in more than 85% of slow sleep (Fig. 10.2), consistent with the occurrence of ESES (Tassinari *et al.*, 1992), suggesting a partial or complete overlap between the two conditions (Kellermann, 1978; Billiard *et al.*, 1981; Dulac *et al.*, 1983; Hirsch *et al.*, 1990; Marescaux *et al.*, 1990). At variance with the ESES syndrome, the persistence (Tiberge, 1988; Hubert-Franc, 1990; Giovanardi Rossi *et al.*, 1999) or even a further increment (Genton *et al.*, 1990) of paroxysmal discharges in rapid eye movement (REM) sleep has been observed in some patients with LKS.

Electrophysiological investigations performed in patients with LKS and widespread, apparently bilateral, paroxysms have shown a unilateral, extremely localized origin of the epileptic activity. Morrell (1995), by using the methohexital suppression test, demonstrated that spike activity on one side anticipated constantly spike activity on the contralateral side by 20–40 ms, suggesting that one hemisphere might "drive" the other (Fig. 10.3). These findings were confirmed by intracarotid injection of amobarbital, which—when performed in the driving hemisphere—suppressed epileptic activity bilaterally; on the contrary, when injected in the driven hemisphere, paroxysmal activity disappeared only in this hemisphere, whereas it persisted in the noninjected, driving side. EEG topographic analysis of the spikes during the methohexital test showed a tangential dipolar pattern across the sylvian fissure, consistent with a source on the dorsal surface of the superior temporal gyrus. Magnetoencephalographic (MEG) (Paetau, 1994; Morrell, 1995) and electrocorticographic (EcoG) (Morrell, 1995) recordings were consistent with these findings. The auditory system has been explored by means of different techniques. Audiometric tests were normal (Rapin *et al.*, 1977; Kale, 1995). Auditory evoked potentials gave normal responses in the cases studied by Nakano *et al.* (1989) and Shu-Xian *et al.* (1989), but Isnard *et al.* (1995) found alterations in central components of early and

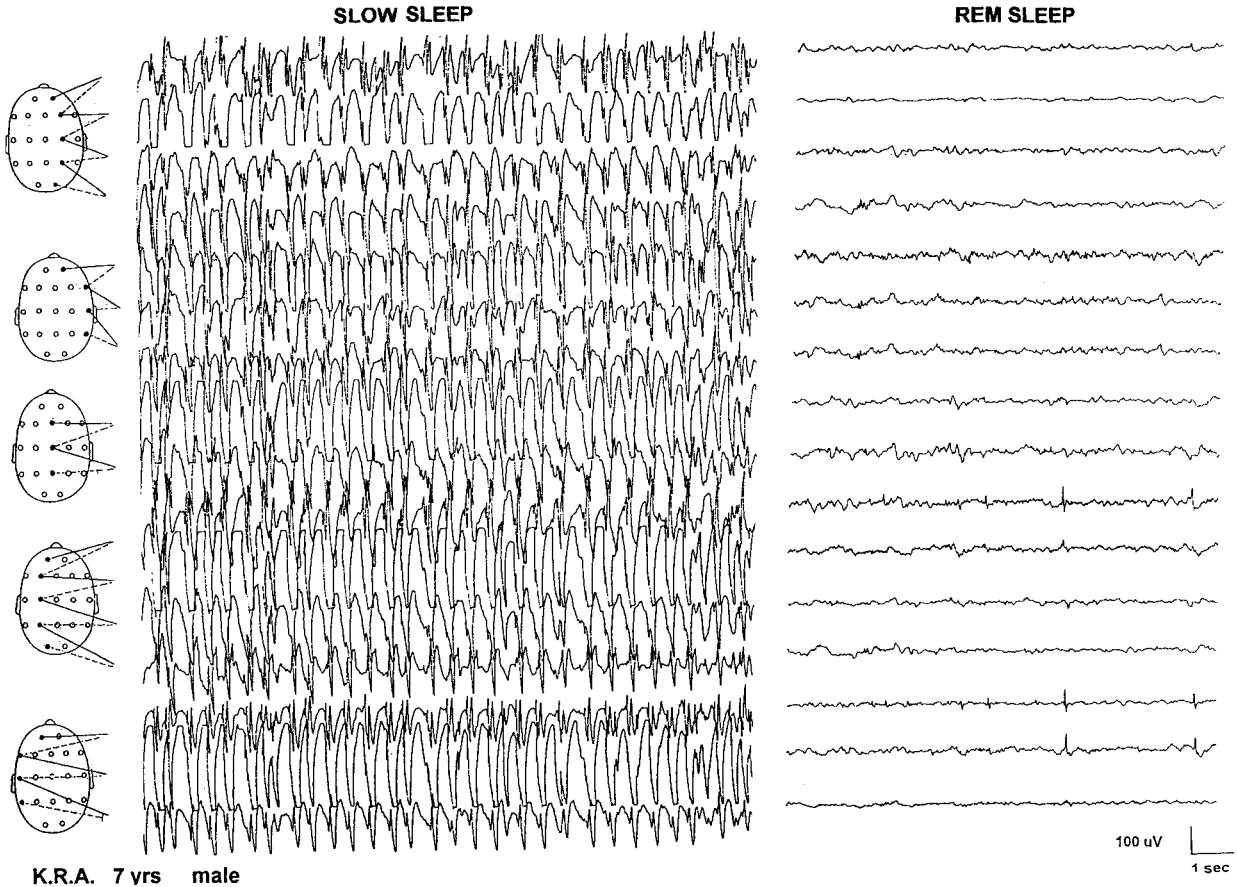

FIGURE 10.2 Same patient as in Fig. 10.1. *Left panel*: during slow sleep, diffuse, 2.5 cycles per second spike-and-wave activity appeared and persisted for more than 85% of this sleep stage. *Right panel*: in REM sleep, diffuse spike-and-wave discharges disappeared, whereas left frontotemporal spikes, without contralateral spread, reappeared.

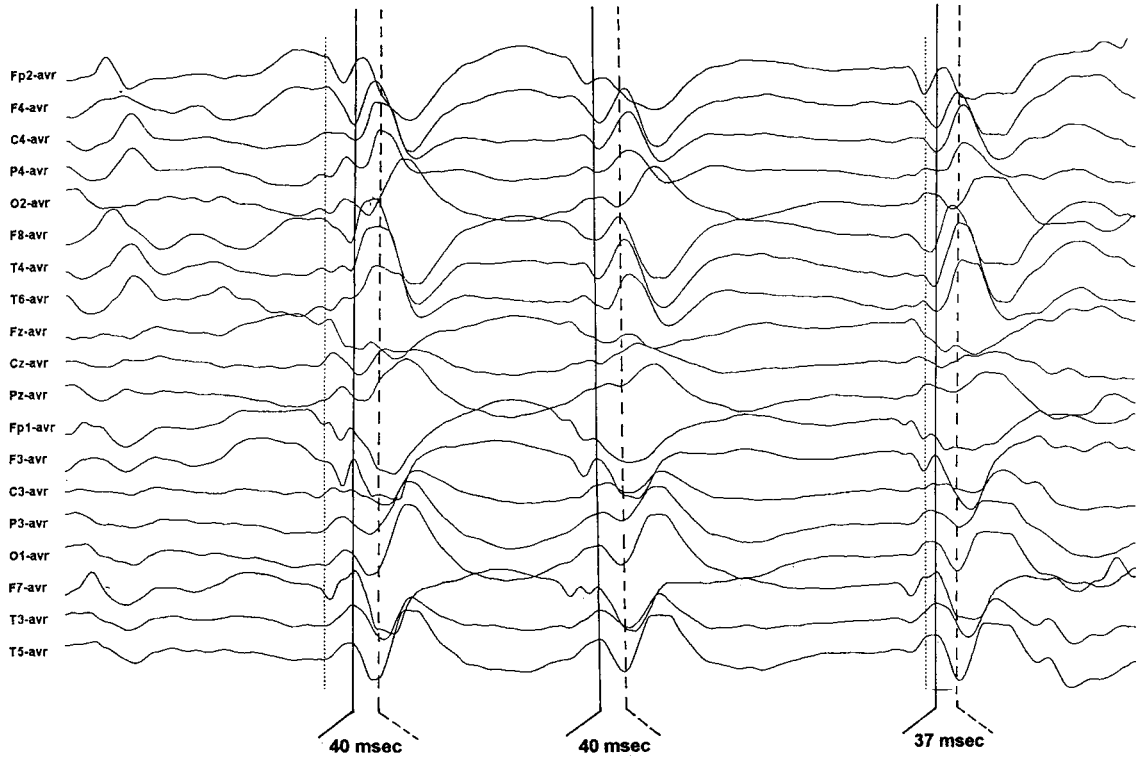

FIGURE 10.3 Same patient as in Figs. 10.1 and 10.2. A fragment of EEG during ESES is reported. Two spike-and-wave complexes are illustrated with an expanded timescale; solid line cursor is positioned at the peak of the spike of the left frontotemporal spike-and-wave complex, whereas dashed line cursor at the peak of the spike of the homologous contralateral spike-and-wave complex. Left spike-and-wave activity constantly preceded contralateral homologous paroxysmal activity with a time lag ranging between 35 and 40 ms, confirming the results reported by Morrell (1995).

middle latency auditory evoked potentials. Seri *et al.* (1998) demonstrated that in a group of six children with LKS spikes in the temporal regions could produce a reduction in amplitude and an increment in latency of the N1 auditory-evoked responses. These results were consistent with a dysfunction of the central auditory pathways and with a deficit in the activation of auditory cortial areas. Paetau (1994) described alterations of the auditory evoked magnetic fields in five children with LKS. The neural generators of the auditory evoked magnetic fields coincided with the sources of the spontaneous spikes, both located along the sylvian fissure and suggested a participation of sound-responsive neurons in the nonprimary auditory cortex, within the middle and posterior sylvian region, in the genesis of epileptic activity.

PATHOPHYSIOLOGY

Originally, Landau and Kleffner (1957) proposed that "persistent convulsive discharge in brain tissue largely concerned with linguistic communication results in the functional ablation of these areas for normal linguistic behavior." Later, serological examination and cerebral biopsy looking for a specific encephalopathy or encephalitis did not show detectable structural epileptogenic lesions (McKinney and McGreal, 1974; Lou *et al.,* 1977; Cole *et al.,* 1988). Data seem to suggest that autoimmune mechanisms might play a role in the pathogenesis of LKS (Connolly *et al.,* 1999). Despite apparently different theories, several authors suggested a functional impairment produced by the interference of the continuous or subcontinuous focal epileptiform discharges during sleep (a form of focal ESES) on the higher functions related to the cerebral area involved (Seri *et al.,* 1998). Morrell argued that the speech systems remain malleable during the first 8–10 years of life as supported by studies of recovery from early brain injuries made by Alajouanine and Lhermitte (1965), and Rasmussen and Milner (1977). A particular sustained focal epileptic activity arising during the speech systems plastic stage and involving meaningful language areas, do not let the neurons and developing synaptic contacts perform and develop normally. The severity and variety of the resulting speech and neuropsychological disruption is probably due to the age of onset, duration, intensity, and localization of the original epileptic focus (Morrell *et al.,* 1995; Tuchman, 1997). Functional abnormalities also have been detected by means of positron emission tomography (PET) and single photon emission computed tomography (SPECT), which demonstrated a metabolic derangement predominant over the temporal lobes (Maquet *et al.,* 1990; O'Tuama *et al.,* 1992; Guerreiro *et al.,* 1996; Da Silva *et al.,* 1997). This hypothesis could explain on the one hand the worse prognosis in children with LKS of early onset and/or with long-standing disease (Toso *et al.,* 1981; Dulac *et al.,* 1983); on the other hand, the better outcome is when aphasia starts after acquisition of written language and leaves writing intact as reported by Beaumanoir (1992) (a sufficient number of normal connections already estab-

lished to mediate a reasonable linguistic behavior). Beaumanoir (1992) suggested that the occurrence of multiple functional spike foci, associated with normal background activity, could be compatible with an immaturity of afferent systems or a sectorial disorganization subsequent to deafferentation.

EVOLUTION AND PROGNOSIS

Aphasia often shows a waxing and waning course characterized by remissions and exacerbations usually but not necessarily related to quantitative variations of paroxysmal activity during sleep (Landau and Kleffner, 1957; Rapin *et al.,* 1977; Mantovani and Landau, 1980; Toso, 1981; Hirsch *et al.,* 1990; Deonna *et al.,* 1997). The recurrence of aphasia or its worsening can occur even many years after the initial episode (Dugas *et al.,* 1995).

The duration of the disease is extremely variable. Spontaneous remissions have been reported within weeks or months after onset (Landau and Kleffner, 1957; Deonna *et al.,* 1977; Mantovani and Landau, 1980; Deonna, 1991; Deonna and Roulet, 1991). However, if symptoms persist unchanged for more than a year, spontaneous recovery is rare (Morrell, 1995). After a variable time, aphasia stabilizes and usually improves before adulthood (Deonna *et al.,* 1989; Hubert–Franc, 1990). Dugas *et al.* (1982) analyzed the long-term outcome of 55 cases with a minimum follow-up of 7 years: 47.5% presented no oral expression or unintelligible or significantly reduced oral language; 34.5% had persistence of oral or written language difficulties that did not prevent a normal life; 18% did not show language abnormalities. However, the long-term deterioration of intellectual functioning is uncommon even when a severe aphasia persists in adulthood (Mantovani and Landau, 1980; Deonna *et al.,* 1989). The frequency and type of seizures do not affect the outcome (Beaumanoir, 1992).

The variables influencing the final severity of language disorder are the following: the early onset of aphasia (Morrell, 1995); the duration, intensity, and localization (speech cortex) of the focal CSWS pattern (Rousselle and Revol, 1995); the spread of paroxysmal activities to the contralateral hemisphere; and the efficacy of antiepileptic treatment (Deonna, 1991). In conclusion, "having CSWS during childhood can impair the acquisition of new and/or the utilization of previous knowledge. If this is the case, are the spike-and-waves really 'interictal'? This is the current concept stemming from the condition of ESES which took a quarter of a century to become, if not understood, at least a matter of discussion" (Tassinari *et al.,* 1995).

TREATMENT

All classical types of antiepileptic drugs have been used. Phenytoin, carbamazepine, and phenobarbital are either ineffective or can even worsen the clinical and EEG picture, whereas partial or transitory improvements have been

obtained with valproate, ethosuximide, or benzodiazepines (Marescaux *et al.*, 1990). Intravenous benzodiazepine can be rapidly and dramatically effective in suppressing the EEG abnormalities and in improving verbal communication, but this result is transitory and brief (Ravnik, 1985; Tassinari, personal observation). Steroid treatment has been claimed to be efficacious by several authors (McKinney and McGreal, 1974; Lerman and Lerman-Sagie, 1989; Marescaux *et al.*, 1990; Lerman, 1991). Marescaux *et al.* (1990) suggest high corticosteroid doses as soon as the diagnosis has been clearly established and continued maintainance treatment for months or years to avoid relapse. In one subject, a spectacular but transient effect on sleep and waking EEG was observed with dextroamphetamine. However, no modification of the language disorder was observed (Marescaux *et al.*, 1990). There are also reports of successful use of i.v. immunoglobulins (Fayad *et al.*, 1997; Lagae *et al.*, 1998).

The surgical treatment, which is performed by means of the technique of multiple subpial transection (MST) proposed by Morrell *et al.* (1989), is an alternative therapeutic option. MST is a procedure that selectively interrupts the intracortical horizontal fibers, preserving the vertical columnar organization; therefore, it prevents the synchronization through horizontal linkages necessary for the epileptic discharge to occur, while not altering the normal physiological transactions mediated by the vertically oriented cortical columns. Over the years, a growing evidence of progressive and long-lasting improvement of language function after MST performed in the region of focal epileptic discharges, as defined by electrocorticographic recordings (Morrell, 1995), has been provided (Morrell *et al.*, 1995; Grote *et al.*, 1999).

A classical surgical approach, by means of left temporal lobectomy, has been performed in two cases resulting in a transitory improvement of aphasia (Cole *et al.*, 1988; Nass *et al.*, 1999). A global educational approach, including language therapy, has been advocated. Deonna and Roulet (1995) pointed out the complexity of psychological and educational management in children with LKS, due to the characteristics of varying severity, and the spontaneous fluctuations of this condition that require constant adaptation of the demands made on the child.

CURRENT PROBLEMS

Although the recognition of LKS, as a syndromic entity, in the International Classification of the Epileptic Syndromes (1989) has given a legitimacy to this condition, still its individuality and nosologic boundaries are a matter of discussion. One of the main problems is the interpretion of the association of a severely altered EEG with abundant paroxysmal activity, in spite of a minor epileptic picture, with acquired aphasia. Some authors (Worster-Drought, 1971; Gascon *et al.*, 1973; Holmes *et al.*, 1981) dismissed a causal relationship between epilepsy and aphasia based on the fact that seizures could precede, or after a long time follow the language disorders; and that, in some cases, there

was a lack of correlation between epileptic EEG abnormalities and severity of the language deficit, with improvement or worsening of speech disturbances independent of the EEG picture. Therefore, the epileptiform activity was considered as an epiphenomenon reflecting underlying abnormalities of speech areas instead of the cause of aphasia. However, this interpretation neglected other clearly documented evidence, demonstrating that aphasia can start acutely and promptly recover, relapses can occur and fluctuations of the course of the aphasia are not unusual. All these features can be compatible with an impairment of function due to continuous epileptic activity. A further argument in favor of a possible epileptic nature of this condition is the dramatic improvement of the disturbances, observed in some cases, with steroid or anticonvulsant therapy. Finally, several electrophysiological findings suggest that epileptic activity originates from a primary focus, with a bilateral secondary synchronisation (Morrell, 1995). It remains to be established which kind of epilepsy can persist for months or years. A similarity with BECTS has been proposed (Dulac *et al.,* 1983; Deonna, 1991), suggesting that LKS also could be included in the group of the so-called "functional" partial epilepsies, although the prognosis is not as good as in BECTS and the course can be severe. Associated variables (such as structural but yet undemonstrable lesions, genetic epileptic predisposition, age, peculiar functional organization, and pattern of brain maturation) might play a role in the clinical expression and final outcome of this condition (Deonna and Roulet, 1995).

Another aspect that remains controversial is the position of LKS with respect to ESES. Some authors distinguished LKS and ESES on the basis of EEG characteristics, pointing out that ESES presumably represents a secondary bilateral synchronization of epileptic activity originating from the frontal regions, whereas in LKS the focal paroxysmal activity is localized mostly in the temporal or parietotemporal areas. On the contrary, the evidence that sleep, in some cases of LKS and in certain stages during the course of the disease, can remarkably activate paroxysmal activities for most of slow sleep (as in ESES), has led other authors to state that the two conditions completely (Hirsch *et al.,* 1990) or partially overlap (Kellerman, 1978; Billiard *et al.,* 1981; Dulac *et al.,* 1983; Marescaux *et al.,* 1990). A point that has to be considered, when the relationship between LKS and ESES is discussed, is that, although the number of sleep recordings in patients with LKS are increasing, it is still difficult to know how many cases show a typical ESES during the course of the disease. However, in some patients, it is evident that the two conditions coexist (see Figs. 10.1–10.3). A focal, temporal, or parietotemporal localization of paroxysmal activities in cases with LKS, without other established clinical, prognostic, and therapeutic differences with ESES, does not seem sufficient to separate these two entities; and this EEG feature may be simply interpreted as the predominant localization of the epileptic activity in that stage of the course of the disease. Indeed, at present, convincing evidence demonstrating that LKS and ESES are two distinct entities is lacking.

It is presumably safe to acknowledge that much of the disagreement about LKS depends on the heterogeneity of the cases classified under this eponym. Landau (1992) himself has raised the issue of the necessity of clear-cut, possibly narrow, diagnostic criteria, to address primary questions, such as etiology, pathophysiology, and rational and empirical treatment of LKS. This approach could eventually shed some light on this condition, characterized by an unexplained cause, no established effective therapy, and a variable and unpredictable prognosis.

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11

SLEEP DISORDERS IN EPILEPSY

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INTRODUCTION

Many patients with epilepsy complain of excessive daytime sleepiness (EDS) or fatigue. These symptoms are commonly attributed to the effects of antiepileptic drugs (AEDs) or seizures. Until recently, there has been little scientific evidence to confirm this suspicion. Whether primary sleep disorders represent a significant cause of EDS in the epileptic population remains to be determined.

The impact of sleep disorders on quality of life is becoming increasingly recognized. In surveys of the general population, 35% of individuals report difficulty initiating or maintaining sleep, and EDS is described by 4–5% of those

queried (Roth *et al.*, 1994). EDS is the most common complaint of subjects referred to sleep disorder centers. Of those referred for polysomnography (PSG) for the evaluation of EDS, sleep apnea is identified in approximately 75%, narcolepsy in 20%, and restless legs syndrome (RLS) or periodic limb movements in sleep (PLMS) in 5% of cases (Partinen, 1994). Obstructive sleep apnea syndrome (OSAS) affects 1–4% of the population with a maximal incidence in middle-aged, overweight males (Partinen, 1994). Individuals with epilepsy may be predisposed to OSAS due to the adverse effects of AEDs, most notably, sedation and weight gain. RLS, a disorder characterized by an irresistible urge to move the legs, may produce insomnia or EDS (Montplaisir *et al.*, 1994). This syndrome is associated with the use of tricyclic antidepressants, medications that are pharmacologically related to carbamazepine (CBZ). Yet, CBZ has been found to be an effective treatment for RLS (Telstad *et al.*, 1984). Long-term use of some AEDs can lead to folate deficiency and peripheral neuropathy, conditions that predispose to RLS and PLMS. Appropriate treatment of sleep disorders can produce a substantial improvement in quality of life and may also improve seizure control.

PRIMARY SLEEP DISORDERS IN PATIENTS WITH EPILEPSY

The incidence of primary sleep disorders in the epileptic population is unknown. The literature contains mostly retrospective studies in which patients with epilepsy and suspected sleep disorders are included. Consequently, the reported incidence of sleep disorders is likely to be overestimated. Prospective studies are required to determine how these figures compare with those of the general population.

In the largest retrospective study, 63 adults with epilepsy were referred for PSG for EDS and suspected OSAS (27), suspected OSAS without EDS (22), spells and EDS or suspected OSAS (10), nocturnal spells (2), or EDS alone (2) (Malow *et al.*, 1997). Multiple sleep latency tests (MSLTs) were performed in 33 cases. Sleep disorders were suspected in 79% of patients. Obstructive sleep apnea syndrome was diagnosed in 71%. The disorder was considered mild in 14, moderate in 21, and severe in 10 patients, including 7 females. Other diagnoses included nocturnal seizures (4), mild OSAS and narcolepsy (1), and insufficient sleep syndrome with probable idiopathic hypersomnia (1). In 13 cases, the diagnosis was uncertain. These included six subjects with PLMS with 20 or greater leg movements per hour generally not causing arousal. Of the subjects who had MSLTs, the average mean sleep latency was 6.8 min, suggesting a moderate degree of daytime sleepiness. Treatment of OSAS with continuous positive airway pressure (CPAP) or with bilevel positive airway pressure (BIPAP) was prescribed in 28 cases. However, only 54% were still using the

device at the time of last follow-up. Seizure control improved with CPAP in five of nine patients having seizures before treatment. In two cases, EDS improved despite higher doses of AEDs or the administration of new AEDs. Treatment with CPAP was discontinued in 12 patients due to poor tolerance (9) and lack of efficacy (3).

Other studies have confirmed a high incidence of primary sleep disorders in subjects with epilepsy and sleep complaints. Of 43 adults admitted for video EEG monitoring (28 with confirmed epilepsy), abbreviated sleep studies were performed to evaluate for suspected OSAS (24); PLMS or nocturnal spells (9); and EDS, cataplexy, or both (10) (Bromfield *et al.*, 1997). OSAS was confirmed in 12 cases (8 with epileptic and 4 with nonepileptic seizures). The disorder was mild in five, moderate in three, severe in two, and restricted to rapid eye movement (REM) sleep in two cases. Hypersomnia without cataplexy was diagnosed in two subjects, and one patient was found to have PLMS. Despite limited follow-up, daytime sleepiness improved with treatment of the sleep disorder in most cases. However, seizure frequency was not significantly affected.

Of 22 patients with epilepsy who underwent PSG for evaluation of EDS with or without snoring, sleep disorders were identified in 18 (72%) (Marsilio *et al.*, 1997). Of these 22 patients, 12 had OSAS, with a mean apnea–hypopnea index (number of respiratory events per hour) of 23. Upper airway resistance syndrome (UARS), a disorder characterized by abnormal increases in resistance of the upper airway in sleep that produce arousal, oxygen desaturation, and EDS, was found in four subjects (Guilleminault *et al.*, 1993). Two patients were diagnosed with PLMS; however, the disorder was of questionable clinical significance in one because leg jerks typically did not disrupt sleep.

Several authors have reported an improvement in seizure frequency following treatment of OSAS (Devinsky *et al.*, 1994; Vaughn *et al.*, 1996; Koh *et al.*, 1997; Barthlen *et al.*, 1998; Wyler and Weymuller, 1981). Seven adults with focal epilepsy and moderate to severe OSAS were treated with CPAP alone (3), CPAP with weight reduction (1), CPAP with pharmacotherapy (1), pharmacotherapy alone (1), and tracheostomy with supplemental oxygen and acetazolamide (1) (Devinsky *et al.*, 1994). Treatment reduced seizure frequency and severity in six cases. However, noncompliance was an issue in three of five patients in whom CPAP was prescribed.

In another series, four of ten patients with OSAS experienced a dramatic improvement in seizures (three patients were rendered seizure free) with CPAP or positional therapy (Vaughn *et al.*, 1996). Seizures occurred exclusively on awakening or in sleep in three of the four patients experiencing the greatest reduction in seizures. A typical body habitus of OSAS was present in only two of these patients. Seizure frequency was reduced in three others after AED adjustments and treatment of the sleep disorder. Three subjects, with seizures unrelated to the sleep–wake cycle, experienced less than a 50% seizure reduction. There was no correlation between severity of OSAS and seizure frequency.

The impact of treatment for OSAS on seizures was reported in 10 epileptic children treated with tonsillectomy (8), tracheostomy (1), and CPAP (1) (Koh *et al.*, 1997). Seizure frequency improved in six cases. After one year of treatment, the mean seizure frequency decreased from 1 or 2 per month to one seizure every 4 months.

Very little is known of the incidence of PLMS and RLS in patients with epilepsy. In one report, three of six patients with untreated epilepsy had PLMS, but the disorder produced sleep disruption in only one case (Newell and Drake, 1994). Restless legs syndrome was described in two subjects taking methsuximide and phenytoin (PHT), respectively (Drake, 1988). In the first case, symptoms resolved after methosuximide was replaced by valproic acid (VPA). Symptoms improved when PHT was replaced by CBZ in a male with a hemiparesis following subarachnoid hemorrhage. No evidence of neuropathy was found in either case.

Daytime sleepiness was assessed in 30 adults with epilepsy using the MSLT (Drake *et al.*, 1994). Of those, 23 subjects reported intermittent tiredness or difficulty sleeping and 20 described feelings of depression and irritability. Another 20 subjects reported feeling sleepy during some of the naps. A mean sleep latency of greater than 8 min was considered normal. The mean sleep latency was greater than 8 min in 10, between 5 and 8 min in 7, and less than 5 min in 3 of the 20 subjects reporting sleepiness. Of the patients who denied feeling sleepy during the test, two failed to sleep during the MSLT, 7 had a mean sleep latency greater than 8 min, and one had a mean sleep latency between 5 and 8 min. The mean sleep latency of the entire cohort was 8.4 min, which is suggestive of mild to moderate hypersomnia, using 10 min as a cutoff by conventional scoring standards (Carskadon *et al.*, 1986). Pathological hypersomnia (mean sleep latency less than 5 min) was found in 10% of cases. Patients who had seizures or were sleep deprived the previous night were excluded. However, the presence of chronic sleep deprivation, concomitant sleep disorders and the remote effects of AEDs were not investigated.

