Current Practice of Clinical Electroencephalography

THIRD EDITION

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Dedication

To Gilbert H. Glaser, founding Chairman of the Department of Neurology at Yale University, who introduced us to the role and possibilities of EEG in neurological research and practice
and
To our wives, Susan and Barbara,
for their seemingly inexhaustible patience, support, and encouragement.

PREFACE

This is the third edition of a textbook that first appeared in 1978 with Donald W. Klass and David D. Daly as editors. Daly remained an editor of the second edition, published in 1990, but Timothy A. Pedley succeeded Klass. Now, in the third edition of *Current Practice of Clinical Electroencephalography*, John S. Ebersole follows Daly, who died unexpectedly shortly after publication of the previous edition.

But there have been other, more important changes that reflect the continued evolution of electroencephalography (EEG) and clinical neurophysiology, and their relevance to clinical practice. This new edition is therefore not simply a revised version of the previous one. The second edition had 23 chapters; the third has 31, and 23 of these are entirely new. We are now firmly in the digital era, and the book strongly reflects this new reality. Advanced display and analytical techniques have extended the utility of EEG beyond the traditional EEG laboratory or epilepsy monitoring unit to the operating room and intensive care unit. New methods of source modeling and detection software are aiding seizure recognition and localization of epileptogenic brain regions. EEG in its broadest sense continues to play a vital role in the study of normal cerebral function and in conditions traditionally categorized as neurological, psychiatric, or psychological but now properly viewed more broadly as brain disorders.

Like its predecessors, this edition of *Current Practice* is not meant to be read from cover to cover following the chapter order listed in the Table of Contents. Residents in neurology and postdoctoral fellows in clinical neurophysiology will have different interests and needs than attending physicians or experienced investigators. We hope, therefore, that the topics and their coverage serve the needs of both novice and expert alike, and as an initial general reference source in the majority of matters related to EEG. Bibliographic citations include both historical and "classical" papers as well as recent publications describing new methods, revised interpretations of EEG data, and new or extended applications. We believe that in-depth knowledge of basic EEG recording methods, normal EEG patterns and phenomena (including changes resulting from development and aging), and the data base of clinical EEG abnormalities are essential to advanced and new applications. To this end, we have aimed to provide a systematic and critical approach to EEG interpretation so that clinical–electrographic correlations are not some mysterious assemblage of meaningless words but rather have practical clinical utility because they are soundly based on physiological principles and evidence from clinical studies.

Because multiauthored textbooks present an array of challenges that sometimes seem insurmountable, we are deeply grateful to our many contributors who generously shared their time, knowledge, and experience. We thank them too for their patience, as this volume has had a much longer gestation than anyone anticipated. We remarked in the second edition that, for those who wonder how editors in the trenches feel, it is useful to recall one of Abraham Lincoln's stories. Lincoln once told of a man who had been tarred and feathered and, while being ridden out of town on a rail, was heard to remark: "If it weren't for the honor, it wouldn't be worth it." We think it was worth it, and we are pleased with the final results; we hope our fellow authors are also.

In closing, we acknowledge with gratitude the many past contributions of David Daly and John Knott, both now sadly deceased, whose earlier work shaped the form of this edition. We also value the tireless efforts and understanding support of Charles Mitchell and Keith Donnellan at Lippincott Williams & Wilkins. Their role has been largely behind the scenes but no less important.

John S. Ebersole, M.D.
Timothy A. Pedley, M.D.

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Chapter 1

The Cellular Basis of EEG Activity[1]

György Buzsáki, Roger D. Traub, and Timothy A. Pedley

Sources of Extracellular Current Flow
Fast (Na^+) Action Potentials
Synaptic Activity
Calcium Spikes
Voltage-Dependent Intrinsic Oscillations
Intrinsic Spike Afterhyperpolarizations: Their Contribution to Cortical Delta Waves
Other Nonsynaptic Neuronal Effects
Neuron–Glia Communication
Ultrafast Cortical Rhythms
Summary
References

At this time, three methods can provide high temporal resolution of neuronal interactions at the network level: electric field recording (electroencephalogram [EEG]), magnetoencephalogram (MEG) (51,70), and optical images (32,86). Each of these has its advantages and shortcomings. MEG is not practical for experimental work on freely moving subjects, because of the large size of magnetic sensors. A major obstacle of the optical imaging method is that its "view" is confined to surface events. Because most of the network interactions occur at the level of the synapses, much of this in the depths of the brain, a search for alternative methods is warranted. In addition, research in both MEG and optical imaging fields faces the same fundamental questions as those that arose decades ago in connection with scalp-recorded EEG: the "reverse engineering" problem of signal interpretation (14,31,63) (see Chapter 4).

Membrane currents generated by neurons pass through the extracellular space. These currents can be measured by electrodes placed outside the neurons. The field potential (i.e., local mean field), recorded at any given site, reflects the linear sum of numerous overlapping fields generated by current sources (current from the intracellular space to the extracellular space) and sinks (current from the extracellular space to the intracellular space) distributed along multiple cells. This macroscopic state variable can be recorded with electrodes as a field potential or EEG or with magnetosensors (superconducting interference devices [SQUIDs]) as a MEG. These local field patterns therefore provide experimental access to the spatiotemporal activity of afferent, associational, and local operations in a given neural structure. To date, field potential measurements provide the best experimental and clinical tool for assessing cooperative neuronal activity at high temporal resolution. However, without a mechanistic description of the underlying neuronal processes, scalp or depth EEG is simply a gross correlate of brain activity rather than a predictive descriptor of the specific functional and anatomical events. The essential experimental tools for the exploration of EEG generation have yet to be developed. This chapter provides a

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basic description of field potential generation in the mammalian archicortex and neocortex and summarizes progress and future directions.

A straightforward approach to decompose the surface (scalp) recorded event is to study electrical activity simultaneously on the surface and at the sites of the extracellular current generation. Electrical recording from deep brain structures by means of wire electrodes is one of the oldest recording methods in neuroscience. Local field potential measurements, or "micro-EEG" (66), combined with recording of neuronal discharges is the best experimental tool available for studying the influence of cytoarchitectural properties, such as cortical lamination, distribution, size, and network connectivity of neural elements on electrogenesis. However, a large number of observation points combined with decreased distance between the recording sites are required for high spatial resolution and for enabling interpretation of the underlying cellular events. Progress in this field should be accelerated by the availability of micromachine silicon-based probes with numerous recording sites (60). Information obtained from the depths of the brain will then help clinicians interpret the surface-recorded events. Such a task clearly requires collaborative work among the fields of neuroscience, silicon nanotechnology, micromachinery, electric engineering, mathematics, and computer science. The stakes are high, because interpretation of macrosignals such as those obtained with EEG, MEG, fast magnetic resonance imaging (MRI), positron emission tomography (PET), or optical imaging methods will still require interpretation of the cellular-synaptic interactions at the network (submillimeter) level.

In principle, every event associated with membrane potential changes of individual cells (neurons and glia) should contribute to the perpetual voltage variability of the extracellular space. Until recently, synaptic activity was viewed as the exclusive source of extracellular current flow or EEG potential. As discussed later, however, synaptic activity is only one of the several membrane voltage changes that contribute to the measured field potential. Progress during the 1990s revealed numerous sources of relatively slow membrane potential fluctuations, not directly associated with synaptic activity. Such nonsynaptic events may also contribute significantly to the generation of local field potentials. These events include calcium spikes, voltage-dependent oscillations, and spike afterpotentials observed in various neurons.

SOURCES OF EXTRACELLULAR CURRENT FLOW

Fast (Na^+) Action Potentials

The largest amplitude intracellular event is the sodium-potassium spike, referred to as the fast (Na^+) action potential when it occurs at the intracellular level, and as unit activity when it occurs at the extracellular level. Individual fast action potentials are usually not considered to contribute significantly to scalp-recorded EEG potentials, mainly because of their short duration (<2 milliseconds). An additional factor is the high-pass frequency filtering (capacitive) property of the extracellular medium, which attenuates spatial summation of high-frequency events. As a result, the voltage of extracellular unit activity decreases much more rapidly with distance between the cell membrane and the recording site than is the case for slower membrane events. However, when a microelectode is placed close to the cell body layer of cortical structures, the recorded field potentials contain both extracellular units and summed synaptic potentials. Furthermore, when action potentials from a large number of neighboring neurons occur within a short time window, such as in response to electrical stimulation of afferents, during epileptic activity, or even during synchronous physiological patterns, these "population spikes" can be recorded with relatively large electrodes and in a larger volume (Color Fig. 1.1) (4,9,25).

Synaptic Activity

In most physiological situations, synaptic activity is clearly the most significant source of the extracellular current flow that produces EEG potentials. The notion that synaptic potentials contribute to the generation of EEG potentials stems from the recognition that for the summation of extracellular currents from numerous individual compartments, the events must be relatively slow (39). The dendrites and soma of a neuron form a tree consisting of an electrically conducting interior surrounded by a relatively insulating membrane with tens of thousands of synapses on it. Each synapse acts as a small battery to drive current, always in a closed loop. Depending on the chemical nature of the neurotransmitter released in the synaptic cleft, the postsynaptic membrane is depolarized (excitatory postsynaptic potential [EPSP]) or hyperpolarized (inhibitory postsynaptic potential [IPSP]). Excitatory currents, involving Na^+ or Ca^{2+} ions, flow inwardly toward an excitatory synapse (i.e., from the activated postsynaptic site to the other parts of the cell) and outwardly away from it. The outward current is referred to as a *passive return current* from the intracellular milieu to the extracellular space. Inhibitory loop currents, involving Cl^- or K^+ ions, flow in the opposite direction. The current flowing across the external resistance of the cortex sums with the loop currents of neighboring neurons to constitute a local mean field (see Fig. 1.1). Viewed from the perspective of the extracellular space, membrane areas where current flows into or out of the cells are termed *sinks* or *sources,* respectively. The active or passive nature of the

sinks and sources is ambiguous, unless the location and types of synapses, involved in the current generation, are identified. Supplementary information may come from simultaneous intracellular recording from neurons dominantly involved in the current generation. Alternatively, extracellular recording of the action potentials and their cross-correlation with the laminar distribution of the field event can provide the necessary clues for the identification of a sink, as opposed to a passive return (inward) current of an active inhibitory source (outward). Cross-correlation of the interneuronal discharges with the field potential in question may further decrease the ambiguity regarding the passive versus active nature of the sink-source dipole (16).

Identification of Synaptic Currents in the Archicortex

Figure 1.1 illustrates the necessary steps in identifying network mechanisms of evoked and spontaneous field events. The example is taken from the hippocampus because it is a simple, three-layered structure consisting of orderly arranged principal cells (pyramidal and granule cells) and interneurons. Therefore, the synaptic interpretation of the extracellular current is much simpler than in multilayered structures. The termination zones of the excitatory paths and the inhibitory connections in the hippocampus are also well studied (14,85). Activation of the excitatory associational input by indirect, trisynaptic electrical stimulation depolarizes the midapical and basal dendrites of pyramidal cells (shown in blue in Fig. 1.1). The passive return current flows out of the cells at the level of the neuronal bodies and distal apical dendrites (shown in red in Fig. 1.1). This change in voltage is reflected by the characteristic distribution of field potentials in different depths. The extracellular voltage is negative close to the excitatory synapse and positive in the cell body layer. The reason for this is the large depolarization of the dendrite and the gradual decrease of intracellular depolarization toward the soma. This synaptic activity–induced intracellular voltage difference between the dendrites and soma (a dipole)–results in a current flow across the membrane (arrows in Fig. 1.1*F*). Simultaneous events in many neighboring pyramidal cells will linearly summate and produce an extracellular voltage fluctuation, which can be measured with closely spaced electrodes. After the impedance characteristics of the extracellular space are determined, the voltage change can be converted into current change (28).

Increased afferent discharge also activates interneurons, some of which terminate on the cell bodies of the pyramidal cells. The discharging basket cells release γ-aminobutyric acide (GABA) and activate Cl^- channels with resulting hyperpolarization of the pyramidal cell somata. Somatic hyperpolarization, in turn, creates a voltage gradient between the soma and dendrites (inhibitory dipole). The created intracellular voltage difference is the driving force of charges across the cell membrane and the consequent spatially distributed current flow in the surrounding extracellular fluid (see Fig. 1.1). Note that the direction of current flow is the same as that when the driving force is apical dendritic depolarization (active sink). Because the directions of current flow are identical for dendritic excitation and somatic inhibition, the excitatory and inhibitory currents sum in the extracellular space, resulting in large-amplitude field potentials.

The contribution of $GABA_A$ receptor-mediated inhibitory currents, however, is believed to be small, because the Cl^- equilibrium potential is close to the resting membrane potential. Thus, the change of the transmembrane voltage is limited. However, in actively spiking neurons, when the cell body is depolarized, the transmembrane potential, mediated by $GABA_a$ synapses, can be large. Another cautionary note is that inhibition may operate also on the dendrites, causing current flow opposite to the direction of excitatory currents. For the identification of excitatory and inhibitory components, represented by the extracellular current flow, a precise knowledge about the anatomical network is essential. Physiological experiments, including recordings from interneurons and pyramidal cells and differential pharmacological blockage of the excitatory and inhibitory synapses, can then provide the necessary knowledge as to which cell types are involved when the associational pathways are electrically activated. These extracellular and intracellular events therefore provide circumstantial evidence that the same neuronal machinery is activated during spontaneously occurring sharp waves (SPWs) as during electrical stimulation of the associational afferent fibers.

Identification of Synaptic Currents in the Neocortex

The strategy just described is, in principle, applicable to any other *a priori* identified rhythmic or sparse EEG event. Complications arise when several dipoles are involved in the generation of the same EEG patterns, especially when these dipoles are phase shifted, as is the case in the generation of the numerous neocortical patterns (10,80,81).

Of the neocortical EEG patterns, two conspicuous low-frequency (<15 Hz) rhythms, the physiological sleep spindles and the spike-and-wave discharges associated with petit mal epilepsy, have been studied most extensively (10,13,44,55,77,81). It is widely accepted that the source of rhythm generation for both patterns is the interplay between the GABAergic reticular nucleus and corticopetal nuclei of the thalamus (10,13,79,81). It is less clear, however, whether synaptic currents of the thalamocortical afferents

can fully account for these rhythms or whether intracortical circuitries are significantly involved in their generation (40). Initially, the "recruiting" response, evoked by repetitive stimulation of intralaminar thalamic nuclei, was thought to be the evoked equivalent of spontaneous spindle waves and spike-and-wave patterns (19,24,41,59,67). Subsequent studies, however, have suggested that spindle waves are more similar to the "augmenting" response, a pattern evoked by repetitive simulation of sensorimotor thalamic nuclei (58,75,76). From the point of EEG generation, this distinction is important because recruiting and augmenting responses have different voltage-versus-depth profiles in the cortex. Thus, a critical issue is the identity of synapses and neurons involved in the generation of these rhythmic patterns. If the thalamocortical synapses are the major source of the extracellular synaptic current, then the major sinks are expected to correspond to the anatomical targets of the corticopetal thalamic fibers.

Use of the approach just described for the hippocampus helped clarify these issues (Color Fig. 1.2) (44). The most striking aspects of the experiment shown in Fig. 1.2 is the general similarity of the spontaneous and evoked field events, which is independent of the initiating conditions. The spatial position of the major current sinks or sources are similar, independently which thalamic nucleus or hemisphere is being stimulated. The differences are expressed mainly in the latencies of the large sink-source pairs. Therefore, the similar spatiotemporal distribution of the main sinks and sources suggest that the major current flow derives from the activity of the intracortical circuitry. The neocortex, in essence, functions as a powerful amplifier during these oscillatory events. Because the thalamocortical network is in a metastable state during reduced activities of the brainstem and basal forebrain (55,77), a weak thalamic or callosal input is capable of recruiting a large population of intracortical neurons. The triggering input may even remain undetectable in the field, and the spread of activity reflects primarily the connectivity and excitability of the cortical circuitry rather than the nature of the initiating input (16,17).

The current source density (CSD) map and the associated multiple-site unit analysis also revealed that at least three dipoles were involved in the generation of the rhythmic field events (Color Fig. 1.3) (44). The most consistent dipole was characterized by a major sink in layer IV (dipole 2). When a surface-positive field component was present, it was associated with a major sink in layer VI and a source in layers II to III (dipole 1). The third, delayed dipole was represented by a surface-negative spike component and a corresponding sink in layers II to III (dipole 3). The relative strength of these respective sinks varied within single episodes of high-wave spike-and-voltage discharge (HVS) (see Fig. 1.3). Although the numerous cell types and the complexity of the intracortical circuitry makes identification of the cellular-synaptic origin of neocortical EEG potentials less accessible, these findings indicate that the use of simultaneous recording of field and unit activity is a proper method for the revelation of the synaptic-cellular mechanisms of extracellular current flow in the neocortex.

Calcium Spikes

In addition to the fast Na^+ spike, an important nonsynaptic event in neurons is a wide Ca^{2+}-mediated action potential. These Ca^{2+} spikes are generated in dendrites and do not propagate to the soma (89). It is believed that their major roles are to boost synaptic inputs and assist plastic modification of synapses (42,53,54,91). Ca^{2+} spikes represent an inward dendritic current and are large in amplitude (20 to 50 mV). They can occur synchronously with dendritic EPSPs, and for this reason they cannot be simply revealed or separated from EPSPs with extracellular recordings. Because Ca^{2+} spikes are activated by a voltage-dependent mechanism, intradendritic depolarization can trigger them.

Figure 1.4 illustrates *in vivo* recording from a distal dendrite of a hippocampal CA1 pyramidal neuron during theta oscillation (43). As the dendrite is progressively depolarized by intracellular current injection, the rhythmic synaptic potentials are superseded by large-amplitude Ca^{2+} events. Are such Ca^{2+} spikes triggered by physiological stimuli? There is evidence that this may well be the case. Patterned stimulation of the visual system evoked putative Ca^{2+} events in layer V pyramidal neurons of area 17 (37). Furthermore, intradendritic recordings during spontaneous SPW bursts revealed that the amount of depolarization, brought about by the converging active presynaptic afferent fibers to CA1 pyramidal cells, is sufficient to trigger voltage-dependent Ca^{2+} spikes (42). This new information, of course, indicates the need for the reinterpretation of the extracellular events illustrated in Fig. 1.1. Provided that Ca^{2+} spikes occur simultaneously in several neurons near the recording electrodes, these large inward currents can significantly contribute to the field sinks observed in the dendritic layers.

To date, the quantitative contribution of dendritic Ca^{2+} spikes to the field EEG has not been determined. They may be quite important in highly synchronous events, such as epilepsy, because synchronous Ca^{2+} spikes in neighboring neurons may be reflected in the field as large sinks. A complicating factor is that, in contrast to EPSPs, Ca^{2+} spikes can actively propa-

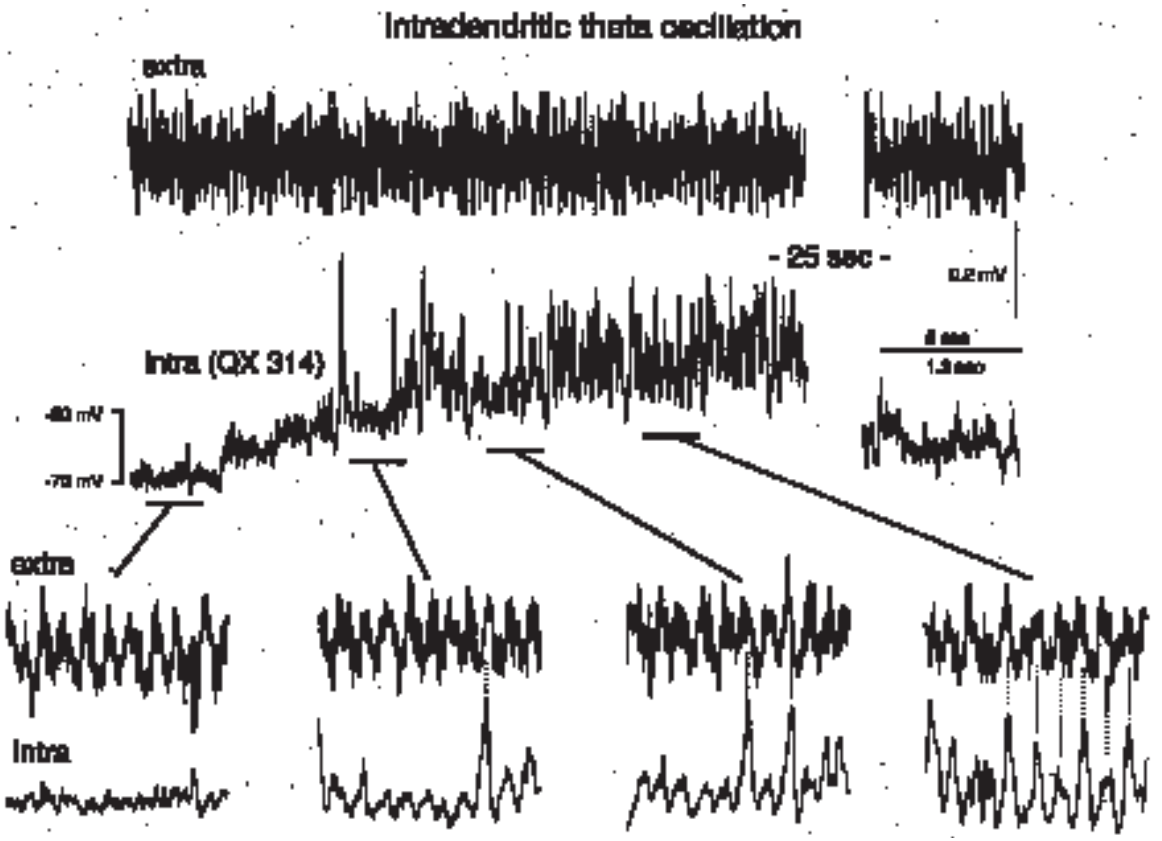

FIG. 1.4. Voltage-dependence of theta frequency oscillation in a hippocampal pyramidal cell dendrite. Continuous recording of extracellular (extra) and intradendritic (intra) activity in a CA1 pyramidal cell. Holding potential was manually shifted to progressively more depolarized levels by intradendritic current injection (0 to 0.8 nA). The marked epochs (*horizontal bars*) are shown at faster speed in the bottom records. The recording electrode also contained QX-314 to block Na^+ spikes (20 mM). Note large increase of intradendritic theta oscillation amplitude upon depolarization. The relationship of the putative high-threshold calcium spikes to the phase of extracellular theta waves in the CA1 pyramidal layer is indicated by *dotted lines.* (From Kamondi A, Acsády L, Wang X-J, et al. Theta oscillations in somata and dendrites of hippocampal pyramidal cells *in vivo:* activity dependent phase-precession of action potentials. *Hippocampus* 1998;8:244–261.)

gate, and large dendritic segments and dendritic locations distant from the initiating site may therefore also be involved.

Voltage-Dependent Intrinsic Oscillations

Experiments similar to that shown in Fig. 1.4 revealed that when intradendritic depolarization is sufficiently strong, the resonant property of the membrane may give way to a self-sustained oscillation of the voltage in the theta frequency range, even in the absence of network-driven theta activity. Intrinsic, voltage-dependent slow oscillations and theta frequency resonance have also been observed in somatic recordings of hippocampal pyramidal cells (49), thalamocortical neurons (63), stellate cells of the entorhinal cortex (2), and layer V pyramidal cells of the neocortex (73). In stellate cells, the main driving force of the oscillation is a persistent Na^+ current (2), whereas another depolarizing current (I_h), in conjunction with the low threshold Ca^{2+} current (I_T), is responsible for the maintenance of the cellular rhythm in thalamic neurons (6).

Voltage-dependent oscillatory activation of ionic channels has been shown also in the gamma frequency range. The membrane potential of sparsely spiny inhibitory interneurons in cortical layer IV can sustain a 40-Hz oscillation by sequential activation of a persistent Na^+ current, followed by a slowly inactivating K^+ conductance (50,51). Similar intrinsic oscilla-

tory properties have been shown in the intralaminar thalamocortical nuclei and GABAergic neurons of the nucleus reticularis *in vivo* (81) and in the dendrites of hippocampal pyramidal cells (65).

In most neurons, the voltage-dependent oscillation is below the threshold to trigger action potentials. However, when action potentials do occur, they are phase locked to the depolarizing portion of the oscillatory cycle. Because these intrinsic, oscillatory membrane fluctuations can occur simultaneously in a number of nearby neurons, their contribution to the extracellular EEG may be substantial. This is perhaps best illustrated in the "low-Ca^{2+}, high Mg^{2+}" model of epilepsy, in which all synaptic activity is completely blocked and the large rhythmic extracellular field potentials are caused exclusively by the voltage-dependent fluctuation of pyramidal cells, coordinated by ephaptic (nonsynaptic) transmembrane effects (33).

INTRINSIC SPIKE AFTERHYPERPOLARIZATIONS: THEIR CONTRIBUTION TO CORTICAL DELTA WAVES

In addition to voltage changes, perturbation of the intracellular concentration of one ion species may trigger influx of other ions by activation of ligand-gated channels. The large Ca^{2+} influx, in association with a dendritic Ca^{2+} spike, is followed by the suppression of fast spikes and hyperpolarization of the membrane caused by activation of Ca^{2+}-mediated increase of K^+ conductance (38,72). These burst-induced afterhyperpolarizations (AHPs) are frequently larger in amplitude and of longer duration than synaptic events. A logical progression of thought is to conclude that they should also be considered important source of the extracellularly recorded EEG potential.

Slow, large-amplitude delta waves (1 to 4 Hz) have been among the most frequently studied neocortical EEG patterns. These irregular, semirhythmic or rhythmic patterns are most frequently observed during stage 4 sleep in the normal brain. The rhythmicity of the cortical delta waves is explained by the triggering effect of the periodic quasisynchronous thalamocortical inputs (22,78). The thalamus can maintain a rhythmic oscillation in the delta range because of the intrinsic properties of thalamocortical neurons and their network connectivity with the GABAergic reticular nucleus (22,78). In short, the "rhythm generator" of delta waves is the thalamus, whereas the "voltage generator" is the neocortex; this situation is analogous to that for sleep spindles and spike-and-wave patterns, discussed earlier.

Delta waves occur with largest amplitude in deep (layer V) cortical layers, and they are recorded as negative waves on the neocortical surface or the scalp. Depth profile measurements in the neocortexes of the cat (15,40,71), rabbit (68), and rat (10,87) revealed that surface negative–deep positive delta waves during slow-wave sleep correlate with the suppression or cessation of discharges of layer V pyramidal neurons. At the intracellular level, the deep positive waves are correlated with hyperpolarization of pyramidal cells (21).

The depth profile of the slow delta waves and the associated unit activity are compatible with the hypothesis that the extracellularly recorded delta waves reflect inhibition of pyramidal cells mediated by GABAergic interneurons (3,69,74). GABA released at the somata of layer V pyramidal cells would open the Cl^- channels and produce an active outward current whose extracellular spatial summation corresponds to deep positivity. A simultaneously occurring passive inward current at the distal dendrites would set up extracellular (surface) negativity. Indeed, with their widespread action, GABAergic interneurons may play an important role in affecting large numbers of pyramidal cells, as discussed earlier. Because subcortical inputs also terminate on GABAergic interneurons (29,30), the subcortical afferents may globally affect the whole neocortical mantle.

A major problem with this "classic" model of delta wave generation is the lack of direct supportive evidence. An explicit prediction of the GABA-interneuron-pyramidal cell model of slow wave generation is that GABAergic cells should fire during the deep positive delta waves. However, experiments directly addressing this issue have failed to find such a correlation in the rat neocortex (10). All putative, physiologically identified neocortical interneurons decreased their firing rates during the deep positive slow waves. Although the duration of the GABA effect may outlast the action potentials by tens of milliseconds (23), the effect may be too short for the postulated delta wave–associated GABA-mediated somatic hyperpolarization. $GABA_B$-receptor–mediated IPSPs may be a possible candidate for producing this hyperpolarization.

An alternative nonsynaptic explanation of the origin of delta wave generation is based on the summation of long-lasting AHPs of layer V pyramidal neurons (10,77). During sleep, pyramidal cells of the neocortex often fire bursts in response to rhythmic thalamic volleys (22,78), and these bursts, in turn, can trigger Ca^{2+}-mediated K^+-conductance changes. The long-lasting nature of AHPs favors the summation of outward somatic currents of individual pyramidal cells, which results in a local positive field in deep layers. Such extracellularly summated currents were hypothesized to form the basis of slow delta EEG waves recorded during sleep (14). Delta waves occur only during slow-wave sleep because subcortical neurotransmitters, such as basal forebrain and brainstem cholinergic neurons, locus ceruleus cells, neurons of

the raphe nuclei, and hypothalamic histaminergic neurons (1,5,10,34,77), are released mostly in the awake brain, and the common property of these neurons is to reduce the calcium-mediated potassium conductance (20,33,52). These actions of subcortical neurotransmitters at the cellular level therefore result in the blockade of delta waves. Using whole-cell recordings *in vivo,* Metherate and Ashe (57) could differentiate between IPSPs and AHPs in cortical neurons of the intact brain. First, they showed, by intracellular injection of cesium, that a large part of the delta EEG wave results from a K^+ current. Second, stimulation of the cholinergic nucleus basalis caused an effect that mimicked the cesium effect. Third, cesium injection blocked the nucleus basalis stimulation effect. These findings directly support the suggestion that delta wave–concurrent hyperpolarizations result from the calcium-activated K^+ current, rather than from GABA-mediated IPSPs. Overall, these examples illustrate that knowledge of the intrinsic properties of the neurons is as important for the identification of sources of the extracellular ion flow as knowledge of synaptic potentials and anatomical circuitry.

OTHER NONSYNAPTIC NEURONAL EFFECTS

Synchronous discharge of large neuronal populations is often associated with large-amplitude extracellular potentials (millivolts to tens of millivolts) and steep voltage-versus-depth gradients. These large field currents, in turn, can influence the activity of nearby neurons by changing their transmembrane voltage (ephaptic effects). Measurement of transmembrane potential changes (as opposed to potentials relative to a distant ground) indicated that such extracellular current loops can depolarize neurons to spike threshold under certain conditions (33,83). Computer simulations of multiple neurons, embedded in a conductive medium, show that such a mechanism is plausible with observed estimates of extracellular resistivity (84). Of importance is that the voltage gradient across pyramidal cell bodies during physiological SPWs and especially during epileptic or interictal spikes is larger than experimentally induced voltage gradients that are known to affect cellular excitability. It is possible, although direct experimental evidence is not available yet, that ephaptic effects could recruit neurons to fire that are otherwise not sufficiently activated by synaptic inputs alone (9,33).

Neuron–Glia Communication

The glial syncytium (astrocytes) is connected through gap junctions, which allow the direct spread of current and the diffusion or transport of small molecules. Although the role of concerted changes in membrane potentials of glial cells in the generation of extracellular currents under physiological conditions has not been studied extensively, work on neuron–glia interactions indicate that the glial syncytium may contribute to the slow field patterns in an important way. Intercellular coupling through gap junctions is required for both propagating Ca^{2+} waves and spreading depression (62). The traveling Ca^{2+}, waves, in turn, can trigger calcium influx into neurons (61,62). The neuron–glia dialogue *in vivo* may be responsible for postictal depression (8,26,35,36,48,82). The increased $[K^+]_O$, resulting from intensive neuronal activity during epileptic afterdischarge, may trigger propagating waves in the astrocytic network, which are reflected by the slowly spreading sustained potentials. In turn, astrocytes at the front of the propagating depolarization wave release more K^+ (47,56), resulting in a large depolarization of neurons. The ensuing depolarization block of spike generation contributes to the termination of the afterdischarge and is regarded as the cause of the consequent "postictal depression" of the EEG (8,82).

Direct currents (DC) or ultraslow change of the extracellular voltage cannot be recorded with conventional EEG devices with high pass-filtered inputs. Nevertheless, the relatively quick changes in the DC level, such as epilepsy-associated spreading depression (8), could be identified mistakenly as slow delta or faster "waves," because of the differential effect of the high-pass filters.