SLEEP COMPLAINTS AND SLEEP HYGIENE

Patients with epilepsy commonly report sleep disturbances. Using a six item questionnaire, the frequency of sleep disorder symptoms was compared with 30 treated patients having epilepsy and 23 normal adults (Hoeppner *et al.*, 1984). Patients with simple and complex partial seizures had a higher incidence of sleep symptoms than patients with generalized seizures and normal subjects. The most common complaint was frequent nocturnal awakenings. Patients with seizures at least every month had more sleep-related symptoms and nocturnal awakenings than those with yearly seizures or less.

As in the general population, poor sleep hygiene is a common cause of daytime sleepiness and insomnia. In a survey of 100 patients with epilepsy,

37% reported poor sleep (Lannon and Vaughn, 1997). These patients had less exercise and more irregular sleep patterns, took more naps, and consumed more caffeine, alcohol, and tobacco within 6 h of bedtime than those without sleep complaints. Environmental barriers to sleep were identified in 40% of patients reporting poor sleep. Patients with poor sleep were less likely to be seizure free and more likely to have daytime sleepiness. Poor sleep hygiene practices were identified in one-third of 270 epilepsy patients in another series (Manni *et al.*, 1998). Inadequate meals, smoking, evening naps, high mental level demanding activities close to bedtime, and sleep deprivation were the most frequent transgressions. Poor sleep hygiene practices were more common in males and younger patients.

EFFECTS OF SEIZURES ON SLEEP AND VIGILANCE

Seizures occurring both at night and during the day can affect sleep architecture and produce daytime sleepiness. In a study comparing the effects of generalized and focal seizures on sleep, nocturnal generalized seizures produced a decrease in sleep time and reduced REM sleep percentage, prolongation of REM latency, and more sleep fragmentation (Touchon *et al.*, 1991). Stages 1 and 2 sleep were increased while the percentage of slow-wave sleep (SWS) was unchanged. REM rebound [an increase in REM percentage after REM-suppressing situations (i.e., sleep deprivation)] was not observed later in a night after a seizure or during seizure-free nights. Focal seizures occurred during REM and nonrapid eye movement (NREM) sleep. When occurring in isolation, focal seizures produced little or no sleep disruption. However, multiple focal seizures in a night produced a significant reduction of REM sleep and duration of REM periods. As compared with control subjects, patients with epilepsy had significantly more disrupted sleep and lower sleep efficiency (total sleep time/time in bed). These findings held true even on seizure-free nights.

The effects of daytime and nocturnal seizures on sleep and vigilance were studied in 11 patients admitted to an epilepsy monitoring unit (Bazil *et al.*, 1997; Castro *et al.*, 1997). The percentage of time spent in REM sleep was significantly reduced and REM latency prolonged in nights after daytime seizures (Bazil *et al.*, 1997). However, daytime seizures did not affect sleep efficiency. After daytime seizures, patients fell asleep more quickly on the MSLT, suggesting that daytime seizures are a significant cause of EDS. As compared with seizure-free nights, nights with seizures were characterized by a reduction of REM and stage 3 sleep (Castro *et al.*, 1997). In addition, REM latency was prolonged and sleep efficiency was reduced. Patients had more severe daytime sleepiness on days after nocturnal seizures as compared with days after seizure-free nights, as measured by the MSLT. These findings were independent of seizure duration.

ANTIEPILEPTIC DRUG EFFECTS ON SLEEP AND VIGILANCE

AEDs produce a variety of alterations in sleep architecture and varying degrees of daytime sleepiness. In seven healthy subjects taking 700 mg daily CBZ of for 10 days (mean serum concentration of 11.8 ± 1.1 μg/ml), SWS percentage increased significantly while REM sleep decreased (Yang *et al.*, 1989). Treatment produced a shortened REM latency, although not statistically significant. The SWS-enhancing effects were thought to reflect the effect of CBZ on 5-HT levels or its effect on adenosine receptors that modulate the release of 5-hydroxytryptamine (5-HT) and catecholamines. The acute and long-term effects of controlled release CBZ (CBZ CR) were studied in seven adults with newly diagnosed temporal lobe epilepsy (TLE) (Gigli *et al.*, 1997). The findings were compared to nine control subjects who underwent PSG after a single 400 mg dose of CBZ CR. The single dose produced a significant reduction of REM sleep and increase in REM fragmentation in the TLE group, and an increase in stage shifts in normal subjects. In patients with TLE, these findings were almost completely reversed after 1 month of treatment with 400 mg twice per day. The first dose produced a significant shortening of the mean sleep latency on the MSLT only in normal subjects. After a single dose, daytime sleepiness was reported more often by controls than TLE patients. Other investigators found no change in sleep macroarchitecture with CBZ therapy in patients with epilepsy (Declerck and Wauquier, 1991). However, administration of the drug to healthy volunteers produced shorter sleep cycle duration.

The effect of therapeutic concentrations of phenobarbital (PB) and PHT was studied in 40 patients with epilepsy using a random, crossover design (Wolf *et al.*, 1984). Treatment with PB shortened sleep latency and produced a reduction of body movements and arousals. An increase in stage 2 sleep, reduction of REM sleep, and higher sleep efficiency were observed, while SWS was not affected. Compared to the baseline, each REM period started later, with the most prolonged latency occurring in the first REM period of the night. Treatment with PHT also shortened sleep latency, but produced a reduction of stage 1 and 2 sleep and an increase in SWS. The frequency of arousals and REM percentage were unchanged. No correlation between sleep architecture and serum concentrations of either drug was found.

Immediate, short- and long-term effects of PHT on sleep architecture were studied in 40 untreated subjects with epilepsy (Röder-Wanner *et al.*, 1987). A single 100-mg dose at bedtime shortened sleep latency and produced a reduction of wake time and an increase in movement arousals and body movements. A decrease in REM sleep was observed in patients with focal epilepsy. During short-term treatment (adjustment to steady state), sleep latency and stage 1 sleep were reduced, SWS was increased, and arousals were more frequent in both REM and NREM sleep. In 12 subjects treated with PHT for a minimum of 4.5 months, most of the short-term effects were reversed. An increase in stages 1 and 2, and a

decrease in SWS were observed, while REM percentage was unchanged. There was no correlation between seizure frequency or serum drug concentration and long-term alterations in sleep architecture. An increase in stage 1 and 2 and a minor reduction of REM sleep after treatment with PHT have also been reported (Declerck and Wauquier, 1991).

In 30 healthy subjects, a single dose of 250-mg primidone (PRM) produced an increase in SWS and a reduction of REM percentage and density (Maxion *et al.*, 1975). No significant changes were found after one 200-mg dose of PHT, although SWS percentage was reduced. A shortened sleep latency and reduction of REM density, but not percentage, were observed in patients with epilepsy on 750 mg daily of PRM for three months. Treatment with 600 mg of PHT per day for the same duration produced no notable effects.

Both ethosuximide (ES) and VPA were found to increase the percentage of stage 1 sleep in 11 patients with absence epilepsy (Wolf *et al.*, 1984). Treatment with VPA resulted in a reduction of stage 2 sleep but no change in SWS. Treatment with ES produced a significant reduction in SWS percentage and a trend for increased stage 2 sleep. In 13 patients with primary generalized epilepsy, doses of ES effective in suppressing absence seizures produced a significant increase in stage 1 sleep and a decrease in SWS, without altering stage 2 or REM sleep percentages (Röder and Wolf, 1981). There was no change in sleep latency, number of stage shifts, body movements, or number of awakenings. Interrupted or light sleep, longer sleep latency, and daytime sleepiness were reported by patients taking ES. Treatment with VPA produced an increase in stage 1 and a trend for reduced stage 2 sleep without affecting SWS, REM, sleep latency, or the number of movements or arousals. Patients treated with VPA complained of difficulty initiating sleep and daytime sleepiness.

The effects of high- (1000 mg/day) and low-dose (500 mg/day) VPA and placebo on sleep were compared in 10 healthy subjects (Harding *et al.*, 1985). As compared with low-dose and placebo, high-dose VPA produced a reduction of REM sleep percentage and an increase in SWS. A reduction of REM sleep was also observed with low-dose treatment when compared with the withdrawal phase of the study. Others have reported only a shorter sleep cycle duration in patients and normal subjects treated with VPA (Declerck and Wauquier, 1991).

With use of the MSLT, daytime vigilance was compared in 20 patients with generalized epilepsy taking PB (10) or VPA (10) monotherapy, 10 subjects with focal epilepsy on CBZ, and 10 healthy controls (Manni *et al.*, 1993a,b). All patients were seizure free for 1 year. Sleep time the previous night was similar between groups. The mean sleep latency was 9, 12.5, 12.5, and 12.9 min for PB, VPA, CBZ, and controls, respectively. No sleep onset REM periods were recorded. Mean serum concentrations were PB 19.3 (6–20), VPA 85.7 (69–106), and CBZ 8.2 (5.5–12) μg/ml. Only two subjects had mean sleep latencies less than 5 min; both were in the PB group. Patients on PB were sleepier based on the MSLT, but this was not accompanied by complaints of EDS.

Of the newer AEDs, only gabapentin has been studied for its effect on sleep. In eight patients treated with 1800 mg per day of gabapentin as add-on therapy, the drug produced a significant increase in REM sleep and mean REM period duration and fewer awakenings (Placidi *et al.*, 1997). Although no PSG analyses have been published on patients taking felbatol, lamotrigine, topiramate, or tiagabine, sleep complaints were commonly reported in premarket trials. The incidence of somnolence and insomnia in patients treated with felbatol was 19 and 18%, respectively (PDR, 1998). Insomnia was a common reason for discontinuation of the drug. Treatment with lamotrigine produced somnolence in 14% and insomnia in 6% of patients (PDR, 1998). Topiramate produced somnolence in approximately 30% of patients treated (PDR, 1998). Somnolence and insomnia occurred in 18 and 6%, respectively of patients receiving tiagabine (Gabatril package insert, Abbott Laboratories, 1997).

PREDICTORS OF SLEEPINESS IN EPILEPSY

Several factors have been identified as predictors of sleepiness in persons with epilepsy using the Epworth Sleepiness Scale as a subjective measure of daytime sleepiness (Malow *et al.*, 1997; Sanchez de Leon *et al.*, 1997). The ESS is a self-administered, eight-item questionnaire designed to ascertain sleep propensity in a variety of everyday situations (Johns, 1992). The scale has been validated in a variety of situations, and was found to correlate with results of the MSLT, the gold standard for the objective measurement of daytime sleepiness (Chervin *et al.*, 1997).

Excessive daytime sleepiness as measured by the ESS was found in 28% of 158 subjects with epilepsy and 18% of 68 control subjects with other neurologic disorders (Malow *et al.*, 1997). Symptoms of sleep apnea and RLS reliably predicted daytime sleepiness. Having epilepsy conferred only a nonsignificant trend for EDS. Patients with epilepsy between the ages of 30 and 45 years were most likely to report daytime sleepiness. In patients with epilepsy, the number and type of AEDs, seizure frequency, epilepsy syndrome, and presence of sleep-related seizures were not significant predictors of daytime sleepiness.

At our institution, 82 consecutive patients admitted to the epilepsy monitoring unit completed sleep questionnaires, the ESS, and Beck Depression Inventory (BDI) (Beck, 1987; Foldvary *et al.*, submitted for publication). An ESS score greater than 8 was considered elevated, suggesting the presence of daytime sleepiness (Johns, 1992). Of the 82 patients, 47% had an ESS greater than eight. Patients were taking a mean of 1.87 AEDs. The group had a mean BDI of 11, and 31% of patients had a score of 15 or higher suggesting symptoms of depression (Beck, 1987). Higher number of AEDs, elevated BDI, and the use of sleeping aids were predictive of daytime sleepiness. No correlation between the ESS and seizure frequency was found.

The causes of EDS in the epileptic population are multifactorial. AEDs, seizures, and concomitant sleep disorders have been found to affect sleep macroarchitecture and produce daytime sleepiness. Patients with epilepsy have a high incidence of sleep complaints and poor sleep habits. Primary sleep disorders should be suspected in patients with persistent hypersomnia, particularly those on AED monotherapy or with low serum drug concentrations and well-controlled seizures. Treatment of sleep disorders and improved sleep hygiene may lead to better seizure control.

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12

NON-RAPID EYE MOVEMENT PARASOMNIAS

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INTRODUCTION

Parasomnias are disorders in which undesirable physical and mental events occur mainly or exclusively during non-rapid eye movement (NREM) sleep, often accompanied by skeletal muscle activity and autonomic arousal. The events may be associated with central nervous system activation, signs of autonomic arousal, and skeletal muscle activity, including simple movements of the extremities, shouts and screams, and complex violent automatisms. Mental phenomena may also occur, including emotions, thoughts, and images. Unlike the dyssomnias, the complaint accompanying parasomnias is related to the undesirable phenomena instead of insomnia or daytime sleepiness. Some features of parasomnias may mimic seizure disorders, and appropriate diagnosis is essential for effective patient management. In the International Classification of Sleep Disorders (American Sleep Disorders Association, 1997), the parasomnias are divided into four groups: the arousal disorders, the sleep/wake transition disorders, the parasomnias related to rapid eye movement (REM) sleep, and the "other" parasomnias. This chapter focuses on three of these groups; the parasomnias related to REM sleep are discussed elsewhere in this volume.

The paroxysmal events that occur with many parasomnias share similarities with daytime spells, but they present a special challenge because patients, who are usually asleep at the onset of the event, are rarely able to describe the physical or mental phenomena accurately. The history from the bedpartner or parent is crucial, but such observers may not see the beginning of an event. Furthermore, responsiveness and level of consciousness, important aspects for diagnosis, are difficult to assess when the patient has just aroused from sleep. Combined video–polysomnographic recordings, useful when the diagnosis cannot be made clinically, allow behavioral analysis of episodes along with assessment of EEG and other physiological measures. Management is based on the prognosis of the disorder, the extent of sleep disruption, the psychosocial impact, and the potential for injury.

Phenomena characteristic of many parasomnias are associated with central nervous system activation, skeletal muscle activity, and signs of autonomic arousal. Visceral contractions, simple or complex movements of the extremities, shouts and screams, and complex violent automatisms may occur. As stated earlier, mental phenomena may include emotions, thoughts, and images.

Parasomniac behaviors can be considered spells and, as with daytime spells, the history is crucial for determining their cause. However, their occurrence during sleep presents an added challenge because patients, bed partners, and

others are rarely able to describe the entire episode. Furthermore, assessment of the level of consciousness and responsiveness, an important tool for determining etiology, is more difficult when the patient has just aroused from sleep.

For parasomniac behaviors that are occurring at least several times per week, video monitoring combined with polygraphic recording, video polysomnography (VPSG), is the most useful diagnostic technique. Video recording permits detailed analysis of behavior, and a synchronizing signal can be used to allow precise temporal correlation of behavior with EEG activity. Modern recording systems allow recording EEG from numerous scalp locations, with playback of EEG data using a variety of paper speeds and montages (Aldrich and Jahnke, 1991). For digital EEG systems, sampling rates must be high enough to permit detection of high-frequency spikes and their differentiation from muscle potentials and other artifacts. Systems that do not permit EEG review at the equivalent of 15 mm/s or faster are inadequate for detection of epileptiform abnormalities; a paper speed of 30 mm/s or the equivalent for paperless recordings is preferred.

Although VPSG is expensive, in part because of the need for continuous observation of behavior and EEG by skilled technologists, the simultaneous analysis of behavior, EEG, and other polygraphic signals usually leads to accurate diagnosis if an episode occurs. Even if a typical episode does not occur during one or two nights of recording, useful information often is obtained that may point to one diagnosis over other possibilities. In one series, diagnostically useful information was obtained in about 65% of patients who were studied (Aldrich and Jahnke, 1991). The degree of sleep disruption, the psychosocial consequences, and the potential for injury and the prognosis determine the approach to management.

AROUSAL DISORDERS

The arousal disorders—confusional arousals, sleepwalking, and sleep terrors—are grouped together because disordered arousal mechanisms are thought to cause a prolonged state that is neither full wakefulness nor sleep in response to a stimulus, internal or external, that usually produces a full awakening (Broughton, 1968). The disorders occur most commonly in childhood, with highest prevalence between ages 4 and 6. The episodes usually occur during the first third of the night, when greater stimulation is required to arouse from slow-wave sleep. They exist on a continuum with considerable clinical overlap among the three disorders: low levels of motor, emotional, and autonomic activation lead to confusional arousals; greater degrees or motor activation may lead to sleepwalking; and intense emotional and autonomic activation leads to sleep terrors. A given individual may have one or more of the three clinical syndromes.

SLEEPWALKING

Sleepwalking is characterized by complex automatisms during sleep typified by getting out of bed and walking. About 20% of children sleepwalk at least occasionally. Most children stop sleepwalking by adolescence, but some continue to sleepwalk into adulthood. About .4% of adults sleepwalk at least once per week and a few individuals who did not sleepwalk as children begin to do so as adults (Hublin *et al.*, 1997). Although they usually respond poorly to voices, they sometimes follow instructions to return to bed.

The duration of sleepwalking varies. Some patients return to bed within a minute or two; others may wander for several minutes and in extreme cases, the episode may last for as long as an hour. During the episode, patients engage in complex coordinated purposeful or semi-purposeful behaviors. Not all patients get out of bed and walk. Some sit up in bed and fumble with the bedclothes or get out of bed and stand by the bedside. Others walk extensively and may leave the home and walk outside. Others eat or drink; in some patients, eating during sleepwalking leads to weight gain or dental problems (Schenck *et al.*, 1991).

Most sleepwalkers have little if any daytime effects, although persons who sleepwalk nightly may develop daytime sleepiness. The major complication of sleepwalking involves injuries suffered during the episode, and sleepwalking or sleep terrors account for more than half of all sleep-related injuries (Schenck *et al.*, 1989a). Patients may trip and fall to the floor or downstairs, and persons who walk outside may suffer from exposure or hypothermia. Violent behavior during sleepwalking may lead to injuries to other family members, particularly to those who are attempting to help the individual return to bed. In at least one case, homicide was apparently the result of sleepwalking (Broughton *et al.*, 1994).

SLEEP TERRORS

Sleep terrors are episodes arising abruptly from sleep of apparent terror. Screaming and agitated behavior with attempts to leave the bed or the room are characteristic, and tachycardia, mydriasis, and sweating are common. The patient is usually inconsolable and partly or completely unresponsive. Injury during the episode is a potentially serious complication due to extreme agitation and "escape behavior," and patients may react violently to attempts to restrain them (Kales *et al.*, 1980b). Morning amnesia is characteristic although some patients vaguely recall a terrifying image or situation and occasionally have more detailed recall of dream-like events. Sleep terrors occur once per week or more frequently in about 1–2% of children between the ages of 6 and 14. Some persons continue to have sleep terrors into adulthood and in occasional cases, the onset of the disorder is during the adult years.

CONFUSIONAL AROUSALS

Confusional arousals, which occur in almost all children at least occasionally, are characterized by a sudden arousal and complex behaviors, but without full alertness, usually lasting just a few minutes. Disorientation, confusion, moaning or incoherent vocalizations, slowed responses, and purposeless clumsy behaviors are typical. Occasionally patients become violent or agitated during the episode, especially if attempts are made to bring them to full awakening. In the morning, amnesia for the episode is the rule. Most episodes last just a few seconds or minutes; rarely, they may last for 15 min or more. The frequency is highly variable; some patients have them almost every night while for others, they occur less than once per month. While they are more common in children, occasional adults have several episodes per week.

BIOLOGICAL BASIS

The behaviors associated with arousal disorders are thought to be caused by incomplete cortical activation in response to an arousal stimulus. Slow-wave sleep provides the usual setting for incomplete activation because depth of sleep, measured by the intensity of a stimulus required to bring a subject to full awakening, is greatest during this stage of sleep. The arousing stimulus may be endogenous, such as a full bladder, or exogenous, such as a ringing telephone. Confusional arousals can also occur in lighter sleep stages, but with lower frequency (Naylor and Aldrich, 1991). Factors that increase sleep depth, such as sleep deprivation and central nervous system depressants, also facilitate arousal disorders.

Children are predisposed to arousal disorders because they have abundant slow-wave sleep from which arousal is difficult. In one study, auditory stimuli of as much as 120 dB did not consistently elicit arousal in young children (Busby and Pivik, 1983). In most children and young adults, confusional arousals and sleepwalking can be induced by stimulation during deep slow-wave sleep. Sleep apnea and other sleep disorders associated with arousal sometimes provide the precipitating factor.

Although the neurological basis for the incomplete activation is unknown, EEG studies support the concept; the EEG during episodes may show nonreactive alpha activity, synchronous delta or theta activity, or drowsy patterns. A genetic component may contribute to susceptibility; for persons with arousal disorders, the prevalence of arousal disorders is increased in first degree relatives and is higher in monozygotic twins than in dizygotic twins (Bakwin, 1970; Hallstrom, 1972; Hublin *et al.*, 1997).

Psychological factors also contribute to arousal disorders. Emotional and physical stress increase the likelihood that sleep terrors will occur in susceptible persons. Furthermore, chronic stress, such as occurs in children from abusive families, probably increases the likelihood of arousal disorders; and some

studies suggest that persistence of sleep terrors into adulthood is often associated with psychopathology (Kales *et al.*, 1980a; Kales *et al.*, 1980b; Llorente *et al.*, 1992). However, many children and adults with sleep terrors and sleepwalking do not have major psychopathology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of arousal disorders depends on the types of behaviors that occur. For patients with sleep terrors or sleepwalking, diagnostic considerations may include nightmares, REM sleep behavior disorder (RBD), epilepsy, nocturnal delirium, panic disorder, and dissociative states. Timing of episodes, the length of time required to attain full alertness after an episode, and amount of recall are helpful distinguishing features. Sleep terrors and sleepwalking usually begin with an arousal from slow-wave sleep and therefore generally occur in the first third of the night, often within an hour or two of sleep onset; patients are difficult to awaken during an episode and are confused and groggy if they are awakened. Patients usually have little recall of episodes, although some report vague images or fragmentary thoughts or emotions. On the other hand, nightmares and the activity of RBD occur during REM sleep and are therefore more common later in the night; full alertness develops rapidly after an awakening from either. The REM sleep behavior disorder is usually associated with dream-enacting behavior, sometimes violent and accompanied by shouting, and sometimes with dream recall. Unlike sleep terrors, autonomic activation is absent or minimal, even with violent episodes. Some patients, however, have violent dreams during NREM sleep and clinical features that suggest an "overlap" between RBD and sleep terrors (Hurwitz *et al.*, 1991).

As with sleep terrors, sleepwalking often can be diagnosed based on the history. Occurrence in children of complex nonstereotyped behaviors during the first portion of the night with amnesia in the morning is almost always due to an arousal disorder. If the presentation is atypical, however, complex partial seizures should be considered, particularly if stereotyped behaviors, tonic postures, or oral automatisms (such as chewing, swallowing, or salivation), have been observed by others. Other features that increase the likelihood of epilepsy include the occurrence of several brief episodes each night and a poor response to usual treatments for arousal disorders.

Diagnostic considerations for confusional arousals include sleep talking, RBD, and partial complex seizures. The lack of stereotypy and dream-enacting behaviors and the predilection to occur during the first third of the night are usually sufficient for diagnosis.

DIAGNOSTIC EVALUATION

For many patients, the history is sufficient to diagnose an arousal disorder; no laboratory studies are required. For example, typical episodes of sleepwalking or

sleep terror that occur in children or young adults generally do not require additional evaluation. Diagnostic studies are more often needed if the history has atypical features, such as stereotyped behaviors, frequent occurrence in the second half of the night, or onset during adulthood. Definitive diagnosis with laboratory studies should also be considered for patients who have injured themselves during nocturnal episodes or describe potentially injurious behaviors.

VPSG is the preferred laboratory study, particularly for patients with episodes that occur nightly or almost nightly. It is most useful if a typical episode is recorded. An abrupt arousal from slow-wave sleep is a characteristic finding, usually associated with tachycardia. During an episode, regular, rhythmic, hypersynchronous delta or theta activity may be seen, and high-voltage EEG slow-wave activity may occur just before the arousal that initiates the behaviors (Fig. 12.1). Even if the behaviors do not occur, the study may be helpful. For example, runs of hypersynchronous delta during arousals from slow-wave sleep are more common in persons with arousal disorders than in other individuals (Blatt *et al.*, 1991). In patients with a history suggestive of sleepwalking or sleep terrors, the occurrence of confusional arousals supports the presence of an arousal disorder. The EEG during a dissociative episode shows a waking pattern while REM sleep behavior disorder is associated with EEG features of REM sleep.

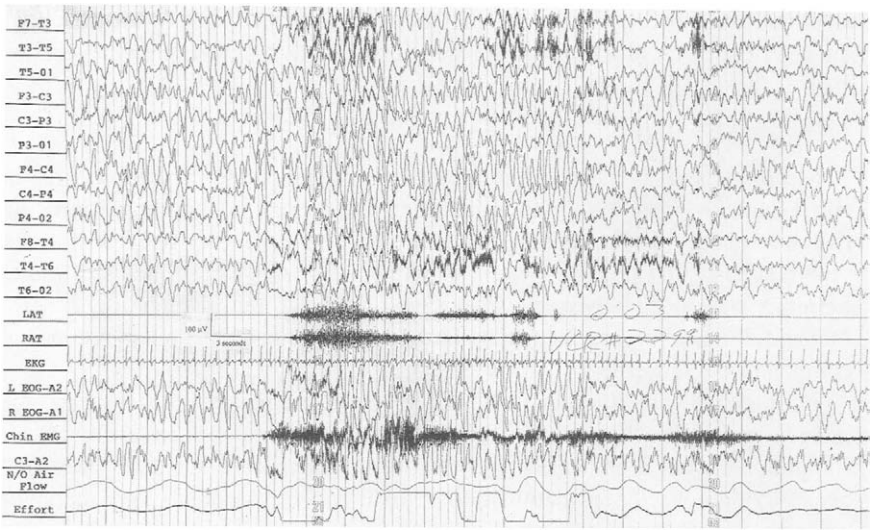

FIGURE 12.1 Arousal from delta nonrapid eye movement (NREM) sleep in child with a NREM arousal disorder. Note synchronous delta activity during arousal from delta NREM sleep, associated with a tonic increase in chin and leg EEG. In contrast to the EEG of an epileptic seizure, the delta activity does not evolve in amplitude or frequency. (From Malow B. A., and Aldrich, M. S. (2000). Neurological Monitoring Techniques, In *Principles and Practice of Sleep Medicine,* 3rd ed., M. H. Kryger, T. Roth, and W. C. Dement, eds., Philadelphia: W.B. Saunders, reproduced with permission.)

MANAGEMENT

Parents are often reassured to know that arousal disorders generally improve with age and resolve before or during teenage years, probably in part because of the reduced amount of slow-wave sleep. For patients with infrequent episodes, reassurance combined with good sleep hygiene, adequate amounts of nighttime sleep, and safety measures may be sufficient. Windows should be locked and sharp objects and toys should be removed from the bedroom floor. For potentially injurious behaviors, or if the activity is excessively disruptive to the family, bedtime doses of 20–100 mg of imipramine, 2–5 mg of diazepam, or 0.5–2 mg of clonazepam are usually beneficial. The medications can be taken nightly for several months and then gradually discontinued, or reinstituted if the behaviors recur. Counseling and psychiatric evaluation or treatment are helpful if family stress or psychopathology are contributing factors. For some patients, hypnosis or behavioral treatments may provide some value (Lask, 1988).