Neuron–glia communication may also contribute to physiological EEG patterns. Sensory evoked responses in scalp recordings with DC amplifiers and nonpolarizing electrodes often contain reliable and relatively long-lasting DC changes, usually referred to as *Bereitschaftpotential* (46) or *contingent negative variation* (88). It remains to be revealed whether and to what extent glial depolarization contributes to these evoked patterns.

Ultrafast Cortical Rhythms

SPW-associated depolarization of hippocampal CA1 neurons sets into motion a short-lived, dynamic interaction between interneurons and pyramidal cells. The product of this interaction is an oscillatory field potential (ripple) within the stratum pyramidale hippocampi and a phase-locked discharge of the CA1 network at 200 Hz in the rat (11). SPW-related ripples are also present in higher mammals, including humans (7). The specific synaptic currents, mediating the high-frequency oscillation, are largely mediated by rhythmic, synchronized IPSPs near the soma of CA1 neurons. The mechanism by which highly coherent discharge of pyramidal cells is

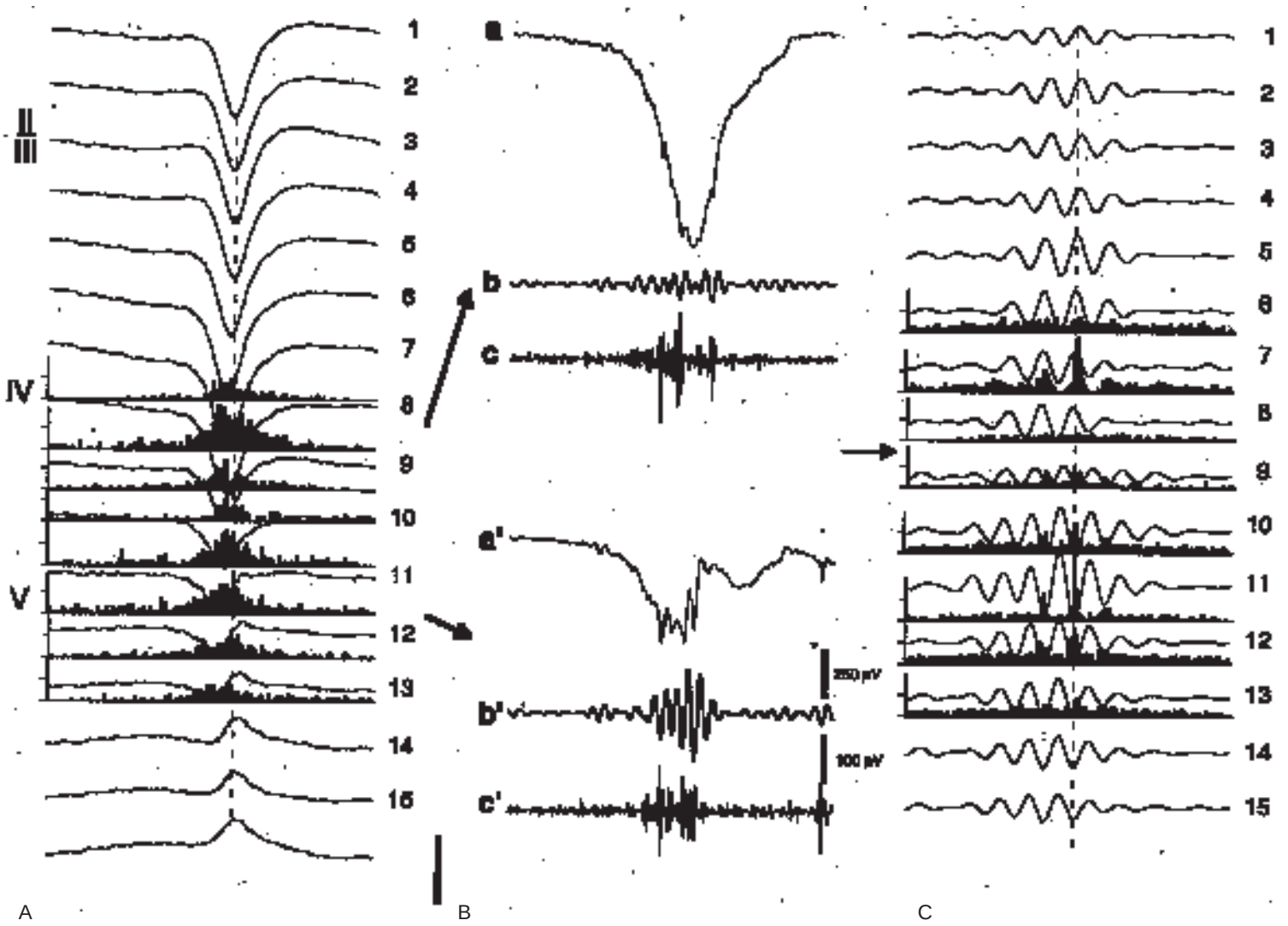

FIG. 1.5. High-wave spike-and-voltage (HVS) pattern—induced fast field oscillation (400- to 500-Hz ripple). **A:** Averaged HVS and associated unit firing histograms from layers IV to VI. **B:** Wide-band (a and a′; 1 to 5 kHz), filtered field (b and b′; 200 to 800 Hz), and filtered unit (c and c′; 0.5 to 5 kHz) traces from layer IV and layer V. **C:** Averaged fast waves and corresponding unit histograms. The field ripples are filtered (200- to 800-Hz) derivatives of the wide-band signals recorded from 16 sites. Note sudden phase-reversal of the oscillatory waves (*arrow*) and phase-locked discharges of units in all cortical layers (*dashed line*). (From Kandel A, Buzsáki G. Cellular-synaptic generation of sleep spindles, spike-and-wave discharges and evoked thalamocortical responses in the neocortex of the rat. *J Neurosci* 1997;17:6783–6797.)

brought about over the entire dorsal hippocampus during the ripple is not understood (18). Three hypotheses have been advanced to explain the spatial coherence of fast ripples. According to the first, the CA3 output produces a voltage-dependent fast discharge in the interneurons, and synchronization of the interneurons is mediated by gap junctions (45). The second explanation, which is based on the reciprocal connections between the interneuronal and pyramidal cell populations, is that fast oscillatory discharges in interneurons would, again, be brought about by the ramp-like depolarizing CA3 output. Chance discharge of just a few CA1 pyramidal cells within approximately 1 millisecond, is hypothesized to reset ongoing oscillatory spiking in the target interneurons and generate a short-lived coherent discharge (90). According to the third hypothesis, zero time lag synchronization of pyramidal neurons is brought about by assumed gap junctions between their axons (25).

Fast field oscillations (300 to 500 Hz) are also present in the neocortex, particularly in association with sleep spindles and spike-and-wave patterns (Fig. 1.5) (44). The maximum amplitude of the field oscillation occurs in layer V, and the ripple waves reverse in phase in the upper part of layer V. The discharge of pyramidal cells are phase locked to the ripples. The physiological significance of the fast ripples has yet to be clarified. It may be that the fast oscillation of interneurons during a strong network drive provides a dissipative mechanism to decelerate and limit population synchrony of pyramidal cells and to prevent the all-or-none discharge of the activated pyramidal cells by protracting the recruitment process and limiting the number of participating neurons.

Because conventional EEG devices are limited in their frequency response, these fast events are often impossible to discern reliably from human scalp recordings (21a). In addition, volume conduction of these fast events is quite limited because of the low-pass filtering properties of lipid membranes, as discussed earlier. Nevertheless, their detection may be of clinical importance because fast oscillatory events may herald the spread or termination, or both, of epileptic activity (8,27).

SUMMARY

Field potential measurements provide an excellent tool for the exploration of network activity in the intact brain. The various rhythms and intermittent EEG potentials can be regarded as time reference points to relate neuronal discharges of single cells. These field potentials (local or global EEG potentials) emerge as a result of synchronous (i.e., simultaneous) changes of the membrane potential of neighboring neurons. Synchronous membrane potential changes can be brought about by synaptic activity (EPSPs and IPSPs) or Ca^{2+} spikes, or they can emerge as a result of intrinsic neuronal patterns (oscillations, burst-induced afterpotentials). The isolated cortical tissue maintains burst discharges of pyramidal cells, followed by long-lasting afterhyperpolarization. The synchronous hyperpolarizations in neighboring pyramidal cells can be measured as slow waves in the extracellular space (synchronization). In addition, these subcortical neurotransmitters induce a gamma frequency oscillation (desynchronized pattern) by activating networks of inhibitory interneurons.

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Chapter 2

Cortical Generators and EEG Voltage Fields

John S. Ebersole

The Source of Electroencephalographic Potentials
Physical Factors Determining Scalp Electroencephalographic Patterns
Electroencephalographic Source Localization Principles
Deep Sources and Scalp Electroencephalography
Functional Factors Determining Scalp Electroencephalography Patterns
Propagation
Effect of Reference on Electroencephalographic Fields
Conclusions
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THE SOURCE OF ELECTROENCEPHALOGRAPHIC POTENTIALS

Cerebral sources of electroencephalographic (EEG) potentials are three-dimensional volumes of cortex. These sources produce three-dimensional potential fields within the brain. From the surface of the scalp, these can be recorded as two-dimensional fields of time-varying voltage. In order to localize and characterize cortical generators of the EEG, the physical and functional factors that determine the voltage fields that these sources produce must be appreciated. In Chapter 1, the cellular mechanisms underlying brain electrical activity were reviewed. This chapter changes the scale from the microscopic to the macroscopic, for the EEG can reveal cortical activity only at a macroscopic level. When considering the combined electrical activity of approximately 10^8 neurons in a cortical area of several square centimeters, rather than a single cell or cortical column, it is necessary to understand several important concepts in order to interpret an EEG properly.

The principle generators of EEG fields that are measured on the surface of the brain or at the scalp are graded synaptic potentials: namely, excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs), of pyramidal neurons (4,6,10,11,13). At the synaptic site of an EPSP, there is an active current sink. Positive ions rush into the cell to depolarize the local membrane. At the same time, at a more distal portion of the cell, a passive current source, consisting of current flow out of the cell, completes a closed circuit. The current flows in the opposite direction with an IPSP. A local active current source is coupled with a distant passive current sink. These currents, generated by synaptic activity, pass through the extracellular and intracellular spaces and set up a potential field around the cell. Near a current sink, the extracellular space is relatively negative, whereas near a current source, it is positive (Fig. 2.1). The current flow and associ-

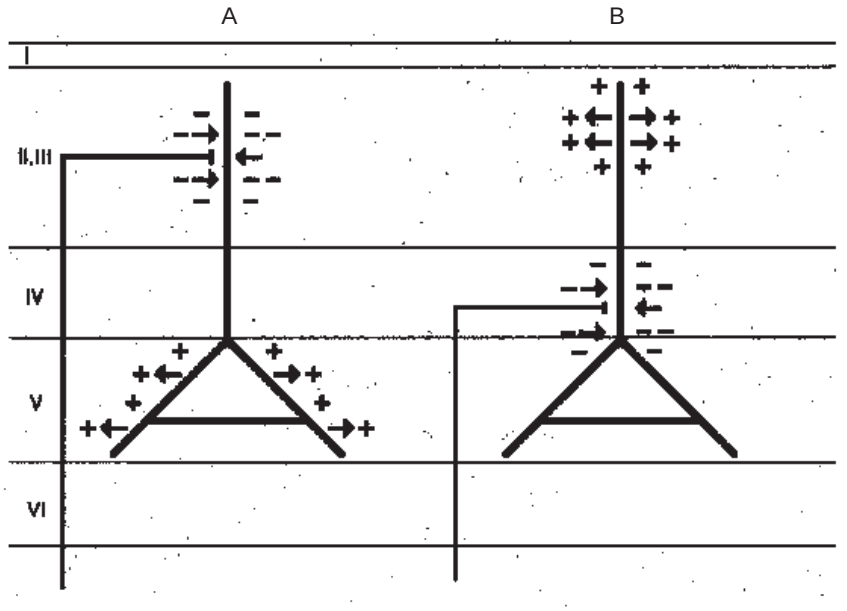


FIG. 2.1. Generation of extracellular voltage fields from graded synaptic activity. **A:** Excitatory postsynaptic potential (EPSP) at the apical dendrite is associated with a flow of positive ions into the cell (an active current sink) and an extracellular negative field. A passive current source at the level of the cell body and basal dendrites is associated with an extracellular positive field. **B:** EPSP on the proximal apical dendrite at the level of cortical layer IV is associated with and active current sink and an extracellular negative field. A passive current source at the distal apical dendrite in layers II and III is associated with an extracellular positive field.

ated field potential around individual cells are very small, and they would not be recordable at the scalp except for the fact that the pyramidal cells are all aligned perpendicular to the surface of the cortex. Because of this geometric arrangement, the voltage fields produced by individual cells can summate to produce a potential large enough to be recorded some distance from the generators, if the activity is synchronous. Summation of potential fields as a result of synaptic currents can more readily occur than can that resulting from fast sodium action potentials because the former events are relatively long in duration (10).

To a first approximation, EEG fields are generated by the large, vertically oriented pyramidal neurons located in cortical layers III, V, and VI. For example, an EPSP at an apical dendrite of a large pyramidal cell that extends through several cortical laminae would produce an active current sink and a negative local field potential superficially in the cortex, whereas the passive current source at the cell body or basal dendrites would result in a positive field potential in the deeper cortical laminae (see Fig. 2.1*A*). The same synaptic event is thus viewed as potentials with opposite polarity, depending on the location of the recording electrode. This juxtaposition of negative and positive charge and resultant current flow is similar to that of a dipole. Pyramidal cells can be thought of as a population of vertically oriented dipoles. Therefore, voltage fields recorded on the surface of the head usually have a dipolar configuration–that is, two maxima: one negative and one positive. The amplitude and the polarity of the potential recorded from the same event likewise depend on the location of the electrode in relation to the dipole source.

The cortex is a multilaminar structure. Current sinks and sources can arise in different locations, depending on the type of input into the cortex. Excitatory input into layer IV, a primary sensory receiving lamina, would produce a local negativity that is reflected in a cortical surface positivity (see Fig. 2.1*B*). Thus, the early components of normal sensory evoked potentials, for example, are commonly surface positive. Epileptic spikes, on the other hand, are commonly surface negative because of depolarization of the superficial laminae (see Fig. 2.1*A*). Electrodes in deeper cortical layers, in the underlying white matter, or even on the scalp at the opposite side of the head record a positive potential. Subsequent repolarization and depolarization cycles, often caused by recurrent excitation and inhibition among laminae, result in the typical sequence of a negative spike followed by a positive afterpotential, which is in turn followed by a negative wave. Spikes that originate in deeper cortical layers may show an initial surface positivity. Propagation of activity from one layer to another also changes the laminar arrangement of extracellular voltage. Mechanistically, a large population of active neurons can be thought of as a collection of oscillating dipoles.

PHYSICAL FACTORS DETERMINING SCALP ELECTROENCEPHALOGRAPHIC PATTERNS

A number of factors determine whether the extracellular voltage field produced by a region of cortex can be recorded from scalp EEG electrodes. These factors are both physical and functional. Physical factors include

source location, orientation, and area. Functional factors include potential amplitude, frequency, and synchrony. A transient potential, such as an epileptic spike, serves as a good example for appreciating these relationships between source character and EEG fields.

It is both logical and correct that the scalp EEG voltage field should be related to the location of its cortical source. However, this relationship is not straightforward. An unfortunately simplistic assumption in traditional EEG interpretation is that the source of an EEG potential must necessarily underlie the electrode recording it; hence the practice of referring to epileptic discharges by the name of the electrode recording the maximal potential. This assumption is true only in limited cases. That a negative field maximum is recorded from a particular electrode does not necessarily mean that the spike source is beneath it, as discussed in detail later.

The importance of source area in determining whether cortical activity will be recordable on the scalp EEG has been appreciated for some time. Using a simulated cortical source beneath a piece of fresh skull, Cooper et al. (3) determined that 6 cm^2 of synchronously active area are probably necessary to produce a scalp-recordable field. Gloor (7,8) also discussed the importance of source area in appreciating EEG fields at the scalp in his dissertation of the "solid angle" theory. In essence, only when a cortical region subtends a large enough solid angle, from the perspective of a given electrode, will that electrode record the potential generated by it. Ebersole and Pacia (5,12), in a series of simultaneous intracranial and scalp recordings, showed that for individual epileptic spikes, the 6 cm^2 estimate was accurate (Figs. 2.2 and 2.3). What was demonstrated in addition, however, was that the area of sources for typical scalp interictal spikes is often substantially larger, often encompassing 20 cm^2 or more of gyral cortex (see Figs. 2.13 and 2.14).

Because of the attenuating properties of the intervening skull, spatial summation of cortical activity is critical for producing a voltage field recordable from the scalp. As commonly observed in candidates implanted for epilepsy surgery, most of the cortical activity recorded from subdural or depth electrodes is not evident in the scalp EEG (1,9). This is not necessarily because the amplitude of the individual cortical potentials is too small; more often, it is because the area of the cortical generator is not large enough. Although they are not well appreciated, this factor, source area, and a closely related factor, source orientation, are the two most important variables in determining whether cerebral potentials are recordable from the scalp. The EEG can detect small and remote sources, but this usually requires the averaging of hundreds to thousands of repetitive signals, such as potentials evoked by sensory stimuli.

Spatial summation of the voltage field generated by multiple cortical sources is three-dimensional. If adjacent active cortical areas have the same orientation, their voltage fields combine, and the resultant voltage field measured at the scalp is the linear sum of the fields of both sources. If, however, adjacent active regions of cortex have a different orientation, the voltage fields summate in relation to the geometry of their respective field vectors. For example, if two cortical areas have an opposite orientation, such as the two sides of a sulcus, cancellation occurs, and no voltage field from them is evident at the scalp (Fig. 2.4, source 3).

Source area is maximal for a given electrode (and the solid angle is maximal) when the orientation of the active cortical region is face-on. This is usually the case when the resultant voltage field is radial and the electrode is directly above the source (see Fig. 2.4, source 2). In this instance, the electrode records the field maximum. As the orientation of a cortical source becomes progressively less radial and more tangential to a recording electrode, that electrode is able to record a voltage field of progressively less amplitude. If the source is directly below an electrode but it is oriented perfectly tangential to the recording electrode, the electrode records no potential, because this location is on the zero isopotential line of the source's scalp field (see Fig. 2.4, source 1 and 4). To summarize the concepts illustrated in Fig. 2.4, cortical sources 4-2 and 4-3 produce voltage fields with a net radial orientation, and, correspondingly, they have a negative field maximum on the scalp directly above them. Sources 4-1 and 4-4 result in a tangential field. The zero isopotential line is located on the scalp immediately above these sources, whereas negative and positive maxima are displaced on either side. In general, midline interhemispheric and basal cortical sources tend to be tangential; lateral convexity cortical sources tend to be radial. Sources on one bank of a sulcus in the lateral cortex may be tangential; however, epileptiform sources are commonly so large that both banks of the sulcus are activated. These opposing fields cancel, as depicted in source 4-3, which leaves only the radial field from the sulcus bottom to predominate.

Taken from the broader perspective of electrodes over the entire head, a radial source produces one field maximum directly above it and another field maximum of opposite polarity on the diametrically opposite side of the head. For a superficial cortical source, the scalp maximum nearest the source is significantly greater in amplitude than that on the opposite side of the head. The negative field voltage gradient is steeper, and the negative

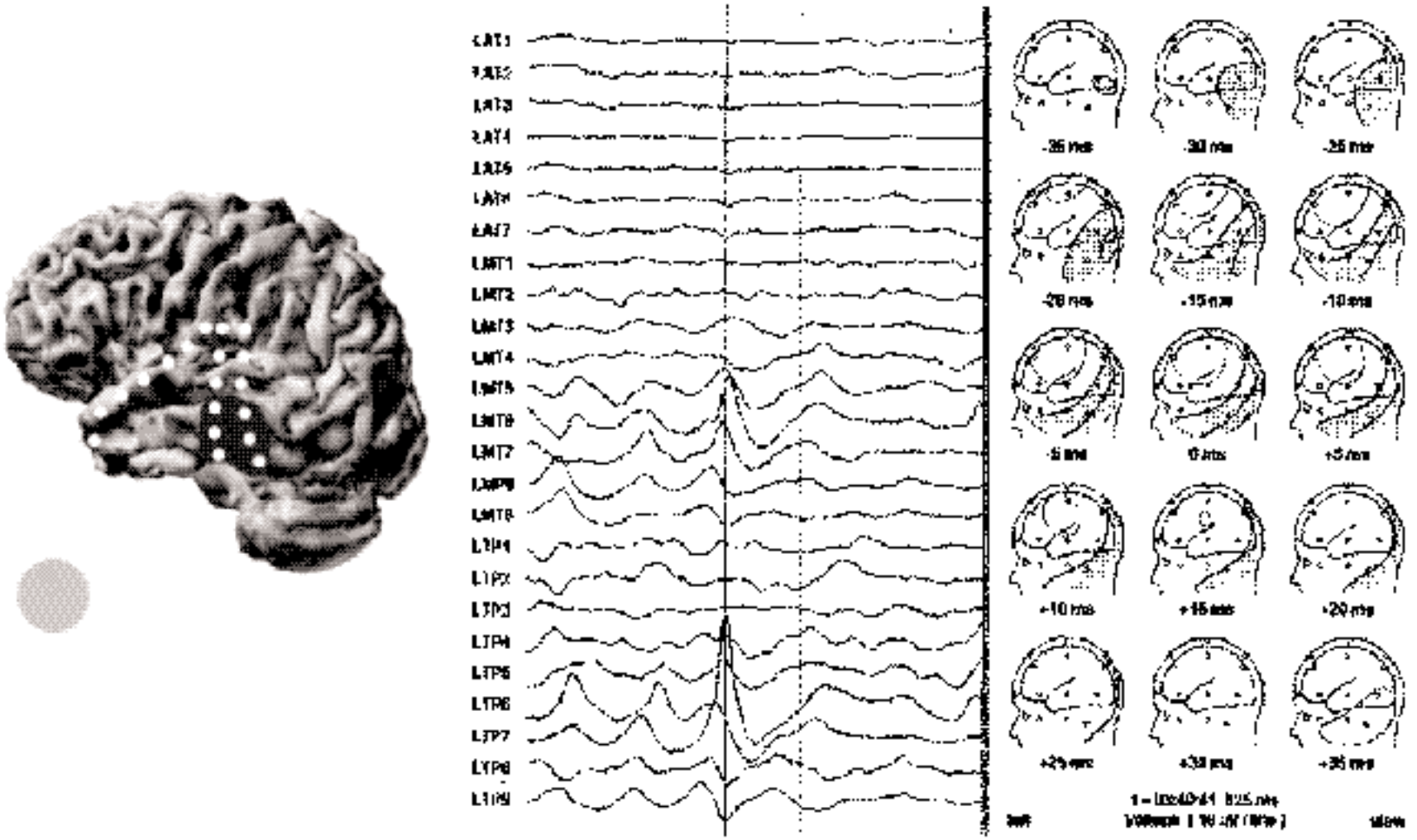


FIG. 2.2. Left: Three-dimensional magnetic resonance imaging (MRI) reconstruction of the brain, illustrating the subdural electrode placements in a patient with left temporal lobe epilepsy. The shaded cortical area represents an estimate of the spike source at the time of the cursor. The shaded circle defines 6 cm^2. **Right:** Intracranial electroencephalogram showing a negative (up) spike involving subdural electrode contacts LMT 5 to 7 and LTP 5 to 7. the map sequence depicts simultaneous scalp voltage topography at 5-millisecond intervals, centered on the cursor, spanning 70 milliseconds. Note that there is no appropriate scalp field associated with the cortical spike.

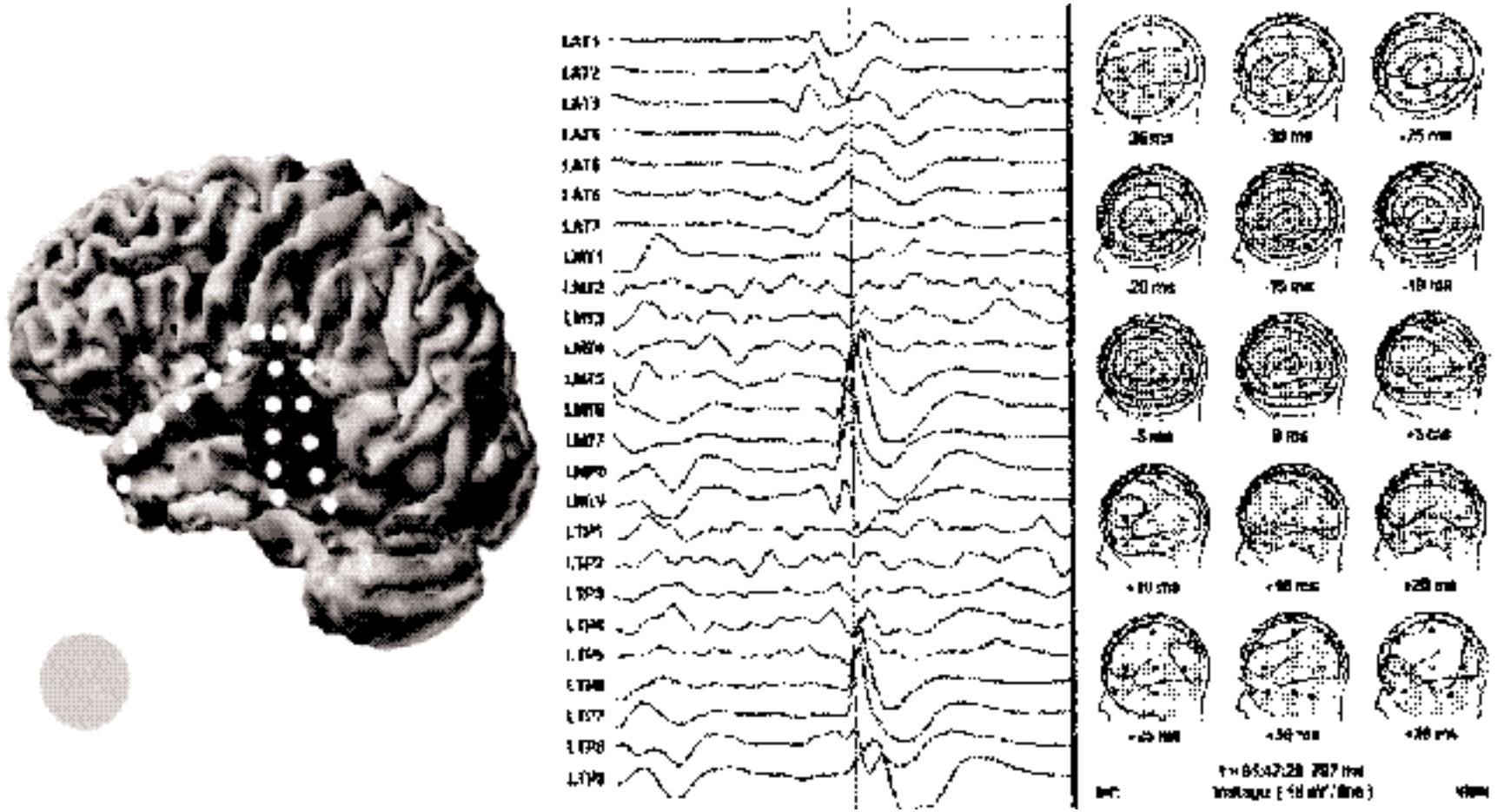


FIG. 2.3. **Left:** Illustration of subdural electrode placements as in Fig. 2.2. The shaded cortical area is an estimate of the spike source at the time of the cursor. **Right:** Intracranial electroencephalogram showing a negative spike (up) involving subdural electrode contacts LMT 6 to 9 and LTP 6 to 8. Map sequence depicts simultaneous scalp voltage topography at 5-millisecond intervals, centered on the cursor, spanning 70 milliseconds. Note that the cortical spike source area is larger than in Fig. 2.2 and that a voltage field with a midtemporal negative maximum is recorded from the scalp.

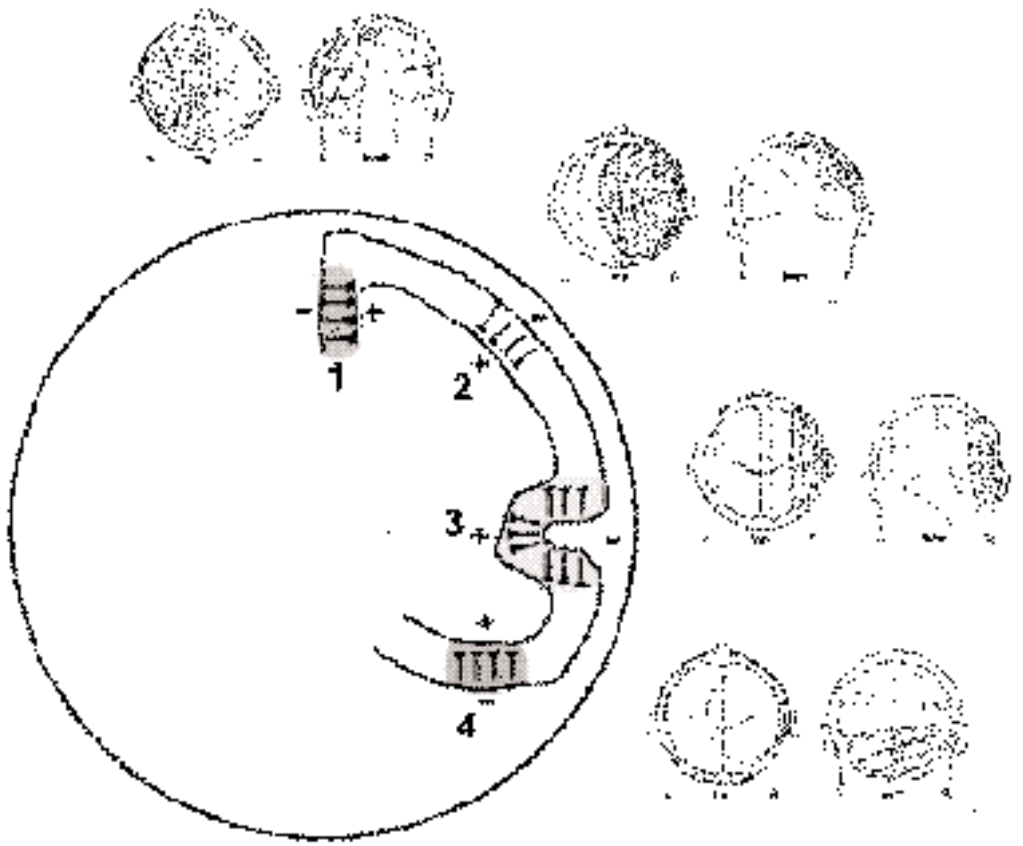


FIG. 2.4. Schematic of a brain cross-section, illustrating four representative cortical electroencephalographic (EEG) sources. Note that the alignment of the pyramidal cells (and thus the EEG voltage field) is orthogonal to the orientation of the cortical surface. Minus (–) and plus (+) signs depict the polarity of the epileptiform potentials generated by these sources. Top and back views of the head show the scalp voltage field generated by each source. The shaded area denotes field polarity (speckled represents negative). Sources 2 and 3 produce radial fields, and the negative voltage maximum is directly above them. Fields from opposing sulcal walls cancel each other in source 3, leaving the radial component from the sulcus bottom to dominate. Sources 1 and 4 produce tangential fields. No voltage is recorded directly above them; instead, negative and positive voltage maxima are displaced to either side.

field size is smaller than for a deeper radial source (Fig. 2.5). In the case of a spike, for example, the negative field maximum above the source is of greater amplitude than is the positive maximum on the other side of the head. For cortical sources whose net orientation is progressively more tangential, the nearest field maximum is progressively displaced away from the region directly above the source. Conversely, the field maximum of opposite polarity moves progressively closer (Fig. 2.6). For a source that is tangential to the skull, both maxima are displaced equally in opposite directions on either side of the source, and the fields are of equal amplitude. The distance between the two maxima is dependent on the depth of the source: The deeper the source, the farther apart are the maxima, and vice versa (Fig. 2.7). The simplistic assumption that the cortical generator underlies the voltage field maximum is not true for tangentially oriented sources. This is a very important concept. Localization and even lateralization are commonly false when cortical sources have an orientation that is even partially tangential.

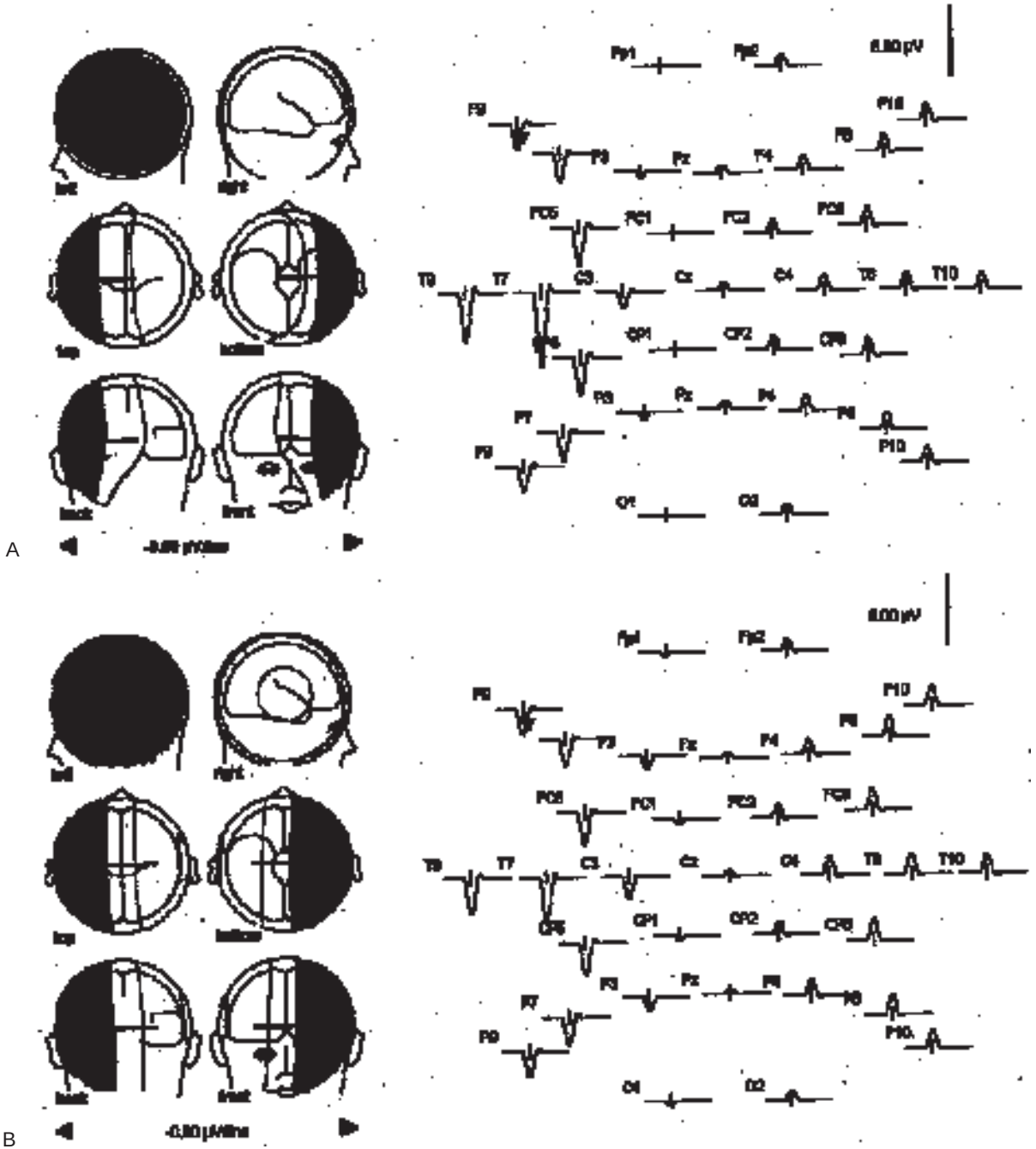


FIG. 2.5. **A:** Computer simulation of the scalp spike voltage field produced by a superficial, radially oriented dipole source (*dot* represents dipole source; *vector* from dot represents source orientation) in the left temporal lobe. Note that the negative field (hatched area) has a steep voltage gradient and a maximum directly above the source. A weak positive field with a shallow voltage gradient exists on the opposite side of the head. Electroencephalographic (EEG) traces of the simulated spike are shown at right. Note the high-amplitude left temporal negative spike (downward deflection in this and following simulations) and low-amplitude right temporal positive potential (upward deflection). (Simulation of EEG traces and voltage field by a forward dipole solution through a three-shell head model was accomplished with "Dipole Simulator" by P. Berg and M. Scherg, see Chapter 23.) **B:** Similar computer simulation of the scalp voltage field produced by a deeper, radially oriented dipole source. Note that the negative field is larger and has a less steep voltage gradient, but the maximum remains directly above the source. The positive field on the opposite side of the head is now of higher amplitude. EEG traces show a lower amplitude left temporal spike and a higher amplitude positive potential.

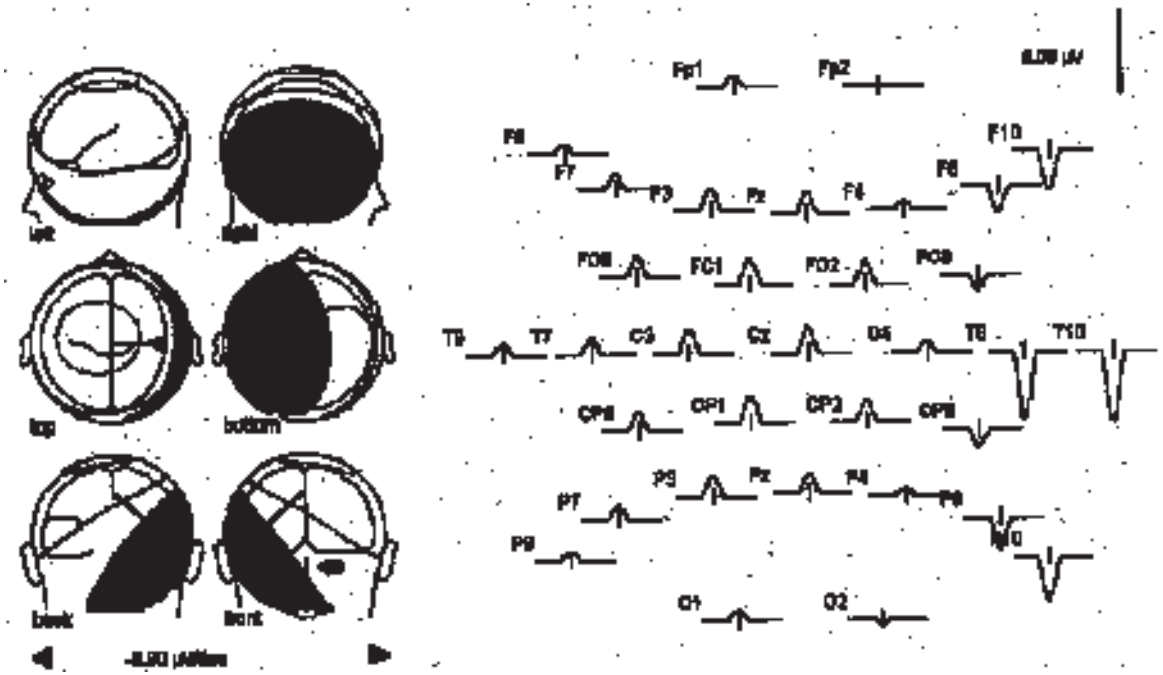
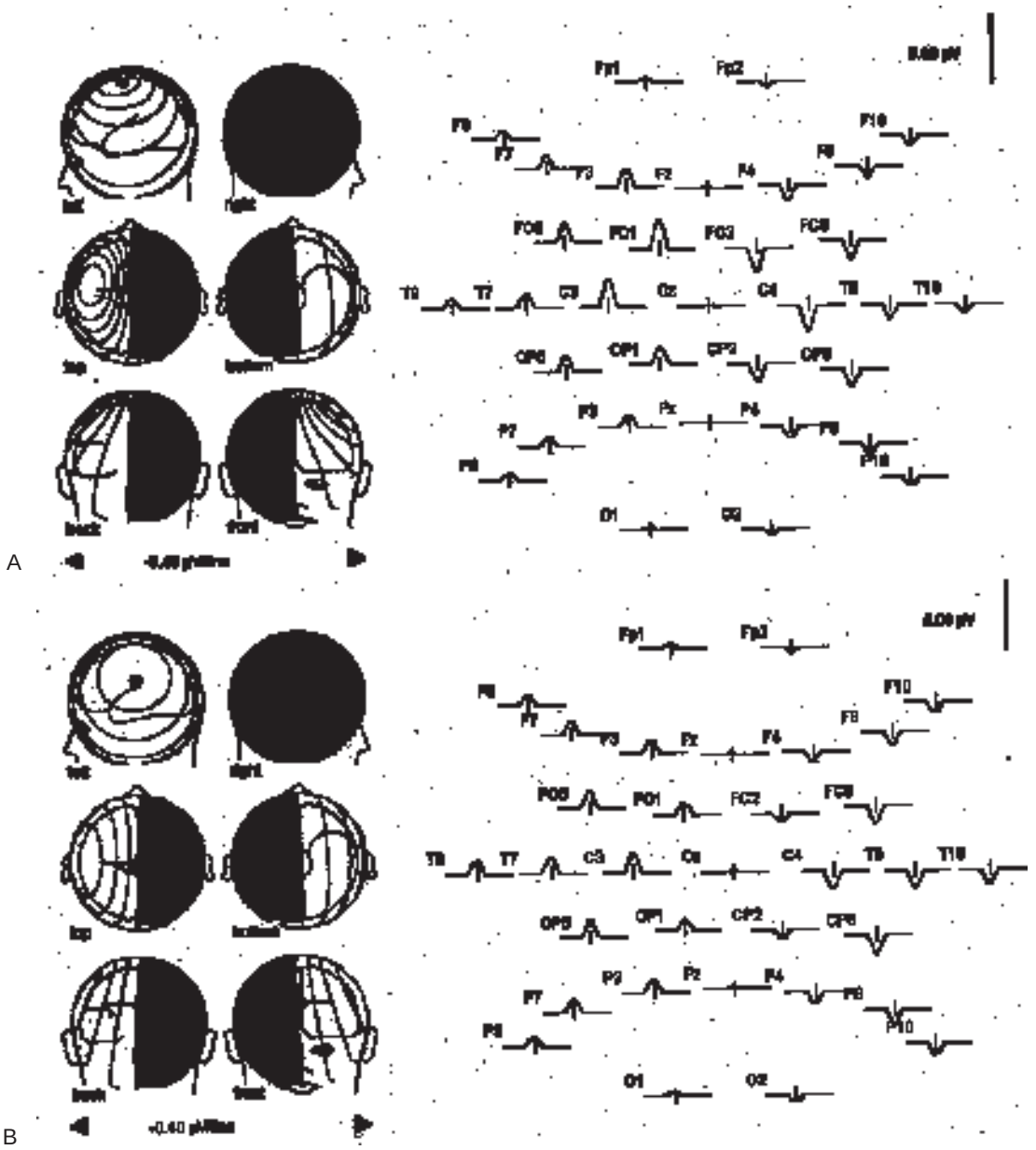


FIG. 2.6. Computer simulation of the scalp spike voltage field produced by a superficial oblique-oriented dipole source (*dot* represents dipole source; *vector* from dot represents source orientation) in the right temporal lobe. Note that the negative field (hatched area) has a steep voltage gradient and a maximum that is displaced downward onto the subtemporal scalp region. A weaker positive field with a shallow voltage gradient has a vertex-located maximum. Electroencephalogram (EEG) traces of the simulated spike are shown at right. Note high-amplitude right subtemporal and temporal negative spike (downward deflection) and the lower amplitude, more widespread vertex positive potential (upward deflection). (Simulation of EEG traces and voltage field by a forward dipole solution through a three-shell head model was accomplished with the "Dipole Simulator" by P. Berg and M. Scherg, see Chapter 23.)



A

B

FIG. 2.7. A: Computer simulation of the scalp spike voltage field produced by a superficial tangentially oriented dipole source (*dot* represents dipole source; *vector* from dot represents source orientation) in the interhemispheric region. Note that both negative (hatched area) and positive fields have a steep voltage gradient and that their maxima are relatively close together and symmetrically displaced on either side of the fissure. Electroencephalogram (EEG) traces of the simulated spike are shown at right. Note high-amplitude right central negative spike (downward deflection) and left central positive spike (upward deflection). Midline Cz electrode directly above the source records no significant activity. (Simulation of EEG traces and voltage field by a forward dipole solution through a three-shell head model was accomplished with "Dipole Simulator" by P. Berg and M. Scherg, see Chapter 23.) **B:** Similar computer simulation of the scalp voltage field produced by a deeper, tangentially oriented dipole source. Note that both the negative and positive fields have a less steep voltage gradient and that their maxima are farther apart and symmetrically displaced on either side of the fissure. EEG traces show a lower amplitude negative and positive spikes and no significant midline voltage.

ELECTROENCEPHALOGRAPHIC SOURCE LOCALIZATION PRINCIPLES

In view of the previous discussion, it becomes obvious that a single voltage field maximum cannot be used to define the location or orientation of a cortical EEG generator. In all instances, except for a purely radial source, the EEG field maxima are displaced from a position directly above it. To characterize a cortical source, the location of both field maxima, negative and positive, and their relative strengths must be taken into consideration. Noting the relative location of these two voltage field maxima provides the easiest and most accurate assessment of source orientation. A three-dimensional line drawn between the two maxima identifies the orientation of the field. Accordingly, the net orientation of the cortex generating the field is orthogonal to this line (see Figs. 2.5, 2.6, and 2.7). As a first approximation, the center of the cortical source should lie somewhere along this three-dimensional line. The amplitude and gradient of the field maxima determines this location–that is, the depth of the source. The source should be proportionately closer to the field maximum of greater amplitude. In the case of sources with tangentially oriented fields, the separation of the negative and positive maxima is dependent on the depth of the source. A three-dimensional line connecting the maxima will travel deeper through the head when the maxima are farther apart (see Fig. 2.7). The center of the source should, again, lie along this line proportionately closer to the field maximum of greater amplitude. Thus, by simply inspecting the scalp voltage topography of any EEG potential, much can be learned about the cortical source generating it.

DEEP SOURCES AND SCALP ELECTROENCEPHALOGRAPHY

Whether an EEG from sources deeper than the most superficial cortex can be recorded continues to be debated (2,7). Recording scalp potentials from deep structures depends on the same factors, and the more important are, again, source area and orientation. Because physiological signals from the cortex are limited in amplitude, effective source area becomes increasingly more important as source depth increases. This argument is particularly relevant in the discussion of the origin of temporal lobe spikes in mesial temporal epilepsy. Because the hippocampus is a rather small and deep structure that is curved in shape, properties that would tend to minimize a voltage field, it is unlikely that potentials isolated to this region could be recordable from the scalp. Simultaneous scalp and intracranial EEG recordings (4,11) have confirmed this assertion (Fig. 2.8). However, propagation of spike activity from the hippocampus into adjacent basal temporal cortex is common. This cortex has a larger area and a net orientation that would allow for summation of voltage fields. Because the basal temporal cortex is tangential to the lateral surface of the skull, voltage fields from this source are not well recorded from standard temporal electrodes. Instead, the negative field maximum is recorded from subtemporal electrodes.

Another factor that favors recording deep sources is the shielding effect of the skull. Ironic as it may seem, signal attenuation produced by the skull improves the chances of identifying deeper activity by affecting superficial sources to a greater extent. If there was no skull and the head was a homogeneous volume conductor, the amplitude of an EEG potential would diminish as the square of the distance from the source. However, the intervening skull has the same effect on EEG signals as would moving cerebral sources farther from the recording electrodes by shrinking the brain to only 60% of the radius of the head (13) (Fig. 2.9). All EEG potentials are reduced in amplitude (Fig. 2.10), but a relatively greater attenuation of surface events makes deep activity more discernible.

FUNCTIONAL FACTORS DETERMINING SCALP ELECTROENCEPHALOGRAPHIC PATTERNS

Several functional factors also affect what can be recorded on a scalp EEG. Amplitude of cortical activity is important, but it has a physiological upper limit. Normal background rhythms and evoked potentials may generate potentials at the brain's surface of several hundred microvolts, and pathological potentials, such as epileptic spikes, may be greater than a millivolt in amplitude. Other functional factors may become equally or more important in determining the eventual scalp voltage field. The synchrony of cortical activity is crucial. The EEG is the measure of spatially and temporally averaged activity of a large population of neurons. The EEG emphasizes the contribution of synchronously oscillating dipolar sources, whereas asynchronous activity may cancel itself despite of its amplitude (Fig. 2.11). Synchronization of cortical neurons may, however, be limited to relatively small regions of cortex. In this case, summation of their voltage fields may not be great enough to produce a field recordable from the scalp. Regions of cortical synchronization commonly become larger with certain pathological

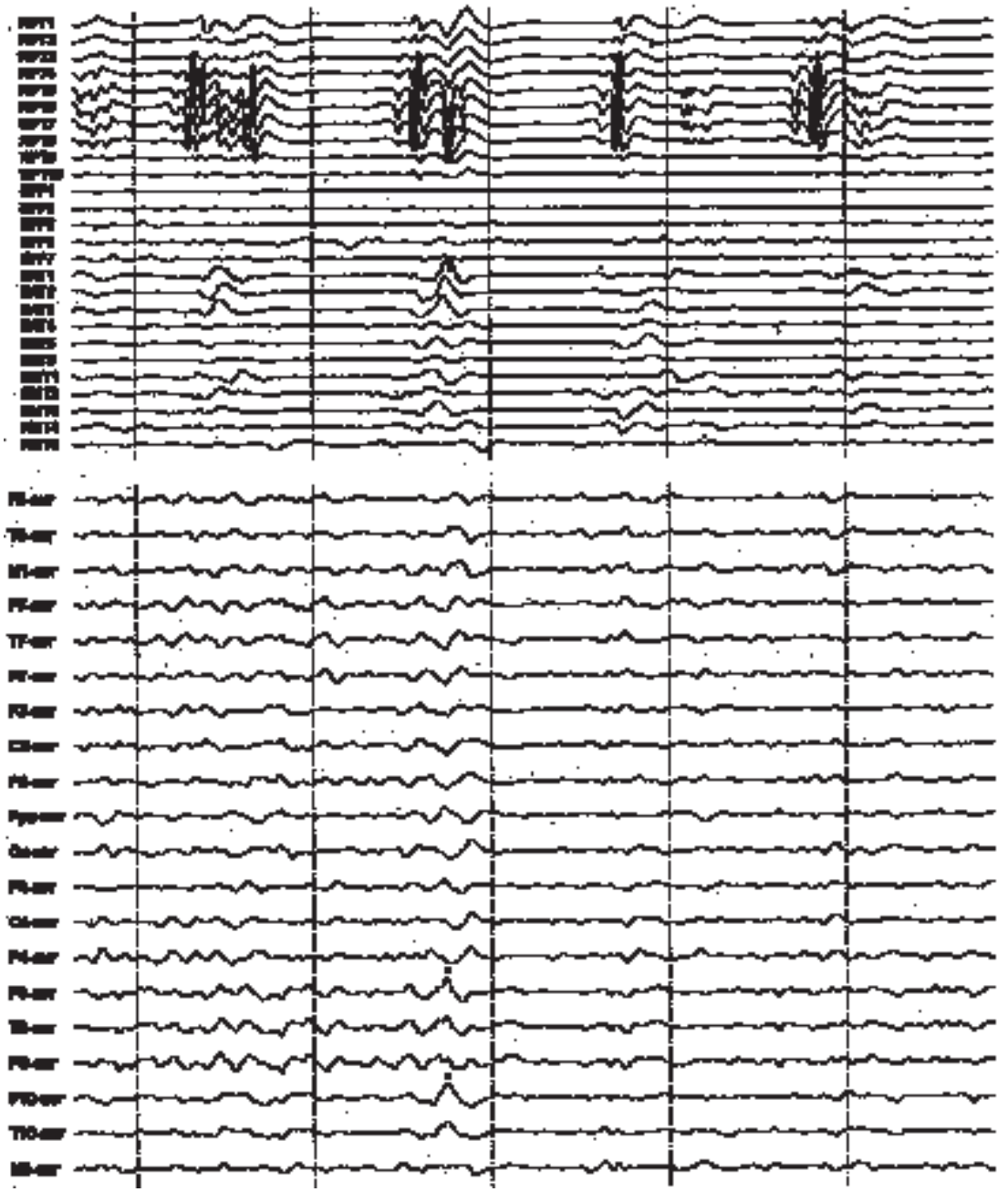


FIG. 2.8. Simultaneous intracranial and scalp electroencephalographic (EEG) recording. Prominent hippocampal spikes are recorded from depth electrode contact RPT4 to 8. No scalp EEG spikes or sharp waves are associated with these spikes unless there are related sharp waves from inferior temporal cortex sources of sufficient size (contacts RAT 1 to 5, RMT 1 to 3). Note that the maximal scalp sharp wave amplitude (*dot marker*) is recorded from the subtemporal electrode, F10.

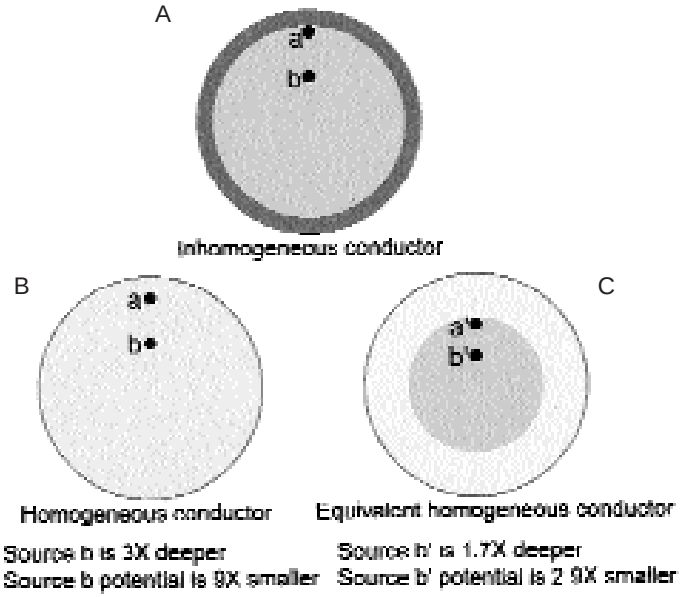


FIG. 2.9. Shielding effect of the skull. **A:** The skull, in particular, makes the head, which is modeled here as a sphere, an inhomogeneous volume conductor. The brain normally occupies approximately 85% of the radius of the head. Brain electroencephalographic (EEG) sources *a* and *b* are superficial and deep, respectively. **B:** If the head were a homogeneous conductor, the amplitude of surface EEG potentials would diminish as the square of the distance (i.e., depth) of the sources. Source *b* is three times deeper than source *a*. Its surface potential for the same activity would be one-ninth the size of source *a.* **C:** The shielding effect of the skull is equivalent to shrinking the brain to 60% of the head's radius. Source *b′* is now 1.7 times deeper than source *a′*. Its surface potential for the same activity would be 1/2.9 the size of source *a′*.

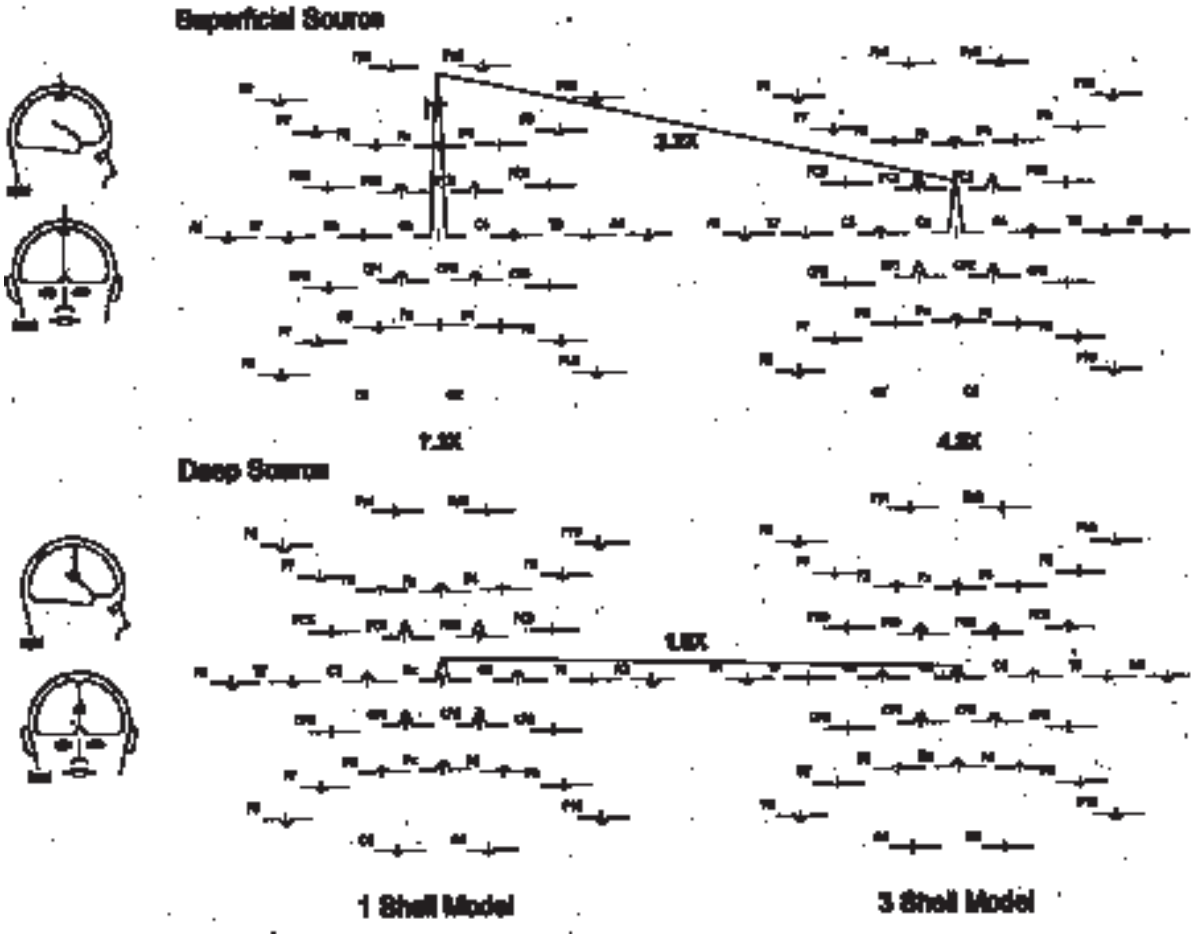


FIG. 2.10. The shielding effect of the skull on the electroencephalogram (EEG) from superficial and deep sources is demonstrated in this computer simulation ("Dipole Simulator" by P. Berg and M. Scherg, see Chapter 23), with the use of a forward solution of a dipole source potential onto the scalp through a one-shell (no skull) and three-shell (with skull) head model. Because the same superficial radial source is below electrode Cz, the presence of a skull reduces the amplitude of the recorded scalp potential by a factor of 3.2. For the same source that is 4 cm deeper, the skull reduces the amplitude of the recorded potential only by a factor of 1.9. Viewed alternatively, without a skull (one-shell model), the scalp EEG potential from the deep source is 1/7.3 the size of the superficial source. However, with a skull (three-shell model), the scalp electroencephalographic potential from the deep source is 1/ 4.3 the size of that from the superficial source. Although the skull reduces the amplitude of the EEG, potentials from deep sources are relatively less attenuated.

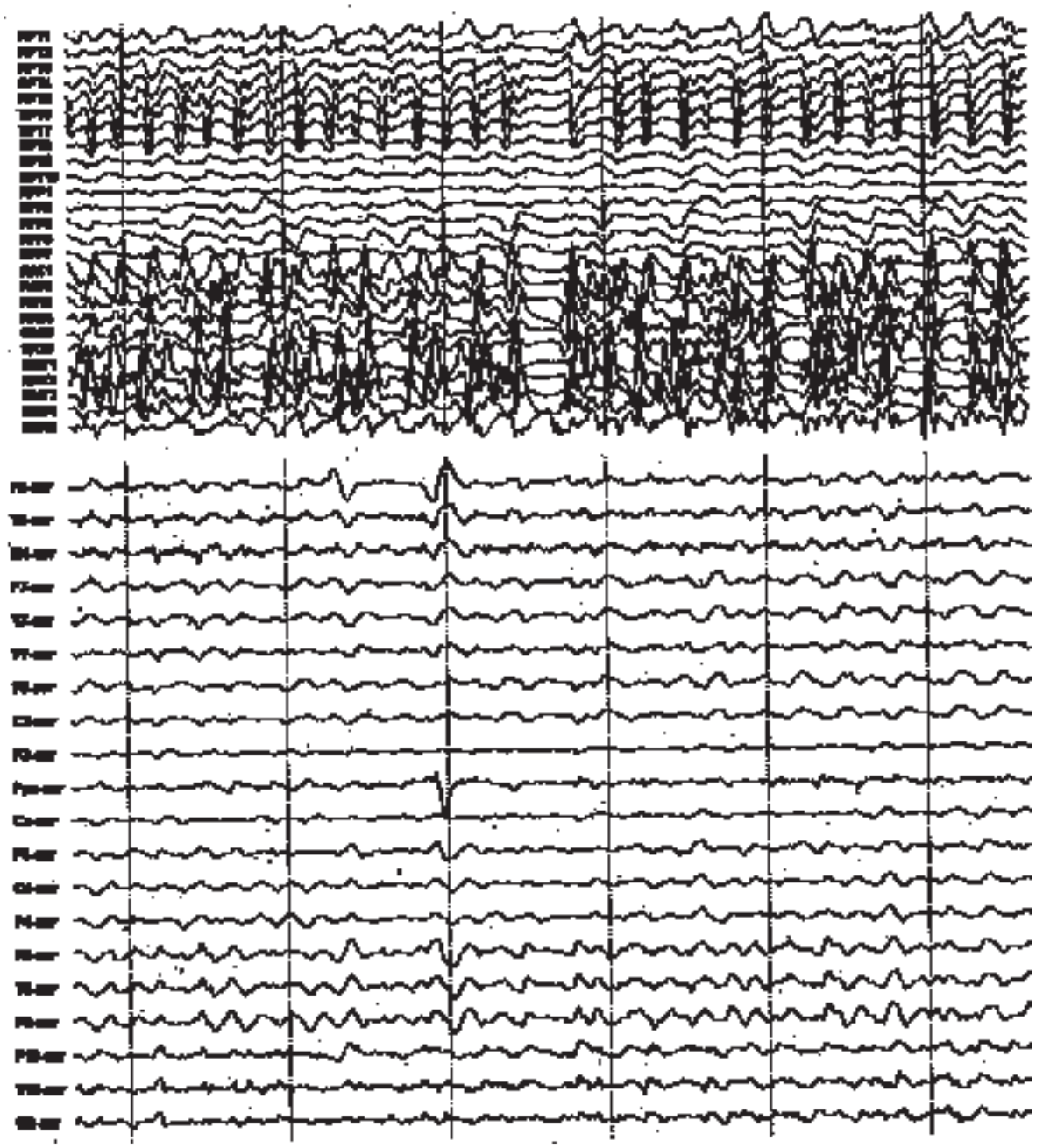


FIG. 2.11. Simultaneous intracranial and scalp electroencephalogram (EEG) recording of a temporal lobe seizure. Although the seizure rhythm from the hippocampus is synchronous (depth electrode contact RPT 4 to 8), seizure rhythms from the temporal neocortex are relatively asynchronous (subdural strip electrode contacts RAT1 to 6 and RMT1 to 5). The scalp EEG shows a poorly developed seizure rhythm despite the high-amplitude cerebral activity.