SLEEP–WAKE TRANSITION DISORDERS

The phenomena associated with the four sleep/wake transition disorders—rhythmic movement disorder, sleep starts, sleep talking, and nocturnal leg cramps—are common during sleep–wake transitions in otherwise healthy persons and may be considered normal events unless they occur with such frequency or severity that they disrupt sleep or cause discomfort, injury, or anxiety.

SLEEP STARTS

Sleep starts, also called sleep jerks or hypnic jerks, are myoclonic jerks occurring at the transition from wakefulness to sleep. Low-amplitude jerks and twitches, usually not perceived, occur in almost everyone at sleep onset; more vigorous jerks that produce flexion of the trunk or gross movements of the extremities are more likely to cause awakenings and to be remembered. A sensation of falling, a fragmentary dreamlike image, or a vocalization sometimes accompanies the movement (Thorpy, 1997).

For patients with vigorous jerks at sleep onset, diagnostic considerations may include periodic leg movements, myoclonic seizures, and excessive startle responses. An EEG is indicated if myoclonic seizures are suspected. Sleep starts generally do not require treatment other than reassurance. Relaxation therapy or other treatments for anxiety are usually successful for the rare patient with sleep-onset insomnia as a result of sleep starts.

SLEEP TALKING

Many people talk during sleep. About 10% of children engage in sleep talking on a regular basis, and in one series of sleep laboratory studies of adults,

sleep talking occurred during 13% of recorded nights (Rechtschaffen *et al.*, 1962). Sleep talking occurs during sleep or during brief arousals and generally consists of just a few words with minimal emotional content; some patients, however, may speak a few sentences and occasionally speech consists of loud or angry comments. Speech during REM sleep tends to be longer and more emotional than speech during NREM sleep. Episodes are often accompanied by mentation appropriate to the speech but subjects rarely recall the content of speech.

Although the cause of sleep talking is unknown, a genetic component may be a factor because children of parents with arousal disorders are more likely to talk during sleep (Abe *et al.*, 1984). Precipitants of sleep talking in predisposed individuals include sleep deprivation, stress, fever, and arousals associated with apneas, arousal disorders, and nightmares.

In addition to primary sleep talking, causes of nighttime vocalizations include confusional arousals or sleep terrors, REM sleep behavior disorder, arousals from apneas, nocturnal dissociative disorder, and talking during awakenings from other causes. In general, laboratory evaluation is unnecessary unless one of these disorders is suspected. Treatment is unnecessary unless talking is a symptom of another disorder.

RHYTHMIC MOVEMENT DISORDER

Rhythmic movement disorder, characterized by stereotyped repetitive movements of the head and neck, or sometimes the trunk, is also called head-banging, head-rolling, body-rocking, or body-rolling depending on the type of movement. Other terms sometimes employed include *jactatio capitis nocturna* and *rhythmie du sommeil*. The movements occur during drowsy wakefulness and stage 1 sleep at a rate of 0.5–2 Hz, rarely during deeper stages of NREM or REM sleep, and may last from a few seconds to as long as half an hour. When head-banging is the principal symptom, patients may repeatedly and forcefully bang their heads into the pillow, headboard, or wall while lying in a prone position. Rolling head or body movements and leg or arm banging may occur instead of or in addition to head-banging. They occur in the majority of infants, but have usually resolved by age 4 (Klackenberg, 1987). In occasional patients, symptoms persist into adolescence or adulthood.

Although the movements may be a source of concern for parents, daytime symptoms are generally absent, although patients occasionally bang their heads hard enough to produce such injuries as bruised foreheads or, rarely, retinal injury or subdural hematoma. For older children and adults, the movements may be embarrassing.

Among infants who have sleep recordings for other reasons, rhythmic movement disorder is a common incidental finding. Other causes in infants of rhythmic muscle activity during polysomnography include bruxism and sucking on a pacifier. The cause of the rhythmic movements is uncertain; a soothing effect

related to vestibular stimulation may contribute. Episodes are more common in infants and children with static encephalopathy.

In most patients, the disorder can be diagnosed based on the history. Seizures may be a consideration, particularly in patients with mental retardation and epilepsy. In rare cases, epileptic seizures may be associated with rocking movements. If epilepsy is suspected, VPSG may be useful. Episodes of rhythmic movements are not associated with EEG abnormalities and show little change in the frequency of movements over the course of an episode. Unlike seizures that typically show an initial increase in the amplitude and frequency of movements followed by a slowing in frequency in the second half of the episode, the frequency of movements remains essentially constant during an episode, although the amplitude may decline at the end of an episode.

Most children do not require treatment and parents should be reassured that the disorder usually resolves. Padding the headboard and crib may reduce bruising or other injuries. For patients with severe head-banging, treatment is difficult although behavior therapy or a benzodiazepine is occasionally useful.

NOCTURNAL LEG CRAMPS

Leg cramps are painful muscle contractions, usually of the calf or foot, associated with bulging and tautness of the muscle. The cramp may resolve spontaneously within a few seconds or it may last for several minutes. Attempts to stretch the muscle by dorsiflexion of the toes or foot may provide relief.

Some patients have leg cramps only at night; others have them day and night; and still others have them only during the day. Nocturnal leg cramps, which affect about 15% of the population, are more common in older age groups. Suspected predisposing or exacerbating factors include prior exercise, fluid and electrolyte disturbances, pregnancy, and caffeine use. The course and severity of the disorder are variable.

Although the cause of nocturnal leg cramps is unknown, familial forms have been described and disturbances of calcium metabolism and other metabolic disturbances may contribute (Weiner and Weiner, 1980; Lazaro *et al.*, 1981; Cutler, 1984; Jacobsen *et al.*, 1986; Ricker and Moxley, 1990). Disorders associated with increased frequency of nocturnal leg cramps include myotonia congenita, the stiff-person syndrome, myokymia, McArdle's disease, hypoparathyroidism, hypothyroidism, lead poisoning, and renal failure (Lazaro *et al.*, 1981; Whitely, 1982).

Visible and palpable muscle tightness helps to differentiate nocturnal leg cramps from claudication, painful neuropathies, and restless legs syndrome. For frequent cramps that disrupt sleep, quinine (325 mg at bedtime) is usually effective. Alternatives include vitamin E (400 International Units), verapamil (120 mg), diphenhydramine (25–50 mg), or procainamide (250 mg).

OTHER PARASOMNIAS

The other parasomnias are disorders in which the phenomena of interest are not closely associated with a particular stage of sleep. Of the other parasomnias, features of three may suggest the possibility of epilepsy: sleep bruxism, sleep enuresis, and nocturnal dissociative disorder. In the psychogenic nocturnal dissociative disorder, conscious awareness becomes dissociated from behavior, and patients perform complex activities for which they are amnestic. Patients are often young women with psychiatric conditions, and the episodes are sometimes accompanied by self-mutilating behavior and injuries.

SLEEP ENURESIS

Clinical Features

Sleep enuresis, defined as recurrent involuntary bedwetting that occurs beyond the age of expected nocturnal bladder control, is a common distressing disorder. The age at which continence is expected varies across cultures while the prevalence of continence is similar. In general, girls attain nocturnal continence earlier than boys. If continence has never been attained, the disorder is called primary sleep enuresis, while enuresis that recurs following a period of at least 3 months of bladder control is called secondary sleep enuresis. Primary sleep enuresis accounts for 75% of cases; however, in older children, up to half have secondary enuresis. Because nocturnal seizures may be accompanied by incontinence, epilepsy is sometimes a part of the differential diagnosis.

The majority of children achieve bladder control by age 4 with a 1–3% prevalence of enuresis at age 12 and a 1% prevalence in young adults (Schmitt, 1984; Klackenberg, 1987; Friman and Warzak, 1990). Daytime enuresis occurs in 15–20% of young bed wetters, mostly before age 6 (Rushton, 1989).

Biological Basis

Genetic factors may play a role in some cases. Enuresis is more common in children of enuretics than in the general population, and in some families, the pattern of involvement is consistent with an autosomal dominant inheritance with greater than 90% penetrance. Linkage to markers on chromosome 13 has been reported (Eiberg *et al.*, 1995).

Primary sleep enuresis is caused by a combination of genetic, maturational, psychosocial, and endocrinological factors; the relative importance of each of these varies across individuals. Anatomic abnormalities of the genitourinary system and other sleep disorders such as obstructive sleep apnea are uncommon in enuretic children although they may contribute to enuresis in some (Friman, 1995). Psychosocial factors that may contribute to or exacerbate enuresis include marital discord, parental separation, sexual abuse, and birth of a sibling.

Maturational factors may also contribute because enuretic children tend to have lower birth weight, delayed developmental milestones, shorter stature, younger bone age, and later onset of puberty (Mimouni *et al.*, 1985; Jarvelin *et al.*, 1991). Although enuretic children have smaller functional bladder capacities on average than nonenuretic children, the contribution of this difference to enuresis is probably small. Reduced nocturnal antidiuretic hormone (ADH) secretion may play a role in some patients (Nergaard *et al.*, 1989).

Diagnosis

Diagnosis of sleep enuresis is based primarily on history. Apart from urinalysis, laboratory investigations are not required for children with primary sleep enuresis, normal physical examination, and no daytime voiding symptoms. Complicated enuresis may require intravenous pyelogram, vesical sphincter electromyography, cystometry, and cystoscopy. Repeated unexplained urinary tract infections along with enuresis in girls suggest possible sexual abuse.

Management

For young children with primary sleep enuresis, education and patience are often sufficient to determine if the child will "outgrow" the bed-wetting problem. If parental expectations contribute, enuresis may become the focus of intrafamily conflict.

Alarm systems are a commonly used and effective behavioral technique. A moisture-sensitive sensor that activates an alarm is placed in the bed or on the bedclothes. The success rate is about 65–80%, but about 10–40% of children later relapse (Maizels and Rosenbaum, 1985). Hypnotherapy has also been tried with some success (Rushton, 1989).

Medications include desmopressin (DDAVP) (25–75 mg daily), an analog of the antidiuretic hormone vasopressin, which reduces nocturnal urine output, or imipramine (25–75 mg at bedtime). Imipramine is superior to placebo but has a success rate of only about 25% with relapses common (Friman and Warzak, 1990; Fritz *et al.*, 1994).

NOCTURNAL DISSOCIATIVE DISORDER

In dissociative disorder, the major symptom is a disruption of consciousness, identity, memory, or perception that has a psychogenic basis. If the disturbance affects consciousness primarily, awareness is dissociated from behavior and patients engage in complex behaviors for which they are amnestic. Identity is primarily affected in depersonalization disorder and multiple personality disorder (American Psychiatric Association, 1994).

While prolonged nocturnal fugues occur in some patients, brief episodes are more common. Patients often have borderline personality disorder or anxiety disorders, and sometimes reenact previous assaults (Schenck *et al.*, 1989b). Video polysomnography demonstrates a waking EEG during the episodes (Rice

and Fisher, 1976; Schenck *et al.*, 1989b). There is a variable response to psychotherapy and psychoactive medications.

SLEEP BRUXISM

Clinical Features

Sleep bruxism, which refers to grinding or clenching of the teeth during sleep, is characterized by rhythmic, chewing movements, or prolonged contractions of the jaw muscles, sometimes accompanied by clicking or grating sounds. Patients may present for evaluation because of daytime symptoms, because of the sounds disturbing bed partners, because of tooth damage, or because of the possibility that the rhythmic activity is caused by epilepsy.

The severity of bruxism typically fluctuates from night to night and is highly variable across individuals. Significant tooth wear, muscular pain, or temporomandibular changes occur in 5–10% of population, with minor tooth wear in 10–20% (Glaros, 1981; Rugh and Harlan, 1988a; Hartmann, 1994). In one study, jaw discomfort was noted in 6 of 18 bruxers and none of 18 control subjects (Lavigne *et al.*, 1996).

Tooth damage is a function of the forcefulness, frequency, direction, and duration of bruxing. The lateral grinding forces of sleep bruxism often lead to greater damage than the more vertical forces of diurnal bruxism. Tooth wear, most commonly on the incisal edges of the anterior teeth and on the cusps of the posterior teeth, is the most striking finding on physical examination. Severe sleep bruxism may also damage supporting structures (Seligman *et al.*, 1988).

Biological Basis

Emotional stress is the most commonly reported precipitant of bruxism (Rugh and Harlan, 1988b). Medications including amphetamines (Ashcrost *et al.*, 1965) and levodopa (L-dopa) (Magee, 1970) may precipitate this disorder; long-term phenothiazine use (Kamen, 1975) and alcohol (Hartmann, 1979) have also been related to bruxism. Bruxism may have a genetic predisposition. Although bruxism has been postulated to be a centrally mediated sleep disorder on the basis of these observations, the specific mechanisms underlying this disorder are poorly understood.

Diagnosis

Because only 20% of bruxist episodes are accompanied by noise, the majority of bruxists are unaware of their bruxing. Wear patterns on the teeth, tooth mobility, and fracture cusps suggest bruxing activity. Other individuals come to medical attention because of muscle or joint pain, fatigue, stiffness on waking, or headaches. The rhythmic myogenic artifact resulting from bruxism appearing on a polysomnogram has a characteristic appearance (Fig. 12.2).

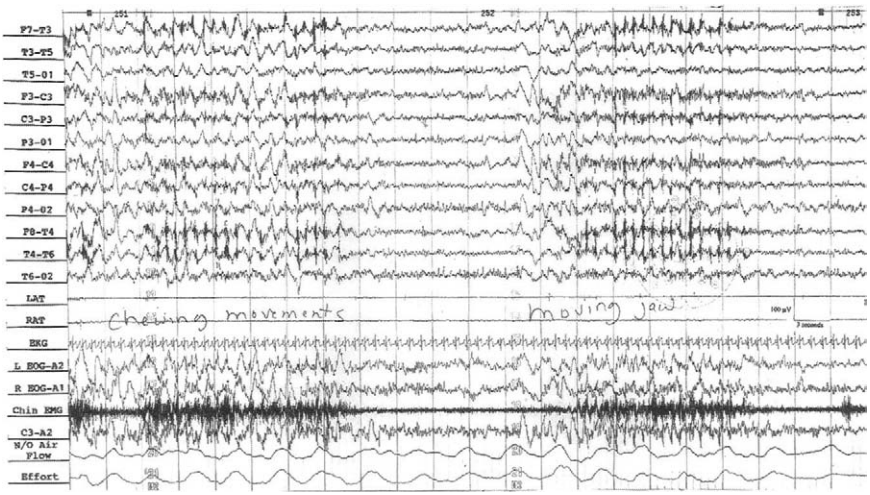

FIGURE 12.2 Chewing movements produced by bruxism cause rhythmic activity with superimposed myogenic artifact in the EEG channels, bearing a superficial resemblance to generalized spike–wave discharges. (From Malow B. A., and Aldrich, M. S. (2000). Neurological Monitoring Techniques, In *Principles and Practice of Sleep Medicine,* 3rd ed., M. H. Kryger, T. Roth, and W. C. Dement, eds., Philadelphia: W.B. Saunders, reproduced with permission.)

Management

A dental guard usually prevents tooth damage and reduces daytime symptoms, although tooth grinding is usually not eliminated. Diazepam (5 mg at bedtime), which may reduce grinding during stressful periods, is not helpful for long-term treatment. Behavioral therapies, including biofeedback, hypnosis, progressive relaxation, and stress reduction may also be helpful.

SUDDEN UNEXPLAINED NOCTURNAL DEATH

Sudden unexplained nocturnal death (SUND) is a rare disorder in which apparently healthy adults die suddenly during sleep. It thus resembles sudden infant death syndrome. Young and middle-aged men from Southeast Asian countries including the Philippines, Japan, Thailand, Vietnam, Cambodia, and Laos are most often affected (Sugai, 1959; Aponte, 1960; Baron *et al.*, 1983). The syndrome has been recognized for almost a century, but attracted increased attention following the immigration to the United States in the 1970s and 1980s of substantial numbers of Southeast Asians. Some affected persons have had episodes resembling sleep terrors in the weeks before death.

The proximate cause of death in cases of monitored death or resuscitation is ventricular fibrillation (Pressman *et al.*, 1993). The factors responsible for the arrhythmia, however, are unknown. Suspected contributors include thiamine or potassium deficiency, stress, and excessive sympathetic discharge during sleep

terrors or REM sleep. Cardiac conduction abnormalities may contribute in some cases.

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13

Rapid Eye Movement Sleep Behavior Disorder

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INTRODUCTION

Parasomnias are defined as abnormal behaviors and/or impaired autonomic nervous system functioning that occur within sleep or during arousals from sleep (ICSD, 1990). Classification of the parasomnias includes both primary and secondary sleep phenomena that can emerge throughout the sleep cycle (Mahowald and Ettinger, 1990). Rapid eye movement (REM) sleep behavior disorder (RBD) is the REM sleep parasomnia that is of greatest interest to neurologists (Schenck and Mahowald, 1996a). RBD is a multifaceted disorder that has a corresponding experimental animal model (Jouvet and Delorme, 1965). RBD can be misdiagnosed as nocturnal seizure disorder, psychiatric disorder, obstructive sleep apnea, or some other condition (Schenck *et al.*, 1986; Schenck and Mahowald, 1990). RBD usually presents as injurious dream-enacting behaviors that are subsequently documented to occur during REM sleep. RBD usually affects middle-aged or older men, but can affect either gender in any age group. In more than half of reported cases, RBD is closely associated with a central nervous system disorder, most commonly a neurodegenerative disorder, narcolepsy, or cerebrovascular disorder (Schenck and Mahowald, 1996a).

ANIMAL MODEL OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER: PARADOX LOST

Rapid eye movement (REM) sleep involves a highly energized state of brain activity, with both tonic (i.e., continuous) and phasic (i.e., intermittent) activation occurring across a spectrum of physiological parameters (Mahowald and Schenck, 1994). REM sleep has several synonyms, the two most compelling of which are: (1) "active sleep" due to a high level of brain activity (comparable to wakefulness), monitored by measuring electrophysiologic activity and by measuring cerebral blood flow, oxygen consumption, and glucose utilization; and (2) "paradoxical sleep" due to the suppression of skeletal muscle tone in the context of a highly activated brain state. This generalized skeletal muscle atonia—"REM-atonia"—is a defining feature of REM sleep, along with REMs and a desynchronized electroencephalogram (EEG) (Fig. 13.1A). The paradox of REM sleep lies in the absence of muscle tone despite a state of brain and mind

(dream) activation. The loss of the paradox of REM sleep in RBD carries serious clinical consequences, namely, sleep-related injuries (Table 13.1).

Jouvet and Delorme (1965) reported that experimentally induced, bilateral, symmetrical, dorsolateral pontine tegmental lesions in cats resulted in permanent loss of REM-atonia, whereas lesions to other brain stem structures had no such

TABLE 13.1 Major Findings in 96 Patients with Chronic REM Sleep Behavior Disorder (RBD) (From Schenck, C. H., *et al.* (1993). REM sleep behaviour disorder: An update on a series of 96 patients and a review of the world literature. *J. Sleep Res.* **2**:224–231.)

Categories	% (*n*)	Comments
Gender		
Male	87.5 (84)	Mean age of RBD onset ($n = 90$)[a] 52.4 (±SD 16.9) years; range, 9–81
Female	12.5 (12)	Mean age at polysomnography[b] 58.3 (±17.4) years; range, 10–83
Prodrome	25.0 (24)	Sleeptalking, yelling, limb twitching, and jerking began a mean 22.3 (±16.1) years before RBD onset; range, 2–48
Chief complaint		
Sleep injury	79.2 (76)	Ecchymoses (76); lacerations (32); fractures (7)
Sleep disruption	20.8 (20)	
Altered dream process and content	87.5 (84)	More vivid, intense, action filled, violent (reported as severe nightmares)
Dream-enacting behaviors	87.5 (84)	Talking, laughing, yelling, swearing, gesturing, reaching, grabbing, arm flailing, punching, kicking, sitting, jumping out of bed, crawling running
Periodic movements of NREM sleep	61.4 (59)	Occur every 15–30 s; infrequently associated with arousals; involve legs/arms, and can occur throughout the entire sleep cycle
Aperiodic movements of NREM sleep	37.5 (36)	Infrequently associated with arousals; involve legs/arms, and can occur throughout the entire sleep cycle
Elevated % of slow-wave (stage 3 to 4) sleep for age (>58 years)	80.0 (52/65)[c]	Not associated with prior sleep deprivation; often pronounced, mean percentage for the 52 elevated cases was 25.8 (±6.6); range, 15–46
Clonazepam treatment efficacy[d]		
Complete	79.1 (44/67)	Rapid control of problematic sleep behaviors and altered dreams, sustained for up to 9 years
Partial	11.9 (8/67)	
Total	91.0 (61/67)	

[a] Six patients had an indeterminate age of RBD onset.

[b] Mean age for males ($n = 84$) and for females ($n = 12$) were significantly different: 60.1 (±16.0) vs. 45.4 (±22.5), ($P = 0.003$, $t = 2.8$, d.f. = 94, one tailed t-test).

[c] Stage 3/4 % elevation was defined as >15% of total sleep time. Thirty-one patients were excluded from analysis who were <58 years old.

[d] To date, 70% (67/96) of patients have received treatment with clonazepam.

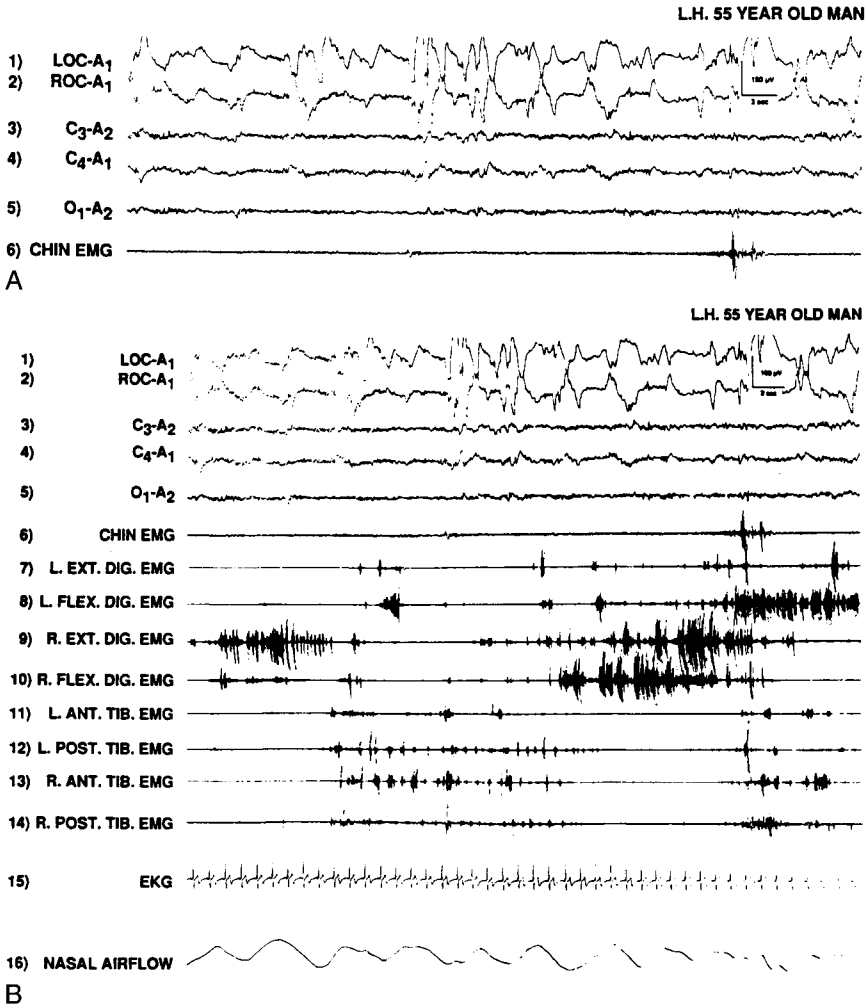

FIGURE 13.1 REM sleep polysomnograms demonstrating the necessity of extensive extremity EMG monitoring in documenting RBD. (A) Shows customary REM sleep, with its distinct electrophysiological profile: the triad of dense, high-voltage REMs (1–2), activated EEG (3–5), and chin EMG atonia with one minor burst of phasic twitching (6). Channels 1–6 are sufficient for scoring sleep stages throughout the night, according to the standard methods and criteria of Rechtschaffen and Kales. However, (B) contains identical channels 1–6 from (A) and reveals that extensor and flexor EMGs of the four limbs have excessive twitching. EKG rate (15) remains constant and respirations (16) are mildly irregular. (Adapted from Mahowald, M. W., and Schenck, C. H. (1990). REM Sleep Behavior Disorder, In *Handbook of Sleep Disorders,* M. J. Thorpy, ed., p. 567, New York: Marcel Dekker, with permission.)

effect. These cats also displayed *de novo* "hallucinatory-type" behaviors during REM sleep that strongly resembled "oneirism" (i.e., dream-enactment). The oneiric behaviors in these cats always occurred during unequivocal REM sleep, with REM sleep retaining all its defining features (apart from loss of REM-

atonia): cortical EEG activation; unresponsiveness to environmental stimuli; periodic cycling with NREM sleep; ponto-geniculo-occipital (PGO) waves; pronounced myosis; and relaxation of the nictitating membranes. Thus, the mechanisms responsible for the oneiric behaviors were postulated to result from disruption of brain neuronal organization during REM sleep.

Further work by Jouvet's group on "paradoxical sleep without atonia" revealed that a stereotypic repertoire of behaviors was displayed, without external provocation, during REM sleep. Attack behavior was most commonly displayed, and sexual or feeding behaviors were never observed (Sastre and Jouvet, 1979; Jouvet *et al.*, 1981). These cats were never inappropriately aggressive during wakefulness—a finding mirrored in human RBD.

Morrison's group, in addition to Jouvet's group, has identified four categories of oneiric behaviors in the cat model of RBD (Henley and Morrison, 1974; Morrison, 1979; Hendricks *et al.*, 1982). The appearance of each behavioral category is dependent on the location and size of the pontine tegmental lesions (Hendricks *et al.*, 1982): (1) minimal syndrome of generalized limb or truncal twitching and jerking, which can intermittently become prominent and violent; (2) orienting and exploratory behaviors, involving staring, head raising, head turning, grasping, and searching; (3) stalking imaginary prey, and episodic attack behavior; and (4) locomotion.

These animal experiments revealed that loss of REM-atonia alone is insufficient to generate RBD. There also must presumably be disinhibition of motor pattern generators in the mesencephalic locomotor region to result in phasic motor overactivation with behavioral release during REM sleep (Morrison, 1979; Hendricks *et al.*, 1982). Studies in dogs have identified a colocalization of the atonia and locomotor systems in the pons, thus providing an anatomic basis for the simultaneous dysregulation of the tonic and phasic motor systems in RBD (Lai and Siegel, 1990).

Supraspinal mechanisms responsible for REM-atonia originate in the perilocus ceruleus (LC)-alpha nucleus of the pons that then excite neurons of the nucleus reticularis magnocellularis in the medulla, which then transmit descending inhibitory projections—more powerful than the competing descending excitatory projections—to the spinal alpha motoneurons, resulting in hyperpolarization and resultant muscle atonia (Pompeiano, 1976; Sakai *et al.*, 1981). Therefore, REM-atonia results from an active process involving a specific neuronal circuitry and is not the result of passive cessation of motor activity.