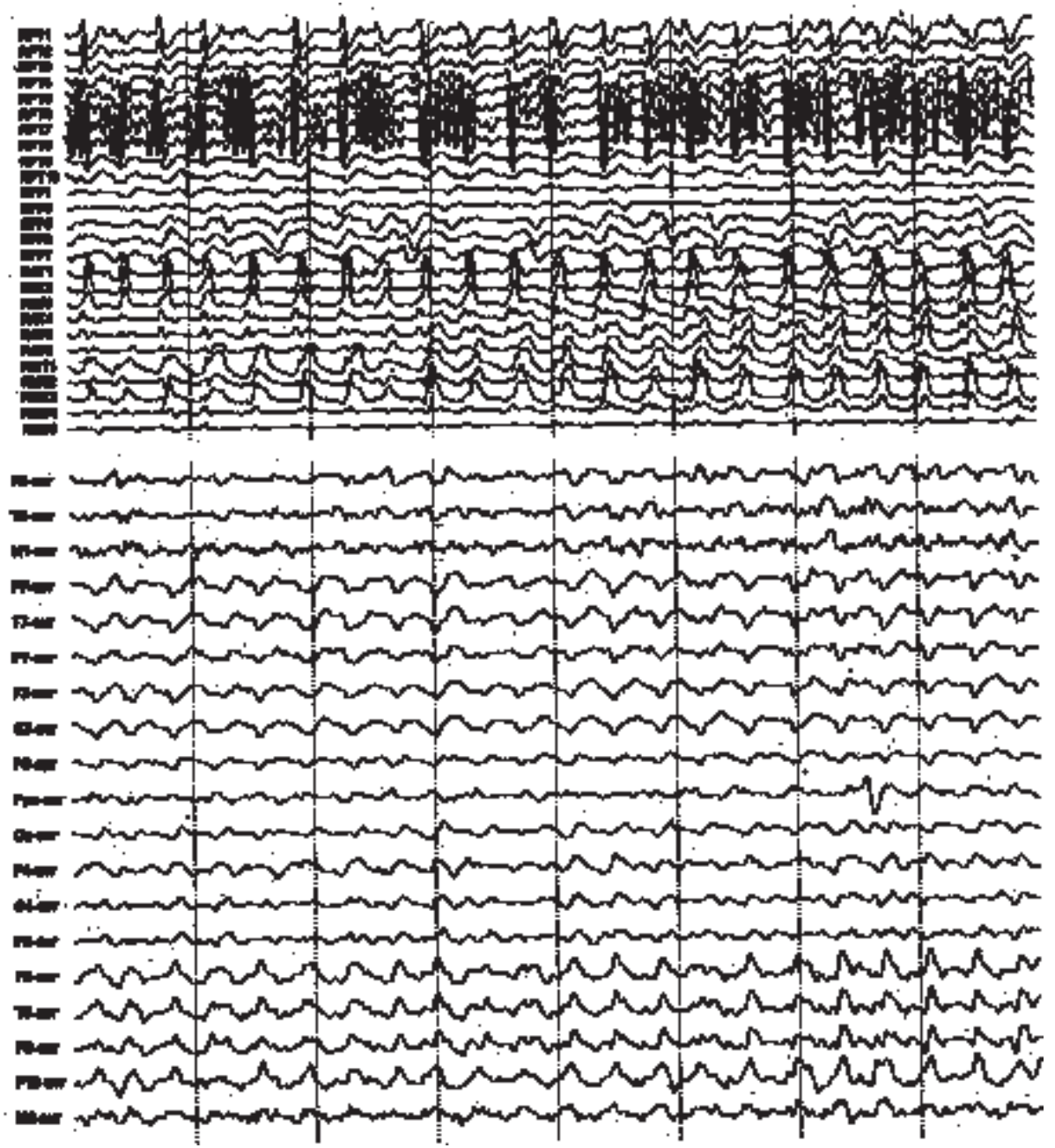


FIG. 2.12. Simultaneous intracranial and scalp electroencephalographic (EEG) recording of a temporal lobe seizure. The seizure rhythm from the temporal neocortex is relatively synchronous (subdural electrode contacts RAT1 to 6 and RMT1 to 4) but of less amplitude than that depicted in Fig. 2.11. The scalp EEG, however, shows a well-developed seizure rhythm.

potentials, such as epileptic spikes or seizures, which makes them easily appreciated on the scalp EEG (Fig. 2.12). Transient patterns of longer duration and thus lower frequency have a greater chance of having at least a partial overlap in activity and thus some summation of their fields.

PROPAGATION

If cortical activation remains localized to one area, which undergoes the usual depolarization and repolarization sequence, the resultant voltage fields on the scalp rises and falls in amplitude and reverses in polarity, but the location of the maxima does not change; nor does the overall shape of the fields. If, however, activity propagates into adjacent cortical regions, the overall geometry of the source changes. A new location to the overall center of activity and a new net orientation of the source cortex exist. These changes result in a different voltage field. Movement of scalp field maxima or change in the shape of the fields over tens of milliseconds suggests propagation of source activity. This is particularly common with epileptiform spikes or seizures (5). Such changes in voltage fields can provide important information concerning propagation direction and extent.

An example illustrating all these relationships is shown in Figs. 2.13 and 2.14. Figure 2.13 illustrates simultaneous EEG recordings from intracranial and scalp electrodes, as well as the scalp EEG voltage topography at the time of the cursor. Note in the intracranial EEG traces the progressive delay of the spike potential, which originates in the mesial temporal tip (LAT1) and propagates posteriorly over basal and lateral temporal surfaces to contacts LAT7 and LMT9. The first recordable scalp field, shown in the topographical maps, has a frontopolar negative maximum that is appropriate for a temporal tip source orientation. The locations of the subdural electrodes are depicted in Fig. 2.14 on a three-dimensional magnetic resonance imaging (MRI) reconstruction of the patient's brain. Also illustrated is the approximate area of cortex undergoing depolarization at five instances during the spike. Shown as well are the five scalp voltage fields produced by this propagating cortical source. As this area of activated cortex propagates posteriorly and laterally, the corresponding scalp EEG field maxima move appropriately for the net source location and orientation. Note also the eventual large size of the cortical source, which approximates 20 cm^2. This example confirms that the voltage field recorded from scalp electrodes is directly related to geometrical features of the cortical spike source. Because of this systematic relationship, source models of scalp EEGs can be used to estimate the location, orientation, and propagation of cortical generators. (See Chapter 23.)

EFFECT OF REFERENCE ON ELECTROENCEPHALOGRAPHIC FIELDS

The measurement of EEG potentials is relative to a reference. Polarity and amplitude are dependent on this comparison. There has been considerable debate about the effect of choice of reference on the appearance of EEG traces and on voltage field maps (see Chapter 4). Most authorities now agree that varying the reference does not alter the contours or gradients of the voltage fields (i.e., the relative differences) or the information concerning source character. What is altered is simply the display of the same data. In fact, EEG source models, such as dipoles, in which topographic voltage distributions are used as raw data for calculation, are reference independent.

The easiest way to appreciate the effect of the recording reference is to think of EEG voltage topography as geographical topography: namely, mountains of one polarity and valleys of another. The reference in this model would be the level of a coexisting ocean that covers part of this landscape. Everything above sea level has an altitude of one polarity, and everything below sea level has a depth of the opposite polarity. With a different sea level, the altitudes and depths of particular points on the landscape change, but the shape of the mountains or the undersea valleys does not change. If the highest mountaintop or deepest ocean valley is chosen to be the reference and all points on the landscape are of one polarity or the other, but the underlying structure has not changed. The same is true for changes in EEG recording reference (Fig. 2.15).

Any reference can be used and data interpreted properly, if the effect of reference on the EEG display is appreciated. There is no such thing as an "inactive" reference, because any point on the head or body carries some electrical potential. Traditionally, reference electrodes were thought to be "active" only when they were within the negative field of a spike. This notion resulted in part from the misconception that outside of this negative field there was no other activity related to the spike. Spikes were commonly thought to have only a negative field maximum, except for the "horizontal dipoles" of benign Rolandic epilepsy. In fact, all spikes have, by electromagnetic necessity, both negative and positive field maxima. Depending on source location and orientation, both maxima may not be recorded in standard 10 to 20 montages, as discussed earlier. Because positive field maxima

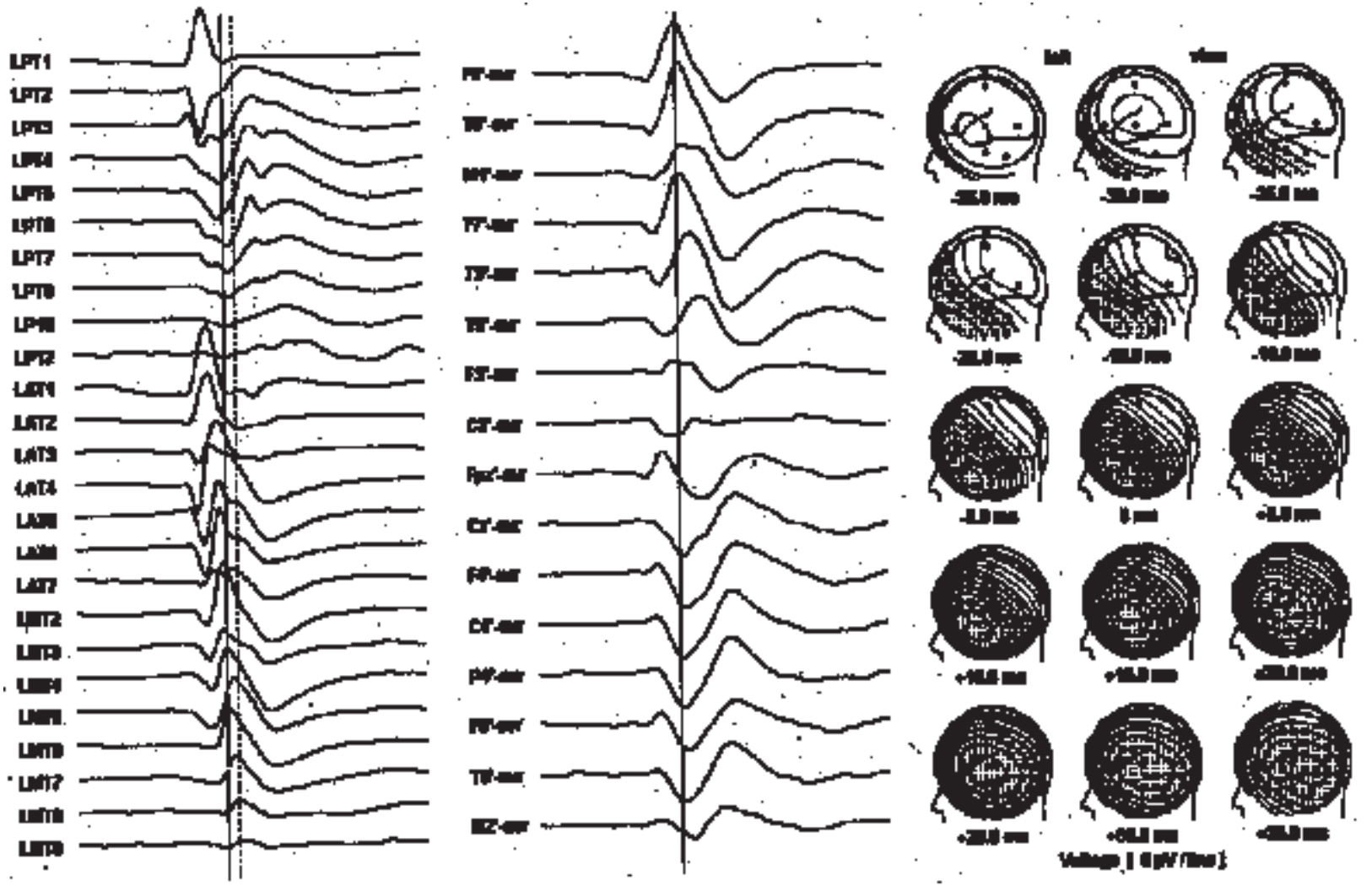


FIG. 2.13. Left: Simultaneous intracranial and scalp electroencephalographic (EEG) recording of a left temporal spike. Subdural electrode placements are illustrated in Fig. 2.14. The intracranial EEG was referenced to the contralateral mastoid; negative polarity is upward deflection of traces. The scalp EEG is displayed in common average reference. **Right:** Map sequence depicts simultaneous scalp voltage topography at 5-millisecond intervals, centered on the cursor, spanning 70 milliseconds. Voltage map shading denotes field polarity (speckled area is negative). Isopotential lines indicate field strength. Note spike onset in temporal tip cortex (LAT 1, LAT 2, and LPT 1), followed by mesial to lateral propagation across temporal tip subdural contacts (LAT 1 to LAT 7) and then midtemporal subdural contacts (LMT 2 to LMT 8). LPT is a longitudinal mesial temporal depth probe. Contact 1 is most anterior; contacts 4 to 7 are located in the hippocampus. Note that the initial scalp voltage field is inferior frontopolar, which is appropriate for an inferior temporal tip source. Over 70 milliseconds, as the spike propagates, the negative field maximum progressively moves into an anterior inferior temporal and eventually into a midtemporal location.

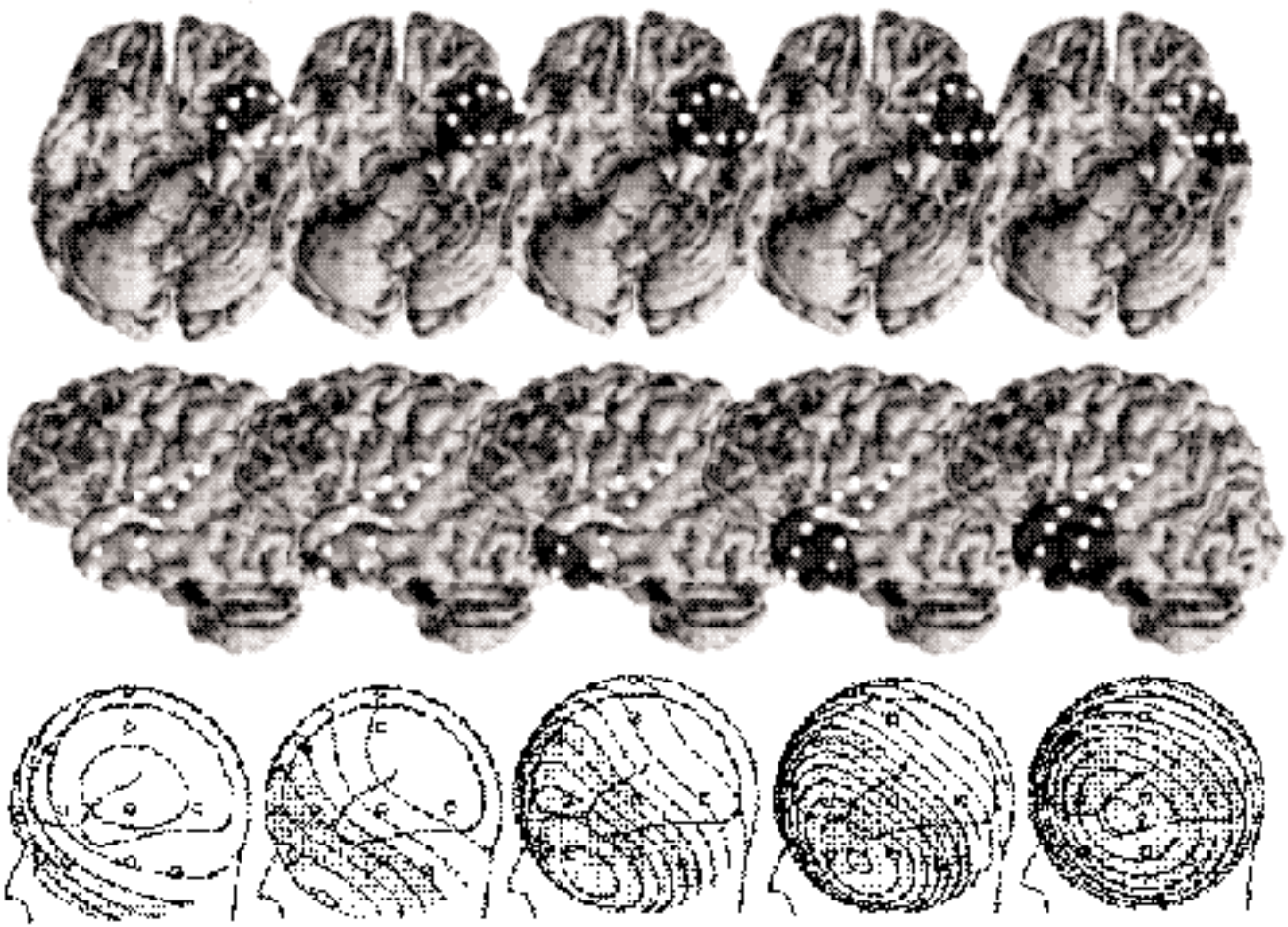


FIG. 2.14. Three-dimensional magnetic resonance imaging (MRI) reconstruction of brain and subdural electrode contacts from patient whose data were depicted in Fig. 2.13. The most anterior strip is LAT. Contact 1 is most mesial; contact 7 is most lateral and superior. The more posterior strip is LMT. Contact 2 is most mesial; contact 9 is most lateral and superior. The darkened cortical area denotes estimated region of concurrent cortical depolarization (negative potential) during propagation of the spike. Source estimate derived from intracranial electroencephalogram of Fig. 2.13. Five time points at 15-millisecond intervals are illustrated, corresponding to latencies –30 to 30 milliseconds in Fig. 2.13. Scalp voltage topography at these times is shown at the bottom. Note the relatively large area of the spike source, its propagation over time, and the close relationship between source geometry and the scalp voltage field. The negative scalp maximum moves from frontopolar to subtemporal to temporal location over 60 milliseconds.

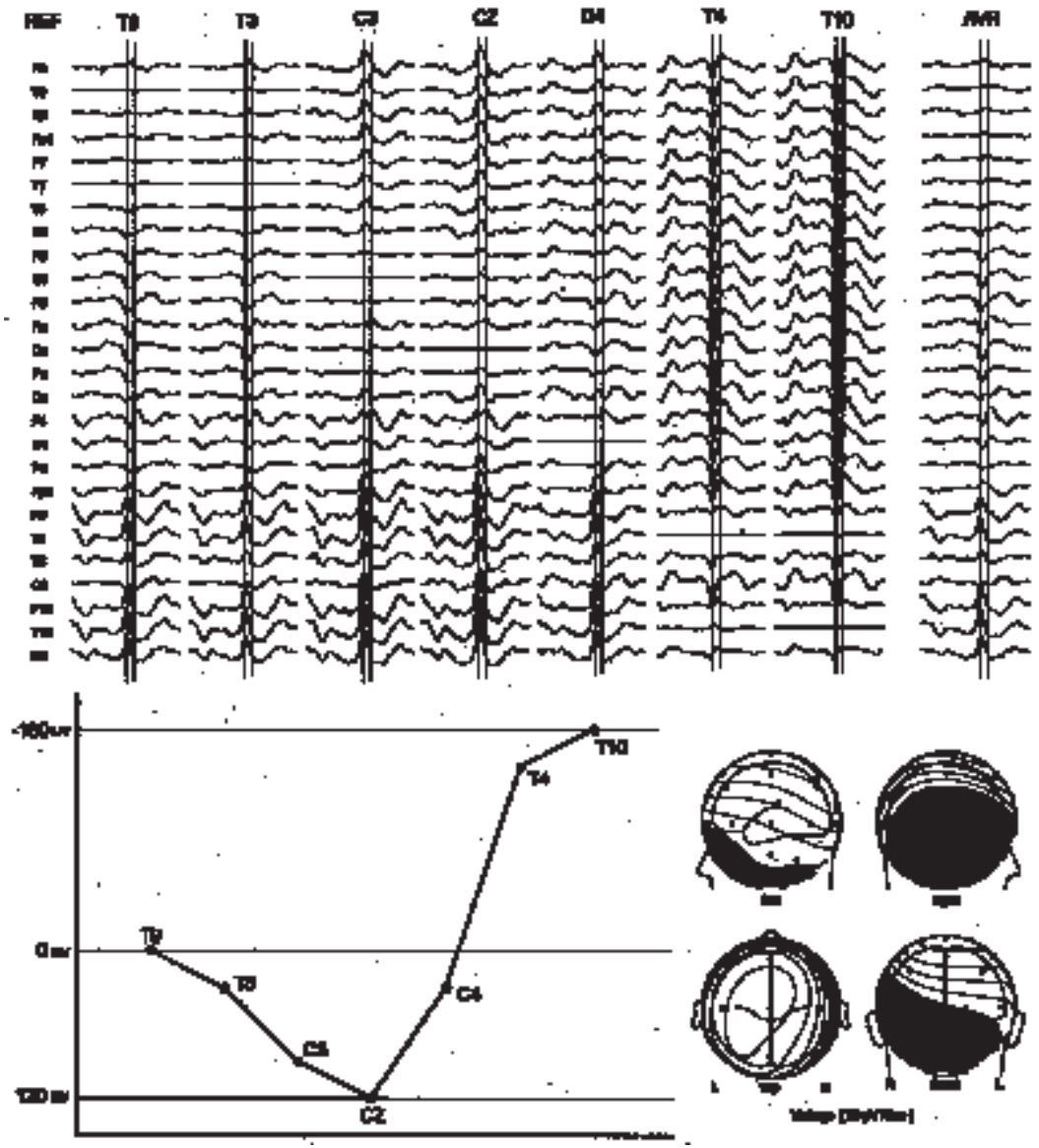


FIG. 2.15. Bottom: The magnitude and polarity of a right temporal spike recorded in common average reference from a midcoronal chain of electrodes is graphed into a two-dimensional landscape. The voltage topography of this spike is illustrated at the right. Isopotential lines are drawn at every 30 μV; the hatched area is negative. **Top:** Electroencephalographic (EEG) traces of this spike are displayed, with each electrode in the midcoronal chain in succession used as the common reference. Note that changing reference alters only where the zero voltage line is placed. The relative voltage differences among electrodes remains unchanged. When T10, the negative field maximum, is the reference, all EEG deflections are positive (downward). When Cz, the positive field maximum, is the reference, all EEG deflections are negative (upward). When T9 is the reference, the EEG deflections are similar to that of the common average reference because this electrode lays on the common average reference zero isopotential line.

were not thought to be present in most spikes, reference manipulations were often performed to eliminate the appearance of positive potentials whenever they did occur.

For example, common average reference derivations were often calculated only after removal of the electrodes recording the largest negative potentials. If the electrodes were not removed, it was said, positive potentials might appear on the opposite side of the head. These were thought to be reference artifacts, rather than the true opposite-polarity field maximum that is produced by any dipolar source. Deleting electrodes with the most negative potential from the average simply shifted the reference "sea level" in a positive direction so that the true positive field would appear to have less amplitude (see Fig. 2.15).

As discussed earlier, however, maximal information about source character can be obtained only by identifying both field maxima. A simple and yet very effective way to do this is to use a common average reference made up from all recording electrodes. If the mean potential recorded from all electrodes is used as a zero reference level, then by necessity both relatively more negative and more positive fields are accentuated and thus more easily identified. This type of reference also makes physical sense. By the laws of physics, the net charge or net potential over the surface of the head from any source should be zero (i.e., positivity balancing negativity). The mean of all recording electrodes is an approximation of this. Obviously, the more electrodes used, particularly from undersampled regions of the head, the more such a reference approximates the true zero potential. To the untrained eye, such a reference may initially cause confusion because fields of both polarities are emphasized. Focal negative spikes from one hemisphere or lobe are accompanied by positive potentials, commonly from the opposite hemisphere. This distribution does not represent bilateral spike sources; rather, it represents the normal dipolar field of any cerebral generator. The greater amplitude and steeper voltage gradient of the negative maximum identifies the source as being nearer to it, whereas its geometrical relationship to the positive maximum conveys the overall field orientation and thus the net orientation of the generating cortex, which is orthogonal to that of the field (see Figs. 2.4, 2.5, 2.6, and 2.7).

CONCLUSIONS

Too often the EEG is thought of as simply time-varying potentials, or wiggles, that supposedly reflect the activity of brain under the recording electrodes. Recognition of the pattern of these wiggles has been the foundation of EEG education. Fortunately, this is not all there is to EEG recording. It is a multidimensional signal and a carrier of abundant information, much of which is not routinely used. Limitations of traditional EEG recording are often artificial and imposed, in part, by simplistic interpretation methods. Practitioners of modern EEG recording must go beyond one dimensional to multidimensional thinking, if more information is to be extracted from the EEG. In order to take EEG interpretation beyond simple description toward an analysis of source location and character, it is essential that the interpreter appreciate the relationships between cortical sources and the EEG voltage fields that they produce.

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Chapter 3

Engineering Principles

Brian Litt and Stephen D. Cranstoun

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- Capacitors
- Inductors
- Power Sources
- Active Circuit Elements

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Electroencephalography (EEG) involves recording and analyzing electrical signals generated by the brain. These signals are small and surrounded by a variety of large electrical potentials originating in the environment. Resolving true electrical brain activity requires three elements: good equipment, meticulous recording technique, and informed interpretation of the data. Improper technique may, in the worst case, lead to injury of a patient from improper grounding or stray electrical currents. This chapter reviews principles of electricity and electronics relevant to EEG technology.

New to this chapter is a review of the basic technical principles underlying digital EEG. Because of the increasing availability of low-cost microcomputers and digital electronic technology, cumbersome banks of amplifiers and chart writers on wheels are rapidly yielding way to portable, paperless personal computer–driven machines, some requiring no more than a notebook computer, a headbox, and some cabling. Reams of remotely warehoused EEG paper and days filled with ink stains and paper cuts are being replaced by high-density, accessible digital storage media, such as recordable compact disks (CDs) and digital video disks (DVD), and by networked computer reading stations. More than just a new fad, digital EEG technology offers great improvements over analog technology, including lower cost; increased diagnostic yield; less environmental pollution and less consumption of natural resources; access to quantitative and automated analysis tools for EEG; and remote transfer, monitoring, and interpretation of EEG records. Clearly, digital EEG is a permanent tool. Every electroencephalographer, medical student, and medical technologist should be familiar with the science and engineering underlying clinical EEG, now supplemented with a practical knowledge of digital computers, principles of digital signal processing, computer networking, and data bases.

ELECTRICAL BASICS

The standard clinical (surface) EEG records potential differences (voltage) between two points, one or both of which are on the scalp. The signals of the EEG are based on the movement of electrical charges in biological tissue. Charge, represented by the symbol Q, is quantized. It exists in units that correspond to the charge of elementary particles, such as protons and electrons. The charge of a single electron is very small; in practice, much larger units of charge are used. In the metric meter-kilogram-second (MKS) system, charge is measured in coulombs (C). One coulomb is approximately equal to the charge of 6×10^{18} electrons (14). Movement of charge is called *current,* usually denoted by I, and is measured in units of amperes (A). One ampere of current represents a flow of 1 C of charge per second (for review, see Purcell [26]). Current flows when electrons move or in association with movement of negative ions (e.g., Cl^-, anionic proteins) or positive ions (e.g., cations Na^+, K^+, or Ca^+). Electron flow is more important in electronic devices, and ionic flow is more important in biological systems. Current flow is conventionally defined from positive to negative. For example, Na^+ ions moving from left to right (or Cl^- ions moving from right to left) would generate a positive current to the right.

According to a fundamental principle of electricity, like charges repel and opposite charges attract. Thus, a collection of freely moving charges will arrange itself in a uniform distribution so that (a) positive and negative charges are as near to each other as possible and (b) positive-positive and negative-negative charge pairs are as far apart as possible. Other physical forces such as gravity, friction, magnetism, moving mass, and nuclear forces can oppose these electrical attractions and repulsions. This results in a separation of charges into more positive and negative areas. Such a system stores electrical potential energy. This energy is released when charges move to restore regional electrical neutrality. The unit of energy in the MKS system is the joule (J). One joule, defined in terms of kinetic energy, is the energy required to accelerate a 1-kg mass by 1 m per square second over a distance of 1 m. This is approximately equivalent to the energy a person would feel after dropping a lemon on his or her foot from waist high. Voltage (V; or E, for electromotive force) is defined as energy per unit charge. One joule of energy is expended when 1 C of charge is moved across a potential difference of 1 V. Voltages are always measured between two points in space. It makes no more sense to say that a single point in an electrical circuit is 5 V than it does to say that a ball is "5 m." In some circumstances, the reference point for height or for voltage differences is implicit. This implicit location of a reference potential is called *ground* ("physical ground" in a discussion of the height of a ball, or "electrical ground" in the case of a voltage difference). The precise meaning of electrical ground is elusive, because two places in the earth are rarely at identical potential with regard to any third point. Nevertheless, potential differences between a circuit element and either ground rod typically are large in comparison with potential differences between two ground points. Exceptions and cautions regarding possible voltages between two different grounds are reviewed near the end of this chapter, in the section on electrical safety.

Table 3.1 lists typical voltages and currents for a few commonly encountered systems.

TABLE 3.1. *Examples of voltage and current for circuits of interest*

System	Volts	Amps
Lightening	100,000,000	10,000
Hoover Dam	50,000	2,000
Static from carpet	2,000	0.000001
Household light bulb	110	1
Car battery	12	200
Flashlight battery	1.5	0.6
Electrocardiogram	0.0015	0.00001
Scalp EEG	0.00005	0.000001

Note: Numbers are rough approximations, for illustrative purposes only. EEG, electroencephalography.

CIRCUIT ELEMENTS

Combinations of a few simple elements can serve as models for many important electrical circuits, simple and complex: resistors, capacitors, inductors, and power sources. These elements are described in detail in numerous electronics texts; only a brief overview is given here (14).

Resistors

In the real world, energy transfer is never completely efficient: Energy carried by currents dissipates into heat by resistance of the conducting medium. Resistance is measured in joule-seconds per coulombs squared, or ohms (Ω). One ohm is the resistance that will cause 1 J of energy to dissipate when a current of 1 A flows through it for a period of 1 second.

Figure 3.1 shows a hydraulic analogy to an electrical circuit. In this system, electrical potential difference is represented by the difference in gravitational potential energy (proportional to the difference in height) between points A and B; current is represented by the flow of water (I), and the resistor is the paddle wheel (R). As resistance increases (done by increasing the paddle wheel radius or by making it more difficult to rotate), flow decreases in an inverse proportional relationship for the same potential difference. This is a statement of Ohm's law:

$$V = I \cdot R$$

where V (or E, for electromotive force) represents the voltage, I represents the current, and R represents the resistance. According to this law, the potential difference across a resistance is equal to the current flowing through it, multiplied by its resistance.

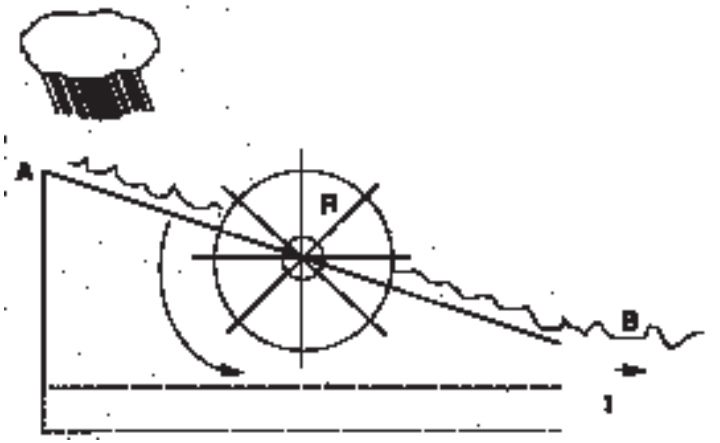

FIG. 3.1. Fluid analog of Ohm's law. A-B is the change in height (which determines difference in gravitational potential energy) driving water flow. I, paddle wheel; R, resists water flow.

Figure 3.2 shows a simple circuit consisting of a voltage source (e.g., a battery) of 10 V and a 100-ω resistor. According to Ohm's law,

$$V = I \cdot R$$
$$10\ \text{V} = I \cdot 100\Omega$$
$$I = 10V/100\Omega = 0.1A$$

In this circuit diagram, the symbol represents a voltage source, with the positive terminal (or anode) drawn as the long line and the negative terminal (cathode), or ground, drawn as the shorter line. The symbol is used to represent a resistor.