CLINICAL FEATURES OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

Although various PSG and clinical features of RBD have been identified by investigators from three continents since 1966 (Mahowald and Schenck, 1994), RBD was not formally recognized and named until 1986–1987 (Schenck *et al.*, 1986; Schenck *et al.*, 1987). RBD was incorporated within the international

classification of sleep disorders (ICSD) in 1990. A typical clinical presentation of RBD is as follows (Schenck *et al.*, 1986):

> A 67-year-old dextral man was referred because of violent behavior during sleep . . . . He had slept uneventfully through adolescence in a small room with three brothers. But on his wedding night, his wife was "scared with surprise" over his sleep talking, groaning, tooth grinding, and minor body movements. This persisted without consequence for 41 years until one night, 4 years before referral, when he experienced the first 'physically moving dream' several hours after sleep onset; he found himself out of bed attempting to carry out a dream. This episode signaled the onset of an increasingly frequent and progressively severe sleep disorder; he would punch and kick his wife, fall out of bed, stagger about the room, crash into objects, and injure himself . . . his wife began to sleep in another room 2 years before referral. They remain happily married, believing that these nocturnal behaviors are out of his control and discordant with his waking personality.

One example of "oneirism" (dream-enacting behavior) in this patient is as follows:

> I was on a motorcycle going down the highway when another motorcyclist comes up alongside me and tries to ram me with his motorcycle. Well, I decided I'm going to kick his motorcycle away and at that point my wife woke me up and said, "What in heavens are you doing to me?" because I was kicking the hell out of her.

This same patient cited another example:

> I was a halfback playing football, and after the quarterback received the ball from the center he lateraled it sideways to me and I'm supposed to go around end and cut back over tackle and—this is very vivid—as I cut back over tackle there is this big 280-pound tackle waiting, so I, according to football rules, was to give him my shoulder and bounce him out of the way, and when I came to I was standing in front of our dresser and I had knocked lamps, mirrors, and everything off the dresser, hit my head against the wall and my knee against the dresser.

This patient had sustained ecchymoses and lacerations during these recurrent nocturnal episodes.

Data on a series of 96 consecutively documented cases of RBD from one center (Schenck *et al.*, 1993) are contained in Table 13.1. These data remain fully representative of the current series of 158 patients (Schenck and Mahowald, 1996a). Data from two other centers (Sforza *et al.*, 1997; Olsen *et al.*, 2000) on their series of 52 and 93 RBD patients, respectively, correspond closely to the data from our center's series of RBD patients. The older male predominance in RBD is striking, although females and virtually all age groups are represented. One quarter of the patients have a prodrome, often lengthy, involving subclinical behavioral release during (presumed REM) sleep. The frequent presence of periodic and aperiodic movements during NREM sleep suggests a strong tendency for generalized sleep motor dysregulation across REM and NREM sleep in RBD. Also, the elevated percentage of stage 3 to 4 NREM sleep in three-quarters of the patients (a finding matched in a series of 25 RBD patients from another center [Iranzo and Santamaria, 1998]) suggests an additional component of NREM sleep dysregulation in RBD. Finally, histories of childhood sleepwalking or sleep terrors are rare in RBD.

Customary cycling among REM and NREM sleep stages is usually preserved, as is the sleep architecture, apart from an elevated stage 3/4 (delta) sleep % (Schenck and Mahowald, 1990). However, a shift toward light sleep with an elevated percentage of stage 1 can occur in some cases (Schenck *et al.*, 1987; Sforza *et al.*, 1988). Sleep-disordered breathing is uncommon in RBD and, when present, is usually mild; it is possible that RBD may protect against obstructive sleep apnea (Schenck and Mahowald, 1992a).

All PSG and behavioral features of RBD are indistinguishable across subgroups, irrespective of gender, age, or the presence or absence of a neurological disorder (Schenck and Mahowald, 1990). This suggests the presence of a "final common pathway" in RBD that can be accessed by a wide variety of pathological states. Figures 13.1–13.3 depict a range of common PSG findings in RBD. One finding that merits particular emphasis is that loss of submental (i.e., background) electromyographic (EMG) atonia is not necessary for the release of excessive phasic EMG twitching during REM sleep, nor for the expression of RBD behaviors. Figure 13.1B illustrates this important point. Our center has also quantitatively analyzed the EMGs during REM sleep in 17 older males with idiopathic RBD and found that submental EMG atonia was preserved in 54% of all 7.5-s time bins containing bursts of phasic limb twitching (Schenck *et al.*, 1992).

RBD behaviors occur within REM sleep, often without associated tachycardia. Complex RBD behaviors are generally aggressive or exploratory, and never appetitive (feeding, sexual). There is a very close association between altered dreams and dream-enacting behaviors, suggesting a mutual pathophysiology: patients do not enact their customary dreams, but instead they enact distinctly altered dreams, usually involving confrontation and aggression with unfamiliar people and animals.

Despite the impressive EMG motor activity and repeated behavioral release during sleep, only a small number of RBD patients complain of excessive sleep disruption and daytime fatigue, and multiple sleep latency testing rarely documents daytime somnolence (Schenck and Mahowald, 1990), apart from cases in which RBD is associated with narcolepsy.

Data on RBD from the world literature (Schenck and Mahowald, 1996a) closely match the data from our center listed in Table 13.1. Approximately half of RBD cases in the published world literature are closely associated with neurological disorders, with great diversity in category and location along the central neuraxis. Three pertinent comments are warranted: first, neurodegenerative disorders and narcolepsy are the most common neurological disorders associated with RBD. Second, the pons is rarely grossly involved, as ascertained by clinical neuroanatomical and neurophysiological testing, which stands in contrast to the animal model of RBD. Third, virtually all the neurological disorders can also manifest as "REM sleep without atonia" and/or excessive phasic EMG twitching in REM sleep, but without the clinical emergence of RBD—in other words, various subclinical forms of

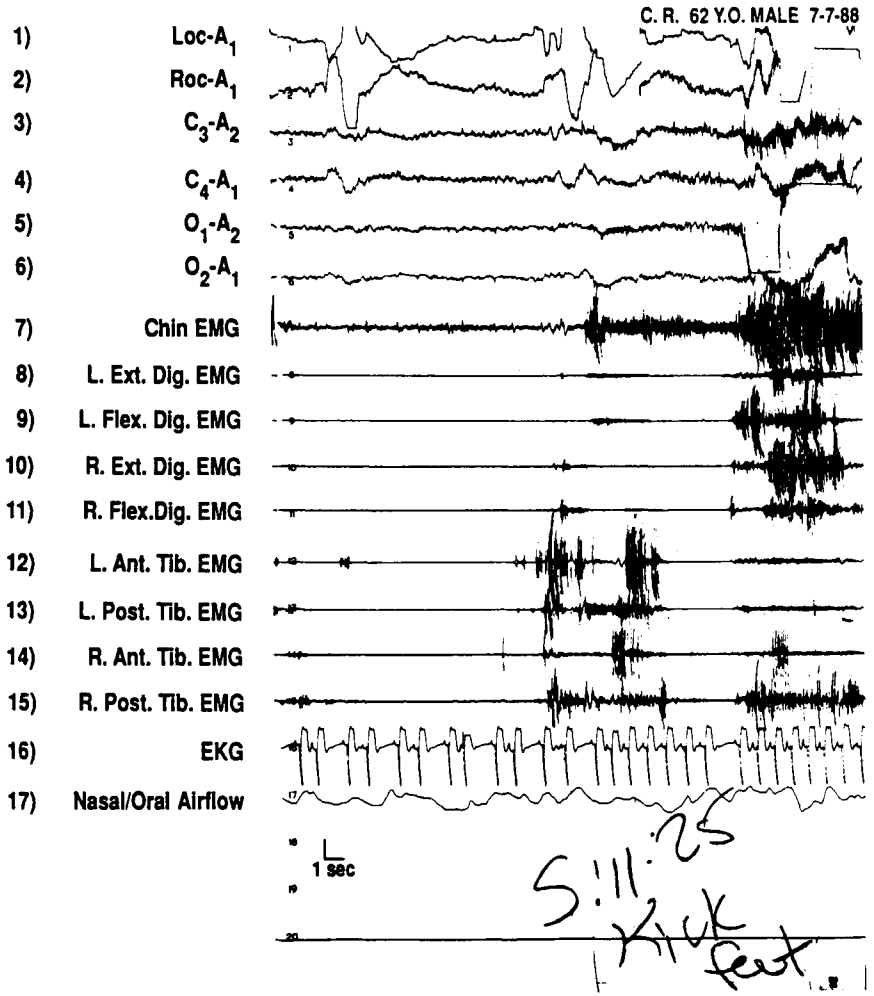

FIGURE 13.2 REM sleep polysomnogram demonstrating selective bilateral extensor and flexor leg twitching (12–15), which corresponds to the technician's simultaneous observation that the patient is kicking his feet. REMs (1–2) and tonic/phasic chin EMG activity appear in conjunction with these vigorous behaviors. EKG (16) is abnormal and reflects a chaotic atrial rhythm that is present throughout the night. EEG (3–6) is activated and respirations are irregular (17). (Adapted from Mahowald, M. W., and Schenck, C. H. (1990). REM Sleep Behavior Disorder, In *Handbook of Sleep Disorders,* M. J. Thorpy, ed., p. 567, New York: Marcel Dekker, with permission.)

RBD can be found in the same neurological disorders that are associated with clinical RBD, and also in individuals without any identified neurological disease. Also, sleep bruxism has been reported to be a subclinical manifestation of RBD (Tachibana *et al.*, 1994).

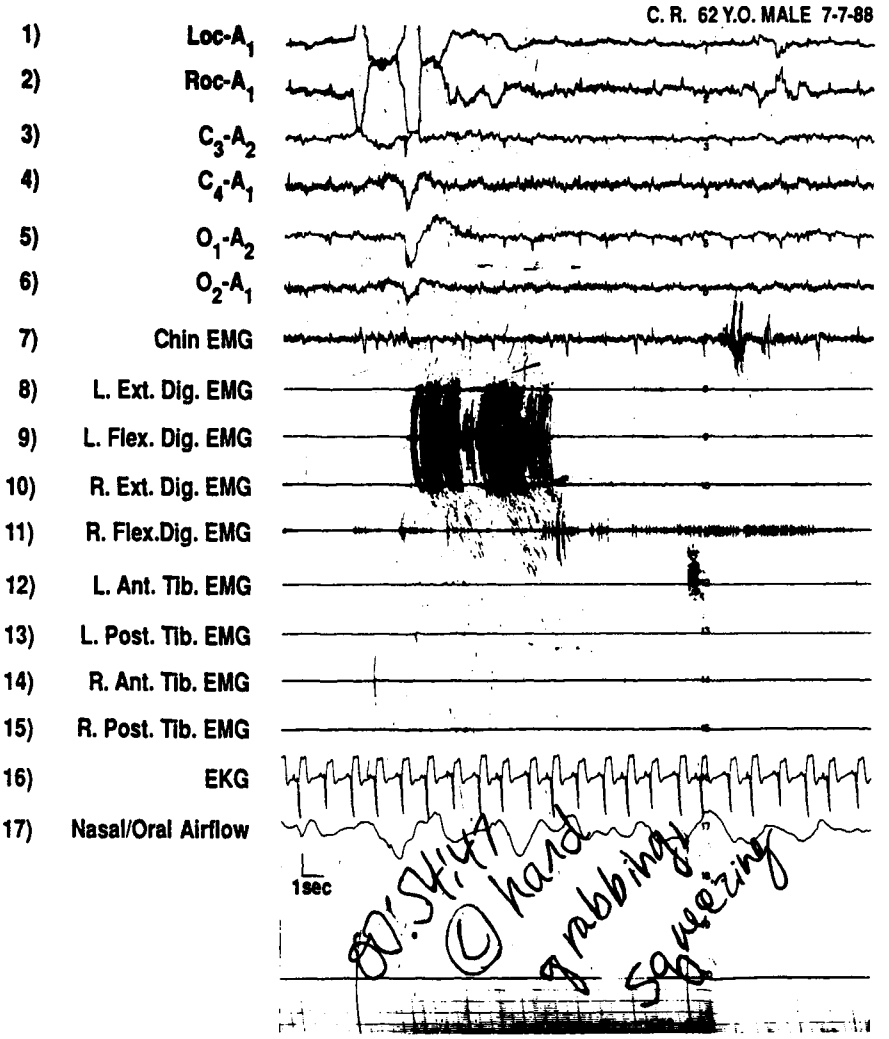

FIGURE 13.3 REM sleep polysomnogram (same patient and same night as shown in Fig. 13.2, revealing selective, dense, high-voltage left flexor arm EMG twitching (9) in conjunction with observed grabbing and squeezing behaviors of the left hand. A burst of REMs (1–2) precedes these gross behaviors. The EEG (3–6) is activated, the chin EMG (7) has minimal tone with occasional twitching, and the leg EMGs (12–15) are completely inactive. (Adapted from Mahowald, M. W., and Schenck, C. H. (1990). REM Sleep Behavior Disorder, In *Handbook of Sleep Disorders,* M. J. Thorpy, ed., p. 567, New York: Marcel Dekker, with permission.)

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER: DIAGNOSTIC METHODS

The evaluation of injurious or disruptive nocturnal behaviors should consist of the following:

1. Clinical sleep–wake interview, includes a review of physician referral information and past medical records; a review of a completed, structured, patient questionnaire, covering sleep–wake, medical, psychiatric, and alcohol/substance use history (including family history); and a review of systems.
2. Psychiatric and neurological interviews and examination.
3. Extensive overnight PSG monitoring with continuous videotaping. Figure 13.1A and 13.1B depicts the PSG monitoring montage that includes the electrooculogram (EOG), EEG, chin and four-limb EMG, electrocardiagram (EKG), and airflow. A PSG paper speed of 15 mm/s is routinely used during the first night of PSG monitoring at our sleep center. Urine toxicology screening is performed whenever indicated.
4. Daytime multiple sleep latency testing is done if there is a complaint or suspicion of daytime sleepiness or fatigue.
5. If RBD is diagnosed, then baseline neuropsychometric testing (Cox *et al.*, 1990) should be considered because Parkinsonism is quite prevalent in RBD, and dementia is common in Parkinsonism. RBD can also be associated with Alzheimer's disease (AD). A brain imaging study, preferably a magnetic resonance scan, may be indicated, depending on findings elicited from the clinical history and/or neurological examination.

MINIMUM DIAGNOSTIC CRITERIA OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

These minimum diagnostic criteria include (ICSD, 1990; Mahowald and Schenck, 1994):

1. PSG abnormality during REM sleep: elevated submental EMG tone and/or excessive phasic submental and/or limb EMG twitching
2. Documentation of abnormal REM sleep behaviors during PSG studies (prominent limb or truncal jerking; complex, vigorous, or violent behaviors), a history of injurious or disruptive sleep behaviors
3. Absence of EEG epileptiform activity during REM sleep

TREATMENT OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

Clonazepam is a remarkably effective treatment in controlling both the behavioral and the dream-disordered components of RBD (Schenck and Mahowald, 1990). Treatment is usually immediately effective at a dose of .5–1.0 mg taken at bedtime (usual range: .25–4.0 mg). Prompt relapse of RBD occurs whenever the patient fails to take clonazepam on any given night. The mechanism of therapeutic action has been shown to involve suppression of phasic EMG

activity during REM sleep instead of restoration of REM-atonia (Lapierre and Montplaisir, 1992). The long-term efficacy and safety of chronic, nightly clonazepam treatment of RBD, and of other parasomnias, at our center has been reported (Schenck and Mahowald, 1996b). Alternative pharmacotherapies at times must be considered in patients not responding to, and/or not tolerating, clonazepam therapy (Schenck and Mahowald, 1990; Mahowald and Schenck, 1994).

DIFFERENTIAL DIAGNOSIS OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

RBD is one of several disorders that can manifest as violent sleep-related (and at times dream-related) behaviors, with forensic implications (Mahowald *et al.*, 1990). Other disorders include sleepwalking and sleep terrors (i.e., disorders of arousal) (Schenck *et al.*, 1989a; Kavey *et al.*, 1990; Blatt *et al.*, 1991; Kavey and Whyte, 1993); nocturnal seizures (Mahowald *et al.*, 1990; Mahowald and Schenck, 1993; D'Cruz and Vaughn, 1997); hypnogenic paroxysmal dystonia (Lugaresi and Cirignotta, 1981); obstructive sleep apnea (with agitated REM-related arousals) (Guilleminault and Silvestri, 1982; Schenck *et al.*, 1989a; Kushida *et al.*, 1995; Nalamalapu *et al.*, 1996); rhythmic movement disorders of NREM and REM sleep, including *jactatio capitis nocturna* (Thorpe, 1990; Whyte *et al.*, 1991); psychogenic dissociative disorders (Schenck *et al.*, 1989b); and malingering (Mahowald *et al.*, 1992).

ASSOCIATED FINDINGS IN RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

ASSOCIATION WITH PARKINSONISM AND OTHER EXTRAPYRAMIDAL DISORDERS

Findings from various centers suggest the following characteristics. First, parkinsonism may be quite prevalent in RBD; second, RBD may be the initial manifestation of a parkinsonian disorder in a substantial number of RBD cases initially considered to be idiopathic; third, a high percentage of parkinsonian patients without sleep complaints may have either subclinical or clinical RBD; fourth, Lewy body pathology may be quite prevalent in RBD; and fifth, similar findings have been reported in various extra-pyramidal disorders.

A review of the world literature on RBD identified 280 published cases, of which 149 (53%) were closely associated with a neurological disorder (Schenck and Mahowald, 1996a). A parkinsonian disorder was the most prevalent neurological condition, affecting 43% ($n = 64$) of neurologically disordered RBD patients (representing 23% of $n = 280$ total cases); narcolepsy was the next most prevalent condition, affecting 25% ($n = 38$) of neurologically disordered RBD patients (representing 14% of $n = 280$ total cases), followed by cardiovascular disorders, dementias, and miscellaneous disorders.

Parkinsonism

The delayed emergence of a parkinsonian disorder in RBD has been reported in a group of 29 male patients ≥50 years of age who were initially diagnosed to have idiopathic RBD (Schenck and Mahowald, 1996c). Of these, 38% ($\frac{11}{29}$) eventually developed a parkinsonian disorder [presumably Parkinson's disease (PD)] at a mean interval of 3.7 ± 1.4 years after the diagnosis of RBD, and at a mean interval of 12.7 ± 7.3 years after the onset of RBD. Only 7% ($\frac{2}{29}$) of those patients had, at the time of publication, developed any other neurological disorder. RBD was controlled with nightly clonazepam treatment in 89% ($\frac{24}{27}$) of patients (both groups). Thus, RBD can be the heralding manifestation of PD (by many years) in a substantial subgroup of older male RBD patients. However, a number of presumed PD patients could eventually be diagnosed with multiple system atrophy (striatonigral degeneration subtype). The findings from that report indicate the importance of serial neurological evaluations after the initial diagnosis of RBD.

In another report, presumed RBD (PSG monitoring was not performed) preceded the onset of PD by 4–5 years in three elderly male patients, and both the PD and RBD were ameliorated by levodopa therapy (Tan *et al.*, 1996).

Two preliminary studies have suggested that RBD and subclinical RBD may be quite prevalent in PD. In the first report, a series of five cases with RBD (four with PD, and one with parkinsonism, dysautonomia, and dementia) involved four males and one female, with mean age of 66 ± 6 years (Silber and Ahlskog, 1992). Three cases involved 14–19-year histories of PD and 1–4-year histories of RBD and dementia. A fourth case involved a four year history of PD and 3-year history of RBD, and a fifth case involved a 1 year history of both PD and RBD. Clonazepam therapy was usually efficacious in these patients. The authors concluded that RBD may complicate both PD and multisystem degenerations, and clinicians should be aware that nocturnal confusional behaviors in parkinsonian syndromes may be a manifestation of RBD and may thus warrant a sleep center evaluation and PSG monitoring.

A second preliminary report involved 10 patients (aged 45–80 years) with untreated PD presenting with parkinsonism, but without sleep symptoms, who underwent two nights of PSG monitoring (Silber *et al.*, 1993). During REM sleep, there was significantly increased submental EMG tone and anterior tibialis EMG twitching in the 10 PD patients compared with 10 controls. Sub-clinical RBD was diagnosed in 40% ($n = 4$) of PD patients and clinical RBD was diagnosed in 20% ($n = 2$) of PD patients. Thus, motor dyscontrol during REM sleep, with or without clinical RBD, was found to be quite common in early PD. Clinicians were prudently urged to maintain a high index of suspicion for RBD in patients with early PD.

In a report of PSG findings in 10 nondepressed, nondemented PD patients, 5 with and 5 without dopaminergic treatment-induced hallucinations, RBD was diagnosed in 50% ($n = 5$) of the total group (in 4 of the 5 nonhallucinators) (Comella *et al.*, 1993). Mean age of the total group was 68 years, and 70% ($n = 7$) were male. Another study found RBD present in all 10 patients with PD

(levodopa-responsive) and daytime visual hallucinations (Arnulf *et al.*, 2000). A unique case of adolescent-onset PD, RBD, and narcolepsy in an African-American female has recently been reported (Rye *et al.*, 1999).

Lewy Body Disease

Lewy body disease, as a postmortem finding, was reported in an 84-year-old man with a 20-year history of RBD, but without any clinically detected neurological disorder (Uchiyama *et al.*, 1995). Postmortem histopathological examination revealed that the patient had Lewy body disease with marked decrease of pigmented neurons in the locus ceruleus and substantia nigra. These findings represent the first documented evidence of a loss of brain stem monoaminergic neurons in clinically idiopathic RBD, and suggest that Lewy body disease might provide an explanation for idiopathic RBD in elderly patients. This report is important in that it calls attention to the possibility that a sizable subgroup of RBD patients with presumed idiopathic RBD may, in fact, turn out to have Lewy body disease as the neuropathological basis of RBD.

A subsequent report involved the case of a 73-year-old man with a 2-year history of parkinsonism and a 15-year history of RBD (Negro and Faber, 1996). The clinical history satisfied operational diagnostic criteria for dementia of the Lewy body type (i.e., mix of parkinsonian symptoms, coarse dementia, fluctuating cognitive performance, and intermittent psychotic symptoms).

Probable diffuse Lewy body dementia was reported in a 72-year-old man with a 17-year history of RBD and a 2 year history of dementia (Turner *et al.*, 1997). The patient had a typically placid disposition during the daytime, but would attack his wife and attempt to choke her during sleep. Cognitive dysfunction began insidiously, but eventually became the dominant clinical concern. He subsequently developed visual hallucinations and illusions in the late afternoon and evening and often thought his wife was an identical imposter. There was marked fluctuation of cognitive capacities, ranging from relatively lucid intervals to intervals of severe cognitive compromise.

Another case was reported of an elderly male patient with RBD and the Lewy body variant of AD identified by postmortem ubiquitin staining (Schenck *et al.*, 1996a; Schenck *et al.*, 1997a).

The potentially close association between Lewy body disease and RBD has been further explored in a study entitled, "REM sleep behavior disorder and degenerative dementia with or without parkinsonism: a syndrome predictive of Lewy body disease?" (Boeve *et al.*, 1997). A group of 21 patients was evaluated, with 90% ($n = 19$) being male. Two subgroups were compared: one group ($n = 11$) with two or more clinical signs of parkinsonism, with mean age of dementia onset of 67 years; a second group ($n = 10$) without parkinsonism, with mean age of dementia onset of 59 years. The clinical features of RBD and dementia in both groups were remarkably similar, with fluctuating cognitive status and visual hallucinations being common. The authors hypothesized that the underlying pathology in both groups was likely to be diffuse Lewy body disease or

the Lewy body variant of AD. Two subsequent studies by the same group of investigators (Boeve *et al.*, 1998; Ferman *et al.*, 1999) on RBD patients with dementia implicate Lewy body disease as the basis of both the RBD and the dementia.

Other Extrapyramidal Disorders

Shy-Drager syndrome (SDS) presenting as RBD has been reported in an elderly male (Wright *et al.*, 1990). RBD emerged at age 53 years as dream-related punching, choking, kicking, and spitting on his wife during sleep, along with leaving the bed and running into walls. The dreams usually involved being attacked. The RBD eventually became severe enough to result in the wife sleeping in another room for her safety, while the patient tied himself to bed with a rope. Despite this impressive nocturnal violence, his waking behavior remained unchanged and he was described as "a loving and caring husband and father and retained his job as a public relations executive. His mood was reported as 'good' and his affect was euthymic." A physical examination at the time of RBD onset was unremarkable—with the notable exception of a 40 mmHg aysmptomatic orthostatic drop in systolic blood pressure. SDS insidiously emerged 5 years after the onset of RBD, and was formally diagnosed 12 years after the onset of RBD, with parkinsonism, symptomatic orthostatic hypotension, anhidrosis, and cognitive impairment being documented.

RBD as the presenting symptom of multiple system atrophy (MSA) was reported in two cases, both involving males, with RBD emerging at ages 42 and 57 years, respectively; and MSA (striato-nigral and olivo-ponto-cerebellar subtypes) emerging 2 or 3 years subsequently (Tison *et al.*, 1995). In one case, the man had sustained nocturnal injuries from leaving the bed and colliding into furniture; and he had also inflicted injuries on his wife and on one occasion had attempted to strangulate her during sleep. In the other case, the man would periodically jump out of bed during sleep, growl, and flail his arms. On one occasion, he dove from bed and engaged in a rugby-style tackle while dreaming that he was tackling someone in a match.

A case of progressive supranuclear palsy and subclinical RBD has been reported in a 70-year-old female who displayed the notable association of inhibition of speech during wakefulness and somniloquy with phasic muscle twitching during REM sleep (Pareja *et al.*, 1996).

In a large systematic study involving 39 consecutive MSA patients [mean age, 60 years (range, 43–80); 67% (n = 26) male], RBD was diagnosed by PSG monitoring in 90% (n = 35) of these patients (Plazzi *et al.*, 1997). Dream-enacting behaviors were reported in 69% (n = 27) of patients; in 44% (n = 12) of this subgroup, RBD preceded the clinical onset of MSA by more than 1 year; in 26% (n = 7) of this subgroup, RBD and MSA emerged concurrently; and in 30% (n = 8) of this subgroup, RBD emerged more than 2 years after the appearance of the first MSA signs. Thus, this study demonstrated that RBD represents the most common clinical sleep disorder in patients with MSA,

and RBD can often herald the appearance of other MSA signs and symptoms by years.

Finally, REM sleep-related talking was documented during PSG monitoring in 86% ($n = 18$) of a series of 21 patients with MSA, and in these patients, sleep talking had begun or had intensified at the time of clinical onset of MSA (Tachibana *et al.*, 1997). Excessive amounts of REM sleep without atonia were documented in all but one patient, and excessive motor activity (apart from sleep talking) during REM sleep was documented in all but two patients, and involved craniofacial, orofacial, or limb movements. Thus, all patients with MSA in this series (save one) had subclinical RBD.