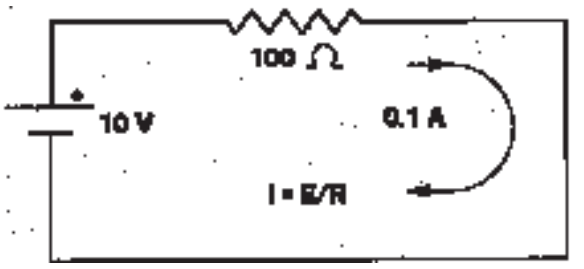

FIG. 3.2. Simple circuit illustrating Ohm's law. $I = V/R = 10\ V/100\ \Omega I = 1/10$ A, where V is a 10-V battery and R is a 100-ω resistor.

Electrical circuit resistors are usually made from materials whose atoms do not easily release electrons, such as carbon. Materials of very high resistance (e.g., rubber, glass, or air) are referred to as *insulators*. Resistive elements in the circuit created during EEG recording include the subject's body, scalp-electrode interface, electrode, wiring, and internal circuitry of the EEG machine.

Resistors may be adjustable to different resistance values. A straightforward example is a potentiometer, in which a dial adjusts the length of a resistive substance through which current must pass. Modern electronic circuits and several important biological circuits (e.g., electrically excitable neuronal membranes) involve the use of resistors whose resistances change as a function of voltage.

Capacitors

A capacitor is a device that stores separated charges. It can be thought of as two conducting plates that are very close together but separated by a thin insulator, so that no charge can flow between the plates. When a potential difference is placed across a capacitor, positive charges accumulate on the plate at the positive end of the circuit. This attracts negative charges toward the other plate. Movement of charges on the plates toward the boundary between them causes a current to flow on both sides of the capacitor, without charges actually flowing across the plates. When repulsion by like charges on each plate of the capacitor balances the force from the applied potential, no more current flows. It is intuitive that a large plate allows more charge accumulation before crowding and mutual repulsion halt currents. Similarly, closer proximity of the plates increases attractive force across plates and thereby increases the currents. The third determinant of capacitance is the type of insulator material between the plates, known as the *dielectric*. In mathematical terms,

$$C = Q/V$$

where capacitance (C) is defined as the amount of charge that a particular device can store for a given potential difference; Q represents the charge (in coulombs); and V represents the potential difference (in volts). The unit of capacitance is the farad (F): 1 F is the capacitance that stores 1 C of charge when a potential difference of 1 V is applied across the two plates of the capacitor. A 1-F capacitor is enormously large and is found only in very specialized applications. Most circuits use capacitors of 10^{-6} F (microfarads, or μF) or of 10^{-12} F (picofarads, or pF).

If the voltage across a capacitor remains constant, charge accumulation on the plates eventually stops current flow. This property can be recognized quantitatively by differentiating the equation $C = Q/V$ with regard to time and by assuming C is a constant:

$$\frac{dC}{dt} = 0 = -\frac{Q}{V^2}\frac{dV}{dt} + \frac{1}{V}\frac{dQ}{dt}$$

$$\frac{dQ}{dt} = \frac{Q}{V}\frac{dV}{dt}$$

$$I = C\frac{dV}{dt}$$

Current is equal to capacitance multiplied by the change in voltage with regard to time. Again, in circumstances in which potential difference does not change in time, there is no current flow because of capacitors. Changing voltages induces current flow in circuits containing capacitors. As an example, Fig. 3.3 displays the capacitor voltage versus time when the switch

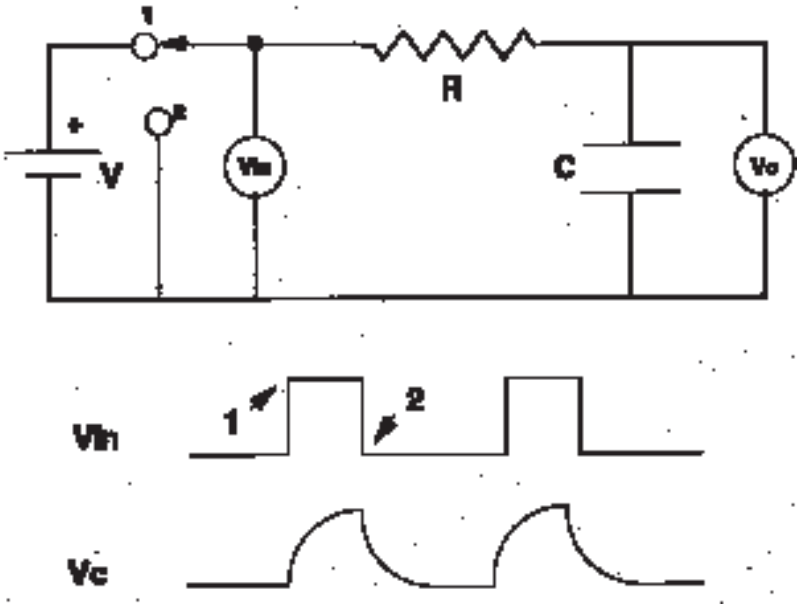

FIG. 3.3. Resistor-capacitor circuit (used as a high-frequency filter) containing voltage source (V), resistance (R), capacitance (C), and voltmeters measuring voltage at input (V_{in}) and across the capacitor (V_c). The switch allows generation of square-wave input shown at bottom of figure (V_{in}). Capacitor charges and discharges exponentially with time constant: $\tau = R \cdot C$.

moves between positions 1 and 2 in the circuit shown. The capacitor serves to "smooth out" and delay the voltage pulse introduced into the circuit. It is evident then that capacitors can serve as resistive elements (resisting current flow), depending on how rapidly current is changing. Capacitors will "pass" alternating current (AC) and block direct (unidirectional) current (DC), after an initial current flow when the DC is first applied. This "resistance" to current flow is called *capacitive reactance* and is usually designated by X_c. Capacitive reactance is inversely proportional to the frequency of an AC and is inversely proportional to the capacitance of the capacitor. The formal formula is

$$X_c = 1/(2\pi fC)$$

where X_c represents the reactance (in ohms); π is approximately 3.14; f is frequency of AC (in hertz [Hz], or cycles per second); and C is capacitance in farads. Energy "lost" in capacitive reactance is not really lost as it is in heat dissipated by a resistor; rather, it is mostly converted to potential energy in the form of charge separation.

Several biological elements have capacitance that alters the EEG signal. These include cerebrospinal fluid, the skull, and the scalp. The electrodes used to connect the patient to the EEG machine also alter the EEG signal. If a train of 1-Hz delta waves in the EEG were led to a capacitor of 1 μF, reactance would be $1/(6.28 \times 1 \times 10^{-6})$, or 159,236 Ω. If a train of 20-Hz beta waves were led to the same capacitor, then the reactance would be approximately 7,962 Ω. In this way, the capacitance of the scalp-electrode interface offers more resistance to current flow at low frequencies than at high frequencies.

Inductors

Inductance is a magnetic phenomenon. Charge in motion generates a magnetic field; therefore, electric current flow produces a magnetic field. A voltage is induced in any conductor that encircles a time-varying magnetic field. This finding is the basis for power generation in hydroelectric plants, in which falling water from a dam or natural waterfall spins a magnet surrounded by a coil of wires, inducing substantial voltages in the connecting circuits.

An inductor is made of coils of wire that encircle the magnetic field that is generated by current flowing in the wire itself. Coils of wire, consisting of many turns, are employed in inductors in order to encircle the magnetic field many times, increasing the induced voltage. In addition, increasing the number of turns of wire increases the magnetic field strength for a given current. Inductance is proportional to the square of the number of turns in the coil.

Magnetic induction is the basis for transformers, which convert one voltage level to another (Fig. 3.4).

The voltage across an inductor is proportional to the derivative, with regard to time, of the current passing through it. The constant of proportionality is called the *inductance.* Inductance is measured in henrys (H) and is conventionally designed by the letter L. Inductance has the same relationship to current that capacitance does to voltage. It is governed by the equation

$$V = L \frac{dI}{dt}$$

A potential difference of 1 V placed across a 1-H inductance causes the current through it to increase at a rate of 1 A per second. Induction may thus be conceived as a form of electrical inertia. "Resistance" of an inductor to current flow is referred to as *inductive reactance,* usually designated by X_L Inductive reactance is proportional to inductance and to the frequency of the current through it. The formula is

$$X_L = 2\pi fL$$

where X_L represents the inductive reactance (in ohms); f represents the frequency (in hertz); and L represents the inductance (in henrys). Energy "lost" to inductance is actually stored in the magnetic field.

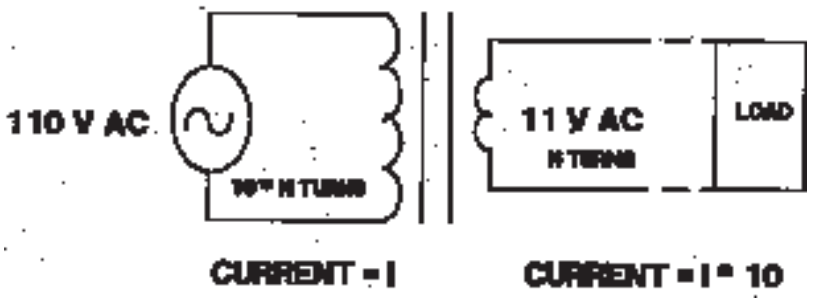

FIG. 3.4. Transformer uses two inductors to change 110 V of alternating current (AC) with current I (through $10 \cdot N$ turns) to 11 V of AC with current $10 \cdot I$ (through N turns). Note that power ($I \cdot V$) is conserved.

Inductance is an important concept in electrical circuits; however, the magnitude of inductive reactance is usually small in circuits relevant to clinical electroencephalography.

Power Sources

Power (P) is energy per unit time, expressed in joules per second, or watts (W). In an electrical circuit, power is calculated as voltage multiplied by current: VI. For a resistor, from Ohm's law, this translates to I^2R, or V^2/R. Power corresponds approximately to the colloquial impression of "strength." A high-voltage, low-current shock does not have much power, just as a high-pressure spray from a garden hose with a very low water flow rate does not have much strength. To continue the hydraulic analogy, a high flow rate in a garden hose with little water pressure produces a soothing wash. Fire hoses combine high water pressure with high flow rates to produce a powerful stream. It is fortunate that high voltages alone cannot kill, or the human race would long ago have been destroyed by static electricity. As discussed later, currents are more dangerous to patients than are voltages.

The two most commonly available sources of electrical power in modem society are batteries and wall sockets. Batteries produce power by chemical interactions between two metals immersed in an acid and produce DC. An everyday wall socket is an AC power source that delivers a sinusoidal voltage at the conventional frequency (in the United States) of 60 Hz. Line voltage may be expressed as

$$V(t) = V_p \sin(\omega t + \theta)$$

where $V(t)$ represents the voltage as a function of time; V_p represents the peak amplitude of the voltage; ω represents the angular frequency (in radians/second), equal to $2\pi f$ (frequency in hertz); t represents the time (in seconds); and θ represents the phase angle (in radians), which corresponds to the amount of offset from the beginning of the sine wave cycle that exists at time = 0. Figure 3.5 reviews some basic characteristics of sine waves.

Most AC voltages are described by the root mean square (RMS) voltage and not by the peak value. The RMS voltage is effective and produces the same average power as would a DC voltage of the same value. For a sinusoid, the RMS value is equal to the peak value divided by the square root of 2. Thus, a wall socket that provides 110 V of AC (VAC) RMS actually delivers peak voltages of 156 V. Most AC voltmeters measure RMS volts.

Electronic circuits usually operate from DC power; however, they usually employ a power supply circuit that converts commonly available AC power into DC. AC power sources are commonly provided because of their advantages in production, storage, and delivery to consumers, in comparison with DC.

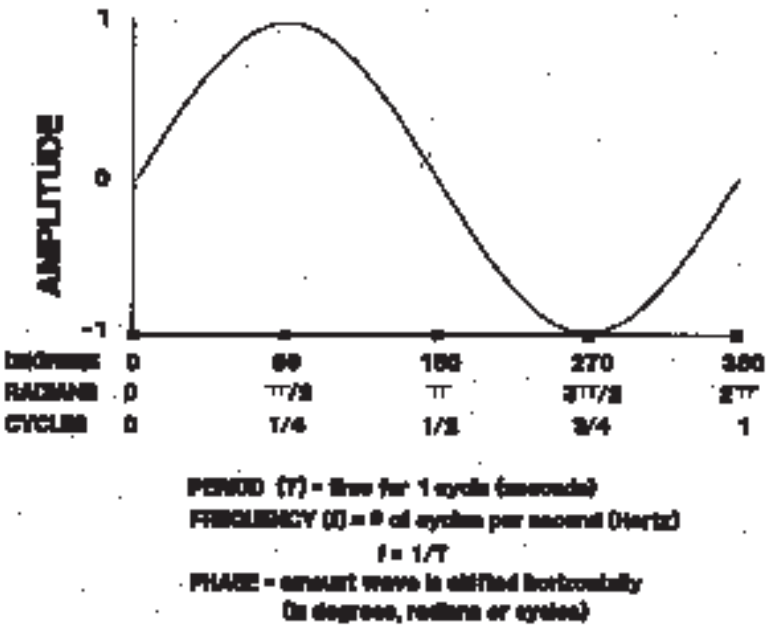

FIG. 3.5. Sine wave demonstrates relationship among degrees, radians, cycles and among period, frequency, and phase.

Table 3.2 summarizes definitions, symbols, and useful formulas pertaining to common electrical terminology.

TABLE 3.2. *Electrical terms and symbols*

Term	Units	Symbol	Comments
Charge	Coulombs (C)	Q	6×10^{18} electrons
Current	Amperes (A)	I	$I = dQ/dt$
Voltage	Volts (V)	V, EMF, E	Joules/coulomb
Energy (work)	Joules (J)	E (or W)	$kg \times m^2/s^2$
Resistance	Ohms (R)	Ω	$V = I \times R$
Capacitance	Farads (F)	C	$I = C \times dV/dt$
Inductance	Henrys (H)	L	$V = L \times dI/dt$
Reactance (capacitance)	Ohms	X_C	$X_C = 1/(2\pi fC)$
Reactance (inductance)	Ohms	X_L	$X_L = 2\pi fL$
Power	Watts (W)	P	$P = I \times V$

Active Circuit Elements

Active circuit elements, which include vacuum tubes, transistors, and integrated circuits, serve as fundamental building blocks for most modern electronic devices, particularly amplifiers and oscillators. Active components add power to a system and provide voltage amplification. Space does not permit discussion of active circuit elements. Information may be found in any standard electronics text (e.g., see Budak [2] and Horowitz and Hill [14]).

CIRCUITS

Sustained current flow requires a closed circuit; otherwise, the circuit functions as a very inefficient capacitor, with charges accumulating at the open circuit ends and inhibiting further charge flow. Circuits comprise the various elements detailed earlier. Even the simplest real-life circuit—for example, a battery with its positive and negative poles connected by a strand of wire—exhibits a certain (small) amount of resistance, capacitance, and inductance. Most circuits contain elements with more explicit resistive, capacitive, or inductive components. Several circuit properties are important for the understanding of EEG technology.

Circuit Elements in Series and in Parallel

Resistors and capacitors can be placed end to end (i.e., in series) or side by side (i.e., in parallel) or in other configurations less pertinent to EEG technology. Any number of resistors in series can be represented by a single resistor of value equal to the sum of all of the series resistors:

$$R = R_1 + R_2 + \ldots + R_n$$

Resistors in parallel can be represented by a single resistor of value equal to the reciprocal of the sum of the reciprocals:

$$R = \frac{1}{\frac{1}{R_1} + \frac{1}{R_2} + \ldots + \frac{1}{R_n}}$$

Figure 3.6 gives some examples of series and parallel resistors and their equivalents.

A similar relation holds for multiple capacitors in a circuit, except that capacitors are additive when positioned in parallel:

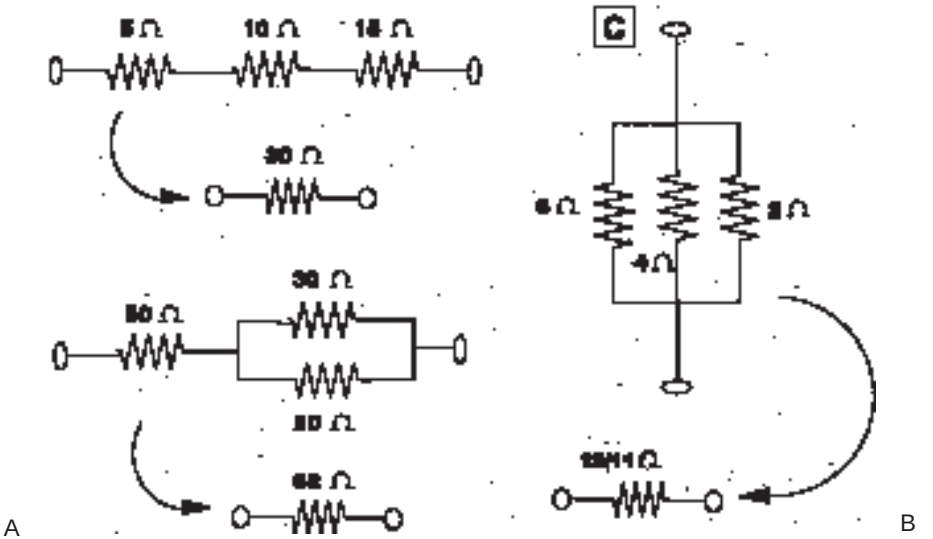

FIG. 3.6. Demonstration of equivalent resistance. **A:** Three resistances in series reduce to one resistance equal to their sum. **B:** Two parallel resistances equal the reciprocal of the sum of the reciprocals of resistances (12 Ω), which adds to 50 Ω resistance in series. **C:** Three parallel resistances reduce to the reciprocal of the sum or the reciprocal (12/11 Ω).

$$C = C_1 + C_2 + \ldots + C_n$$

Capacitors in series decrease total capacitance by the formula

$$C = \frac{1}{\frac{1}{C_1} + \frac{1}{C_2} + \ldots + \frac{1}{C_n}}$$

It is possible to construct an endless number of complex circuits from a voltage source, resistors, and capacitors, if they can be arranged in serial and parallel combinations. Three basic rules of electrical circuits are useful in analysis of current flow and potential difference across any circuit element:

1. *Thévenin's theorem* states that any system made up of resistors and voltage sources enclosed in a box with two terminals protruding can be exactly modeled by a system composed of one voltage source and one resistor in series. The value of the equivalent voltage source is found

from the voltage appearing at the terminals when no current is drawn from the terminals. The value of the equivalent resistance can be found by dividing the equivalent voltage by the current that flows when the terminals are short-circuited.

2. *Kirchhoff's voltage law* states that the sum of the voltages across circuit elements in a complete loop (starting and finishing in the same place) must be zero. Because of this, all elements in parallel have the same voltage across them.
3. *Kirchhoff's current law* asserts that the net current flow into a node (junction point) anywhere in a circuit must be zero; that is, total current exiting a node equals total current entering a node. This means that all elements in series have the same current passing through them.

In Fig. 3.7 these laws are applied to analyze simple circuits used in EEG machinery. Figure 3.7 shows a circuit made up of an ideal voltage source and two resistors in series. To analyze the circuit, Ohm's law is first applied:

$$V = I \cdot R$$
$$V_{in} = (R_1 + R_2) \cdot I$$
$$I = \frac{V_{in}}{(R_1 + R_2)}$$
$$V_1 = I \cdot R_1 = V_{in} \cdot \frac{R_1}{(R_1 + R_2)}$$

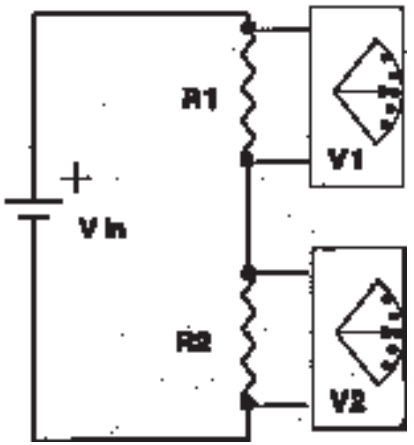

FIG. 3.7. Simple voltage divider. If $R1$ and $R2$ are selected appropriately, V_{in} can be divided up into V_1 and V_2 in any ratio desired. $V_1 = V_{in} \cdot R1/(R1+R2)$; $V_2 = V_{in} \cdot R2/(R1 + R2)$.

$$V_2 = I \cdot R_2 = V_{in} \cdot \frac{R_2}{(R_1 + R_2)}$$

Assume that

$$V_{in} = 11\text{V}, R_1 = 1\Omega, \text{ and } R_2 = 10\Omega$$

Therefore,

$$V_1 = 11V \cdot \frac{1\Omega}{} = \underline{11\text{V} \cdot \Omega}$$
$$V_1 = 1V$$

and

$$V_2 = 11V \cdot \frac{10\Omega}{} = \underline{110\text{V} \cdot \Omega}$$
$$V_2 = 10V$$

This circuit is called a voltage divider. It can be used to produce smaller voltages in any ratio desired, depending on the ratio of the resistances.

Figure 3.8 illustrates a more complex voltage divider with two switches. This circuit, which is actually the sensitivity setting circuit from an EEG amplifier, allows selection between two resistors with switch 1 and allows selection among 12 resistors with switch 2 (32).

Analysis of circuits containing multiple capacitors is analogous to the exercises above.

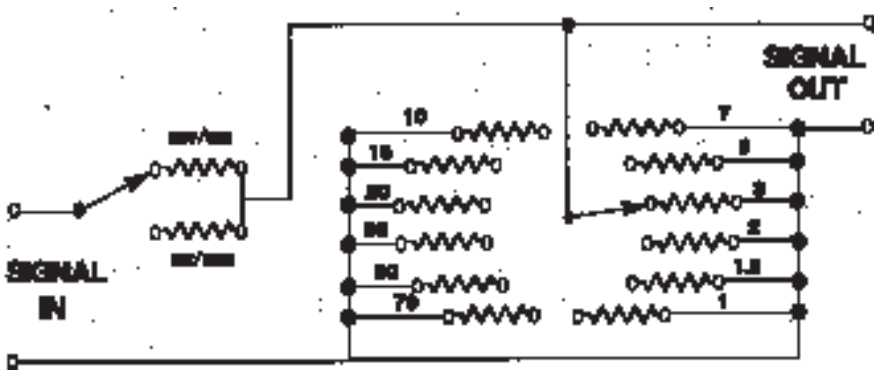

FIG. 3.8. Electroencephalographic sensitivity switch circuit. A voltage divider with selectable values for $R1$ and $R2$ via two switches. This circuit governs output voltage amplitude to the electroencephalogram pen system.

Time Constants

Figure 3.9 shows a capacitor and a resistor in series with a power source connected via a switch. The input voltage (V_{in}) and the output voltage across the resistor (V_c) are measured, as shown, by two imaginary voltmeters. This circuit does not pass DC because of capacitive reactance. As discussed earlier, it resists current flow in inverse proportion to the frequency. A point less evident is that the resistor-capacitor (RC) circuit will also alter the timing of applied electrical signals. The bottom of Figure 3.9 shows what happens when a square-wave voltage is applied to the circuit at V_{in}. By Kirchhoff's voltage law, voltage across the capacitor and the resistor must sum to the voltage generated by the power supply. When the switch is in position 1, electrons travel to the right plate (P_R) of the capacitor and begin to charge that plate negatively. In the first small slice of time, few negative charges on the left plate (P_L) of the capacitor are repelled from this charge buildup, and thus there is little voltage across the capacitor. The entire voltage therefore appears across the resistor. Later in time, P_R becomes more negatively charged, and more negative charges are repelled from P_L. A voltage appears across the capacitor, and less is measured across the resistor. Later still, electrons slow their migration to P_R, because they are repelled in proportion to the number of electrons already there. The equation to describe a process whose rate is dependent on its amount is called an *exponential* equation, and the inverse (reversed axes) is a *logarithmic* equation. Many processes in nature are exponential or logarithmic: for example, unrestricted population growth, cooling of a brick, radioactive decay, and the wearing away of a stone's surface in a stream. The process of charging the capacitor in the RC circuit is exponential, so that the rate of charging is inversely proportional to how much it is already charged.

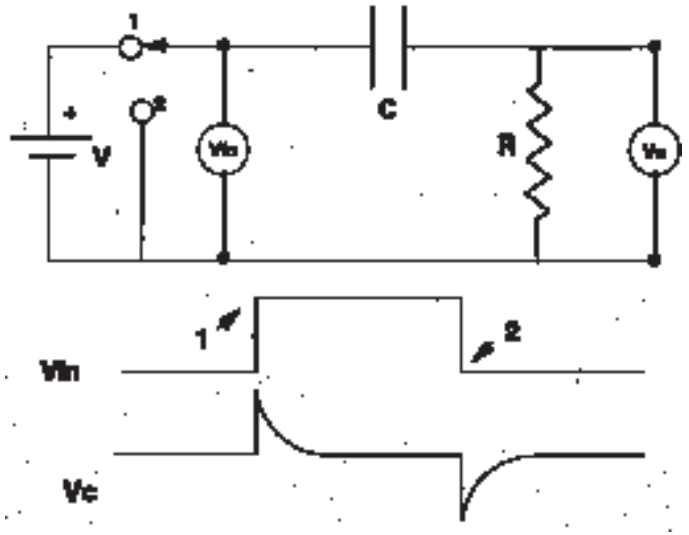

FIG. 3.9. Resistor-capacitor circuit employed as a low-frequency filter, demonstrating exponential decay of output to square-wave input signal. Circuit contains voltage source (V), capacitance (C), resistance (R) and voltmeters measuring voltage across the input (V_{in}) and across the resistor (V_c). Output at V_c illustrates low frequency filtering (and differentiation) of input (V_{in}).

The formula for the voltage across the resistor (V_c) is

$$V(t) = Ae^{-t/\tau}$$

where $V(t)$ represents the voltage across the resistor at time t; A is a constant representing maximum voltage; and τ is called the *time constant*. The term e represents the base of natural logarithms (approximately 2.718) and is also the one constant for which the proportionality between the rate of change of an exponential process and the process itself is unity.

The inverse equation may be obtained by taking the logarithm of each side:

$$\ln(V(t)) = \ln(A) - t/\tau$$

Theoretically, the capacitor in an RC circuit never becomes fully charged; instead, it only approaches the full battery voltage in ever-decreasing increments (the more it is already charged, the less it charges in the next time slice). Consequently, a convenient convention is needed to describe how long it takes an RC circuit to charge. One possibility would be to use the $t_{1/2}$, the time required to charge a capacitor to halve its final value. Engineers prefer to use the natural logarithm as a yardstick and to utilize $1/e$, which is approximately 1/(2.718), which equals 0.368, or approximately 37%, as a standard measure rather than the 50% point. Conventionally, the time constant of a series RC circuit, τ, is the time required for the voltage across the resistor to fall to 37% of the initial value. This is arithmetically equivalent to the time required to charge the capacitor to 63% of its final value. The time constant of an RC circuit can be calculated as the product of the resistance and capacitance:

$$\tau = R \cdot C$$

The bigger the resistor, the smaller the amount of current that is delivered to the capacitor (by Ohm's law) and the longer it takes to fully charge. The

larger the capacitor, the longer the first plate takes to "fill" with electrons and develop a repulsive force on the second plate.

Once the capacitor in an RC circuit is nearly fully charged (this being an exponential process), a switch may be opened to prevent the charge from leaking off. If the charged capacitor is then removed from the circuit and placed in series with a resistor, then as soon as a complete circuit is formed, the capacitor will discharge through the resistor. The rate of discharge is also exponential (or logarithmic, depending on which axis in the voltage-time relation is chosen as the independent variable). Initially, charges rush off each plate, repelled by like charges on the same plate and attracted by opposite charges on the other plate. As charges redistribute more equally, there is progressively less force driving the movement of charge. The time constant, τ, also defines the time required for the charge to decline to 37% of the initial value. To avoid confusion over 63% versus 37% and charging versus discharging, it is useful to remember that time constants represent a "majority" of the appropriate change: (a) an increase to 63% of maximum voltage on charging or (b) a decrease to 37% of initial voltage on discharging. The direction of current flow is, of course, opposite to that of the initial charging period, and voltage measured across the resistor therefore jumps to a negative value (see Fig. 3.9).

A circuit with a 1×10^6 Ω (1 MΩ) resistor in series with a 1-μF capacitor would have a time constant of 1 second. Any constant stepped voltage drop applied across the resistor would decrease voltage to 37% of its final value in 1 second. Similarly, a circuit with a 100-Ω resistor in series with a 1-μF capacitor would exhibit a time constant of 0.0001 second. Applied voltage steps downward would decline to tiny fractions of their initial values within a few hundred microseconds.

If there are several circuits like the one in Fig. 3.9 (employed as a low-frequency filter) in series, then the overall time constant is less than any individual time constant and may be estimated by the reciprocal of the sum of reciprocals of the time constants of each circuit (6,14):

$$\tau = \frac{1}{\frac{1}{} + \frac{1}{} \ldots + \frac{1}{}}$$

Simple Filters

The analysis of an RC circuit demonstrates that low frequencies are filtered by recording across the resistor of the circuit. How much filtering is done depends on (a) the frequency content of the input voltage and (b) the time constant of the circuit. Low-frequency filtering is used in every clinical EEG recording in order to prevent DC potentials (e.g., tissue-electrode polarization) from overwhelming the biological signals. Figure 3.10 shows examples of calibration voltage pulses passed through EEG circuitry with time constants corresponding to filters with cutoff frequencies of 0.1, 0.3, 1.0, and 5.0 Hz. Note that on many EEG machines, the time constants are given in seconds. The time constant in seconds is calculated from the following equation, which governs its relation to the cutoff frequency. The shorter the time constant is, the more attenuated the low-frequency components of the signal become. A low-frequency filter is sometimes referred to as a *high-pass filter,* because it allows high-frequency signals to pass. Another way to characterize a low-frequency filter is by specifying the frequency (assuming a pure sine wave input) at which output is reduced to a fixed fraction of the input. This frequency, called the *cutoff frequency,* is inversely related to the time constant and multiplied by a factor of $1/(\pi)$ (to convert from frequency in radians to cycles per second):

$$f_{cutoff} = \frac{1}{} = \frac{1}{} = \frac{0.16}{}$$

With a time constant of 1 second, the cutoff frequency is 0.16 Hz. A time constant of 5 seconds yields a cutoff frequency of 0.03 Hz. A τ of 0.1 second corresponds to a cutoff of 1.6 Hz. High-pass (low-frequency) filters pass at least 70% (more precisely, $1/\sqrt{2}$) of the signal amplitude for inputs of frequencies higher than the cutoff frequencies.

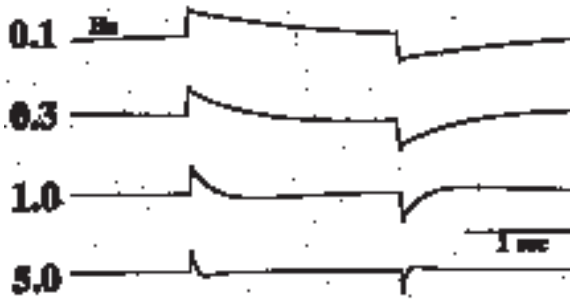

FIG. 3.10. Response of low-frequency filters to 50-μV square-wave calibration input, with respective cutoff frequencies of 0.1-, 0.3-, 1.0-, and 5.0-Hz.

Low-frequency filtering causes an advance in the timing of voltage peaks for a sinusoidal input signal. One way to envision the mechanism of this phase shift is to recognize that the later portions of a slow wave occur at a time when the filter capacitor is resisting accumulation of additional charge on the plates. The later portions of the slower waves are therefore attenuated, and the peak of the wave is shifted to the left (i.e., the filter *differentiates* the input voltage with regard to time). At the cutoff frequency, the peak is shifted earlier by $\pi/4$ radians (45°, or one-eighth of a cycle) (32). This can be very significant in practice if filtering is applied to one channel and not another. For example, assume a 5-Hz theta wave is recorded in two different EEG channels having low-frequency filters set to different cutoff frequencies. If channel 1 has a cutoff of 0.1 Hz and channel 2 has a cutoff frequency of 5 Hz, then the wave in channel 2 will appear to have occurred 25 milliseconds before the wave in channel 1, even though they both came from the same source. If the EEG reader is not aware of these filter settings, he or she may misinterpret this type of record.

High-frequency filtering may be obtained from an RC circuit by taking the output across the capacitor. Rapidly changing input voltages (high frequencies) generate little potential difference across the capacitor and thus generate little output. Slowly changing currents, in contrast, build up substantial voltages across the capacitor plates (the capacitor has time to charge). A high-frequency filter is a low-pass filter. The cutoff frequency is defined as the reciprocal of $2\pi\tau$ ($1/[2\pi\tau]$), just as with high-pass filters. Figure 3.11 shows the effect of two high-frequency filters having cutoff frequencies of 35 Hz and 15 Hz on a spike-and-wave discharge. Spike amplitudes become noticeably attenuated at a lower high-frequency cutoff; slow waves are barely altered, except that they are made smoother.

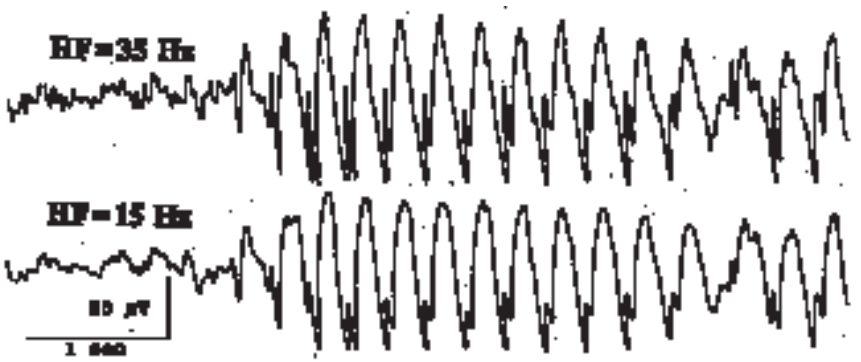

FIG. 3.11. High-frequency filtering of spike waves to show attenuation of spike component with 15-Hz high-frequency cutoff. Data are reproduced from an ambulatory cassette electroencephalographic (EEG) monitor played back to a standard EEG machine for paper output.

High-frequency filtering also produces phase shifts in the timing of sinusoidal (or approximately sinusoidal) signals, because it takes time for a capacitor to charge and develop a voltage across the two plates. In this case, the phase shift causes a delay in the peak of the waveform. This delay becomes significant only for high-frequency signals. At the cutoff frequency, a sine wave is delayed by one-eighth (45°, or $\pi/4$ radians) of a cycle (32).

Impedance

Impedance is a term used for the combined effects of resistance, capacitive reactance, and inductive reactance. The formula for calculating the impedance of a series circuit is

$$Z = \sqrt{R^2 + (X_C + X_L)^2}$$

where Z is in ohms and the remaining terms are as defined earlier. Inductive reactance is subtracted from the capacitive reactance, because their values have opposite phase. In the practice of EEG, inductive reactance can usually be ignored. Impedance, represented by Z, replaces resistance in the analysis of AC circuits. In AC circuits, Ohm's law takes the form

$$V = I \cdot Z$$

This equation describes only the amplitudes of the waveforms considered. V, I, and Z are each a function of frequency, and they may be shifted in phase in comparison with one another. These phase shifts can have significant effects on the behavior of AC circuits; however, a proper treatment of this subject requires complex mathematics that are beyond the scope of this discussion.

Impedance can be significant in several aspects of EEG. The most important of these is probably safety considerations (see later section on electrical safety): dangerously low circuit impedances can allow high currents to pass through tissue with potentially disastrous consequences. Impedance is also important in comparing amplitudes in different EEG channels. High impedance (typically in a poorly affixed electrode) causes the EEG machine amplifiers to work improperly and distorts the resulting signal in that channel. Impedance is also an important factor in coupling the output of one amplification stage to another. The EEG machine is

designed so that electrodes should have impedances in the range of a few thousand ohms, whereas the input impedance of the machine is in millions of ohms. If the impedance of the input is too low, the second stage may draw significant current from the primary stage and distort the measurement. Suppose, for example, that a 100-μV EEG signal is inputted into a circuit with a 1,000-Ω resistor. Assume that the input impedance of the EEG machine is 10^6 Ω and therefore in a position to draw negligible current from the circuit. Current through the circuit will be 0.1 nA (10^{-9} A). In contrast, now suppose that the EEG machine has an input impedance of 1,000 Ω. Total circuit impedance is now 2,000 Ω, and current through the circuit is 50 nA. Because of the low-input impedance, the output signal is attenuated and measured as 50 μV rather than 100 μV, as in the first case. This illustrates that the high-input impedance of a good amplifier produces its output voltage largely independently of electrode impedance. It is essentially the voltage divider seen earlier in this chapter, with one resistance being *much* larger than the other. As a result of this design, the electrode impedance during normal EEG recording can vary by a factor of almost 10, with only minor alterations in the quality of the EEG. Very high electrode impedances, which approach those of the EEG machine input, cause the phenomenon called *impedance mismatch,* which results in signal attenuation, as demonstrated in the example earlier.

THE DIGITAL WORLD

Introduction to Digital Computers

The rapid and continuing spread of computers into all aspects of people's personal and professional lives requires that much information gathering, storage, and communication be converted to their language, the language of numbers. Properly referred to as *digital* computers, these devices primarily manipulate, store, and display numbers, or their equivalents, in various forms. Their strength lies in the fact that they perform these tasks extremely fast, executing simple commands at speeds measured in millions of instructions per second (*mips*) and performing calculations measured in millions of floating point operations per second (*megaflops*). Conceptually, a digital computer can be envisioned as a group of individual devices, such as a calculator (central processing unit [CPU]), information archive area (hard disk), computer monitor, floppy disk drive, keyboard, printer, and temporary memory storage area in which data are temporarily kept for manipulation (random access memory [RAM]). These devices are all connected both to each other, by a communication cable called a *bus,* and to a clock. Each device is assigned a priority, according to its importance, and an interrupt flag, which is turned on when the device needs to do something and turned off when it is waiting for instructions. Figure 3.12 depicts a schematic of this arrangement. The clock keeps track of time, so that events can occur in a synchronized manner. In a typical instruction cycle in a computer's life, the clock ticks, and the CPU goes looking around the bus to determine which devices need to be serviced. It checks the devices in order of priority around the bus to determine which get served first. The CPU services the devices as necessary before moving on to the next request. If an instruction is given to copy data from the floppy drive to the hard disk, the floppy drive sets its interrupt flag to "on" and asks for service. The CPU, cycling around devices on the bus, notices this and moves a piece or pieces of data from the floppy drive to the hard disk, as requested, all the while taking brief periods to look around the bus for other tasks to complete, which it prioritizes. If no other devices need service, it may continue this operation until the file is copied and then turn the flag on the floppy drive to "off." If other devices with higher priority request attention, then the floppy drive will wait until

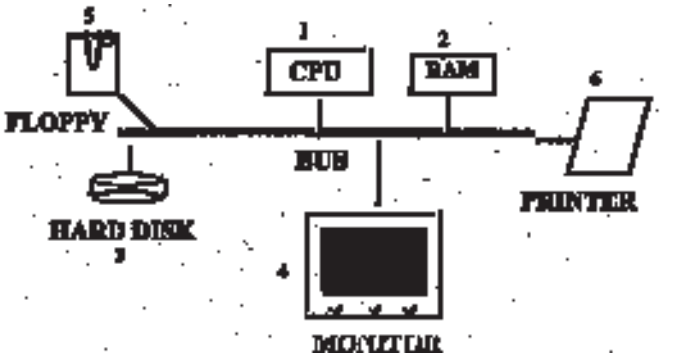

FIG. 3.12. Schematic diagram of personal computer architecture. A fast clock is built into the central processing unit (CPU), which is connected to random access memory (RAM), peripheral structures (such as the floppy and hard drives, printer, and fax machine), and computer monitor. State-of-the-art machines have a variety of other design features and peripheral devices, such as "burst cache" memory, network access, and digital video disk (DVD) drives. Despite these tremendous advances, the basic machine design reduces to the operations described in the text.

the more important tasks are completed. Devices with lower priority may wait until the current job is finished before they are serviced. If many devices request attention at one time, as frequently happens, then the CPU may take turns servicing them, but it distributes service time according to device priority. The faster the clock ticks (as of this writing, personal computers have clock speeds of over a billion cycles per second [gigahertz]), and the larger the capacity of the bus, the faster and more efficiently the computer operates. As computers become even faster, this rule breaks down somewhat as the rate-limiting steps in some processes change; for instance, they may change to time it takes for the reading heads to access the hard disk drive or transfer information to and from memory. More ingenious ways of speeding up these processes continue to be dreamed up by engineers, such as "burst cache", an ultra-fast hard-wired section of memory that holds critical information for brief periods, and putting more and more microscopic devices on the machine's CPU chip, so that transfer distances and times are minimized. Because theoretical limits to the density of integration of these chips are approached, completely new types of computing strategies, even using living cells to store information, are under development.

Computer programs that directly access machine hardware and allow users to give commands to this system via the keyboard or to run programs are called *operating systems* or software *platforms* (e.g., Windows, Macintosh Operating System (MOS), Disk Operating System (DOS), UNIX, and LINUX). The actual machines and their individual components together form *hardware platforms*. Other computer programs that run on these computers and can be started or stopped by commands through the operating system are called *applications*. The computer programs that provide interfaces, displays, and commands through which users interact with digital EEG machines are examples of such applications. In most cases, however, the hardware platforms that constitute these machines are the same standard personal computers that are used to balance checkbooks or surf the Internet, with the exception of some specialized hardware, which is discussed later. The easy-to-use graphical windows through which these programs are run are called GUIs (pronounced "gooeys"), for graphical user interfaces.

Analog and Digital Signals

The basic currency of EEG is electrical activity generated by the brain and recorded by scalp electrodes after it is conducted through the intervening tissues. On a standard EEG machine, filters and amplifiers process brain signals so that they can be conducted to pens, which transfer these signals in a continuous flow of ink to the EEG paper that scrolls beneath them. Throughout this process, brain activity, although transformed, remains continuous and uninterrupted. In this scheme, brain activity remains an *analog* signal, as it is analogous to the source signal, and every point in time can be mapped back to every point in the source signal if one knows the "recipe" for transformation is known. A *digital* signal is different in that it is discontinuous, consisting of a sampling of the source signal in time with spaces left between the data points. Rather than begin a smooth, continuous line drawn on paper, a digitized signal can be written as a table of numerical values. When these values are plotted on a graph, they form a representation of the original signal, with spaces between the data points. Engineering theory provides mathematical rules, which determine how many points, or *samples,* are necessary to uniquely resolve a particular kind of signal or waveform. These rules, to some degree, are governed by what clinicians wish to do with the data and are discussed later Table 3.3 reviews a number of common items that can be represented in analog or digital form.

TABLE 3.3. *Analog and digital comparisons*

Reference	Analog machine	Digital machine	Comments
Time	Pendulum clock	Digital clock	The pendulum clock has smoothly moving hands; the digital clock has discrete numbers.
Music	Long-playing vinyl record	Compact disk	The stylus traces groves in vinyl records, generating an electrical signal that is carried to the speakers. Numbers burned onto a compact disk are read by a laser, generating discrete voltages sent to speakers.
Art	Oil painting	Newspaper photograph	The painting has smooth, continuous brush strokes. Dots or pixels compose the newspaper photograph; they can be seen through a magnifying glass.

Analog-to-Digital Converters

The heart of a digital EEG machine is the *analog-to-digital converter* (ADC). This device usually consists of a circuit board installed in a computer and is composed of several conceptual parts: (a) a clock, (b) a voltmeter or series of voltmeters, and (c) very rapidly accessible memory storage. The signal from a single EEG channel is inputted into a corresponding channel in the ADC board, the voltage across the input in the board is measured, and its numerical value is written down in memory. The clock ticks off a certain measure of time, and the process is repeated at regular intervals, yielding a table of evenly spaced numbers. The number of times per second that the voltage is measured is called the *sample rate* and is measured in samples per second (hertz). The higher the sample rate, in general, the better the reproduction of the input signal. ADC boards are measured (and priced) according to their number of input channels; their *throughput,* or the total number of samples per second that can be acquired by the entire device; and their resolution (described later). The throughput can usually be directed to and divided among any number of channels in the device. This number may be only one channel, if very fast sampling is required, or the total number of channels available, depending on the application. For example, if an ADC board has 32 input channels and a total throughput of 6,400 samples per second (6.4 kilohertz [kHz]), it can sample each of 32 channels at a maximum of 200 Hz each. The device could also sample two channels at 3.2 kHz each.

ADCs are also distinguished by their design for data sampling, including boards that sample each channel in turn and stagger them in time (it takes at least a few milliseconds to sample each channel), sample-and-hold devices that sample sequentially and then align data points in time, and devices that sample all channels simultaneously. Another important characteristic of ADCs is their *resolution* or *precision.* This is a measure of how finely the voltage can be subdivided when measured (e.g., to 1, 0.1, or 0.01 V). This precision is measured in *bits,* each bit being a place in a binary number. The total number of voltage values that can be resolved is 2^n, where n is the number of bits. If V_r is the maximum range of the board, then the input is resolved in steps, whereby ΔV is $V_r/2^n$. For example, if the board can resolve only two bits and is measuring on a scale of −100 to 100 μV, then there are 2^2, or four, possible values for the EEG signal, each data point being rounded to the nearest 50 μV. At this resolution, such a signal would look very rough, as measurements are rounded to the nearest 50 μV, without any possible values in between. This type of resolution is far different from the smooth lines drawn by pens on paper that are used with analog machines. Bits are used to measure resolution because the language of computers is *binary* numbers, in which each bit is a little electrical switch that is turned either on (a value of 1) or off (a value of 0). When these switches grouped together (usually in multiples of 8, 16, 32, or 64 at a time), they become binary numbers. For example, in the number 101 in binary, the first place on the right has the decimal value of $1 \cdot 1 = 1$, the 0 in the middle (twos) place has the decimal value $0 \cdot 2 = 0$, and the 1 in the most leftward (fours) place has a decimal value of $1 \cdot 4 = 4$. Therefore, the binary number 101 is equal to $(1 \cdot 4) + (0 \cdot 2) + (1 \cdot 1)$, or 5, in the decimal system. The number of bits, n, in a binary number can then resolve into a maximum of 2^n divisions. ADC used in early digital EEG machines were eight-bit devices, able to resolve EEG signals into $2^8 = 256$ divisions. Therefore, in a range −150 to +150 μV, steps of 300/256 μV, or 1.17 μV, can be resolved. This initial resolution partially contributed to slow acceptance of these new devices because the tracings did not look as good as on paper. Most current EEG machines have 16-bit resolution and, for an input range of ±150μV, can resolve 300/65,536 μV, or 0.00457 μV. Table 3.4 depicts the resolution of a voltage range of −1.0 to 1.0 V as a function of the number of bits of the ADC.

Of importance is that the input voltage (2,000 μV in this case) is not the actual input voltage that is divided up by the ADC. Rather, all brain activity, once brought into the machine, is amplified by a certain multiplier (called *gain;* the inverse of this is *sensitivity,* the term commonly used to refer to controls to adjust amplitude on the EEG) that brings it into the standard input range of the ADC device (a typical range is ±5 V). In the earlier case, recording ±1,000 μV would require a gain of 5,000 to bring it to ±5 V.

Although it may not seem at first that a typical electroencephalographer can tell the difference between 8-, 12-, and 16-bit resolution, these differences, particularly at the lower end of resolution, are easily apparent on rou-

TABLE 3.4. *Voltage steps for digitizers of various resolutions*

No. bits	No. levels	ΔV for V_r = 2000 μV
1	$2^1 = 2$	1,000 μV
2	$2^2 = 4$	500 μV
3	$2^3 = 8$	250 μV
4	$2^4 = 16$	125 μV
8	$2^8 = 256$	7.8 μV
12	$2^{12} = 4{,}096$	0.49 μV
16	$2^{16} = 65{,}536$	0.031 μV

tine reading of clinical records. For this reason, digital EEG technology was not widely used until 12- and 16-bit machines became available.

Visual Resolution: How The Electroencephalogram Looks to the Reader

As noted earlier, a frequent criticism of digital EEG, particularly when this technology first became available, was that it just did not look as good as on paper. At first glance, this is true. Paper EEGs are larger than most early computer monitors, the tracings are continuous waveforms in dark black ink, and large areas of the paper are devoted to each channel with, in general, plenty of space between channels. Digital EEG systems initially used 15-inch monitors; channels were often crammed together with little space between them, depending on the number of channels; and waveforms just did not appear as crisp as paper EEGs. Newer digital systems have improved a great deal on these early systems, making use of larger monitors with higher resolution and with better and more flexible graphical displays. A number of important characteristics should be kept in mind in assessing how a digital EEG tracing looks to a reader. Many of these parameters can be adjusted to improve the appearance of the EEG, although some may be hard-wired into the EEG machine.

Data Sample Rate

Low data sample rates may leave considerable spaces between data points, when tracings are magnified to rapid paper speeds on digital displays. Higher sample rates give an EEG recording the appearance of a smoother, connected line in the horizontal (time) dimension.

Data Resolution

Data resolution, mentioned earlier in the context of ADC, is a function of the ADC and consists of the number of bits in which the EEG signal is recorded. The more bits of data resolution there are, the better the signal looks, because smaller incremental changes in voltage are displayed, giving the appearance of a smooth, connected line rather than a jumpy, step-like tracing in the vertical dimension. On older eight-bit EEG machines, this stepwise quality to EEG tracings was sometimes quite evident. On newer systems, this is much rarer, inasmuch as tracings are viewed on standard gain settings with multiple channels displayed on the screen at one time; however, it is possible to adjust display parameters so as to allow the reader to view the limitations of a given data resolution—in many cases, primarily by spreading smaller epochs of time over the screen (e.g., 1 to 2 seconds) at high gains (see later discussion).

Monitor Resolution

This feature, sometimes neglected in discussions of digital EEG display, is, along with monitor size and dot pitch, an important determinant of how a digital signal looks when the EEG pattern appears on a monitor. Monitor resolution is the number of pixels in each direction that can be used to fill in points on the EEG tracing. For example, a common resolution of computer monitors is $1{,}024 \times 768$ pixels. If 10 seconds of the EEG are displayed (for the time being, without regard to pixels dedicated to channel labels, screen borders, and so forth), then each second of the EEG on the horizontal axis has 102 pixels devoted to its display. If the EEG is sampled at 250 Hz, then less than every other data point can be displayed. In the vertical direction, there is a more severe restriction, because typical EEG tracings may have 32 channels or more. In this case, again without regard to pixels devoted to borders or labels, each channel may have only 24 pixels devoted to it in the vertical direction. If the EEG has a dynamic range of 300 μV, then very sharp waveforms, such as spikes, which may change by 150 μV over a fraction of a second, may look quite choppy. Larger monitors may help to better visualize tracings and allow space for each channel, in comparison with paper. This increased size of the viewing area should also be coupled with higher resolution, when possible (and affordable), so that the increased size does not serve to emphasize the distance between data points and does not further accentuate the noncontinuous nature of digital waveforms. Smaller monitors have the advantage of crowding each channel in such a way as to make it appear more continuous to the eye, but this is overridden by the disadvantage of making the reader strain to make out what can turn into a jumble of waveforms crammed into a small space.

Other Items: Dot Pitch and Color

Other items that can affect the appearance of the EEG are the dot pitch of the monitor and how color is applied to tracings. Their effect is, in general, smaller than that of the items just described. Dot pitch is the diagonal distance between display pixels. The smaller the pitch is, the higher the screen resolution is and the greater the number of pixels that the screen can contain. Changes in color for different groups of channels are sometimes used for ease of reading, although less commonly by more seasoned electroen-

cephalographers. The authors' preference is to make the tracings black against a white or easy-to-read light background, but choice of colors and tracing displays are usually a matter of personal preference.

Recording "The Right Stuff": Nyquist's Theorem and Aliasing

A few important engineering rules govern how digital EEG signals must be acquired in order to guarantee that the EEG records the appropriate signals. The most important of these is called *Nyquist's Theorem,* which states that, in order to reliably digitize a signal of a given frequency, *F,* the signal must be sampled at a rate of more than two times *F.* For example, if the signal to be recorded has components of interest at 100 Hz, then a sample rate of greater than 200 samples per second (also properly stated as 200 Hz) is required. The reason for this sampling requirement is something called *aliasing.* Aliasing occurs when a signal of a certain frequency is sampled too slowly to resolve its frequency content, so that the resulting samples, when put together, compose a signal whose frequency is lower than that of the source signal. The true frequency of the signal "folds back" on one-half the sampling frequency, giving the aliased frequency. Once this aliasing has taken place, it is impossible to recover the original signal from the samples. This is best demonstrated by an example. Suppose an electroencephalographer wants to record a brain rhythm that occurs at 75 Hz, which requires a minimum sampling rate of 150 Hz, but the bargain-basement device that the purchasing department acquired for the electroencephalographer has a maximum sampling rate of 100 Hz per channel. Not believing in Nyquist's theorem, the electroencephalographer records the activity. An aliased signal of 25 Hz will therefore be recorded, introducing error into the data. Figure 3.13 depicts this phenomenon for a 5-Hz sine wave sampled at 8 Hz, which is less than the Nyquist frequency of 10 Hz. The sine wave reconstructed from the samples is only 3 Hz. Just as the term "alias" in common speech means a false name, so is an aliased signal a false representation of the source signal.

One method to significantly reduce aliasing is through the use of *antialiasing* filters. These simply are low-pass filters whose cutoff frequencies are equal to or less than one-half the sampling rate, the highest frequency component of the signal that can be resolved without aliasing. This ensures that higher frequency components are eliminated before digitization. Another way to be sure that a signal is not aliased is to *oversample,* which is sampling at a rate higher than that required by Nyquist's theorem. For example, most commercial EEG machines have sampling rates of at least 250 Hz to sample a bandwidth of 0.1 to 100 Hz. There are many practical reasons for doing this.

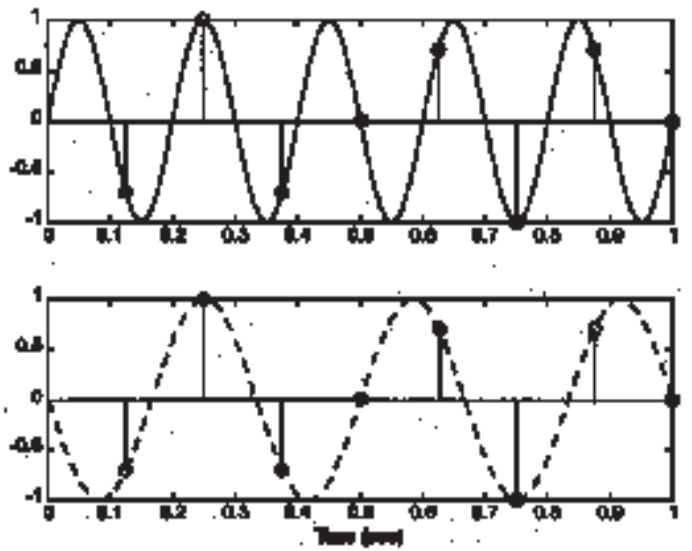

FIG. 3.13. Example of aliasing in an under sampled signal. ***Top:*** The original analog signal, a 5-Hz sine wave, and the discrete points sampled at eight times per second (*open circles*). ***Bottom:*** The analog sine wave reconstructed from the samples. Note that the frequency of the reconstructed signal is only 3 Hz.

Most important is that most commercial filters, such as those used in antialiasing, remove only approximately 37% (30% on Grass machines) of signal power at the cutoff frequency. This means that there is still significant power higher than the cutoff allowed into the EEG. Oversampling prevents this portion of the source signal from being aliased. When oversampling is combined with antialiasing filters, the aliasing can be eliminated.

Referential Recording

One important difference between analog and digital EEG machines is that digital machines use the principle of "referential recording." In this scheme, a separate electrode, called the *reference,* or a combination of electrodes such as the ear or mastoid electrodes (A1 and A2, or linked ears), are used as the second input ("grid 2" in older EEG language) into the differential amplifier for each channel. In this recording convention, the potential difference at the reference is subtracted from each electrode location (e.g., Fp1 − ref, Fp2 − ref), so that each data point stored in memory consists of

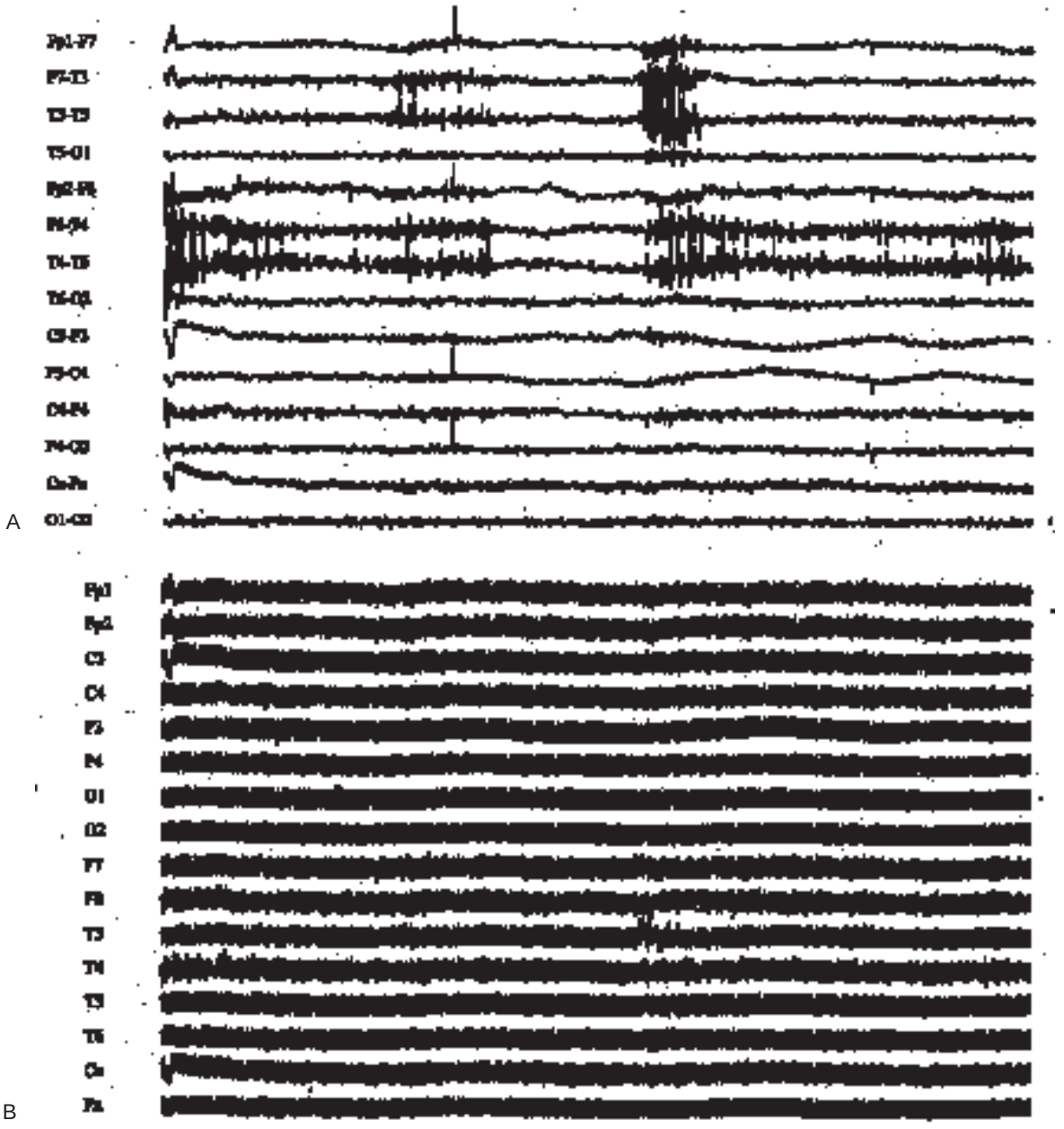

FIG. 3.14. Example of a referential digital recording, viewed in both a bipolar montage **(A)** and then the "machine reference" montage **(B),** with the potential at each electrode location minus the reference displayed. In this case, with the references (lined ears) off the patient, the bipolar record appears to demonstrate low voltage and muscle artifact (a). On the machine reference, notice the 60-Hz artifact in all channels, which indicates that the reference is either of high impedance or off the patient. The data viewed in *A* are not physiological.

the voltage derived by subtracting the potential at each electrode location minus the reference. This convention allows the reader to convert this simply by subtracting or adding channels appropriately. For example, to get the channel Fp1 – Fp2, the technician needs only to take the data in memory for the channel Fp1 – ref and subtract Fp2 – ref:

$$(Fp1 - ref) - (Fp2 - ref) = Fp1 - ref - Fp2 + ref = Fp1 - Fp2$$

The reference channel activity thus cancels, and the result is Fp1 – Fp2. In this way, simply adding and subtracting the appropriate channels can yield any conceivable montage. This is to be distinguished from bipolar recording, in which the montages remain fixed and can be changed only by physically changing the wiring in the machine, which may be accomplished through the channel selector or montage selector on analog machines (see later discussion). Referential recording has numerous advantages over bipolar recording in that it allows the reader to revise the montage at will when examining a particular section of the EEG to get numerous views of a particular discharge. In addition, referential recording allows use of a variety of computed references, such as an "average reference," Laplacian reference, or individualized custom references for each patient by combining signals from multiple channels mathematically. One potential disadvantage of referential recording is that the data in all channels may be compromised if the reference electrode or electrodes are disrupted or are of high impedance, particularly in the presence of significant external noise. In these cases, the noise may overwhelm the signal in all channels, leaving the reader a tracing of very low amplitude with little to no signal content. A quick review of EEG data on the machine reference montage demonstrates high-amplitude 60 Hz artifact in all channels, indicating the reference problem. For this reason, the authors recommend that each digital tracing be viewed briefly both during recording by the technologist and later on review by the reader first on a "machine reference" montage (each channel minus the reference) to check for high impedance in the reference electrode (see Figure 3.14). The authors have personally seen records misinterpreted as low voltage with little normal background because of such technical difficulties.

THE ELECTROENCEPHALOGRAPHIC MACHINE: AN OVERVIEW

The EEG machine has been the subject of study, development, and use since the 1920s. Although the basic elements are similar to those employed in the days of Hans Berger, many of the components and circuits have been vastly improved. One-channel machines have expanded to machines with 8, 16, 20, 24, 32, 64, 128, and even more channels. Vacuum tube–based amplifiers have given way to transistorized amplifiers and then to integrated circuits of increasing complexity and smaller size. The electronics that once constituted machines of several hundred pounds that were pushed around the hospital by burly EEG technologists now can be worn on a patient's belt. Paper output has persisted for a surprisingly long time, arguably because electroencephalographers tend to be very conservative and concrete. Nevertheless, oscilloscopic output devices and methods for computerized signal analysis have been around for decades and steadily attract devotees. The paperless EEG is in a race with the paperless office. In the next section, the major components of a typical modern EEG machine are considered in view of the engineering principles described earlier, with new emphasis on integration of digital signal technology. Figure 3.15 shows a block diagram of the circuit containing the patient and EEG machine, which consists of both

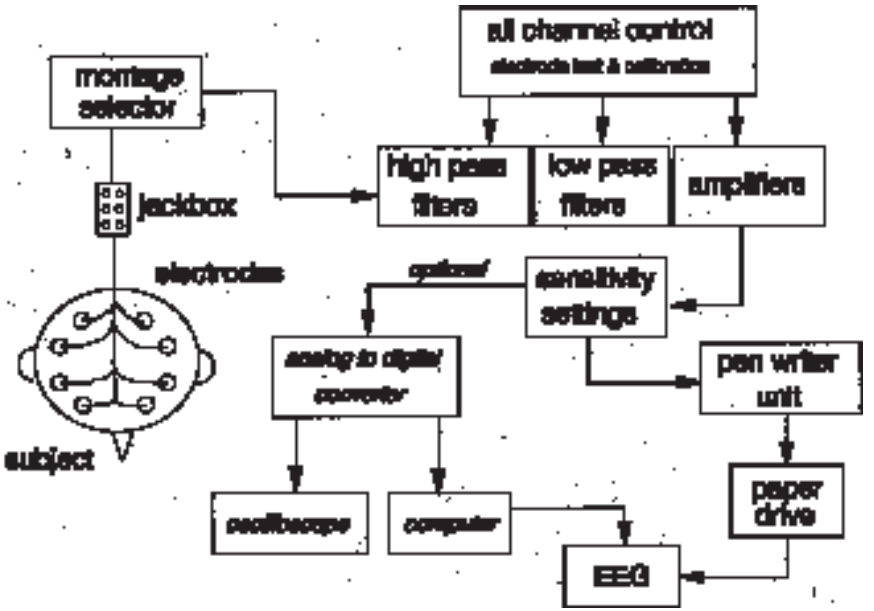

FIG. 3.15. Block diagram of major functional units of the electroencephalographic (EEG) machine. Filters and amplifiers are contained in EEG amplifier units. Paper, ink, and drive train are replaced in digital EEG machines by an analog-to-digital converter, a computer monitor (oscilloscope), and a computer.

digital and analog components. The machine's main functional units are defined in individual blocks.