Brain Mechanisms in Combined RBD–Extrapyramidal Disorders

What brain mechanisms may be involved in subclinical and clinical RBD associated with various extrapyramidal disorders? The pedunculopontine nucleus (PPN) is likely to be prominently involved in the disruption of the REM-atonia circuitry, for at least three reasons. First, there is a strong reciprocal connectivity between the PPN and the substantia nigra (Garcia-Rill, 1991), the main site of pathology accounting for the cardinal signs of PD (Koller, 1992). Second, the neuropathology of PD includes prominent neuronal loss within the PPN (Jellinger, 1991). Third, the PPN has strong links with both the REM-atonia and REM-phasic generator circuitry (Lai and Siegel, 1990; Garcia-Rill, 1991; Shouse and Siegel, 1992). The retrorubral nucleus is located near the substantia nigra, and appears to be implicated in the linked PD–RBD pathology (Lai and Siegel, 1990). The retrorubral nucleus projects to the caudate and putamen (extrapyramidal motor system); experimental lesions to the retrorubral nucleus in cats releases abnormal motor activity during both sleep and wakefulness, ranging from myoclonic twitches to rhythmic leg movements and locomotion (Lai and Siegel, 1997). In addition, the substantia nigra also is closely connected to the REM-phasic generator circuitry and may play a major role in the genesis of PGO waves, a characteristic REM sleep phasic event (Datta *et al.*, 1991). In regard to MSA, pontine involvement has been revealed by both gross neuropathological examination and histochemical studies, as cited by Plazzi *et al.* (1997). Functional magnetic resonance brain imaging studies and postmortem brain analyses are required to definitively elucidate the underlying neuropathology responsible for combined RBD–extrapyramidal disorders. In this regard, it is important to consider that extrapyramidal dysfunction has just been found in idiopathic RBD, with reduced striatal dopamine transporters being identified by single-photon emission computed tomography (SPECT) in 5 patients compared to 7 controls (Eisensehr *et al.*, 2000).

ASSOCIATION WITH NARCOLEPSY

A close association of RBD with narcolepsy has been described in two reports. In the first report, combined narcolepsy–RBD was documented in a series of 10 cases (80% male); mean age of narcolepsy onset was 23 ± 15 years

(range: 12–59), and mean age of RBD onset was 29 ± 17 years (Schenck and Mahowald, 1992b). RBD emerged in tandem with narcolepsy in 5 cases, and early in the course of narcolepsy in three cases. Treatment of cataplexy (with tricyclic antidepressants) either induced or aggravated RBD in three cases. There was strong expression of the narcolepsy tetrad in all 10 patients. An additional 7 patients in this report had subclinical RBD. For the entire group of 17 RBD and subclinical RBD patients, 71% were male and the age range was 8–74 years. In the second report (Mayer and Meier-Ewert, 1993), records of 14 narcoleptic patients with RBD were retrospectively analyzed in a controlled design, and the (testable) suggestion was made that sleep motor dyscontrol in narcolepsy may start as a NREM sleep parasomnia in childhood and then "the onset of narcolepsy might represent the turning point for its intrusion into REM sleep."

PARASOMNIA OVERLAP DISORDER

Our center has reported on a group of 33 RBD patients with PSG-documented overlapping NREM–REM sleep motor parasomnias consisting of sleepwalking, sleep terrors, and RBD (Schenck *et al.*, 1997b). Mean age was 34 ± 14 years; mean age of parasomnia onset was 15 ± 16 years (range: 1–66); 70% (n = 23) were males. An idiopathic subgroup (n = 22) had a significantly earlier mean age of parasomnia onset (9 ± 7 years) than a symptomatic subgroup (n = 11) (27 ± 23 years) whose parasomnia began with neurological disorders, n = 6 [congenital Mobius syndrome, narcolepsy, multiple sclerosis, brain tumor (and treatment), brain trauma, indeterminate disorder (exaggerated startle response/atypical cataplexy)]; nocturnal paroxysmal atrial fibrillation, n = 1; posttraumatic stress disorder/major depression, n = 1; chronic ethanol/amphetamine abuse and withdrawal, n = 1; or mixed disorders (schizophrenia, brain trauma, substance abuse), n = 2. The rate of psychiatric disorders was not elevated; group scores on various psychometric tests were not elevated. Of the 33 patients, 45% (n = 15) had previously received psychological or psychiatric therapy for their parasomnia, without benefit. Treatment outcome was available in n = 20 patients; 90% (n = 18) had substantial parasomnia control with bedtime clonazepam (n = 13), alprazolam and/or carbamazepine (n = 4), or self-hypnosis (n = 1). This series of cases thus demonstrated striking motor–behavioral dyscontrol extending across NREM and REM sleep.

ASSOCIATION OF RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER WITH SPECIFIC HUMAN LEUKOCYTE ANTIGEN HAPLOTYPES

Narcolepsy, like RBD, is a prominent disorder of REM sleep dysregulation. Narcolepsy has a very strong association with HLA class II genes, with the DQB1*0602 (DQw1 group) allele being expressed in nearly all cases. Our center performed HLA class II antigen phenotyping in a group of 25 Caucasian males who had RBD but not narcolepsy: 84% (n = 21) were DQw1

(DQB1*05,06) positive [and 28% (n = 7) were DR2 positive]; DQB1*0501 (n = 9) and DQB1*0602 (n = 7) were the most common phenotypes (Schenck *et al.*, 1996b). The 84% DQw1 rate in RBD was significantly greater (p = .015) than the 56% DQw1 rate found in a local Caucasian comparison group (n = 66), and was greater than the 39–66% DQw1 rates in 12 published Caucasian groups (n = 40–418 per group). In contrast to the nearly 100% DQw1–DR2 linkage in narcolepsy, only 28% of RBD patients in this report were DR2-positive. The strong dissociation between DQw1 and DR2 in RBD can be contrasted with the very strong DQw1–DR2 association in narcolepsy. Narcolepsy and RBD, therefore, have strikingly convergent (DQw1) and divergent (DR2) HLA findings.

CONCLUSION

The recognition of RBD has demonstrated multiple physiological and clinical relationships; has shed additional scientific light on the "bumps in the night"; has opened up new areas of research on sleep and neurological disorders, particularly extrapyramidal disorders and narcolepsy; and has underscored the vital link between basic research and clinical medicine.

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14

NOCTURNAL PAROXYSMAL DYSTONIA AND FRONTAL LOBE EPILEPSY

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NOCTURNAL PAROXYSMAL MOTOR PHENOMENA

The nature of paroxysmal motor phenomena occurring during sleep has been a matter of debate for many years. Various sleep disorders associated with motor activity such as sleepwalking (somnambulism), sleep talking, night terrors (pavor nocturnus), periodic limb movement disorder, and rapid eye movement (REM)

behavior disorder (RBD) have been described and constitute well-recognized entities (ICSD, 1990). Epileptic motor seizures may manifest themselves at any time of the day or night. However, some types of seizures, especially those originating from the mesial or orbitofrontal region, preferably occur during sleep (Niedermeyer and Walker, 1971; Tharp, 1972; Waterman *et al.*, 1987); have a peculiar semiology characterized by complex movements with dystonic, choreic, or ballistic features, asymmetrical tonic postures, and bizarre vocalizations, often with preserved consciousness (Tharp, 1972; Talairach *et al.*, 1973; Geier *et al.*, 1977; Bancaud and Talairach, 1992; Salanova *et al.*, 1995); and are not always associated with epileptiform abnormalities on scalp EEG (Williamson *et al.*, 1985; Morris *et al.*, 1988), thus leaving room for diagnostic uncertainties. In addition, Tassinari and colleagues (1972) have pointed out that true parasomnias may coexist in patients with known epilepsy.

However, some nocturnal motor events do not fit readily into any of these categories.

EPISODIC NOCTURNAL WANDERINGS

Pedley and Guilleminault (1977) described six patients with frequent, unusual sleepwalking episodes associated with complex automatisms and vocalizations, which they termed *episodic nocturnal wanderings*. No ictal seizure discharges were recorded, but interictal epileptiform abnormalities were seen in four patients. These episodes responded to antiepileptic medication, prompting the authors to suspect an atypical form of epilepsy.

DIURNAL PAROXYSMAL DYSKINESIAS RESPONSIVE TO ANTICONVULSANTS

Diurnal paroxysmal dyskinesias that respond to anticonvulsants have been observed as well. Initially described as a seizure disorder (Lishman *et al.*, 1962; Stevens, 1966), paroxysmal kinesigenic choreoathetosis—characterized by recurrent brief attacks of unilateral or bilateral dystonic, choreic, ballistic, or athetoid limb movements precipitated by sudden movement—soon acquired the identity of a movement disorder, mainly due to the lack of evidence for a cortical seizure discharge and the existence of rare symptomatic cases secondary to basal ganglia lesions (Fahn, 1994). Just as in another form of paroxysmal dyskinesia, paroxysmal nonkinesigenic dystonic choreoathetosis, first described by Mount and Reback (1940) and characterized by prolonged episodes of bizzarre dystonic posturing that do not respond to antiepileptic medication, familial occurrence was noted (Lance, 1977), and many cases follow an autosomal dominant transmission pattern (Fahn, 1994).

HYPOGENIC PAROXYSMAL DYSTONIA OR EPILEPSY?

Lugaresi and Cirignotta (1981) described five patients with recurrent nocturnal episodes of agitation during nonrapid eye movement (NREM) sleep, consisting of violent limb movements and tonic spasms of 15–45-s duration with preserved consciousness, responsive to carbamazepine. Impressed by the resemblance of these clinical manifestations to the attacks of paroxysmal kinesigenic choreoathetosis and the absence of epileptiform EEG changes, they coined the term "hypnogenic paroxysmal dystonia." Further, they proposed the existence of a distinct nosological entity akin to the former disorder, suggesting that the paroxysmal motor events, although a possible epileptic origin was discussed, might represent dystonic episodes triggered by arousals. Later Lugaresi *et al.* (1986) presented a larger group of patients with similar symptoms, in addition to two patients with longer lasting attacks unresponsive to medication (one of which was diagnosed with Huntington's disease at a later date), and again raised the question of a possible new syndrome of sleep-related motor attacks of uncertain nosologic classification, comprising two variants with short- and long-lasting attacks. A subsequent publication by the same group of researchers (Tinuper *et al.*, 1990) seemingly resolved the controversy by demonstrating that the nocturnal episodes of three of their patients had an epileptiform EEG correlate, thus concluding that nocturnal paroxysmal dystonia was indeed a form of frontal lobe epilepsy. They also noticed episodes of different duration in the same patients and suggested that these represented fragments of different intensity of the same type of seizure. Meierkord *et al.* (1992), using a more systematic approach, compared the semiology of motor attacks among groups of patients with nocturnal paroxysmal dystonia, daytime frontal lobe seizures, and proven epileptic nocturnal motor seizures, concluding there were no clinical features that would allow a distinction between these groups. Similar observations had been made by Fusco and colleagues (1990), who described the clinical and EEG characteristics of a group of patients with nocturnal seizures of mesial frontal lobe origin consisting of repetitive rhythmic movements and dystonic postures with preserved consciousness, accompanied by bizarre vocalization, and suggested that this type of epilepsy was probably underdiagnosed.

OTHER SLEEP-RELATED PAROXYSMAL EVENTS

Other sleep-related paroxysmal events were identified as epileptic as well. Peled and Lavie (1986) described 14 patients with hypersomnia secondary to recurrent nocturnal arousals, which were shown to be associated with paroxysmal epileptiform discharges occurring exclusively during stage 2 or 3 of NREM sleep; three patients showed dramatic improvement after treatment with

anticonvulsants. Montagna *et al.* (1990) made similar observations, concluding that, even though epileptic in nature, paroxysmal arousals constituted a clinical entity distinct from nocturnal paroxysmal dystonia characterized by attacks of even shorter duration. However, the same authors, in a subsequent review (Montagna, 1992) and strengthened by additional videopolygraphic recordings in three patients (Sforza *et al.*, 1993), pointed out again that stereotyped episodes of increasing complexity and duration could coexist in the same patient and therefore probably represented clinical variants of the same disorder. In addition, they stressed the peculiar periodic recurrence of these paroxysmal motor events at 20–60-s intervals throughout lighter stages of NREM sleep, similar to the periodic oscillations of other physiological phenomena observed by Lugaresi *et al.* (1972). Based on studies by Terzano *et al.* (1985), who found that EEG activity during NREM sleep could be divided into 40-s periodic sequences of greater and lesser arousal that they termed cyclic alternating pattern, the authors concluded that periodic fluctuations in cortical–subcortical excitability could exert a modulating influence on the nocturnal motor attacks, thus explaining their tendency to occur in the vicinity of a K-complex. The argument was picked up by Terzano and colleagues (1997), who confirmed this hypothesis in six patients with a diagnosis of nocturnal paroxysmal dystonia (without epileptiform EEG features). Additional evidence for the epileptic nature of some instances of episodic nocturnal wanderings and paroxysmal arousals, respectively, was subsequently presented by Plazzi *et al.* (1995) and Zucconi *et al.* (1997).

NOCTURNAL FRONTAL LOBE EPILEPSY

Finally, an overview of the clinical and EEG features of 100 consecutive cases of presumed nocturnal frontal lobe epilepsy was published by Provini *et al.* (1999). Although the authors propose that all patients are affected by the same disorder, namely, nocturnal frontal lobe epilepsy, they again emphasize the usefulness of a clinical distinction of their patients' multifaceted nocturnal motor manifestations into three subgroups, maintaining the previously introduced terminology. *Paroxysmal arousals* would constitute brief (<20 s) episodes characterized by sudden eye opening, head raising or sitting up in bed, often with a frightened expression and sometimes vocalization; *nocturnal paroxysmal dystonia* would describe episodes of intermediate duration (20 s–2 min) and include more complex behavior with wide, often ballistic movements, dystonic posturing or choreoathetoid movements of head, trunk, and limbs and vocalization; and the term *episodic nocturnal wandering* would be applied to the episodes of longest duration (1–3 min), characterized by stereotyped, paroxysmal ambulation, often agitated and accompanied by screaming and bizarre, dystonic movements, which set them apart from classical sleepwalking episodes.

Although some of the patients, as previously reported, present all three types of seizures, the distinction into the three groups is corroborated also by other statistically significant clinical associations. These involve the presence of an unremarkable personal history and absence of daytime or secondary generalization of seizures in patients with paroxysmal arousals, a family history of epilepsy and a higher overall frequency of seizures including secondary generalization of seizures in patients with nocturnal paroxysmal dystonia, and a family history positive for parasomnias and a personal history of sleepwalking in patients with episodic nocturnal wanderings. In about half of the cases, no interictal or ictal epileptiform EEG abnormalities were seen, but the authors are confident in making a diagnosis of frontal lobe epilepsy based on the stereotypy and the mode of occurrence of the nocturnal attacks, as well as the response to antiepileptic medication in several of the patients.

AUTOSOMAL DOMINANT FRONTAL LOBE EPILEPSY

The first familial cases of nocturnal paroxysmal dystonia were reported by Lee *et al.* (1985). The authors described a family with five affected members in three generations, suggesting an autosomal dominant inheritance pattern. However, given the absence of EEG abnormalities in three family members studied in detail, an epileptic origin of their motor manifestations was thought to be unlikely. The existence of an idiopathic frontal lobe epilepsy syndrome with onset in childhood and benign course was proposed by Vigevano and Fusco (1993) based on observations in 10 children; familial occurrence of seizures was noted but no specific inheritance pattern was identified.

Autosomal dominant frontal lobe epilepsy was first described by Scheffer *et al.* (1994), who collected six families with 39 affected individuals in Australia, the United Kingdom, and Canada, and were able to demonstrate monogenic inheritance with an autosomal dominant transmission pattern. A more extensive description of the clinical characteristics of five of these families, which proved to be quite homogeneous, was published the following year (Scheffer *et al.*, 1995). Their seizures were characterized by daily clusters of brief nocturnal motor attacks thought to be typical for frontal lobe seizures, often preceded by an aura that could include virtually all kinds of sensory or psychic phenomena. Onset of seizures was in the first two decades of life in most cases, and there was considerable intrafamilial variation in the severity of the seizure disorder. Seizure frequency overall tended to decrease over time and only a few individuals over 50 years of age still reported recurrent attacks. Diagnosis was made mostly on the basis of clinical symptoms, because most patients did not have interictal epileptiform EEG abnormalities and only 3 out of 10 patients studied with video EEG showed ictal changes compatible with epilepsy. However, as in previously

reported patients with similar symptomatology, treatment with carbamazepine was often effective. The first gene found to be responsible for this new syndrome was identified only shortly thereafter by Phillips *et al.* (1995) in a large Australian kindred and mapped to chromosome 20q13.2-q13.3; Steinlein *et al.* (1995) discovered a corresponding missense mutation in the neuronal nicotinic acetylcholine receptor alpha-4 subunit (CHRNA4), resulting in a substitution of serine with phenylalanine. More families, mostly of Caucasian descent, were described in the literature (Oldani *et al.*, 1996, 1998; Nakken *et al.*, 1999), and all affected individuals shared overall similar clinical characteristics. The attacks were highly stereotyped intraindividually, but intrafamilial variation of symptoms was again emphasized. Hayman *et al.* (1997) were able to study two patients from unrelated families with ictal single photon emission computed tomography (SPECT) and demonstrated focal frontal seizure onset, yet in different locations. Evidence for genetic heterogeneity emerged as well: Steinlein *et al.* (1997) reported a novel mutation in the M2 domain of the CHRNA4 gene in a Norwegian family, consisting of the insertion of an extra leucine into the amino acid chain. Both CHRNA4 mutations are thought to produce a decrease in receptor function (Steinlein *et al.*, 1997), and the authors propose that varying proportions of defective acetylcholine receptors could account for clinical variations between individuals. More mutations were discovered in the following years. Phillips *et al.* (1998) found evidence of another acetylcholine receptor defect with linkage to chromosome 15q24 in an English family and excluded the presence of the hitherto known mutations in an additional six families. Hirose *et al.* (1999) reported on a new CHRNA4 mutation, and the first mutation discovered in an Asian (Japanese) family, resulting in the replacement of serine 252 in the M2 domain of CHRNA4 with a leucine. Nevertheless, in most of the approximately 40 families reported to date the genetic defect has not yet been identified, and additional discoveries are likely to occur.

SUMMARY

Paroxysmal nocturnal motor events characterized by complex, often stereotyped dystonic or choreic movements with sudden onset and variable duration often defy precise classification. Over the years, different hypotheses regarding their origin have been advanced, and they have been variably diagnosed as sleep disorder, movement disorder or epilepsy. More recently, evidence has been mounting that many of these motor manifestations indeed represent seizures originating from the frontal lobe, although epileptiform EEG abnormalities are often lacking. Autosomal dominant transmission has been described in several families, and different mutations affecting the alpha 4 subunit of the neuronal nicotinic acetylcholine receptor (CHRNA4) have been discovered.

However, it should be borne in mind that "not everything that shakes is epilepsy," and that a diagnosis of epilepsy on clinical grounds alone leaves room

for the doubt that the paroxysmal motor events displayed by some of the reported patients might actually have a different etiology. There is certainly strong evidence for a genetic basis of the symptomatology in many of the patients diagnosed as having nocturnal frontal lobe epilepsy, but an autosomal dominant inheritance pattern has been demonstrated also in many patients with paroxysmal dyskinesias. The discovery of a channelopathy in patients with frontal lobe epilepsy may provide a future link between epilepsy and some paroxysmal movement disorders, and perhaps NREM parasomnias as well.

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15

CATAPLEXY

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INTRODUCTION

Cataplexy may present as drop attacks and thus must be distinguished from atonic seizures. Hunt (1992) described episodes of "sudden shock like loss of postural control for short duration associated with or without loss of consciousness" as epileptic events and called this a "drop seizure." Kremer (1958)

popularized the term *drop attacks*. Stevens and Matthews (1973) defined "idiopathic drop attacks," which they tried to distinguish from epileptic drop attacks, as "a falling without warning, not associated with loss of consciousness, not apparently due to any malfunction of the legs, not induced by changes in posture or movement of the head and not accompanied by vertigo or other cephalic sensations, not associated with myoclonic jerks." Finally, Lee and Marsden (1997) defined a drop attack as "a sudden fall, with or without loss of consciousness, due either to collapse of postural muscle tone (a negative phenomenon) or abnormal muscle contraction in the legs (a positive phenomenon)."

Introduction of the notion of the positive and negative motor phenomena has helped distinguish drop attacks. Negative motor phenomena (i.e., inhibition of muscle tone) is commonly seen in an "atonic seizure." These epileptic seizures occur usually but not exclusively in children. It is characterized by a sudden loss of postural tone that may be total and associated with an abrupt fall, but may be slight and associated only with a drop of the head with slackening of the jaw, or the dropping of the limbs. The patient usually arises immediately but may remain motionless and unresponsive for several minutes. For clinical neurophysiologists, frequently the first diagnosis to be considered is an atonic seizure. This is particularly true in prepubertal children. However, drop attacks can be related to many causes; even if eliminating the non-neurological causes and focusing on the negative motor phenomena, epilepsy is not the only clinical problem to face very young children. In a study of prepubertal narcolepsy (Guilleminault and Pelayo, 1998), none of the children 5 years or younger, finally diagnosed with the narcolepsy syndrome, were investigated initially except for epilepsy. A mean of three referrals to different specialists and a delay of 2–5 months after onset of symptoms and the first clinical evaluation occurred before the possibility of a narcoleptic syndrome was considered. The reason for these delays was that the presence of abrupt unexplained falls were interpreted by parents as being secondary to clumsiness. In these children, the falls led to repetitive bruising. This clumsiness was described as consisting of sudden dropping and breaking of objects such as plates and trays that seemed to be related to localized weakness. The dissociation between a key manifestation of the narcolepsy syndrome, cataplexy, and other causes of drop attacks is rarely considered not only in prepubertal children but also in older pubertal children and young adults (fortunately not as often).

Henneberg (1996) first used the term calaplexy in 1916. The clinical manifestation had been previously described in the literature by other names such as *fall* or *astasia*, terms used by Gelineau (1880) in his description of a new syndrome that he called narcolepsy. Henneberg had mentioned *cataplectic inhibition*, deriving his term from the Latin word *cataplessa*, meaning to strike down with fear or the like. Adie (1926) defined cataplexy as an abrupt and reversible paralysis, which a narcoleptic patient might experience. Daniels (1934) provided the definition that still applies today. He said that cataplexy was a state of helplessness into which a narcoleptic patient may be precipitated by emotional stress; he is

not unconscious but a mass of toneless muscles; and he promptly recovers, none the worse from the experience.

Cataplexy is one of the four symptoms of the narcolepsy syndrome, first described by Yoss and Daly (1960). Unlike the other three (sleep paralysis, hypnagogic hallucinations, and daytime sleepiness), cataplexy is thought to occur only with narcolepsy, and is therefore considered the hallmark of this syndrome. A few cases of independent cataplexy have been reported in family clusters, but these have not been well documented. The presence of cataplexy is the most reliable marker of the narcolepsy syndrome, more reliable, in fact, than any neurophysiological [i.e., electroencephalographic (EEG)] finding.

Cataplexy was first reported in dogs (Anic-Labat *et al.*, 1974). The symptom is also seen in other animals such as bulls, goats, and ponies, but the dog model is the only one that has been extensively investigated.

CLINICAL FEATURES

Cataplexy is a negative motor phenomenon. Cataplectic attacks can take many forms. In the most extreme case, voluntary muscle control is completely abolished and the patient is rendered paralyzed temporarily. He or she may collapse suddenly to the floor, which can cause minor injuries. Patients who suffer complete attacks are often able to brace themselves so that they actually "slide" down to the floor or collapse into the nearest chair. In a second form of the attack, the patient reports a fleeting sensation of weakness extending throughout. The third and most common manifestation of cataplexy features a combination of sagging of the jaw, flexion of the head, drooping of the shoulders, and transient buckling of the knees. During these partial attacks (the second and third form), speech may be slurred, and during more pronounced attacks (the first form) weakness of abdominal muscles and irregular breathing have been observed, though long diaphragmatic pauses have never been recorded. Generally, ocular motility and breathing are not affected during the cataplectic attack.

In humans, attacks are usually brief. A review of 150 narcoleptic patients at Stanford indicated that 110 had attacks lasting 1 min or less, 25 had attacks lasting between 1 and 5 min, 10 reported attacks lasting between 5 and 10 min, and 5 reported attacks lasting between 10 and 20 min. In fact, a single patient may have attacks of different duration at different times. It is thought that very long cataplexy attacks may represent a combination of cataplexy, and the abnormal appearance of rapid eye movement (REM) sleep.

There is a great variation in the frequency of attacks over the life span of a narcoleptic patient. In general, the frequency is highest right after the symptom's first appearance (typically, anywhere between the ages of 15 and 30 years), around the time the other symptoms of the narcolepsy syndrome appear (Anic-Labat *et al.*, 1974). A survey of our 150 narcoleptics during the first 2 years after the appearance of cataplexy indicated that 4% had fewer than one

attack per week, 21% had fewer than one attack per day but more than one per week, 69% had between one and four attacks per day, and 6% had more than four daily attacks. Over time, most narcoleptics report a decline in the frequency of attacks, usually beginning around 10 years after the first appearance of the symptoms. This decline may be partially attributed to patients' increased ability to avoid emotional situations or to "harden" themselves against them. Indeed, subjects have often commented that their personality changes due to their cataplexy. Attacks may increase again in frequency during menopause or periods of grief, particularly in elderly patients with the loss of a loved one.

It is typical for narcolepsy–cataplexy to develop during the second decade. In one report, 51 prepubertal children (29 boys) (Guilleminault *et al.*, 1998) were reported with narcolepsy syndrome and 26 of them had an abrupt fall as the first symptom. This indicates that cataplexy, even if uncommon, may be seen early in life, during the same age range when atonic seizures are seen. In 29 cases, the first suspected diagnosis was epilepsy, even after clinical evaluation by specialists, and EEGs were performed long before clinical questions of sleep disorders were asked. The several features that enhance the clinical diagnosis of cataplexy are discussed next.

TRIGGERING FACTORS

Cataplexy is usually triggered by emotions. A survey (Anic-Labat, 1998) of 300 narcoleptics indicated that laughter, feelings of amusement, or being "tickled by oneself, repartee, or a joke" induced cataplexy in 93% of the patients. Other emotions found to trigger cataplexy include anger (90% of patients), excitement and elation (82%), surprise (61%), athletic activities with an emotional content, such as winning or hitting a good shot (60%), elation (59%), "response to a call for action" (38%), sexual intercourse (37%), and embarrassment (36%). Surprisingly, driving an automobile was reported to trigger cataplexy in less than 1% of the patients. Sleepiness and tiredness was cited as a trigger in 50% of the patients, and 36% of the patients said that in some attacks they could not identify the immediate trigger. A given individual usually reports several different triggers over time.

A self-administered questionnaire was validated on 983 subjects who consulted a sleep disorder center (Anic-Labat, 1998). This questionnaire included 51 cataplexy-related items. Responses to the items were composed between subjects with clear-cut cataplexy ($n = 63$) and all other patients ($n = 920$). Nonnarcoleptic subjects were found to experience muscle weakness with various intense emotions (1.8–18%) or athletic activities (26.2–28.8%). Factor analysis and Receiver Operating Characteristics Curve Analysis were used to determine the most predictive items for clear-cut cataplexy. Cataplexy was best differentiated from other forms of muscle weakness when triggered by three typical situations: when hearing or telling a joke, while laughing, and when angry.

DISTRIBUTION OF THE MUSCLE WEAKNESS

In very young children, abrupt and complete falls may occur. In children younger than 6 years of age, bruises associated with these falls were commonly noted (Guilleminault, 1998). Attacks were also partial and abrupt loss of tone of the limbs, the parts of the body most noted by parents, because they were often associated with dropping of objects. However, the existence of dropping of objects as a marker of the part of the body involved may have biased against the recognition of weakness of the head or another part of the body.

In older subjects, the analysis of a questionnaire (Anic-Labat, 1998) revealed that cataplexy manifestations frequently involved the face and the jaw. Surprisingly, muscle tone loss indicating frequent unilateral partial cataplexy was only marginally significant.

ABRUPTNESS OF THE ATTACK

It is characteristic to emphasize the abruptness of atonic seizures and the risk of frequent injury due to falls. However, in young children, the speed of fall may not allow one to distinguish cataplexy from drop attacks related to an atonic seizure.

Bruises are also common in children with cataplexy. Compared with non-negative phenomenon drop attacks, cataplectics of all ages had a greater risk of injuries. Subjects were often able to break their fall with their arms and slowly collapsed to the floor, succeeding in partially breaking the fall and avoiding injury.

REFLEXES DURING THE ATTACK

Normal tendon reflexes in the region affected by muscle atonia are abolished during cataplexy. H- and T-reflexes have been systematically investigated. The H-reflex was elicited by percutaneous electrical stimulation of the tibial nerve in the popliteal fossa using rectangular 1-ms shocks at a rate of one every 1–3 s. The amplitude of the reflex was monitored with a surface electrode placed on the distal third of the leg.

The maximum H-response (H-max) was obtained and adjustment to H-max/2 (one-half the maximum response) was calculated. During generalized attacks, the H-reflex was abolished but then returned to normal at the end of the attack. Increased intensity of stimulation from H-max/2 to H max had no effect on the elicitation of the reflex. T-reflexes were also abolished. During partial attacks involving the jaw and shoulder, the H-max/2 reflex was very briefly abolished, but a significant decrease was noted during the course of the attack (Anic-Labat, 1974). Thus, monosynaptic (H) and polysynaptic reflexes are abolished during cataplexy and return to normal at the end of the attack.

ASSOCIATED SYMPTOMS

Cataplexy can precede the appearance of the other symptoms of the narcolepsy syndrome by months or even years. Most commonly the other symptoms are seen preceding the appearance of cataplexy or occur concomitantly with its development. The most common symptom is daytime sleepiness. Initially it may be referred to as hypersomnia, tiredness, and fatigue; however, over time, the hypersomnolence becomes apparent, with the need to take short naps in the daytime to maintain vigilance to perform adequately at work or at school. Hypnagogic hallucinations, sleep paralysis, and automatic behavior are not pathognomonic of narcolepsy. They are seen in association with other sleep disorders and are also noted in the general population.

Human Leukocyte Antigen Markers and Narcolepsy

By following up the work of the Japanese researchers led by Honda *et al.* (1983); Honda and Juji (1998) and by using the multiracial U.S. population, it was demonstrated that susceptibility to narcolepsy–cataplexy is very closely linked to a subtype of human leukocyte antigen (HLA)-DQwI, DQB1-0602, which is most commonly associated with DQAI–0102. This DQw1 subtype is normally seen with DRw15 (DR2) in Japanese and most Caucasians, but 30% of the African-American population is DRwl5 negative. We also demonstrated that certain Caucasians (sporadic and familial cases) not only are DRwl5 negative but also do not present with DQBI-0602 and DQAI-0102. This suggests a genetic heterogeneity in the appearance of the narcolepsy syndrome, even if these individuals are rare (Mignot *et al.*, 1997).

In summary, even if the presence of HLA DQ1 (DQ beta 1-0602) is neither necessary nor sufficient to confirm narcolepsy, its presence in association with cataplexy is a reinforcing factor in favor of the diagnosis.

Multiple Sleep Latency Test

The multiple sleep latency test (MSLT) is performed following nocturnal polysomnography, a standardized test, which consists of five naps lasting 20 min each, performed at 2-h intervals. The presence of short sleep latencies (i.e., mean <8 min), and sleep onset rapid eye movement (REM) (i.e., within 15 min of sleep onset) during at least two naps of the MSLT also confirm the diagnosis of narcolepsy, in association with a history of episodes of cataplexy.

PATHOPHYSIOLOGY OF CATAPLEXY

The muscle atonia seen in cataplexy is the result of postsynaptic hyperpolarization of the spinal cord motor neurons, with active inhibition of muscle tone (Glen *et al.*, 1978). The spinal cord makes no essential contribution to the muscle atonia of cataplexy or normal REM sleep. Lesions of the ventral quadrant of

the spinal cord, especially the ventrolateral funiculus corresponding to the ventrolateral reticulo spinal tract, inhibit muscle atonia. Because there is a strong analogy in man and dog between cataplexy and the muscle atonia seen during normal REM sleep, it may be that similar final pathways are involved. Siegel (1985) has shown in the cat, using transection experiments and cellular unit activity recordings, that pontine and medullary mechanisms are needed to produce muscle atonia. If transection is made at the pontomedullary junction, no muscle atonia is seen, while in midbrain decerebrate cats, complete bilateral inhibition of the antigravity muscles is seen. Therefore, pontine mechanisms contribute to medullary induction of atonia.

It has been shown that chemical destruction of the locus ceruleus α (LCα) and the perilocus ceruleus α (peri-LCα) neurons with local injections of kainic or ibotenic acid result in permanent abolition of muscle atonia and REM sleep (Sakai, 1985). Thus, the dorsolateral pontine tegmentum seems to be involved in the muscle atonia of REM sleep. LCα and peri-LCα appear to contain cholinergic neurons and receive noradrenergic afferents from the LC complex.

In summary, while we understand that the central neurological defects responsible for cataplexy ultimately impact the spinal cord motor neurons, causing hyperpolarization and active inhibition of muscle tone, investigations of receptors in the brains of narcoleptic humans and dogs have yet to fully explain the etiology of the disease.

PHARMACOLOGICAL MANIPULATIONS IN CATAPLEXY

Several compounds have been administered intravenously (i.v.) during H-reflex studies and during long-term investigation of cataplexy in humans; more sophisticated studies have been performed using animal models, particularly narcoleptic–cataplectic Dobermans (Delashaw *et al.*, 1979; Foutz *et al.*, 1981; Mignot *et al.*, 1988).

The effects of REM sleep-modulating agents and tricyclic antidepressant compounds have been investigated. Compounds with norepinephrine and serotonin reuptake-blocking properties have been shown to suppress cataplexy in man. The most potent were compounds combining norepinephrine and serotonin reuptake-blocking properties with atropinic effect. Drugs such as protriptyline, imipramine, and clomipramine were shown to significantly reduce cataplectic attacks. Atropine i.v. injections reversed cataplectic attacks in humans, and more specific reuptake blockers—such as viloxazine, a specific norepinephrine reuptake blocker, and fluoxetine, a serotonin reuptake blocker—were shown to suppress cataplexy without inducing the atropinic side affects (e.g., impotence) often seen with tricyclic antidepressants with anticholinergic properties. Earlier studies had also shown that levadopa (L-dopa), a precursor of dopamine, might have an effect on cataplexy.

The fact that clomipramine and, to a lesser extent, fluoxetine suppress cataplexy shed light on the neurochemical control of cataplexy. Progressively, it was shown in humans that both drugs have active metabolites: desmethylclomipramine and norfluoxetine (Nishino *et al.*, 1993). These active metabolites strongly inhibit norepinephrine reuptake. This finding, associated with the findings that amphetamine and the amphetamine drugs that act presynaptically to release norepinephrine, improve cataplexy, and viloxazine, a norepinephrine blocker without serotonin activity, also controls human cataplexy, suggests the involvement of a norepinephrine synapse.

More specific pharmacological studies have been performed in Doberman pinschers. First, we documented that nicotinic cholinergic stimulation had no effect on muscle atonia (Delashaw *et al.*, 1979). However, muscarinic cholinergic stimulation with arecoline and physostigmine salicylate, an anticholinesterase with a short biological half-life, increases cataplexy in Dobermans, while cholinergic blockade using atropine sulfate or scopolamine hydrobromide, compounds which cross the blood–brain barrier, eliminates the symptom (Delashaw *et al.*, 1979). Methyl atropine and methyl scopolamine, which do not cross the blood–brain barrier, are completely ineffective.

In conjunction with these pharmacological investigations, a comparison of the muscarininc receptors in different parts was carried out (Kiliduff *et al.*, 1986). The comparison revealed that M2 subtype muscarinic receptors are upregulated in the pontine reticular formation of narcoleptic dogs, more particularly in the nucleus reticularis pontis caudalis, the nucleus reticularis giganto cellularis, and the interpenducularis. Further studies demonstrated that the norepinephrine reuptake blocker nisoxetine also had a strong effect on canine cataplexy. These findings suggest the possibility of the involvement of a neurotransmitter other than norepinephrine, as well as the involvement of a second synapse.

To resolve this issue of serotonin activity, a specific investigation of serotoninergic reuptake inhibition properties was performed (Nishino *et al.*, 1993). Fluoxetine, zimelidine, clomipramine, and amitriptyline were investigated in the animal model; and their activity was compared with that of their active desmethyl metabolites: norfluoxetine, norzimelidine, desmethylclomipramine, and nortriptyline. These active metabolites more potently block adrenergic uptake and more potently suppress cataplexy. These results demonstrated that anticataplectic potency is positively correlated with adrenergic reuptake inhibition and negatively correlated with serotoninergic uptake inhibition. These studies provide further support for the concept that the adrenergic system is the main monoaminergic system involved in the regulation of cataplexy and that muscarinic cholinergic and adrenergic synapses are involved in the pathway responsible for the symptom.

To distinguish the roles of the different norepinephrine receptor subtypes, selective studies of alpha- and beta-adrenergic compounds were performed. Central beta-1 and beta-2 adrenergic receptors were found not to play a significant

role in the muscle atonia, but alpha-1 adrenergic compounds were very active. Prazosin, an alpha-1 antagonist, significantly worsened canine cataplexy. This same compound, used as an antihypertensive agent in human narcoleptics, also significantly worsens cataplexy. Further investigation demonstrated that there are at least two alpha-1 receptor subtypes, classified as alpha-1a or alpha-1b. Drugs with a high affinity for alpha-1b receptors, such as Prazosin and phenoxybenzamine, were found to increase cataplexy, while alpha-1b agonists reduced the attacks (Mignot *et al.*, 1988; Fruhstorfer *et al.*, 1989; Nishino *et al.*, 1993).

The alpha-2 adrenergic system has also been investigated (Fruhstorfer *et al.*, 1989). Alpha-2 agonists were found to increase cataplexy, while alpha-2 antagonists such as yohimbine reduced the symptom. However, treatment of human narcolepsy with yohimbine in a double blind study we performed did not demonstrate positive results. Also, the effect of yohimbine in canine cataplexy seems transitory. Alpha-2 receptors are located pre- and postsynaptically, but results to date suggest the presynaptic alpha-2 receptors are more actively involved in cataplexy. Analysis of brain tissue from narcoleptic and control dogs showed a general increase in catecholamine in the narcoleptic dog brain. Further chemical studies revealed a higher concentration of dopamine D2 receptors in discrete regions, particularly the amygdala, of cataplectic dogs (George *et al.*, 1964).

In interpreting these findings, it must be remembered that receptors may be pre- or postsynaptitic and that several synapses may be involved in muscle atonia; that is, there must be a descending pathway associated with normal REM sleep muscle atonia. Muscarinic cholinergic and catecholaminergic systems—especially cholinergic and adrenergic systems undoubtedly play a role in human and canine cataplexy, although how they interact remains unclear.

Pharmacological coadministration experiments were performed to investigate the interaction of cholinergic and adrenergic systems. Pretreatment with muscarinic cholinergic antagonists such as atropine sulfate or scopolamine hydrobromide, followed by administration of the alpha-1b antagonists prazosin, block the effect of Prazosin and improve canine cataplexy. This suggests that the cholinergic muscarinic synapse is farther down on the descending pathway, impinging on the spinal cord motor neurons involved in cataplexy.

Some investigations were performed at Stanford involving dialysis and *in situ* injection. George *et al.* (1964) showed that injections of carbachol, a cholinergic agonist, into the pontine tegmentum of the cat produce abrupt muscle atonia, with development of the REM and pontogeniculooccipital waves seen during REM sleep. Injection of carbachol into the pontine reticular formation induced status cataplecticus in our cataplectic Dobermans. Acetylcholine release in the same region confirmed the previous pharmacological studies. Still, the pontine reticular formation is not the only muscarinic cholinergic region in the central nervous system, and our pharmacological investigations support the existence of a multisynaptic descending pathway involved in the muscle atonia of cataplexy.

The basal forebrain muscarinic cholinergic system (nucleus basalis, substantia-innominata, diagonal band, and medial septum) is linked to the limbic (emotional) system and sends and receives information to and from the entire cerebral cortex, the thalamus, and the limbic system. Injection of carbachol into the basal forebrain of cataplectic dogs induced status cataplecticus with very long-lasting muscle atonia, while atropine sulfate reduced cataplexy. Such injections had no effect on muscle tone of control dogs, but increased (at the same dosage) alertness. Bilateral injection (compared with unilateral injection in cataplectic dogs) of a much higher dose (50 versus 10 nmol in cataplectic dogs) of carbachol finally induced muscle atonia of abrupt onset in control dogs. These findings suggest that a hypersensitivity of the muscarinic cholinergic system exists in different parts of the cataplectic dog brain. The hypersensitivity of this system is, as mentioned, directly linked to the limbic system, which is known to be involved in the control of emotions.

CONCLUSION

Cataplexy, a negative motor phenomenon, may be the first symptom of narcolepsy. The syndrome has a prevalence that varies, depending on the study between .03 and .06%. It must be recognized, particularly in young children, and must always be considered in the differential diagnosis of atonic seizures.

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16

VIDEO ELECTROENCEPHALOGRAPHY AND POLYSOMNOGRAPHY

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INTRODUCTION

The relationship between epilepsy and sleep was recognized in antiquity by both Hippocrates and Aristotle. The systematic study of the occurrence of seizure in relation to the sleep–wake cycle has been reported since the end of the nineteenth century (Gowers, 1885; Fere, 1890). In the latter half of the twentieth century, Janz (1962) popularized the term *sleep epilepsy*, referring to those patients whose seizures were restricted to sleep. Parasomnias refer to a group of disorders that originate from sleep and are characterized by prominent motor phenomena and associated autonomic nervous system changes. Clinically, there is a group of patients who present with paroxysmal events occurring in sleep, characterized by motor phenomena or unusual behaviors that are features common to both epileptic seizures and parasomnias. In addition, on rare occasions, psychogenic disorders may also mimic these paroxysmal events. A clinical description is often insufficient to distinguish one disorder from another. Therefore, use of combined video electroencephalography (EEG) and polysomnography (PSG) has proved invaluable. The ability to simultaneously study the clinical semiology of the event, define the associated sleep stage or arousal, and also have a comprehensive recording of the EEG patterns often supplies ample information to make a definitive diagnosis.

EPILEPSY

There are several types of epilepsy in which the seizures occur predominantly during sleep or are restricted only to sleep. These include benign focal epilepsy of childhood and frontal lobe epilepsy (FLE), particularly those patients with supplementary sensorimotor area (SSMA) seizures. Also included in this group are certain patients with idiopathic generalized epilepsy. When seizures occur only during sleep, they may often be confused with parasomnias.

BENIGN FOCAL EPILEPSY OF CHILDHOOD

The syndrome of benign focal epilepsy of childhood, also referred to as benign rolandic epilepsy or benign childhood epilepsy with centrotemporal spikes,

is a common form of childhood epilepsy. The children are of normal intelligence, have a normal neurological examination, and present with sleep-related seizures. Approximately 75% of the seizures occur during sleep (Lerman and Kivity, 1975; Loiseau *et al.*, 1973). The seizures are focal motor (usually involving the face and arm), present with oropharyngeal sensorimotor phenomena, or are generalized tonic–clonic in nature. The oropharyngeal seizures manifest as hypersalivation, guttural sounds, and mouth movements and at times sensations in the mouth (dryness or prickling tongue sensation). The interictal EEG is characterized by sharp waves with a stereotyped morphology and typically has a distribution in the centrotemporal region (Lombroso, 1967).

FRONTAL LOBE EPILEPSY

Patients with FLE may present with one of three distinct clinical seizure types: (1) asymmetrical tonic seizures (SSMA), (2) focal motor seizures, and (3) complex partial seizures (Salanova *et al.*, 1995). Patients with SSMA seizures frequently have asymmetrical tonic involvement of the extremities, at times assuming a typical fencing posture. There may be associated vocalization, thrashing movements, and kicking with preserved responsiveness. The seizures are usually brief in duration, less than 30 s, and arise from the mesial surface of the superior frontal gyrus in the SSMA. Complex partial seizures of frontal lobe origin are characterized by unresponsiveness at the onset of the seizure with prominent automatisms consisting of repetitive arm movements, bipedal movements, whole body movements, bilateral arm tonic activity, and version of the head and eyes. The seizures of frontal lobe onset frequently occur in sleep and at times tend to occur in clusters. In a review of SSMA seizures in patients evaluated in the Epilepsy Monitoring Unit at the Cleveland Clinic Foundation, 65% of the seizures recorded were from sleep (Anand and Dinner, 1997).

There is a group of patients with a familial occurrence of seizures of frontal lobe onset that has been described, referred to as autosomal dominant FLE (Scheffer *et al.*, 1995). The seizures usually begin in childhood and persist throughout life. The neurological examination and imaging in these patients is normal.

GENERALIZED EPILEPSY

There is a small group of patients who present with generalized tonic–clonic seizures restricted to sleep. This has been referred to as pure sleep epilepsy (Young *et al.*, 1985; Gibberd and Bateson, 1974; Park *et al.*, 1998). In the study by Park and colleagues (1998), the patients with sleep-related generalized tonic–clonic seizures demonstrated an excellent response to antiepileptic drugs (AEDs) with 81% becoming seizure free. These results are similar to those of other patients with idiopathic generalized epilepsy. The occurrence of diurnal seizures in this group of patients was extremely rare, 4.8%.

Tonic seizures occur most often in childhood but onset can also occur in adulthood. They occur primarily in sleep, always non-rapid eye movement

(NREM), last 10 s on average, and can involve axial, proximal, and distal muscles. When the abdominal or respiratory musculature is involved, the resulting brief respiratory disturbance may cause an apnea. There can also be associated autonomic changes including increased blood pressure, tachycardia, dilatation of the pupils, and flushing of the face.

PARASOMNIA

The parasomnias refer to clinical disorders consisting of undesirable physical phenomena that occur predominantly during sleep (DCSC, 1990). They have been classified based on the stage of sleep from which they originate. They include both normal and abnormal phenomena. Included in the category of NREM parasomnias are hypnic jerks and hypnic imagery, considered to be normal, in addition to confusional arousals, sleep terrors (pavor nocturnus), and sleepwalking (somnambulism), referred to as disorders of arousal. These all originate from deep NREM sleep, stages 3 and 4. They are all common in childhood and decrease in frequency as age increases. These individuals tend to have a family history of similar disorders. REM parasomnias include nightmares and REM behavior disorder (RBD). A third group consists of disorders that may occur during any or all sleep stages and includes bruxism, enuresis, rhythmic movement disorder (including head-banging), sleep talking (somniloquy), and posttraumatic stress disorder. The following parasomnias may at times need to be considered in the differential diagnosis of seizures associated with sleep.

CONFUSIONAL AROUSAL

Confusional arousal is thought to be a partial manifestation of sleepwalking or sleep terrors. It is characterized by the individual arousing from sleep, usually in the first third of the night, and displaying features of confusion. The individual is disoriented and responds slowly and inappropriately to simple commands or questioning. The episode may be precipitated by factors that increase deep sleep including sleep deprivation with rebound and circadian rhythm disturbance (shift work and jet lag). PSG demonstrates these episodes occurring as arousals from deep NREM sleep.

SLEEPWALKING

Sleepwalking is fairly common in children (1–7%) and is also not rare in adults (2.5%) (Bixler *et al.*, 1979; Klackenberg, 1982). Sleepwalking may occur in an agitated fashion and may result in injury to the individual. Inappropriate behavior may occur, such as urinating in a closet. Sleep deprivation and conditions causing sleep disruption such as obstructive sleep apnea may be associated with sleepwalking. PSG again demonstrates the onset of this disorder from stage 75% NREM sleep.

SLEEP TERRORS

Sleep terrors are characterized by arousal from sleep with inconsolable crying, associated autonomic activation and intense fear. This parasomnia usually occurs in prepubertal children. PSG demonstrates the episodes originating as arousal from stage 75% NREM sleep, usually in the first third of the sleep time, associated with prominent tachycardia.

RAPID EYE MOVEMENT BEHAVIOR DISORDER

RBD is characterized by the emergence of prominent motor activity from sleep, associated with dream content (Schenck and Mahowald, 1990). The motor activity is often violent including punching, kicking, or running from bed with resultant injury to the patient or bed partner. The individual usually is acting out his or her dreams or nightmares. The PSG may demonstrate the presence of augmented electromyographic (EMG) tone during REM sleep. The motor phenomena such as kicking or punching activity, if recorded, occur during the REM state.

PSYCHOGENIC SEIZURES

Psychogenic seizures usually manifest during the individuals' daytime waking hours. However, on rare occasions individuals may present with paroxysmal events restricted to the sleep period. Video recording of such patients demonstrates that the patient awakens from sleep and the EEG demonstrates a normal waking EEG pattern prior to and during the time of the recorded paroxysmal event. In addition to the normal EEG pattern during the ictus, the clinical features of the psychogenic seizure often allow one to identify these events as being nonepileptic in nature.

VIDEO ELECTROENCEPHALOGRAPHY–POLYSOMNOGRAPHY

As mentioned earlier, paroxysmal events in sleep characterized by prominent motor activity or complex behavior may represent manifestations of epileptic seizures or sleep disorders and on rare occasions psychogenic seizures. Frequently, it may be difficult to make a definitive clinical diagnosis based solely on the history. In this situation, video EEG–PSG may prove extremely valuable in defining the nature of the paroxysmal events. If one of the recurrent episodes is recorded, careful analysis of the clinical semiology may allow one to determine if the event is consistent with epileptic seizure, parasomnia, or psychogenic seizure. However, at times, the exact nature of the episode may prove very difficult to distinguish solely on the basis of the clinical features. Simultaneous recording of the EEG may demonstrate associated ictal epileptiform

activity, allowing one to identify the epileptic nature of the recorded behavior. This is particularly true for seizures originating from the supplementary sensorimotor area that may be characterized by bilateral extremity and truncal thrashing movements and vocalizations associated with preserved consciousness.

In the evaluation of these episodes, because of the absence of associated changes in the EEG recording, these episodes were initially thought to represent a sleep disorder, which was termed nocturnal paroxysmal dystonia (Lugaresi *et al.*, 1981). However, it was later recognized that these patients with nocturnal paroxysmal dystonia were in fact patients with SSMA seizures with the ictal EEG activity restricted to the mesial aspect of the superior frontal gyrus and thus frequently not seen in the scalp EEG recordings (Bleasel and Morris, 1997). There may be prominent EMG activity during the seizures, which may obscure the EEG tracing, making it difficulty to discern the presence of any associated ictal EEG pattern. Frequently, the ictal EEG may be characterized by low-amplitude, fast activity, restricted to the vertex region, making it difficult to recognize. Utilization of a transverse montage may facilitate the recognition of this ictal pattern. At times, these patients have also been misdiagnosed as having psychogenic seizures because of the presence of prominent asymmetrical motor activity in conjunction with retained consciousness without any recognized changes in the EEG recording.

In a study of the diagnostic value of video EEG–PSG, Aldrich and Jahnke (1991) reviewed their experience with 122 patients who presented with suspected parasomnias and subsequently underwent video EEG–PSG monitoring (Table 16.1). The patients were divided into three groups. Group I consisted of 59 patients presenting with prominent motor activity without a prior diagnosis of epilepsy. Group II consisted of 27 patients presenting with minor motor activity without a prior diagnosis of epilepsy. Group III, 36 patients with known epilepsy, had unexplained movements occurring in sleep. Table 16.1 displays the patients evaluated. The video EEG–PSG study resulted in a definitive diagnosis being made in 43 (35%) of the 122 patients. It is interesting that approximately half the patients with motor events in sleep had a final diagnosis of epileptic seizures, while approximately half were given a diagnosis of a parasomnia. It is also important to note that three patients were diagnosed as having psychogenic seizures. The video EEG–PSG studies supported a specific diagnosis of epilepsy, parasomnia, or psychogenic seizures in another 37 (30%) of patients. The studies were inconclusive in 42 (34%) of the 122 patients.

We have reported on a group of six infants and children who presented for evaluation of apnea and in whom a combined video EEG–PSG study was performed (Kotagal and Dinner, 1991). In three of the six patients, the apnea represented a manifestation of an epileptic seizure. Zucconi and colleagues (1997) reported on two adults who presented with a history of awakening from sleep with a sensation of choking and abnormal motor activity as well as daytime sleepiness, and who had been previously diagnosed with obstructive sleep apnea. These patients underwent video EEG–PSG and were found to have

TABLE 16.1 Patients Evaluated with Video EEG–PSG

Group	I	II	III	Total
No. of patients	59	27	36	122
Studies leading to definitive Dx	18	8	17	43 (35%)
Epilepsy	4	1	15	20
Parasomnias	13	6	1	20
Psychogenic	1	1	1	3
Studies supporting specific Dx	23	3	11	37 (30%)
Epilepsy	3	1	8	12
Parasomnias	19	1	3	23
Psychogenic	1	1	0	2
Inconclusive studies	18	16	8	42 (34%)

Modified from Aldrich and Jahnke, 1991.

frontal lobe seizures that were responsible for the sleep disruption with only mild associated apnea. The presence of the FLE had not previously been diagnosed and further supports the value of combined studies. These two reports underline the value of combined studies in a select group of patients who present with a history of sleep-related breathing disorders.

In a published study from our institution, Foldvary *et al.* (2000) discussed their results comparing among other things, the ability to recognize arousals and seizures based on the number of EEG channels as well as paper speed. In a blinded EEG analysis, comparing 4, 7, and 18 channel montages at 10 and 30 mm/s, the overall sensitivity for seizure (temporal or frontal) or arousal detection ranged from 70% (4-channel montage at 10 mm/s) to 81% (both 7 and 18 channel montages at 30 mm/s). In total, the readers were able to correctly identify 77% of the events, arousals being more easily recognized (88%) than seizures (74%). Although other factors contributed to the overall results, the study affirms that accuracy was improved with increased numbers of EEG channels.

TECHNICAL ASPECTS

Following is a description of some of the physiological parameters used in combined EEG–PSG.

ELECTROENCEPHALOGRAPHY

The EEG is an integral part of any monitoring. Sleep staging can generally be performed using one or two channels of EEG, recording from the central regions, C3 or C4. However, use of the entire 10–20 system is essential when

seizures are a part of the differential diagnosis. In addition, the ability to record a complete bipolar, referential, or transverse montage can prove invaluable when the differential diagnosis includes seizures versus parasomnias. When a digital EEG system is employed, this is easily accomplished because the montages can be reformatted to display the EEG in a manner that optimizes the visualization of the temporal or the vertex regions. As is shown in Case No. 2, a seizure can oftentimes be completely obscured using one montage, yet becomes perceptible and often quite clear when utilizing another. Also, the ability to apply filtering after acquisition with digital EEG may improve one's ability to interpret underlying EEG activity. Alternately, we are frequently in a position to exclude a seizure as a diagnosis. The ability to apply a variety of montages in the evaluation of a recorded event can help make that classification easier as well. Application of silver–silver chloride or gold disk electrodes with collodion has proven reliability. Impedances should not exceed 5 kiloohms (K Ω), and filtering systems should not attenuate signals between .5 and 70 Hz. The standard chart paper speed for EEG is 30 mm/s; however, 10 mm/s is usually used with PSG. Clearly, the ability to change paper speed during the review process, as allowed with most digital systems, is the ideal.

ELECTROOCULOGRAPHY

The electrooculogram (EOG) is the second parameter necessary for differentiating sleep stages, and at least two channels are the recommendation. Electrodes can be placed 1 cm lateral to and above one outer canthus, while a second is placed 1 cm lateral to and below the contralateral outer canthus. By referencing these electrodes either to one or to both ear or mastoid electrodes (A1, MN1), horizontal, vertical, and oblique eye movements can all be recorded. If the need arises to distinguish lateral from vertical movements (e.g., lateral eye movements of REM sleep), a supranasion electrode can be referenced. A low-frequency filter setting of .1 Hz (or a time constant of .3 s) results in a well-defined signal.