Just as the function of an automobile is to serve its driver, the function of an EEG machine is to serve the patient. The entirety of EEG technology is devoted to faithful representation of the electrical signals generated by a patient's brain. These signals arise primarily from spontaneous synaptic activity in cerebral cortex. Regional voltage differences in brain are communicated via the conductive components of the head to the scalp. At that site, biology meets technology.

Electrodes

Electrodes conduct electrical potentials from patient to the EEG machine, usually with help from a conductive paste connecting skin to electrode. The electrically conducting paste that is used to couple the electrode and the skin serves two functions: It transmits potentials from the brain to the EEG machine, and it decreases movement artifacts. Electrodes are made of metal, but not all metals make equally good EEG electrodes. Proper electrodes must be good electrical conductors (an indicator of available mobile charge) and must make good contact with the electrolyte paste that covers the skin. Electrodes establish this contact through double layers of charge.

When metals are placed into a conducting solution, such as a solution that contains free ions to carry current flow, there is the opportunity for charge to move between the metal and the solution. Diffusion of ions leads to a separation of metal ions from the metal electrode. How far the charge strays and how great a potential difference is developed depend on the balance between an ion's mobility in solution and the retarding force from charge separation. In the steady state, a layer of charge is established on the metal surface, and a layer with opposite polarity is established in the solution near the metal. This system resembles the charged plates of a capacitor. If a voltmeter is connected across the solution by connecting one lead to the metal and another to the solution, a small potential is measured. This indicates that a small steady-state current of ions is flowing between the metal and solution. The potential measured in this manner is called the *electrode potential.* Electrode potentials may be measured in the range of up to 1 V: that is, four to five orders of magnitude larger than the voltage of the EEG (6).

When a voltage (such as that from the EEG machine) is applied to an electrode and an electrolyte solution, the double layer between the two is disturbed, and current flows between the electrolyte solution and the electrode. This current is added to the steady-state electrode-electrolyte current. If the electrode potential is large in comparison to the signal of interest, the electrode is said to be *polarized* or *nonreversible.* Such electrodes have large resistances and capacitances, which distort the EEG pattern. In order to detect the EEG signal with polarized electrodes, low-frequency filtering to remove the DC electrode potential is required. Furthermore, the electrode itself serves as a low-frequency filter because of capacitance at the double layer.

Reversible electrodes are electrodes that do not easily become polarized. One way to produce such electrodes is to deposit a metallic salt containing an ion in common with the conducting solution on the electrode. An example of this is the silver chloride (AgCl) electrode. Such an electrode may be fabricated by immersing silver wire in a solution of electrolyte-containing chloride and placing a positive voltage across the electrode. Chloride ions migrate to the surface of the silver and impart a distinctive gray color. When a chloride-treated silver electrode comes into contact with NaCl solution on the skin, currents of Cl^- ions flow freely between the electrode and the solution and prevent the electrode from becoming polarized. Polarization is avoided because the electrode and the solution can communicate with ions (namely, Cl^- ions from electrode and electrolyte, respectively) that exhibit identical mobilities in solution. Silver chloride electrodes are useful for recording DC and potentials of very low frequency.

Reversible electrodes can also be constructed from noble metals, such as platinum and iridium. For a more in-depth consideration of these electrodes, see Cooper (5), Cooper et al. (6), or Weyer (33).

The ability of different kinds of electrodes to reproduce a square-wave test voltage is illustrated in Figure 3.16, taken from Cooper et al. (6). In this illustration, the distortion of the waveforms results from the electrode impedance, which is a function of the electrode capacitance and resistance. Notice that the silver chloride electrode best reproduces the waveform. Figure 3.17, adapted from Niedermeyer (24), shows a simple circuit that models the interface between electrode and skin. In this diagram, R_{eq} is the resistance resulting from the electrode-skin junction. R_D and C_D are the resistance and capacitance of the electrode double layer, and R_d and C_d are the frequency-dependent resistance and capacitance of the system related to diffusion, which compose the Warburg impedance (10,25).

Large electrode resistances, greater than 5,000 Ω for skin electrodes or 15,000 Ω for needle electrodes, can result in noise artifacts in the EEG recording (6,30). This happens because strong electric fields present around the EEG machine induce small currents in the electrodes where they meet large impedances (e.g., at the scalp-electrode junction). By Ohm's law ($V = I \cdot Z$), high electrode impedance leads to high voltages, even in the presence of small

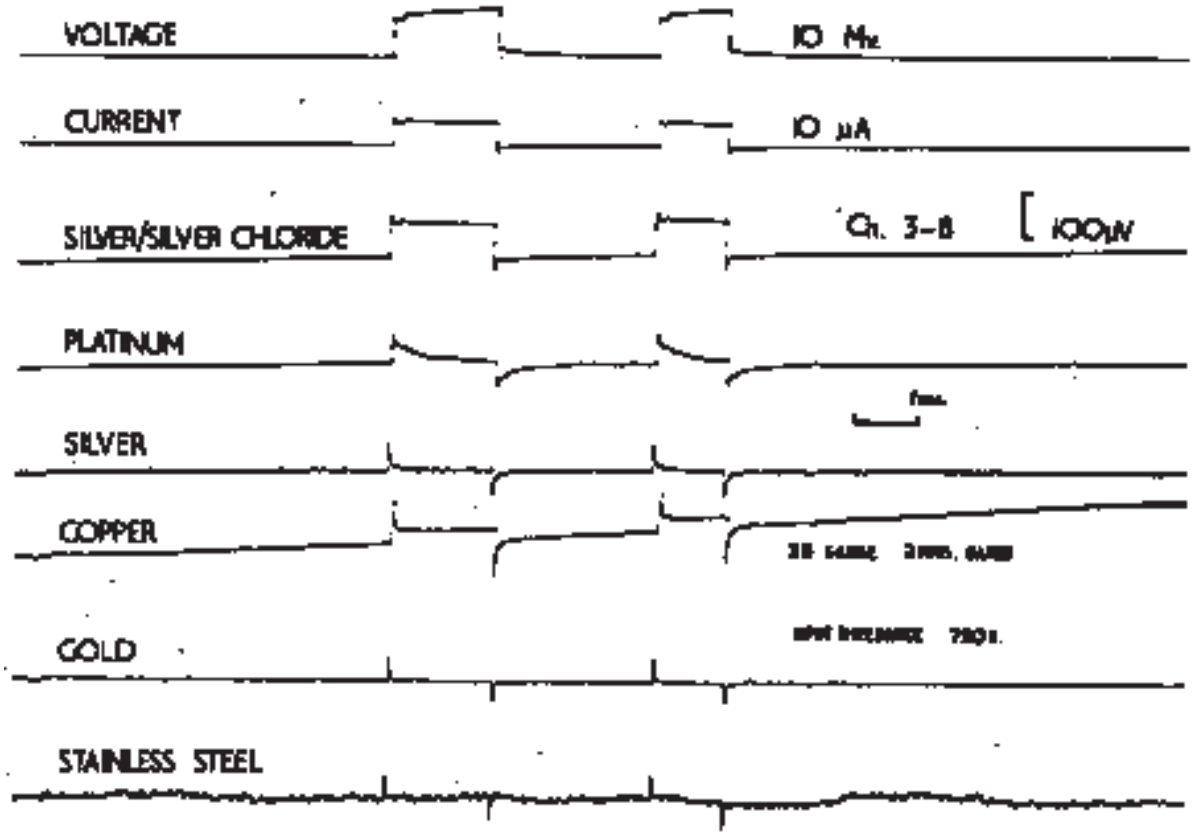

FIG. 3.16. Ability of various types of commonly used electroencephalographic electrodes to reproduce a 10-mV, 10-mA square-wave input. (Adapted from Cooper R, Osselton JW, Shaw J. *EEG technology.* London: Butterworths, 1980.)

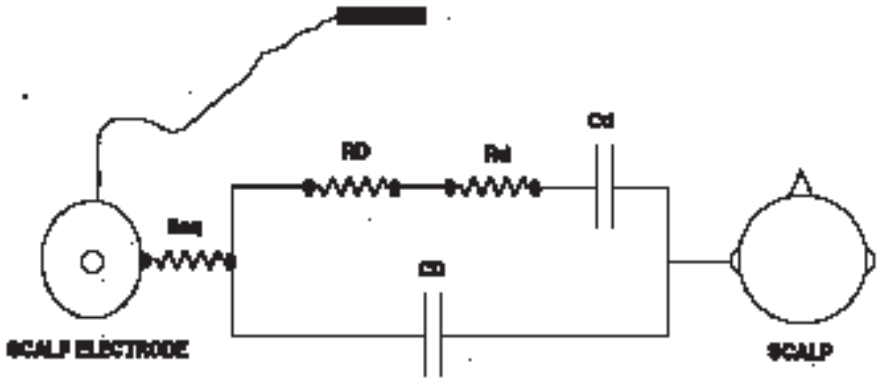

FIG. 3.17. A simplified model of the electrode-tissue interface. R_{eq} is the resistance of electrolyte material (e.g., gel) between tissue and metal; R_D and C_D are the resistance and capacitance of the electrode double layer; R_d and C_d are the time and frequency dependent diffusion impedances (these are very large if electrode becomes polarized). (Adapted from Niedermeyer E, Lopes da Silva FH, eds. *Electroencephalography: basic principles, clinical applications, and related fields,* 4th ed. Baltimore: Williams & Wilkins, 1999.)

currents. Because of a small area of contact with the subject, a needle electrode has high impedance and is more susceptible to line (60-Hz) artifacts. In certain circumstances (e.g., the use of needle sphenoidal electrodes to record activity from the anterior-inferior temporal lobe), the benefits of a needle electrode may outweigh the drawback of high impedance. Electrode impedances are tested after application by ohmmeters. These devices pass a small constant current through the electrode circuit and a remote reference (e.g., *on* the forehead or ear) attached to the patient. Voltage change is measured, and Ohm's law is used to calculate impedance. Impedance is frequency dependent, and the ohmmeter should therefore use frequencies in a range relevant to the EEG, such as 10 to 30 Hz. DC ohmmeters induce polarizations in electrodes and in validate the measurement. High DC currents can also cause discomfort for the patient.

Before placement of an electrode, the scalp must be prepared by being rubbed vigorously with alcohol or with a skin preparation agent. This action removes dirt and oil from the electrode site and lowers the impedance of the scalp-electrode junction. Obviously, excessive cleaning can be irritating to the patient. Similarly, some patients are sensitive to paste containing salt solutions or bentonite. Several varieties of electrode attachment media, including sodium chloride pastes or gels, conducting sponges, and other specialized electrolytes, are available. Scalp electrodes are usually cupped, with a hole at the peak, to facilitate contact with electrode paste. Electrodes may be held in place by viscous gels, by mechanical restrictions (bands or rubber caps), or by collodion. Collodion is a glue formulated from pyroxylin (an element of gunpowder) in ether, alcohol, or camphor; it is liquid when applied, but it is able to dry to a strong adhesive within minutes. It is suitable for patients who cannot keep still or who need electrodes in place for more than a few hours. Ether is highly flammable. Flames, excessive heat, or pure oxygen should not be near collodion applications, and collodion should be used only in well-ventilated areas. It must be remembered that collodion is not an adequate conductive medium: Conductive gel must be injected into the cup electrodes and refreshed periodically. A blunt needle is usually employed for this task. Collodion is removed with acetone scrubs (6).

Common Types of Electrodes

Each of the commonly used electrodes has a simple design: a metal contact surface, flexible and insulated wire, and a connecting pin to mate with the headbox or jackbox of the EEG machine. Wires are usually color-coded for easy tracing in troubleshooting (4).

Scalp electrodes (Fig. 3.18*A*) are suitable for most routine recordings and are usually of the reversible type. They are most often made of chloride treated silver disks 4 to 10 mm in diameter. Electrodes fabricated from platinum, gold, or tin are sometimes used. Properly applied electrodes demonstrate resistances of a few hundred ohms. Resistances smaller than this usually indicate a short circuit in the electrode. According to the international standards for the EEG, electrode resistances should be less than 5,000Ω and greater than 100 Ω (1). Positioning of scalp electrodes and methods for constructing montages of electrode pairs are considered elsewhere in this book.

Subdermal electrodes (see Fig. 3.18*B*) are fine metal electrodes made from stainless steel or platinum and are approximately 10 mm long and 0.5 mm in diameter. Skin is cleaned with a presurgical scrub such as iodophor or benzalkonium chloride (Zephiran), and the electrodes are inserted through the horny layer of the skin into the subdermis. Insertion is made to the needle hub, in a direction nearly parallel to the scalp. Subdermal electrodes are attached quickly and simple to use, but their disadvantages are many. First, they are painful and consequently are best used on comatose patients. They have a high resistance (generally 10,000 to 15,000 Ω), which makes them more susceptible to noise. Subdermal electrodes can cause infection and must be sterilized before each use; therefore, in the era of serious, transmissible viral illnesses, such as hepatitis, Jakob-Creutzfeldt disease, and acquired immunodeficiency syndrome (AIDS), the use of subdermal electrodes should generally be avoided. In the rare occasions when they are employed, most institutions require that they be discarded after a single use.

Clip electrodes (see Fig. 3.18*C*) are cup electrodes filled with conducting paste and clipped to the earlobes, usually for referential recordings. Their properties are similar to those of scalp electrodes. Because of their location, these electrodes are prone to movement artifacts. Some electroencephalographers prefer to place the A1 and A2 electrodes (left and right ears, respectively) over the mastoid processes (sometimes they are then labeled M1 and M2), obviating the need for clip electrodes.

Nasopharyngeal electrodes (see Fig. 3.18*D*) have historically been used in conjunction with standard scalp electrodes in order to improve detection of inferior temporal or frontal discharges. They are made from a 10- to 15-cm-long segment of flexible insulated wire with an uninsulated 2-mm gold tip. Nasopharyngeal electrodes can be purchased or fabricated from insulated silver wire by stripping 5 mm of insulation from the tip and heating the wire with a match. The silver melts, forming a little ball at the tip. A pin connector is soldered at the proximal end. The wire may then undergo chloride treatment by immersion in 1N HCl or NaCl and passage of 1.5 to 9V of pos-

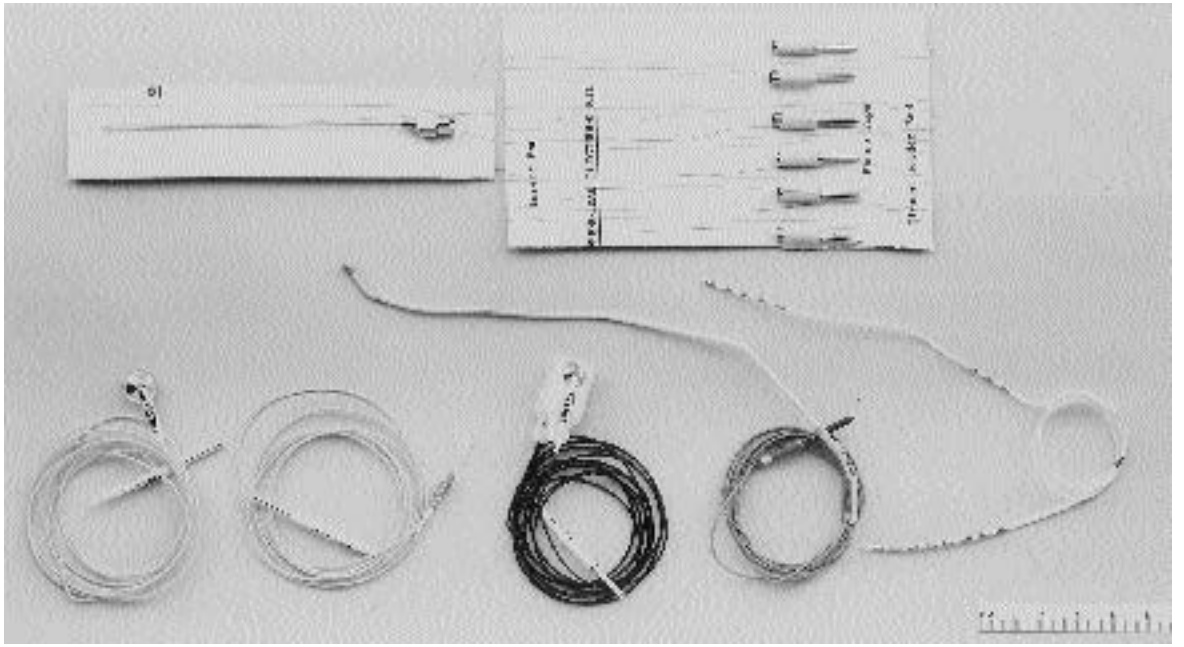

FIG. 3.18. Photograph of commonly used electroencephalographic electrodes. **A:** Scalp cup electrode. **B:** Subdermal or "needle" electrode. **C:** Clip electrode for recording from the earlobe. **D:** Nasopharyngeal electrode. **E:** Sphenoidal electrode with needle introducer. **F:** Depth electrode, with eight recording contacts.

itive battery current through the wire until it is evenly gray. A 1,000- to 10,000-Ω resistor should be placed in series with the silver wire to limit current flow (if current flow is too high, chloride deposition may be uneven). Any thick-gauge wire can serve as a reference in the solution. Electrodes should then be thoroughly washed and sterilized. A physician or an experienced technologist inserts one electrode in each of the patient's nostrils. Wires are bent into an "S" shape, threaded along the nasopharynx, and rotated outward to their position within 2 cm of the anterior mesial surface of the temporal lobes. Insertion technique was reviewed in detail by MacLean (23). Nasopharyngeal electrodes may increase the yield of interictal spike detection, but only by about 5% (28). Unfortunately, they are uncomfortable for the patient and highly prone to respiratory motion artifact. Nasopharyngeal electrodes are now rarely used clinically, having been replaced by a ring of subtemporal electrodes (e.g., T1, T2, and cheek) or sphenoidal electrodes, which substantially increase the ability to record anterior and deeper temporal discharges without being subject to the same respiratory and motion artifact seen in nasopharyngeal electrodes.

Sphenoidal electrodes (see Fig. 3.18*E*), as initially described by Silverman in 1960 (29), are used to record discharges from the anterior tip of the temporal lobe. Electrodes are usually made from thin, straight insulated stainless steel wire about 50 mm long and 0.5 mm in diameter, with a small uninsulated ball at the tip. Sphenoidal electrodes are introduced through a needle cannula into the temporal and masseter muscles; the insertion point is between the zygoma and sigmoid notch of the mandible. Penetration is directed slightly anteriorly so that the tip rests lateral to the foramen ovale at the greater wing of the sphenoid bone. In theory, there is risk of injury to branches of the trigeminal and facial nerves, and rare complications have been reported; in practice, however, these electrodes are well tolerated. Infection is a potential risk but is very rare. Sphenoidal electrodes were traditionally sterilized after each use and destroyed after use on a patient with a known or suspected transmissible viral infection. At present, these electrodes are disposable, and it is rare that they are reused, even after sterilization. Some authors have held that sphenoidal electrodes are more sensitive than scalp or nasopharyngeal electrodes (31), but others have disputed this

(13,28). More recent studies claim that sphenoidal electrodes offer limited advantages over cheek electrodes in detecting and localizing temporal epileptiform discharges (19), although many epilepsy centers continue to use them as part of initial (phase I) epilepsy monitoring (18). Other studies report that introducing these electrodes under fluoroscopic guidance, to ensure exact placement, can maximize the diagnostic yield of sphenoidal electrode recording (9,16,17).

Tympanic electrodes (not shown in Fig. 3.18) are another type of basal electrode used for recording from the mesial temporal lobe or for recording brainstem auditory evoked potentials. The electrodes usually consist of a thin insulated conducting wire with an uninsulated 7-mm-diameter stainless steel, gold, or platinum ball wrapped in felt. The electrode tip is soaked in a conducting solution and threaded through the external auditory meatus to lie next to the tympanic membrane. A conservative approach is recommended, stopping the procedure as soon as the patient senses any discomfort in the internal auditory canal. These electrodes must be carefully placed, to avoid trauma to the eardrum, and must be sterilized between uses. In practice, these electrodes are rarely used.

Wieser and Moser (34,35) have described foramen ovale electrodes (not shown) for recording mesial temporal or frontal discharges. These electrodes are fine silver wires insulated with polytef (Teflon) and mounted on a stainless steel wire 0.1 mm in diameter. The external diameter of the array is 0.33 mm. Up to four contact points, separated by 15 mm, are recommended. Electrode impedances range from 200 to 700 Ω. Electrodes can inserted with the use of local or general anesthesia, in meticulous sterile procedure. A guide needle punctures the cheek 3 cm lateral to the corner of the mouth and is aimed as directed (34). The foramen ovale and the subarachnoid space are penetrated by the introducer, after which the electrode is inserted into the caudal end of the ambient cistem. In this study (34,35), two of 37 patients experienced transient sensory deficits, and about half of the patients experienced minor discomfort.

Depth electrodes (see Fig. 3.18*F*) are arrays of electrodes designed for introduction directly into the substance of the brain by a neurosurgeon. They are used to detect and localize voltages not visible with scalp EEG recording. Typically, depth electrodes are composed of a fine array of thin stainless steel, platinum, or gold insulated wires of different lengths, ending in uninsulated tips. The electrodes most commonly used at present consist of plastic-encased wires with 1- to 3-mm uninsulated bands exposed at regular intervals, so as to allow spatial sampling along the mesial and neocortical temporal structures. Chloride-treated silver can irritate brain tissue after direct contact for several days. In contrast, stainless steel, gold, and platinum are relatively inert and safe. Depth electrodes are usually implanted stereotactically (according to a three-dimensional coordinate reference frame), although some experienced neurosurgeons prefer to place the electrodes freehand or with radiographic guidance, under sterile protocol. Electrodes may remain in place for days or weeks. Orientation, targets, and methods for implantation differ among institutions. Other chapters in this text review various approaches. The amygdala, hippocampus, entorhinal or orbitofrontal cortex, and supplementary motor areas of the frontal lobe are popular placement targets. Depth EEG recordings usually demonstrate excellent signal-to-noise ratio, because these electrodes have relatively low impedance, are relatively unaffected by muscle and movement artifact, and bypass the high-resistance skull. Depth EEG clearly increases the ability to detect and localize epileptiform activity in selected patients (30), but it has disadvantages. First, not all deep brain sites can be studied with this technique, and thus there is a possibility of sampling error. Epileptiform activity originating in a particular depth electrode only indicates that the electrode is closer than the others to the seizure focus and not necessarily that it is within the seizure focus. Second, the technique is invasive, with risks for hemorrhage, infection, reactive meningitis edema, and headache. Use of these electrodes should be restricted to experienced centers.

The current explosion in research on implantable devices to treat neurological conditions, such as movement disorders (Parkinson's disease, tremor) and now epilepsy requires that the use of depth and cortical electrodes be used not only to record the EEG but also for stimulation in deep brain structures (e.g., the thalamus) and on the cortical surface itself. Although these applications have not resulted in drastically new designs for intracranial electrodes, they are now available in a wide variety of configurations, with different electrode spacing and geometries, depending on the intended site of implantation. The development of new designs, materials, and implementations of chronic indwelling electrodes for brain recording and stimulation is expected to evolve considerably over the coming years.

Cortical electrodes (Fig. 3.19) are used to record directly from the surface of the brain during neurosurgical procedures (12). The technique is usually referred to as *electrocorticography* (ECoG). Epileptiform events can be localized in relation to brain anatomy, enabling a "tailoring" of the resection during epilepsy surgery. Unfortunately, the relatively brief time available for recording, the need to restrict recording to the craniotomy site, and EEG suppressant effects of most anesthetics limit the practical value of ECoG. Some investigators believe that location of corticographically recorded discharges at

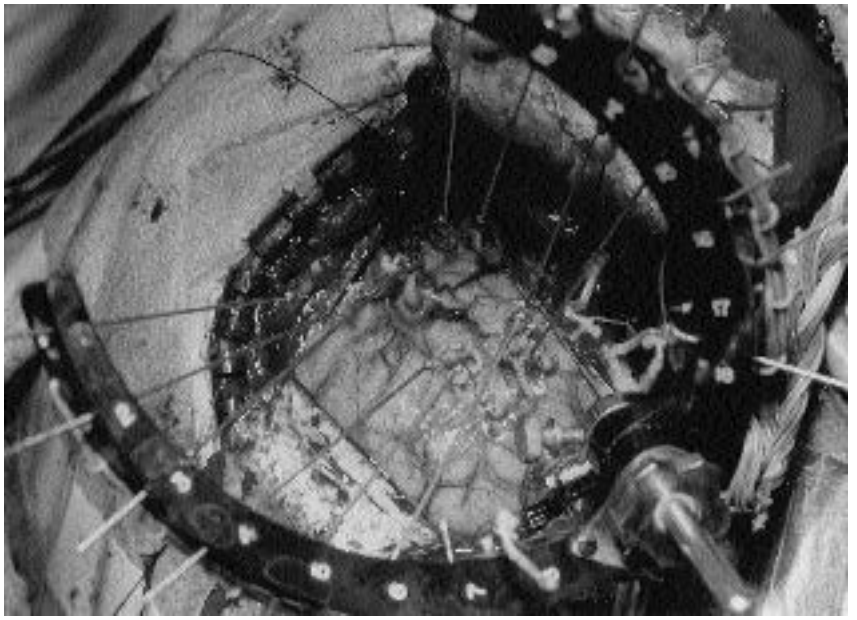

FIG. 3.19. Intra-operative photograph of electrocorticography (EcoG) apparatus with cotton wick electrodes soaked in sterile saline. Electrodes are held in place by a metal halo attached to the surgical table. This apparatus is mainly of historical interest, inasmuch as most corticography is now performed with subdural grids moved from place to place during surgical procedures. (Photograph courtesy of Dr. Sumio Uematsu.)

the time of surgery, and persistence of these discharges after resection, may have prognostic value for surgical outcome (15), although this is debated.

An old cotton wick ECoG apparatus, now mostly of only historical interest, is shown in Fig. 3.19. In this apparatus, cortical electrodes are usually made from stainless steel, silver, or platinum. Although metal ball electrodes may be placed directly on the cortex, brain pulsations can make this hazardous. In the past, it was common to make electrodes in this manner, connected to the brain by cotton wicks soaked in a sterile isotonic saline solution. Electrodes were held in an adjustable halo frame anchored to the skull or surgical table. Such equipment has been replaced by moving subdural strips and grids of electrodes over the cerebral cortex (see following discussion). Recording in the operating room with these electrodes is now standard practice in most institutions.

Subdural electrodes (Fig. 3.20) are designed to be in contact with cortical tissue of conscious, cooperative patients for periods of a few days to a few weeks. The goal of subdural recording is localization of seizure foci in relation to important functional areas of brain (11,21). In the epilepsy surgery of the past several decades, this facilitated the critically important distinction between "bad brain" (epileptogenic areas) and "good brain" (normal areas). Seizure discharges are identified and localized by recording. Areas of cortex involved in sensorimotor, speech, reading, or cognition are identified by stimulation through pairs of adjacent electrodes, which causes transient suspension of function in these regions. Benefits and risks of this technique are discussed elsewhere in this book. In order to study a large region of cortex, subdural grids may be assembled in an approximately hand-sized array, with up to eight rows and eight columns of electrodes. These electrodes are usually flat 3-mm disks fabricated from stainless steel or platinum. Electrodes are embedded in a sheet of flexible plastic, usually with center-to-center electrode separation of 1 cm (see Fig. 3.20). Grids may be cut to size during implanta-

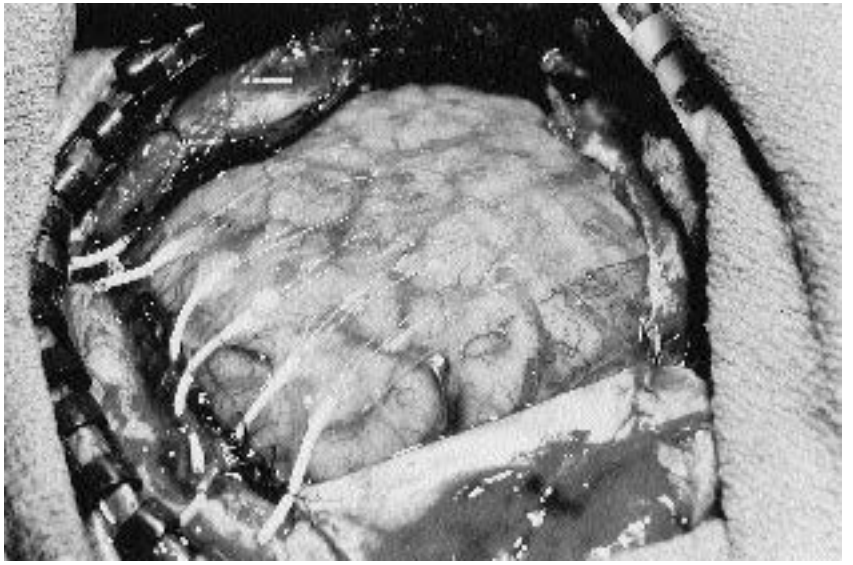

FIG. 3.20. Subdural stimulating-recording grid of electrodes photographed just before anterior temporal lobectomy. An 8×5 array of electrodes is illustrated. Cut wires, visible in the upper left, connect to a 2×8 array of electrodes placed inferiorly to the temporal lobe. (Photograph courtesy of Dr. Sumio Uematsu.)

tion. Placement requires a full craniotomy. Aggressive surgical resection of regions demonstrating early onset of seizures outside of the temporal lobe has declined somewhat, as a result of only fair clinical outcomes and newer ideas related to the role of neuronal networks in the generation of focal seizure onsets. Despite this change in thinking, implantation of intracranial electrodes, grids, strips, and depth electrodes continues to be common, although surgical resection is somewhat more limited to cases with focal lesions or functional abnormalities in which the chances of a good outcome are high.

Epidural electrodes in single or double-row strips are less invasive than subdural grids (they can be placed through a burr hole) and often provide important information about seizure foci (36). Because a smaller area is covered, the true focus of seizure onset is less likely to be in the field of recording. In addition, epidural electrical stimulation is painful, unless dural nerves are cut (12).

THE ELECTROENCEPHALOGRAPH MACHINE: PRACTICAL ISSUES

Over the years, EEG recording devices have evolved into many different forms, each uniquely addressing the challenge of presenting the electrical activity of the brain to the electroencephalographer in a faithful and useful manner. Special credit is due the Grass Corporation for their historical efforts to further EEG technology. The following section traces a signal through an EEG machine, from patient to paper (and digital computer screen; see Fig. 3.12). The purpose of this review is to develop in the student an appreciation for the function of the different components of a generic EEG machine. Discussion of specific machines can be found in the manuals distributed with them. Such manuals are not only a technical necessity for proper operation and maintenance of an EEG machine but are also a useful source of general information about EEG technology.