ELECTROMYOGRAPHY

Submental EMG is the third physiological parameter used to determine sleep staging. One channel is sufficient, usually consisting of two electrodes placed submentally and referenced to one another. This would also allow the use of one of these electrodes to later be referenced to either ear electrode (A1 or A2) should the other become detached during the recording. Using a low-frequency filter setting of 10 or greater eliminates unwanted slow-frequency artifacts while allowing muscle activity to be recorded provided the high-frequency filter is set at 70 Hz. The sensitivity can be adjusted while the patient is awake, with 2 μv/mm as a standard setting. The chin EMG decreases as the patient enters into NREM sleep and progressively decreases as the depth of NREM sleep increases. EMG dramatically decreases in REM sleep. EMG activity can also

prove helpful as a measure of muscle tone when seizures are a part of the differential diagnosis, specifically tonic, clonic, or atonic. The recorded EMG shows an increase in tone with tonic or clonic seizures, while an atonic seizure conversely shows decreased EMG activity. It can also be beneficial to use additional EMG electrodes when the clinical description of the events to be recorded is available. If particular movements have been described, placing electrodes to record this muscle activity may help more precisely correlate it (or not, as the case may be) with the EEG activity occurring simultaneously, such as with a focal motor seizure involving the arm. In the case of RBD a full complement of both flexor and extensor electrodes placed on bilateral upper and lower extremities is the recommendation (Schenck and Mahowald, 1996).

ELECTROCARDIOGRAPHY

Electrocardiography (EKG) is another useful parameter routinely utilized in both standard EEG and PSG recordings. Changes from the baseline can be indicative of certain scenarios. Bradycardia or even asystole can suggest apnea. Tachycardia may occur with seizures and certain parasomnias such as sleep terror.

Gold disk electrodes as well as a number of disposable "snap electrodes" all have been shown to provide an excellent signal. A single channel is usually sufficient, with the potential recorded between two electrodes placed for this purpose or with a single electrode referenced to an already existing placement, such as an ear electrode (A1 or A2). Additional electrodes should be placed and available for use should this become necessary. Placement of the electrodes should be carefully documented whether using thoracic, abdominal, or even arm or leg positions. Frequently, a chest or shoulder electrode referenced to any one of several available intercostal electrodes allows a sufficient signal. Amplification of the EKG signal is usually one-tenth of the EEG signal and a similar filter range of 1–70 Hz can suffice.

RESPIRATION

The measurement of airflow and respiratory movement has become standard practice for the recording of all PSG. It is, of course, essential in the diagnosis of apnea as well as hypopnea or respiratory pauses. There is also a known association between these as well as other breathing disturbances and a variety of other sleep-related conditions, such as parasomnias and seizures. Air exchange is commonly monitored using a thermistor or thermocouple, simultaneously recording both nasal and oral airflow. Nasal pressure transducers are an alternative method. Respiratory movement or effort can be recorded in a variety of ways. The use of intercostal electrodes, abdominal and thoracic strain gauges, and abdominal and thoracic belts all have proven to be dependable. The use of pulse oximetry to monitor blood oxygen levels collects vital information concerning the severity of any recorded desaturations.

CASE EXAMPLES

The utilization of video EEG or video PSG is oftentimes the only way to accurately make a diagnosis. Through the use of an adequate number of EEG channels, alone or in conjunction with various other physiological parameters, and with the additional data observed from videotape, an accurate diagnosis can frequently be reached. Following are several examples of patients seen in our clinic for whom it was necessary to collect all these data before we could arrive at an accurate diagnosis.

CASE NO. 1

Patient No. 1 was a 29-year-old female referred for a complaint of nocturnal spells. These began 2 years prior to this evaluation; however, the patient was known to have had episodes of both somnambulism and somniloquy as a child. The current events were noted by her family to be different.

The events usually occurred between 3:00 and 5:00 A.M. and lasted approximately 10 min. The episodes would begin stereotypically with the patient gasping for air saying, "I can't breathe," with her hands clasped to her chest. During the episodes the patient might rearrange furniture, pull out electric plugs, or get a drink from the faucet, sometimes leaving the water running. She was known to have been incontinent of urine on two occasions. It was impossible to wake the patient during these episodes, and she remained amnestic of the events. She would only be aware that something had occurred because she would experience diffuse aching the following day.

The patient had additional complaints of excessive daytime sleepiness, multiple awakenings throughout the night, and loud snoring. However, no apneas had been witnessed. Her past medical history was significant for one episode of brief loss of consciousness during a motor vehicle accident.

Prior testing included a computerized tomography (CT) scan of the head and routine EEG, both reported as normal. She was given the diagnosis of seizures and placed on gabapentin, 100 mg bid, but had stopped this on her own when additional episodes occurred despite the medication. The patient underwent a combined overnight EEG and PSG with simultaneous video recording.

The standard 10–20 system of electrodes was placed, as well as additional electrodes to record EOG, EKG and EMG. Airflow, respiratory effort via thoracic and abdominal belts, and oxygenation were also recorded, as well as body position and snoring.

Two arousals were recorded during the study. Both occurred out of slow-wave sleep. The patient sat up in bed for less than a minute as though awake, then proceeded to lie back down. The EEG was characterized by rhythmic delta activity lasting from 10 to 30 s (Figs. 16.1 and 16.2). No epileptiform discharges were seen. The patient's EEG was interpreted as normal, specifically there were no epileptiform discharges during the entire recording. Other than these arousals her

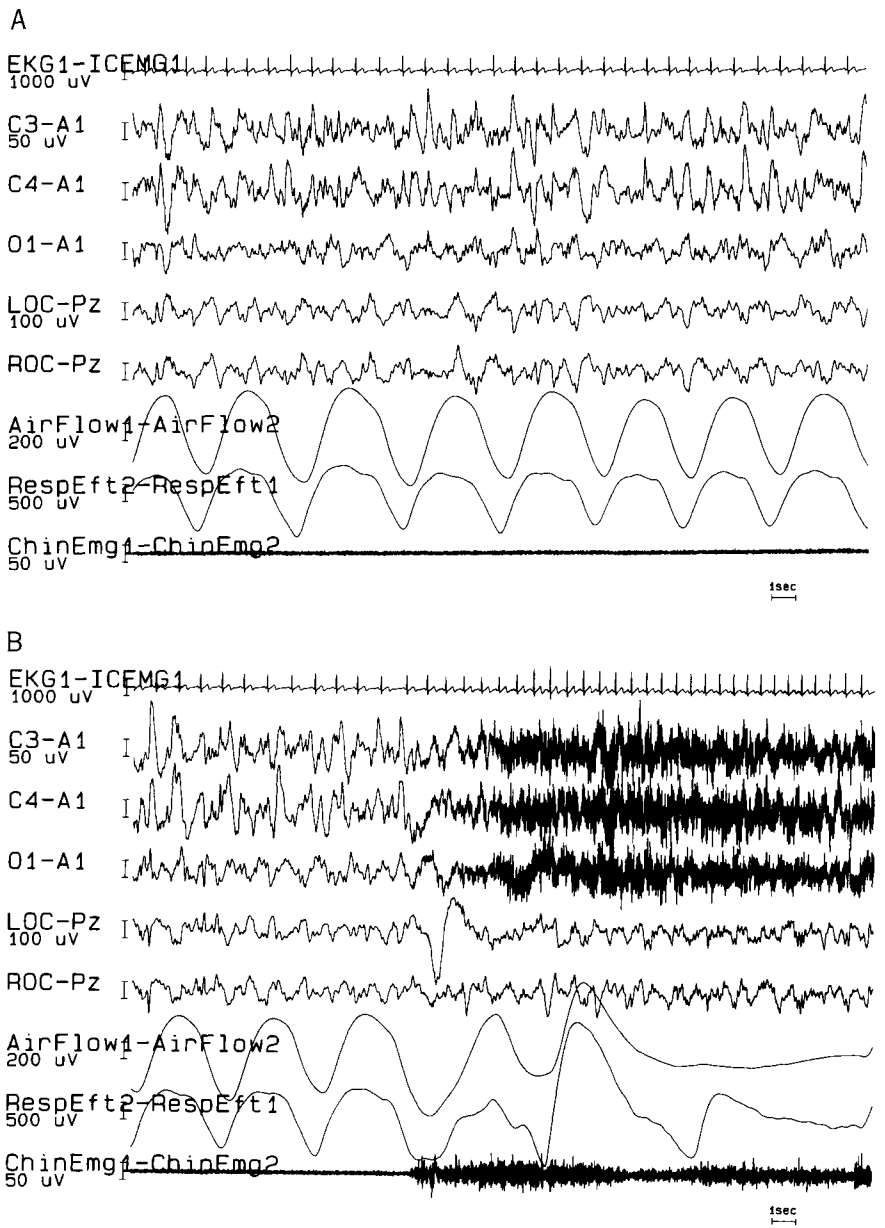


FIGURE 16.1 Patient No. 1 with an arousal from slow-wave sleep shown with a PSG montage in 30-s epochs. (A) Stage 3/4 sleep with high-voltage delta activity. (B) Demonstrates a clear arousal from slow-wave sleep with EEG obscured by EMG artifact and increased EMG in the submental leads.

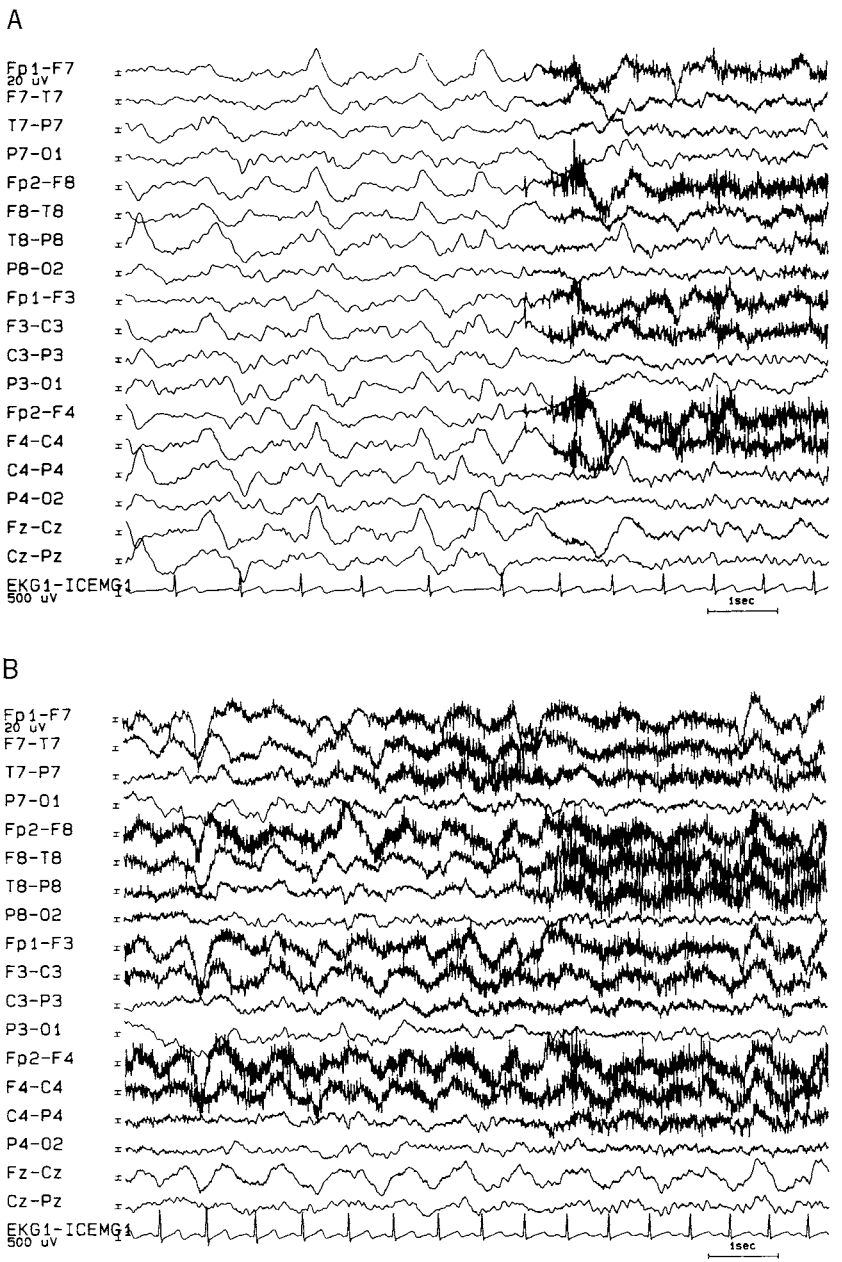


FIGURE 16.2 This demonstrates the arousal of Patient No. 1 with a clear representation of EEG during the arousal using 10-s epochs. (A) Bipolar EEG montage demonstrating slow-wave sleep, the epoch ending in an arousal. (B) Continuation of the arousal with a 6–7 Hz background evident and no apparent epileptiform activity.

PSG was unremarkable. The diagnosis based on the combined video EEG–PSG was of arousals from slow-wave sleep, consistent with a NREM parasomnia.

The patient was started on a trial of nortriptyline, 25 mg h.s. At follow-up 2 months later, the patient reported feeling much improved, alert in the daytime, sleeping better, and most importantly, having had no additional nocturnal events. Six months after the combined recording, the patient continues to remain without any nocturnal events.

CASE NO. 2

Patient No. 2 is a 25-year-old male referred for evaluation of two types of episodes, one of which occurred primarily at night. The first type consisted of brief episodes of staring during wakefulness with unresponsiveness for which the patient is amnestic. This behavior was new, and the frequency was unknown. The second type of event, which began at 5 years of age, occurring primarily in sleep, was described as shaking of the right arm and leg, followed by generalized shaking that often woke the patient from sleep. If these events occurred in the daytime, a stereotypical feeling of anxiety that lasted 30 s preceded them. There was also occasional altered sensation in the involved extremities. The patient stated that he never lost consciousness with these events, and that although brief, they occurred multiple times each day, often as many as eight.

His past medical history was significant for a left occipital skull fracture without loss of consciousness at the age of 4 years. He had no other risk factors for epilepsy. Prior testing had included CT, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, and single photon emission computed tomography (SPECT) scan, all thought to be essentially normal, as well as both EEG and PSG. The sleep study had shown moderate obstructive sleep apnea. Routine EEG had been read as normal. The patient had undergone a prior epilepsy workup, and while nine of these typical events had been recorded on video EEG, no EEG changes were observed. The patient had been treated unsuccessfully with a number of anticonvulsant medications to no avail, and was currently taking phenytoin and carbamezepine.

The patient underwent combined video EEG and PSG in hopes of further defining these spells. The 10–20 system of electrodes was placed, as well as additional physiological parameters of the standard PSG. Two of the patient's typical events were recorded. Both involved facial grimacing and right upper extremity tonic posturing, followed by generalized complex motor movements (back arching and pelvic thrusting). Although the interictal EEG remained normal, EEG during these events showed low-voltage, generalized fast activity followed by rhythmic alpha and then sharply contoured theta activity in the left centroparietal region (Figs. 16.3 and 16.4). The PSG again showed mild obstructive sleep apnea as well as a short REM latency.

The combined study confirmed a diagnosis of left FLE.

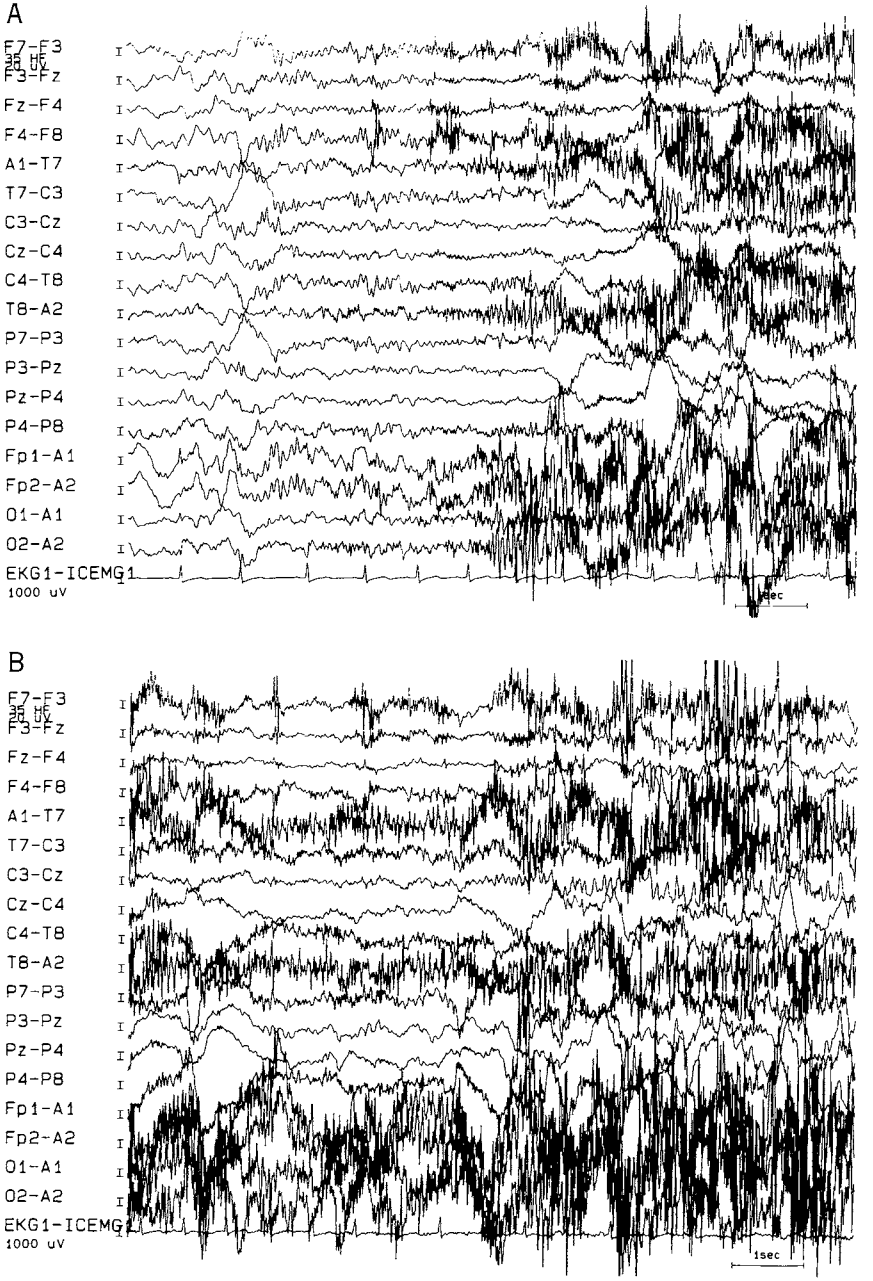


FIGURE 16.3 EEG recording of the focal motor seizure recorded in Patient No. 2. (A) Stage 2 sleep with an arousal using a transverse EEG montage in a 10-s sample. Diffuse low-amplitude beta activity maximal in the parasagittal region can be seen beginning in the third second. (B) The subsequent 10-s EEG recording with a sharply contoured rhythmic pattern of alpha frequency seen in the sixth second at electrodes C3 > P3. (C) Continues this pattern of sharply contoured alpha at C3 > P3 until replaced by generalized low-voltage suppression in the seventh second.

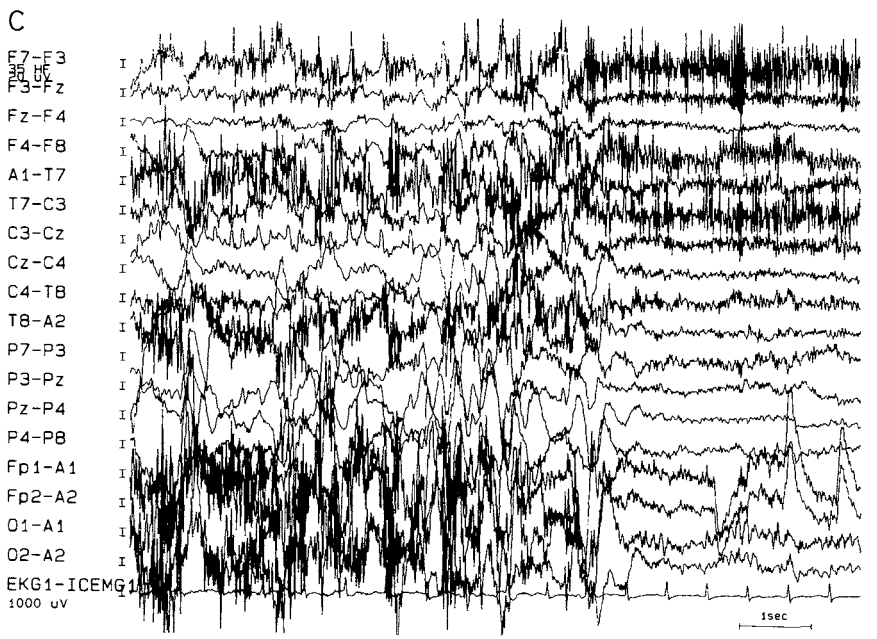


FIGURE 16.3 *(Continued)*

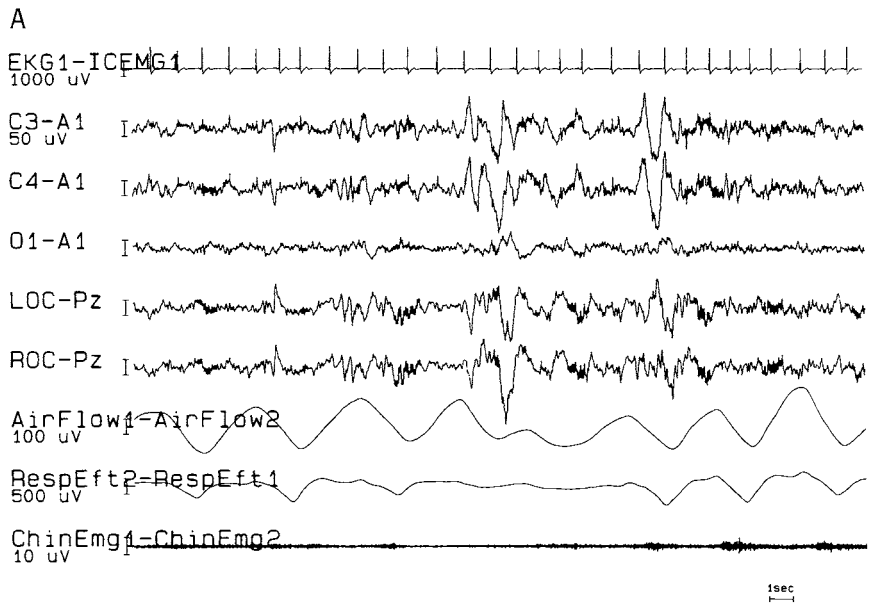


FIGURE 16.4 The PSG of the recorded event of Patient No. 2 proves difficult to read when viewed in 30-s epochs. (A) The patient in stage 2 sleep. (B) Sleep with an arousal in the 12th second completely obscured by EMG and movement artifact. (C) Continues with this artifact and ends with the patient awake. No seizure activity is evident on PSG.

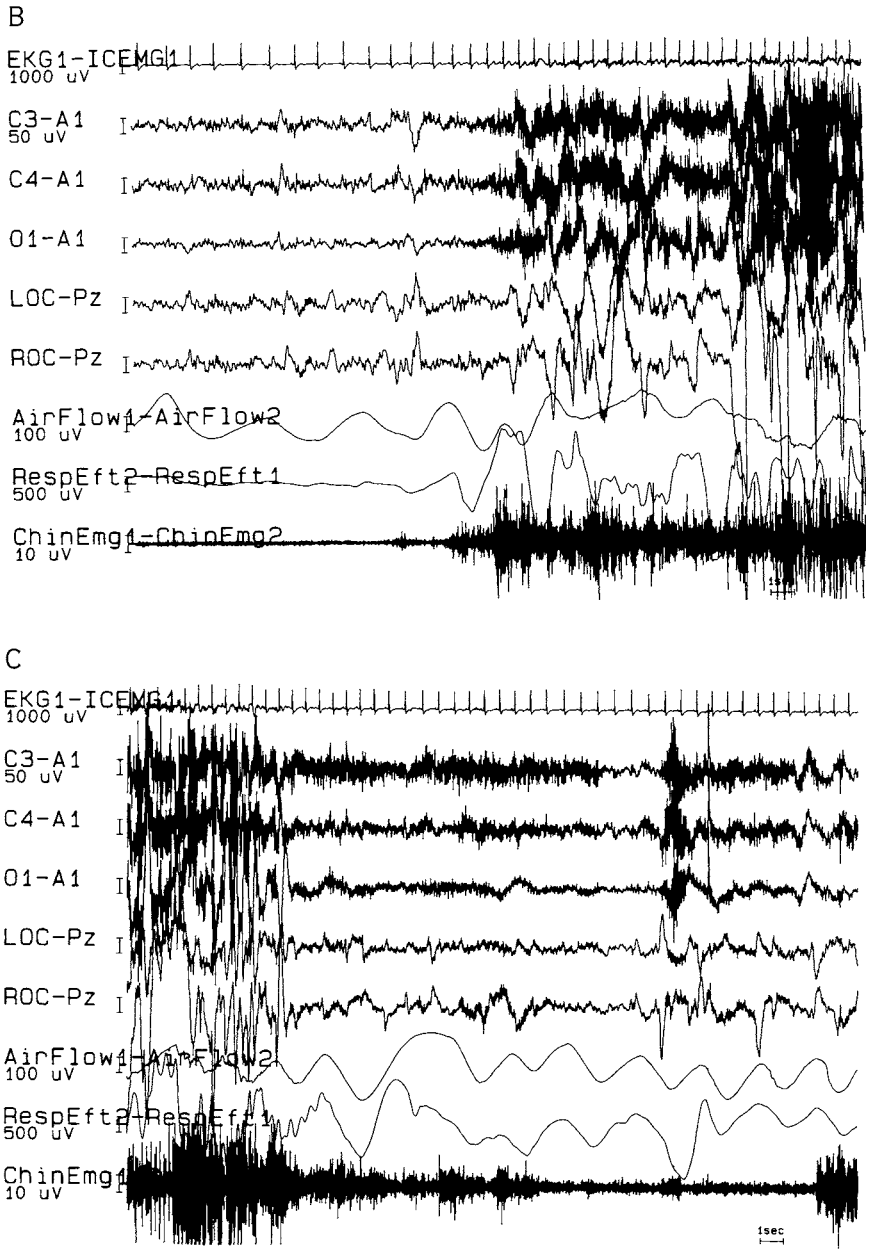


FIGURE 16.4 (*Continued*)

CASE NO. 3

Patient No. 3 is a 13-year-old boy with Lennox-Gastaut syndrome, mental retardation, and spastic quadriparesis who was admitted to the hospital for episodes of apnea in sleep. Although the patient had a known generalized seizure disorder, these spells were felt not to be seizures by his caregivers.

Other than the Lennox-Gastaut syndrome, the patient had been fairly healthy. Onset of generalized seizures began at age 1 year. At the current time they consisted of flexion of the trunk, but were stable on medication. Ten months prior to this evaluation the patient underwent an orthopedic surgical procedure. During rehabilitation the patient had a prolonged cardiac arrest, requiring cardiopulmonary resuscitation (CPR) and intubation. A tracheostomy subsequently had to be performed. (It later closed spontaneously.) Since this time the patient has also experienced myoclonic seizures mostly involving the upper extremities; however, these also were felt to be under good control on medication and were seen rarely. He was presently taking lamotrigine, topiramate, and lorazepam.

The new events for which the patient was being evaluated were episodes where the caregivers noted that the patient appeared to stop breathing while asleep. There were no other clinical signs associated with these events. However, during one episode, the patient did appear to awaken, sat up partially, and was not breathing, appearing to have some sort of respiratory obstruction. He eventually began breathing again on his own after chest compressions were initiated by the caregiver.

The question thus posed to the primary physician was whether these events represented obstructive sleep apnea, possibly secondary to the patient's tracheostomy, a primary central apnea phenomenon, or a new form of seizure. It was decided that the patient should undergo combined video EEG–PSG to further elucidate the etiology of these apneic spells.

One event was recorded during the night. While sleeping, the patient appeared to cease breathing for approximately 20 s. When touched, he opened his eyes but did not interact. Testing of consciousness was not performed. At the onset of this event, PSG showed a 46 s central apnea, with oxygen desaturating to 48% and pulse rate increasing to 166 from a baseline of 96 (Fig. 16.5). Ten seconds prior to the clinical apnea, the EEG showed 100–200 μv generalized delta activity, which then evolved into generalized theta rhythms and finally generalized spike and slow wave (Fig. 16.6). The EEG seizure lasted for approximately 5 min, at which time the EEG returned to baseline. After approximately 5 min, the patient raised his head, moved some, and then returned to sleep. There was some snoring recorded; however, the PSG was essentially normal, save for the central apnea and hypoxia recorded. No additional apneas were recorded. The patient's awake recording showed slow background rhythms and generalized slow spike and wave complexes, consistent with his Lennox-Gastaut syndrome. Valproate was added to the patient's drug regimen in the hopes of controlling this new seizure type. At follow-up 18 months later, the patient remained seizure free.

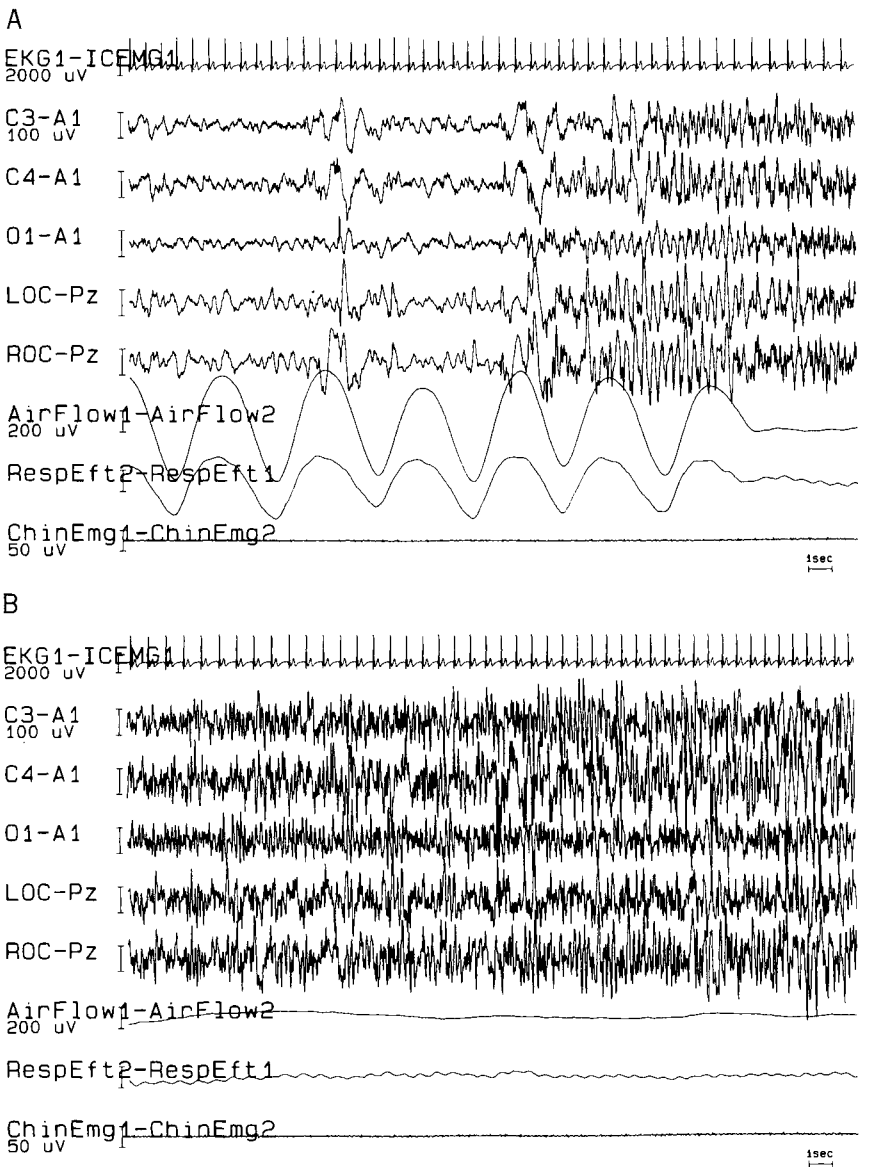


FIGURE 16.5 Two consecutive 30-s samples demonstrating the recorded seizure of Patient No. 3 using a sleep montage. (A) Stage 2 sleep followed by an arousal with the onset of a central apnea. (B) Continuation of the apnea, which lasted 46 s, with the EEG obscured by EMG artifact for 5 min.

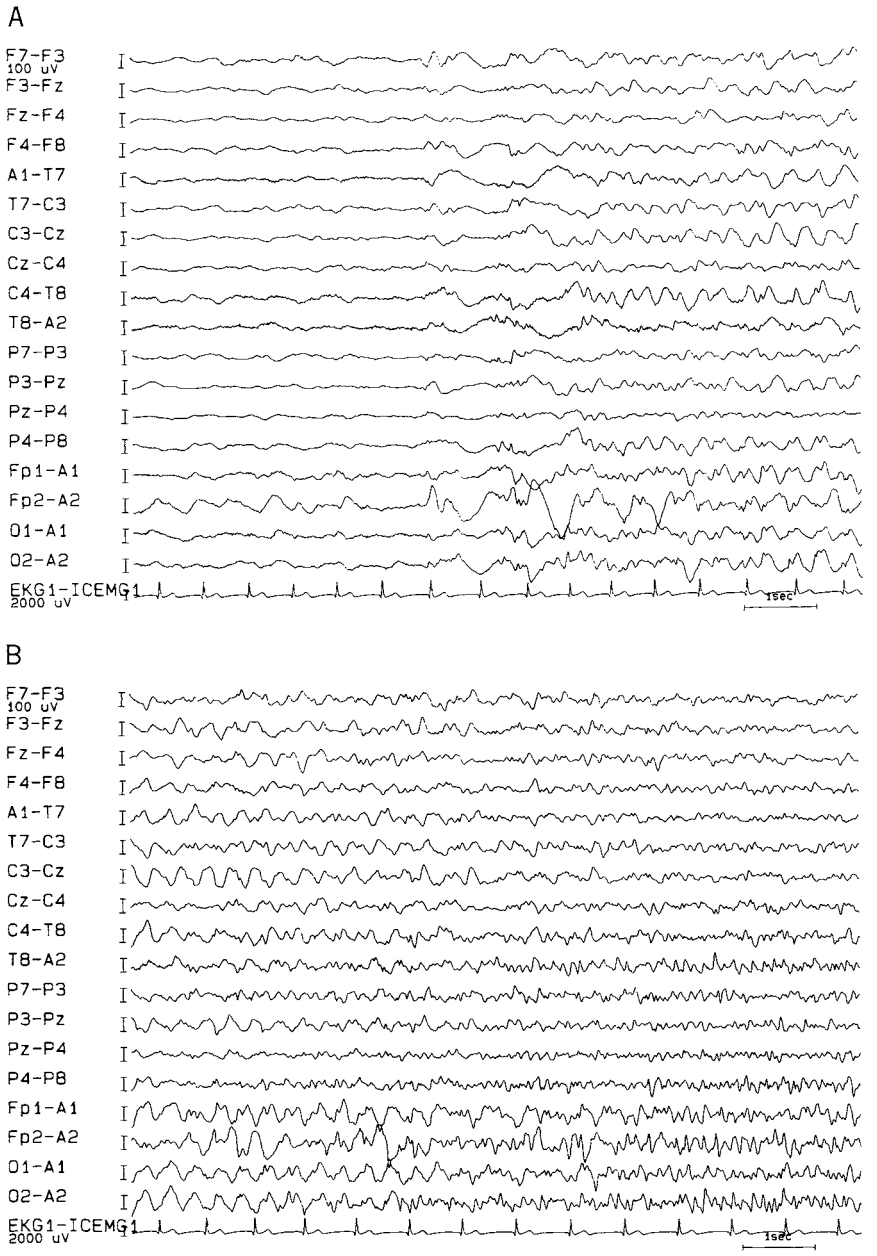
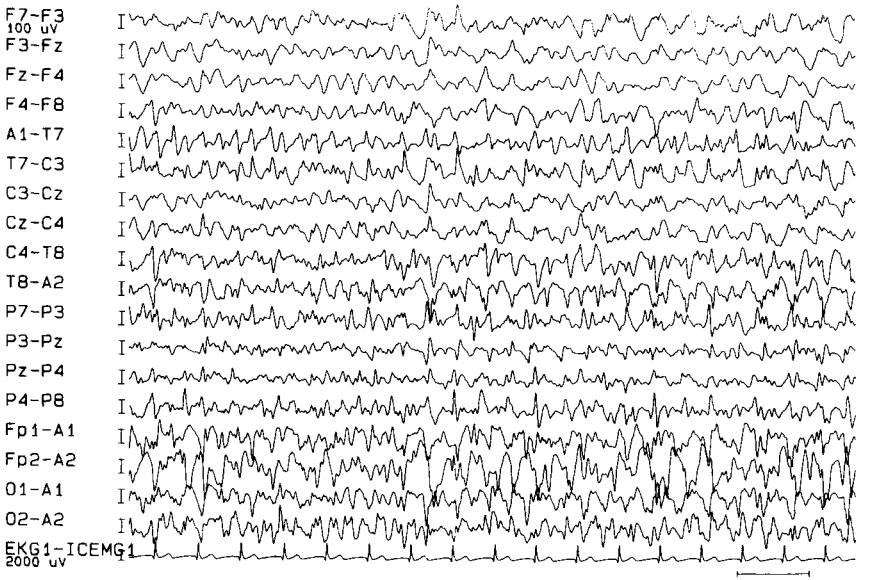


FIGURE 16.6 Four 10-s pages show the same episode using a full array of electrodes with a transverse EEG montage. The evolution of a generalized seizure is clearly evident. (A) Stage 2 sleep with an arousal of generalized delta activity that lasted 10 s. (B) Progression from delta to a faster theta pattern lasting 40 s. (C) Generalized theta interspersed with multiregional spikes that continued for approximately 60 s. (D) The seizure in the fourth minute, now as generalized slow spike and wave activity that lasted almost 3 min.

C



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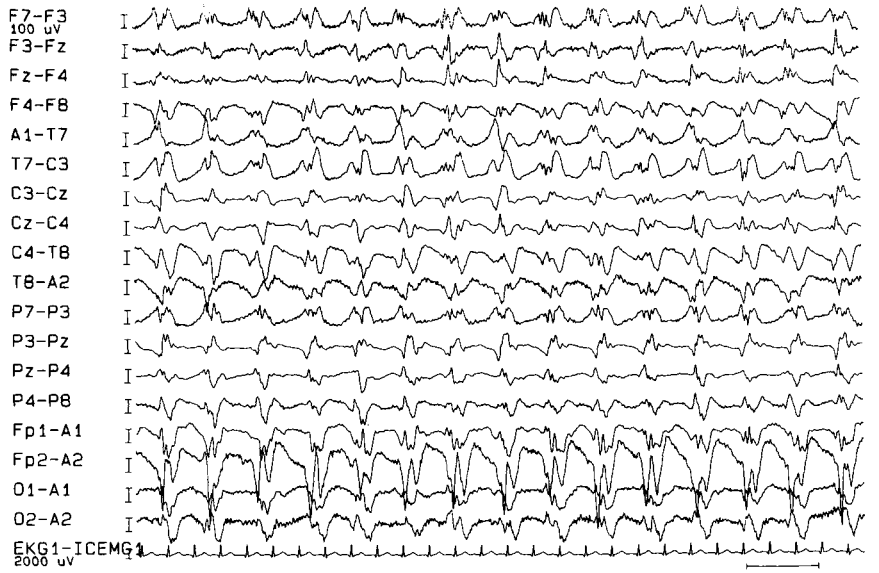

FIGURE 16.6 *(Continued)*

As seen in the preceding examples, nocturnal events can often pose a difficult diagnostic dilemma. One clear-cut problem is the fact that so many of the clinical components of a number of parasomnias may be similar to the clinical features of seizures. The other difficulty is that because these are phenomena of sleep, they are infrequently witnessed. Often when witnessed, this is by someone who was asleep him- or herself prior to the events, and so is perhaps not fully cognizant of details or descriptions that might be helpful in making a definitive diagnosis by history. However, with a combination of EEG, PSG, and video, especially if one is fortunate enough to capture a typical event, one can frequently arrive at a diagnosis. Even when an event does not occur, supportive information can often be obtained to suggest a diagnosis; either the presence of interictal epileptiform discharges supporting a diagnosis of epilepsy or the arousal from stage 3/4 NREM sleep supporting a diagnosis of NREM parasomnias.

SUMMARY

In summary, we have discussed some of the parasomnias and epileptic seizures that need to be considered in the differential diagnosis of paroxysmal events occurring in sleep and the value of combined video EEG–PSG in the diagnosis of these events. Although each test independently can offer valuable information, with especially difficult cases, a more extensive combined video EEG–PSG can frequently result in the correct diagnosis in a more timely fashion.

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17

POSTICTAL STATE

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When brought to the hospital he was unconscious of his condition—who brought him in or with whom he had been associating. . . . To this state succeeded tremor of the limbs . . . and vacant converse with spectral and imaginary objects on the walls . . . his answers were incoherent and unsatisfactory. . . . I found him in a violent delirium . . . he became quiet, and seemed to rest for a short time; then gently moving his head, he said "Lord help my poor soul!" and expired.

—John J. Moran, MD,
speaking about his patient Edgar Allan Poe (Bazil, 1999)

INTRODUCTION

The postictal state is an ambiguous and poorly understood phenomenon. The means by which the various pathophysiological mechanisms produce differing postictal manifestations are still unknown. It is commonly assumed that various phenomena seen in the postictal state represent a manifestation of neuronal exhaustion in a selected neuronal pool. The clinical symptomatology of the postictal state is almost as diverse as the variations of ictal semiology. The postictal period correlates to a time in which neuronal, behavioral, and electroencephalographic return to the baseline is achieved. The clinical manifestation of the postictal period may vary with the seizure type as well as the intensity and duration of the seizure. These manifestations can vary even in the same patient from seizure to seizure.

The postictal state encompasses lethargy, confusion, psychosis, sleep, and coma. The elements of the postictal state have not been as well studied in a fashion that the ictal stages have been by historical data, physical examination, video electroencephalographic (EEG) monitoring, and functional neuroimaging. Family members often misinterpret the postictal period as a continuation of the ictus, leading to exaggerated estimates of the seizure duration. Many times it is even confusing to a trained clinician. The differentiation between these two states using EEG data can still remain ambiguous. The distinction is further blurred in conditions such as status epilepticus where certain EEG patterns such as periodic lateralized epileptiform discharges (PLEDs) are still debated as to whether they represent an ictal or a postictal phenomenon. Most postictal phenomena are ignored because they have poor lateralizing value. However, there are some postictal phenomena such as postictal aphasia and postictal hemiparesis (Todd's paralysis) that carry lateralizing value as to the ictal onset zone. This chapter focuses on various changes in cognition, behavior, alertness, and consciousness that occur after an epileptic seizure.

POSTICTAL DELIRIUM/PSYCHOSIS

There are patients who have a profoundly disturbed postictal recovery during which they display a delirious confusional state. At times, the reaction may appear violent, during which time the patient may appear hypervigilant. Postictal aggression usually occurs in the setting in which an attempt is made to restrain the patient (Delgado-Escueta, 1981; Fenwick, 1986). For this reason, the recovering patient should be surrounded by as little commotion as possible and not be restrained because this only tends to further agitate and confuse the individual.

These types of reactions are rare and are thought to be seen in patients with deteriorated or poorly controlled seizures. In some cases, postictal delirium may be accompanied by visual hallucinations (Niedermeyer, 1990). Some authors have found that directed violent behavior and suicidal attempts were more commonly a feature in patients with postictal psychosis instead of acute interictal psychosis or postictal confusion (Kanemoto *et al.*, 1999).

Postictal psychosis, defined as a time-limited disturbance with diverse psychiatric symptoms that is temporally related to seizures or a flurry of seizures, has been described in patients with focal as well as generalized seizures. These cases are at times associated with abrupt anticonvulsant withdrawal (Savard *et al.*, 1991; Kanner, 1996; Baumgartner, *et al.*, 1995). The prevalence of this entity is unclear in patients with epilepsy, but has been reported as 6–10% (Kanner, 1996; Kanemoto *et al.*, 1996). There is usually a lucid interval prior to the psychosis. The duration of the psychosis can last a few days or continue for up to 3 months (Lancman *et al.*, 1994; Logsdail and Toone, 1988). Patients with postictal psychosis usually present with mood disorders and other positive psychiatric symptoms such as paranoid delusions, and auditory, visual, and sensory hallucinations (Logsdail and Toone, 1988; Mendez, 1991; So, 1991). Postictal psychosis has also been noted in cases following electroconvulsant therapy (Zwil, 1997). The speculated pathophysiological mechanisms of postictal psychosis vary from neuronal exhaustion after being hyperexcited by frequent epileptiform discharges, to dopaminergic hypersensitivity, to γ-aminobutyric acid (GABA)-mediated mechanisms (Savard *et al.*, 1991; Lancman, 1994; Ring *et al.*, 1994; Szabo *et al.*, 1996). Most patients have a benign prognosis, although as many as 15% of patients may develop chronic psychosis (Logsdail and Toone, 1988).

Occasionally patients with complex partial seizures may experience periods of aimless wandering (poriomania) that may represent a prolonged postictal automatism (Mayeux *et al.*, 1979). The postictal EEG often shows either a generalized or a lateralized delta slow activity. The postictal lateralized slowing that patients may show on their EEGs may be a lateralizing sign of the ictal onset zone. The postictal EEG recording may also have a lack of interictal spikes that may have been evident as interictal activity prior to the seizure.

POSTICTAL LETHARGY/CONFUSION

It is often difficult to distinguish postictal confusion versus an impairment of comprehension. Differentiating postictal aphasia, abulia, and disorientation are also difficult. Care must be taken when diagnosing postictal confusion in patients with left temporal lobe epilepsy (TLE) because it may actually represent a postictal language dysfunction. In a study of patients with complex partial seizures of 32 patients with right TLE, 28 (88%) had initial postictal confusion with impaired comprehension and normal language function. In 33 patients with left TLE, 14 (42%) postictally had impaired comprehension with no paraphasia. These patients were much more likely to have paraphasic errors (36%) as compared with right TLE patients (6%). In this group of patients, a flattened effect and a prolonged disorientation for place was more commonly observed in patients with right TLE. (Devinsky *et al.*, 1994).

Postictal confusion is often used to discern between typical absence seizures and complex partial seizures. There is no postictal period in typical absence

seizures that helps in distinguishing them from complex partial seizures (Delgado-Escueta *et al.*, 1983). A lack of postictal confusion after seizures may also be seen in children with supplementary sensorimotor seizures (Connolly *et al.*, 1995). The postictal period in complex partial seizures can vary in length usually from 2 to 10 min and is characterized by disorientation and inattention with very little motor activity (Goldensohn and Gold, 1959; Malamudu, 1967; Mohan *et al.*, 1975). There is usually a partial impairment of consciousness during which time patients may react either appropriately or inappropriately. In a study of patients with TLE and mesial temporal atrophy, prolonged postictal confusion, defined as a period of disorientation in time and space with recent memory disturbance lasting more than 10 min following complex partial seizures without secondary generalization, was more commonly seen in patients with bilateral mesial temporal abnormalities in terms of either atrophy or spiking (Gambardella *et al.*, 1995). In a separate study using the same criteria for prolonged postictal confusion the authors found a significant tendency for prolonged postictal confusion, to occur in patients with amygdala atrophy (Guerreiro *et al.*, 1999). Postictal confusion may present as isolated amnesia. Rarely episodic amnesia may be the presenting complaint resulting in a diagnostic dilemma (Zeman *et al.*, 1998). Prolonged periods of antrograde and retrograde amnesia can occur as postictal phenomena. In one case report, a prolonged postictal amnesia lasting more than a month occurred in a patient who had a flurry of complex partial seizures over an entire day (Palmini *et al.*, 1992).

POSTICTAL SLEEP

Postictal sleep is a common phenomenon after a generalized tonic–clonic seizure. The patient may pass through several stages from sleep to delirium to drowsiness before awakening. During the late postictal state, the heart rate begins to normalize from the typical ictal tachycardia. There is a decrease in muscle tone with bladder sphincter relaxation and incontinence that typically occurs in the early postictal phase. In the immediate postictal phase, there is partial obstruction of the airway resulting in stertorous respirations. Deep tendon reflexes are diminished and the plantar responses are sometimes extensor. The patient then may pass into sleep. If the seizure occurs during the night, the patient may sleep through the postictal period and awaken with complaints of tongue soreness, muscle aches, or nocturnal enuresis. Patients may often experience postictal morning headaches or unexplained bruises.

Although postictal sleep is a frequent occurrence after a generalized tonic–clonic seizure, it may also occur after complex partial seizures. The characteristics of postictal sleep have not been well studied. Some authors differentiate between sleep that occurs after a seizure and results from a compulsory need to sleep after a complete recovery of consciousness, and sleep in which the postictal events move directly from a period of confusion to sleep without ever a complete recovery to baseline (Tassinari *et al.*, 1987). Whether these two manifestations of postictal sleep differ in their electrographic correlates or pathophys-

TABLE 17.1 Generalized Tonic–Clonic Seizures

Epilepsy type	Postictal sleep (%)	Frequency of sleep (%)	Hours of sleep[a]
Generalized epilepsy	100	90	3.6
Temporal lobe epilepsy	67	61	2.2
Extratemporal lobe epilepsy	88	72	4.4

[a] For those who could answer this question.

iology is not known. It remains unclear if postictal sleep represents some stage of normal sleep or an encephalopathic recording.

A study was performed to evaluate postictal sleep in a series of patients with intractable seizures (Nair *et al.*, 1999). The patients' epilepsy syndromes were defined based on history, physical examination, high-resolution magnetic resonance imaging (MRI) scan of the brain, outpatient EEG recordings, and video EEG monitoring. Patients were asked to indicate if they slept after either a generalized tonic–clonic seizure or a complex partial seizure. They were then asked to specify how often and how long they slept after such seizures. A total of 61 patients were included in this study. Of those, 36 were male and 25 were female. Of the 61 patients, 2 had generalized epilepsy, 25 had TLE, and 30 patients had extratemporal lobe epilepsy. Of the 61 patients, 49 (80%) had postictal sleep. The average time spent sleeping after a seizure in 46 patients was 3 h. Only 3 patients were unable to determine the duration of their postictal sleep. After a generalized tonic–clonic seizure, all patients with generalized epilepsy had experienced postictal sleep and reported that they tended to sleep after 90% of their generalized tonic–clonic seizures. Those with focal epilepsies had a lower percentage of postictal sleep (88% in extratemporal and 67% in TLEs). This group also reported a lower frequency of postictal sleep with generalized tonic–clonic seizures (Table 17.1). In those seizures that were not generalized tonic–clonic (either complex partial or dialeptic), patients with TLE reported more frequent sleep after complex partial seizures than those with extratemporal lobe epilepsy (Table 17.2), as has been reported by other authors (Rodin, 1976).

TABLE 17.2 Seizures Other Than GTCS

Epilepsy type	Postictal sleep (%)	Frequency of sleep (%)	Hours of sleep[a]
Generalized epilepsy	33	92	3.6
Temporal lobe epilepsy	56	71	1.9
Extratemporal lobe epilepsy	37	74	3.0

[a] For those who could answer this question.

TABLE 17.3 Etiologies for Focal Epilepsies

Etiology	Number of cases
Neoplasm	5
Vascular malformation	3
Encephalomalacia	5
Cortical dyplasia	6
Encephalitis/meningitis	7
Hippocampal sclerosis	13
Cryptogenic	16

The reasons for patients with extratemporal lobe epilepsy being less prone to postictal sleep may be due to the fact that those seizures are of shorter duration or may be linked to the spread pattern of the seizures and to which specific neuronal population is involved with the ictus. The etiologies for the patients with focal epilepsies were diverse (Table 17.3) (Nair *et al.*, 1999). Two out of six patients with generalized epilepsy reported sleeping after a dialepic seizure. Both of these patients were not likely to have typical idiopathic generalized epilepsy because one patient had a history of seizures associated with alcoholism and the other had a history of recreational drug abuse.

POSTICTAL COMA/ENCEPHALOPATHY

Postictal coma is sometimes seen after a generalized tonic–clonic episode. It is unclear if this phenomenon differs from patients who experience brief or prolonged periods of postictal sleep. Of the 61 patients studied, only 4 patients (6.6%) reported having postictal sleep in which they slept for 12 h or more (Nair *et al.*, 1999). Occasionally patients with seizures can present as episodic hyersomnolence that lasts 24–72 h and resolves with anticonvulsant therapy (Wszolek *et al.*, 1995). Other cases with prolonged postictal encephalopathy have been reported following seizures in patients who were taking clozapine (Karper *et al.*, 1992).

Some patients with prolonged confusional states may actually represent cases of nonconvulsive status. This can occur in patients with no history of prior seizures, and may be seen in patients who abruptly discontinue their anticonvulsants. Cases of nonconvulsive status can be diagnosed with EEG monitoring (Fagan and Lee, 1990; Treiman, 1995). There are cases of more prolonged periods of postictal confusion that last for several days, up to 4–10 days. The EEGs during these periods consist of encephalopathic patterns. Other causes such as metabolic, toxic, drug-related toxicity, and nonconvulsive status should be ruled out.

Many of these patients with extremely protracted periods of postictal confusion also had mental retardation, diffuse structural abnormalities, or prior history of status epilepticus. These episodes often follow a flurry of seizures (Biton *et al.*, 1990). In elderly patients, postictal coma following either a partial or a generalized seizure may indicate an underlying diffuse or focal brain pathology. A variety of etiologies such as strokes, primary or metastatic brain tumors, alcohol withdrawal, or central nervous system (CNS) infections may be the culprit. Elderly patients may be more susceptible to more prolonged recovery from seizures as compared with younger patients (Willmore, 1976). This may be an effect of a compromised vascular responsiveness that results in a poor response to an increase in neural metabolic demands from seizures (Plum *et al.*, 1968). This, in addition to lactic acidosis, hyperthermia, and hypoxia, may combine to cause an elderly patient to enter into a postictal coma (Meldrum and Horton, 1973). Therefore, supportive care with supplemental oxygen, treatment of the seizure disorder with an anticonvulsant, and searching for an underlying cause are all important aspects of management to avoid a more prolonged postictal state. Care must be taken when selecting an anticonvulsant because some cases of iatrogenic coma can result, especially in the elderly, from treatment with an anticonvulsant such as phenobarbital with excessively sedating properties.

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SUBJECT INDEX