Jackbox and Montage Selector

The EEG signal is conducted from the subject through conducting electrodes to the electrode board, also called the *electrode box* or *jackbox*. Electrodes are identified on the jackbox in accordance with the International 10-20 system electrode nomenclature. All electrodes except midline electrodes are identified by a number and a letter; all midline electrodes carry the subscript "Z" instead of a number. Odd-numbered electrodes are on the left side of the head, and even-numbered electrodes are on the right. Electrodes are labeled according to the brain region proximate to their location: frontopolar electrodes are labeled "Fp"; frontal, "F"; central, "C"; temporal, "T"; parietal, "P"; and occipital, "O." Ear or aural electrodes are labeled "A," and mastoid electrodes are labeled "M." It is important to note that only the F7 and F8 electrodes may appear to be misnamed, inasmuch as they record more from the anterior temporal than frontal regions. The jackbox contains an additional input for a ground electrode; a scalp electrode affixed to the midline forehead or other relatively neutral site connects to this input. Numbered inputs are available on most jackboxes to accommodate special electrodes or transducers. Safety issues pertaining to proper grounding are considered later in the chapter. A jackbox may be electrically or optically isolated to limit the possibility of passing current to the patient (4,32).

The jackbox for digital EEG machines has additional components that are not seen in analog machines. For example, there is one or more additional inputs for the reference electrode. This electrode is often placed somewhere between Fpz and Fz in single reference devices, although it can be located in any place that is relatively noise free and where a good contact with the scalp can be maintained. In some machines, two electrodes, usually A1 and A2 (linked ears) are used together to form the reference. As explained earlier, in digital EEG machines, each channel is stored as G1-Ref, where G1 (grid one) is a particular electrode of interest and Ref is the potential at the reference electrode. It is important to note here a vulnerability specific to digital EEG machines that can render recordings devoid of information. If the reference electrode becomes detached in the presence of an electromagnetically noisy environment, this noise may actually saturate the recording amplifier in the reference channel. In this instance, the EEG signal in each channel (each channel being G1-Ref) is overwhelmed by noise. When individual channels are subtracted in a typical display montage (e.g., longitudinal bipolar), the record appears to be very low voltage and with little activity. This pattern can be hard to recognize as a technical artifact for technicians who are not familiar with this problem. For this reason, it is the authors' opinion that EEG technologists should always look at the machine reference montage for a short time at the beginning of the record (each channel minus the reference) to see whether the reference is detached or of very high impedance. This is usually demonstrated by the presence of high-voltage line artifact (60-Hz noise) in every channel. It is remarkable that in most cases in which the reference is of high impedance, the EEG record can appear completely normal on other montages, unless the reference amplifier is saturated, although the machine reference montage demonstrates widespread 60-Hz artifact (see Fig. 3.14).

Another important feature of digital EEG machines is that ADCs and amplifiers are frequently reduced in size and installed as part of the jackbox itself. This requires a little more careful handling of the jackbox than sea-

soned EEG technicians are used to with their analog predecessors. Again, it is important to consult individual machine manuals to determine the design and care of particular pieces of equipment.

From the jackbox, the EEG electrode inputs are carried to the montage selector board of the EEG machine, a two-dimensional array of pushbuttons. Each row across the board contains one button per jackbox input. Vertically, the array is organized into channels, with two rows of buttons per channel. Each channel's output is equal to the potential of the electrode selected in row 1 minus the potential of the electrode selected in row 2. The top input of the pair is sometimes referred to as "grid 1" (G1) and the bottom as "grid 2" (G2), from the days of vacuum tube technology; more recently, they have been referred to as "input 1" and "input 2." For example, in channel 1, if the O1 button is depressed in the first row and the O2 button is depressed in the second row, then the output of channel 1 will be O1 minus O2. One electrode's potential can be an input into more than one channel. With 21 electrodes and 16 channels, there are 21^{16}, or 1.43×10^{21}, possible montages. This impractical number calls for a certain choice of a limited number of montages in a recording session. Reasons for choosing particular montages are discussed in other chapters. Once a montage is determined, it may be programmed into the EEG hardware (usually by boards inserted into slots) so that it can be implemented with a single-switch selection. This master electrode selector switch spares the technologist from having to specify each channel of each montage with each recording.

Montage selection and recording are quite different in digital EEG machines. Because all recording is performed referentially, simple addition and subtraction are performed to derive any montage without requiring selections of particular recording configurations in advance. Remontaging is performed at the click of a mouse or touch of a button, which changes only the way that the computer displays prerecorded information or information being recorded. This scheme also makes available other computer-calculated montages, which may enhance information embedded but not readily visible in the EEG. Such examples include average reference and Laplacian montages, in which global or local averages of the potential at specified electrode locations are used to provide a more balanced reference or to enhance local features of the EEG in particular regions.

Amplifiers

From the montage selector board, EEG signals move on to amplifiers. Amplifiers in EEG machines are compound devices and should be distinguished from an amplifier whose sole function is to increase voltage. EEG amplifiers also contain filters, voltage dividers, input and output jacks, and calibration devices. Amplifiers designed to receive small inputs (e.g., microvolts or millivolts) are often called *preamplifiers,* and those designed to receive large inputs (volts) are called *amplifiers;* however, this distinction is arbitrary. An amplifier multiplies an input voltage by a constant. Because EEG signals are very small, the assumption is that this constant will be a number greater than 1, usually in the range of 2 to 1,000; however, step-down amplifiers are also available. The amplification factor is referred to as *gain* and may be expressed as V_{out}/V_{in}. More commonly, gain is expressed as a logarithmic ratio in order to compress representation of the wide range of possible input voltages. The unit of gain is the *decibel* (dB):

$$decibels\ (dB) = 20 \cdot log\left(\frac{V_{out}}{V_{in}}\right)$$

An amplifier that increases input voltage by a factor of 10 has a gain of 20 dB.

Amplifiers are designed to receive input voltages within a certain range, called the *dynamic range.* Inputs smaller than this range may be lost in background noise. Voltages exceeding the maximum recommended input may be distorted or may cause damage to the equipment. Flexible control of the dynamic range is achieved with a sensitivity setting on an EEG machine. Sensitivity has units of either millivolts per centimeter or microvolts per millimeter and is defined as the amount of voltage required to deflect the recording pens a given distance. A typical sensitivity setting for the EEG is 7 μV per millimeter, leading to pen deflections of 3 to 20 mm for typical EEG input voltages. An electrocardiographic monitoring channel, in contrast, may require a sensitivity of 1 or 10 mV per centimeter. The sensitivity control switch is a voltage divider, which attenuates the input to a level consistent with faithful reproduction by the EEG amplifiers and output system. In practice, an EEG technologist adjusts the sensitivity of the EEG machine so that EEG signals of interest produce a pen deflection large enough to read, but not so large that it runs into the pen output of adjacent channels.

Figure 3.21 shows an EEG signal at several sensitivities. To increase the amplitude of the pen deflection, the voltage to the writer-unit must be increased by increasing the gain. Inexperienced technicians are sometimes confused by the concept that to increase the gain, they must use a sensitivity setting with a smaller numerical value. A moment's thought clarifies this. At a sensitivity of 5 μV per millimeter, a 100-μV signal deflects the pen 20 mm (100 ÷ 5). At a sensitivity of 10 μV/mm, the pen deflects only 10 mm

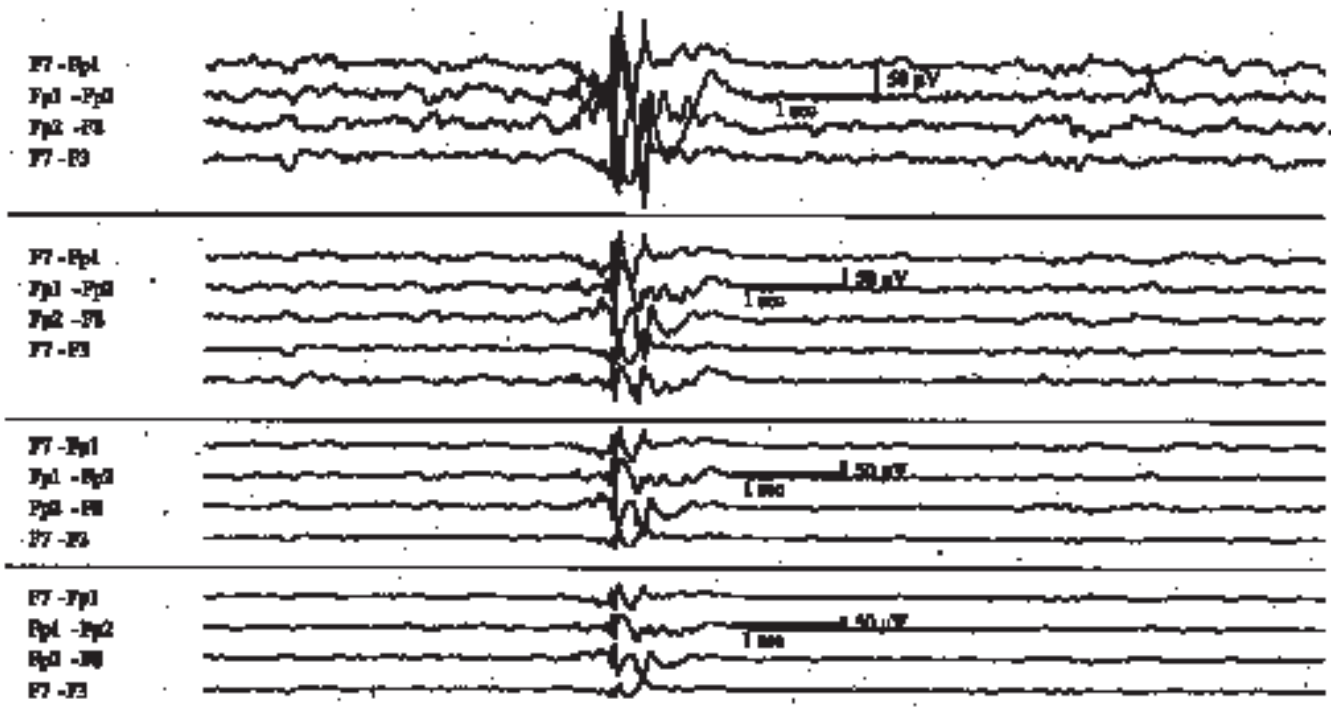

FIG. 3.21. Illustration of effect of sensitivity setting on electroencephalographic (EEG) tracing. The same EEG input is displayed at sensitivities of 5, 10, 15, and 20 μV per millimeter. As sensitivity is increased, the waveform, which initially appeared to be some sort of artifact, is revealed to be a generalized, high-voltage spike and slow-wave discharge. Before the era of digital EEG, such discharges passed without a chance of definitive interpretation, unless the technologist was very fast or the discharge was repeated.

(100 ÷ 10). At the beginning of every recording, to verify the accuracy of amplification, the technologist calibrates each channel with a known standard voltage, typically 50 μV for a sensitivity of 7 μV per millimeter. At the end of the recording, the technologist documents an appropriate voltage calibration for every sensitivity setting used (e.g., 50 μV for a sensitivity of 7 μV per millimeter, 100 μV for a sensitivity of 10 μV per millimeter, or 200 μV for a sensitivity of 20 μV per millimeter).

Of importance is that this type of calibration loses much of its meaning for digital EEG machines. In this case, amplifiers may be testable by the machines that would put a known current pulse into the inputs of the amplifiers and verify that they, the ADC, and the analog and digital filters are functioning properly. In machines that synthesize only a pretended calibration signal and display it, this process serves little or no purpose.

The EEG amplifier itself has a frequency response that is linear over a wide range of input voltages. In practice, the settings that the technologist chooses for the filters determine the range of linear frequency response. Figure 3.22 displays the relationship between frequency and amplification for a typical EEG amplifier (4). It is important to choose an amplifier whose frequency response is linear over the expected range of input voltages so that high- or low-frequency components will not cause distortion. Thus, amplifiers for EEGs and amplifiers for evoked responses differ substantially in amplification and settings for filters (see later discussion).

Signals from each electrode are led to a differential amplifier, which subtracts one signal's voltage, in relation to some reference electrode (the isolated ground electrode [isoground] on the scalp in most machines), from another signal, in relation to the same reference, and amplifies the difference signal. This process removes voltages (e.g., noise) common to both electrodes. Although one of the input pairs could be connected to the machine's ground circuit, this would expose the signal to massive amounts of noise generated by line current and electrical appliances. The two inputs for each channel are therefore kept isolated (floating) from the system ground. When a distant electrode is chosen as the common reference for

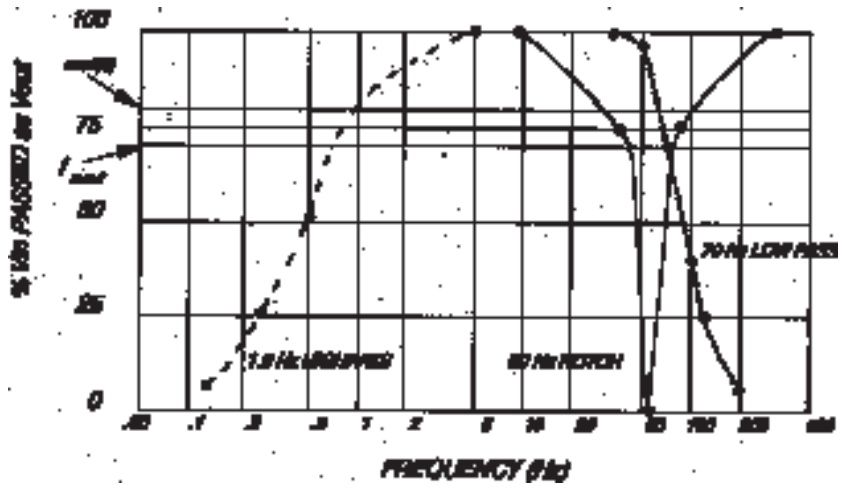

FIG. 3.22. Frequency response of 1.0-Hz high-pass, 60-Hz notch, and 70-Hz low-pass filters. The conventional cutoff frequency, at which input is attenuated by approximately 30%, is marked "cutoff." The cutoff frequency of this particular machine, defined by the manufacturer to be the point at which the input is attenuated by 20%, is marked "cutoff (G)." (Adapted with permission from Grass Instruments® EEG machine instruction manual.)

several channels, the montage is said to be *referential*. The older term *monopolar* is inaccurate, because a voltage must always be recorded between two points. Montages linking nearby electrodes are called *bipolar*. Referential montages are more sensitive to regional changes in EEG potential. Bipolar montages, which are configured to record more localized potentials, are less disturbed by noise. Both types of montage should be used in a clinical EEG recording.

Signals common to both inputs of a differential amplifier are canceled. Such signals are said to be *in phase,* or *common mode,* which implies that they vary together over time. Noise from a 60-Hz line current is an example of a signal likely to be in phase at all inputs. Unfortunately, differential amplifiers are not perfect and do not completely cancel common-mode signals. The ability of an amplifier to reject in-phase and amplify out-of-phase potentials is measured by the common-mode rejection ratio (CMRR) of the amplifier. The CMRR can be measured by connecting a voltage source to two amplifier inputs so that each input "sees" the same signal. The output voltage, which should be close to zero, forms the denominator of the CMRR. This is compared to the output voltage when the voltage source is connected to one input and the machine ground is connected to the other (the numerator of the CMRR). The ratio of these output voltages is the CMRR. Good EEG amplifiers have CMRRs of at least 1,000, and many have CMRRs of 10,000. Under ideal circumstances, CMRRs of 100,000 may be achieved. It is important to note that common-mode rejection is effective only over a limited range of common-mode voltages. It is possible that in extreme circumstances (e.g., if an electrode falls off the head), the voltage of common-mode signals may exceed the amplifier's input range. In this case, the output is unpredictable. It is also important that the reference electrode used be reasonably close to the recording electrodes. This maximizes chances that major noise signals will be common mode and canceled. If the reference electrode is placed at a distant location (on the leg, for example), the widely spaced electrodes may act as an antenna and pick up signals that may exceed the common-mode range of the amplifiers.

When recording is done with differential amplifiers, the polarity convention for display of EEG signals is that negative waveforms cause an upward deflection and positive waveforms cause a downward deflection. For example:

1. If input 1 is negative with regard to input 2 (i.e., input 1 minus input 2 is negative), the pen (or waveform displayed on the computer monitor) deflects up. If input 1 is positive with regard to input 2 (i.e., input 1 minus input 2 is positive), the pen or monitor waveform deflects down.
2. If input 2 is negative with regard to input 1 (i.e., input 1 minus input 2 is positive), the pen or monitor waveform deflects down. If input 2 is positive with regard to input 1 (i.e., input 1 minus input 2 is negative), the pen or monitor waveform deflects up.

This convention leads to the principle of *phase reversal* of the EEG signal, by which negative potentials can be localized to an electrode demonstrating phase reversal between two channels sharing a common electrode. Figure 3.23 illustrates this principle. The montage in this instance is a simplified, linked bipolar montage. Channel 1 represents the differential voltage between Fp1 (electrode 1) and F7 (electrode 2). Channel 2 shows a differential input from F7 (electrode 1) and T3 (electrode 2). Because the pen deflects down in channel 1, F7 is negative with regard to Fpl. Because the pen deflects up in channel 2, F7 is also negative with regard to T3. At F7 there is therefore a local maximum of extracellular negativity. Such extracellular negativity occurs during interictal spikes near an epileptic focus, as a result of sudden influx of positive ions (sodium and calcium) into the depolarizing neurons. Of course, many other EEG events, including those

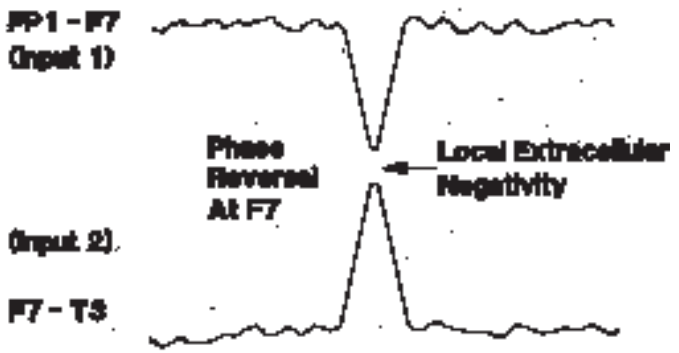

FIG. 3.23. Schematic drawing of a phase reversal, representing site of local extracellular negativity, which in this illustration is at the F7 electrode.

derived from normal spontaneous brain activity, may result in instances of local extracellular negativity. In practice, electroencephalographers first identify potentials with the morphology of interictal spikes or sharp waves and then attempt to determine a physiological field, perhaps including a phase reversal, for the potential. The electrode common to the two channels showing phase reversal may be assumed to be near the origin of the discharge. Extracellularly positive potentials (generally of less practical importance to electroencephalographers) cause phase reversals with pen deflections away from each other in adjacent channels. These are seen on occasion on scalp EEGs, usually in the case of transversely oriented dipoles in the generating tissue. This method of localizing discharges is applicable only to recordings with linked bipolar montages.

Outputs of one amplifier may be used as input to another. This allows a series of amplifiers, each with a limited dynamic range, to boost the EEG signal substantially. As the signal becomes amplified, it becomes large in relation to ambient noise, and differential amplification may no longer be required. Internal amplifiers may thus be single ended (one active input measured with regard to ground). The principles of differential amplifiers and common mode rejection explained earlier are central to most systems for recording clinical EEGs and unchanged in digital EEG machines.

Electroencephalogram Filters

After EEG signals are subtracted and amplified, the output is filtered to remove specified frequency components, as described earlier. The high-pass filter attenuates components of the signal that have frequencies less than a specified value; the low-pass filter removes components with frequencies higher than a certain value. A special filter, a 60-Hz notch filter, is available to remove electrical noise generated by line current. The ideal in EEG recording is to minimize the use of filters—for example, by using a low cutoff frequency of 0.1 Hz and a high cutoff frequency of 70 Hz. Filters distort both the amplitude and the interchannel phase of signals. In some circumstances, high-frequency artifacts from muscle and low-frequency artifacts from movement or sweat potentials mandate use of more stringent filtering. Figure 3.24 illustrates how filtering can rescue a nearly uninterpretable tracing. The use of filters should always be documented on the EEG recording, so that the electroencephalographer can interpret their possible influence.

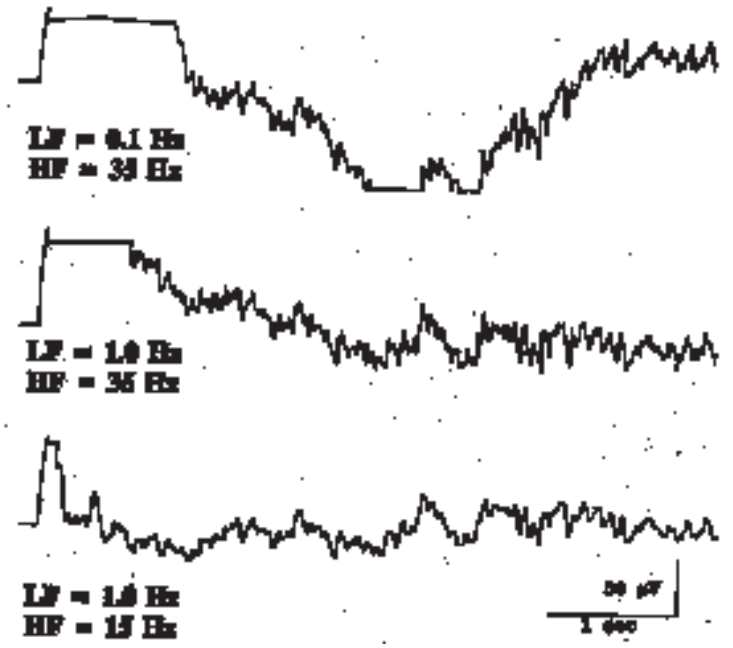

FIG. 3.24. Effects of different low- and high-filter cutoff frequencies on a noisy electroencephalographic (EEG) tracing. Note enhanced readability at the expense of lost detail in the most severely filtered tracing at the bottom. Data reproduced from an ambulatory cassette EEG monitor played back to paper output.

Of importance is that the principles of filtering remain the same in digital EEG machines, except that most filtering is performed post hoc—that is, after the signal has been acquired and stored. Most digital EEG machines record and store EEG broad band—that is, with the filters open as wide as possible, without introducing aliasing, artifacts, or severe distortion into the data. Because the data are to be displayed, computer programs are used to filter the data as they are projected to the computer monitor. In reality, the source data, recorded with less stringent filtering (e.g., 0.01 to 100 Hz), remains untouched by digital filtering. Of importance is that digital filters induce the same changes into the EEG, such as phase shifts, as do analog filters, although the digital environment allows for correction of these changes, if desired, because this requires only numerical manipulation of the digital data.

Ancillary Electroencephalographic Controls

Typical EEG machines offer several controls to validate proper functioning of electrodes and amplifiers and to provide flexibility in presentation of data. A few of the more important controls are considered as follows:

Individual channel controls: It is a convenience to use the *all-channel control* to set gain and filters for all channels; however, this is not practiced if input signals vary widely, as is the case when cardiac, electromyographic, or movement monitors (or transducers) are used to measure respiration or intracranial pressure, or during recording from invasive electrodes. Such circumstances require individualizing of gain and filters for each channel. In the digital environment, channels can be individually displayed, filtered, and manipulated numerically post hoc, after acquisition.

Calibration signal: A calibration signal is an internally or externally generated input of known voltage. The operator chooses a calibration voltage (square-wave pulse) ranging from 1 to 10 mV or more. This signal is passed through all stages of EEG signal processing, from the first stage of amplification to pen output. In addition to serving as a voltage reference, the calibration procedure can (a) show differences in channel amplitude or pen alignment that might introduce artifact and (b) show the effect of filter settings on a square-wave input. No EEG tracing is complete without a voltage calibration signal for each filter and sensitivity setting used during the recording session. As mentioned earlier, the actual implementation of calibration signals varies from one digital EEG machine to another. It is important to consult the manual for individual EEG machines to understand the details of how this procedure is performed for any given piece of hardware.

Electrode test switch: The electrode test switch conducts an artificial (e.g., 30-Hz sine wave) signal through each electrode to the pens. Electrodes with impedances less than approximately 1,000 Ω produce no pen response. Electrodes of higher resistance generate pen deflections of about 0.5 mm for each 1,000 Ω of resistance (Fig. 3.25). Testing electrodes entails passing current through electrodes to the patient. This is of theoretical concern with cortical or depth electrodes. The test current is, however, very small and is probably below a level able to produce biological effects. For the Grass Model 8 EEG machine, test current is 0.035 μA (9). In digital EEG machines, this procedure is performed the same way as in analog devices, but impedances are usually displayed as numbers, in ohms or kilohms on the EEG machine screen. Some digital machines do not record these numbers as part of the EEG record, which

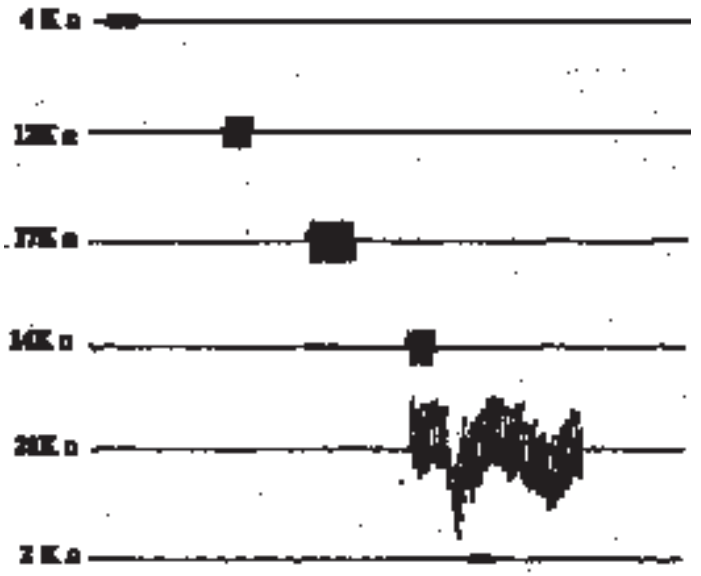

FIG. 3.25. Illustration of electrode test output from six electroencephalographic electrodes. The resistance of each electrode is marked to the left of its tracing (assuming a resistance of 2,000 Ω per millimeter). Electrodes 2 to 5 would need to be reaffixed before resumption of recording, because their resistances are more than 5,000 Ω.

is a disadvantage with regard to later interpretation. Electrode tests should be performed at the beginning and end of each recording session, according to accepted EEG standards (1).

Baseline adjustment: The baseline adjustment for each channel is used to set the pen tracing baseline to coincide with the 0-V line on the EEG paper. This permits maximum travel of the pen. There is no equivalent control in digital EEG machines.

Sensitivity adjustment: As an EEG machine ages, the amplification factors for individual channels may drift out of the specified range. The sensitivity adjustment is a turn-screw used to set the sensitivity in conjunction with the all-channel calibration signal. The sensitivity of each channel can be adjusted to produce equal output for the same input signal. Amplifiers in digital EEG machines must also be checked and calibrated in a similar manner over time. The Biomedical Engineering section of hospital facilities that service this type of equipment usually undertakes this responsibility. Procedures for testing and adjusting this equipment vary between manufacturers.

Event markers: Event marker buttons provide a quick and convenient way for the technologist to annotate time of occurrence for an event of interest. On digital EEG machines, this feature is usually more sophisticated, allowing technologists to type specific comments into the record, with the computer keyboard or with a light pen that allows them to write longhand on the computer screen, or to display a variety of preset comments from a series of "hot keys" programmed on the computer keyboard.

Trace restore: High-amplitude, low-frequency signals cause the pens to deflect and slowly return to baseline. If the return to baseline requires several seconds, EEG information may be lost. The trace restore button quickly neutralizes amplifier blocking so that recording can continue. This feature is usually omitted in digital EEG machines; however, many digitally controlled amplifiers have preprogrammed features to suppress these types of artifacts.

Output and input jacks: When output other than paper tracing is desired, it is necessary to have a means of transmitting the EEG signal to another output device. Examples of such outputs are analog tape recordings, oscilloscopes, and analog-to-digital devices for computer input. Some EEG machines provide several outputs in order to facilitate impedance matching of the output and input equipment. Similarly, EEG machines may have input jacks to allow playback of external signals in the machine circuitry. This input may be before or after the initial stage of amplification and filtering. One commonly employed input is a marker for photic stimulation. Attention must be given to the proper range of input voltages for each input jack. The high-quality amplifiers used in analog EEG machines still offer the advantage that their output signals can be digitized at very high rates, with the appropriate filters in place; thus, they are very important in the basic science community, in which they remain extremely popular in research on biological signals. Many digital EEG machines provide an analog output to allow playing the recording back into a standard paper EEG machine to generate old-fashioned paper tracings. With the growing acceptance of digital EEGs and the widespread availability of affordable universal reader software for the majority of EEG programs and manufacturers, it is expected that this feature will be used less over time.

Penmanship

The final link between the patient and a legible EEG tracing is the writer. Most EEG machines involve the use of a pen-ink-paper system in which pen tips move back and forth in proportion to voltage while EEG paper is transported by rollers at a constant velocity under the pens. Several varieties of ink-writing systems are available. The most common system uses a coil of wire to generate a magnetic field in proportion to the applied voltage. This field is opposed by the field of a nearby stationary magnet, which results in deflection of the pen. This type of apparatus is called a *galvanometer.* Mechanical force from a spring on the pen mounting restores the pen position to baseline.

Because the pen moves in an arc rather than in a straight line, there is a small error in representing the amplitude and time to reach the peak of particular waveforms in the EEG signal. In addition, the pens are mechanical devices with mass and friction, which exert effects on the paper as it scrolls by. They are thus filters, unable to respond with perfect fidelity to EEG signals. Pens are high-frequency filters because of mass, and they usually cannot respond to frequencies higher than approximately 90 Hz. Pens may be low-frequency filters because of friction. Friction is usually considered more of a problem at low frequencies than at higher ones, because it takes more energy to initiate movement in an object than to keep an object moving. The effect of pen friction is to decrease and delay response to low frequencies. Finally, the resonance of the system is a function of both the electrical and mechanical characteristics of the pen writing system. A sensitive system might respond quickly to an input, but it

may oscillate when the input pulse is very sharp, as with a square wave or a spike. At the other extreme, a pen system can be overdamped, with little or no oscillation in response to very sharp input signals but with substantial attenuation and delay of the input signal (see Cooper et al. [6] for a detailed discussion).

In routine practice of EEG, pen-writing systems are entirely satisfactory, despite the qualifications just listed. In special applications involving high-frequency recordings, alternative methods are needed. Such methods include rectilinear ink jet recorders, oscilloscopic data presentation, analog tape, and digital recording of the EEG. Again, with the increasing popularity of digital EEGs, these factors will likely become less important over time. Of historical interest is that experienced EEG technologists often rely on the sound that the pens make on paper to detect certain conditions: for example, the 3-Hz waveforms of absence epilepsy. This sound was thought to be so important in the past that early digital EEG machines actually synthesized the sound of pens writing on paper while the EEG scrolled by on the computer screen, so as to preserve these auditory cues.

Paper Transport

The writer unit is the final part of the EEG machine to influence the EEG record. This is the system by which the paper is pulled below the pens in order to provide a written tracing of the EEG. The writer unit consists of a small rotating wheel (pressure roller) connected to a motor. The switch controlling the writer is usually a lever with three settings: "off" (no paper or pen movement), "chart" (allows the paper to move, but the pens do not conduct the EEG signal to the paper), and "chart and pens" (the paper moves and the pens conduct the EEG signal to the paper). On most machines, at least three speeds are offered: 15, 30, and 60 mm per second. The slowest time setting is used to conserve paper or to highlight slow activity. The setting of 30 mm per second is standard in the United States, although 15 mm per second is common in other parts of the world. The 60-mm per second chart speed is used to examine fast activity or interchannel latency relationships that are not easily discerned at slower paper speeds. This setting serves to draw out the tracing, thereby allowing the reader to see more detail. Figure 3.26 shows some examples of an EEG tracing containing ictal activity seen on three different paper speeds. One area in which digital EEGs demonstrate superiority over analog EEG is in the ability to replay segments of the EEG at different gains and paper speeds. Single events that may occur suddenly and be uninterpretable when written on paper may be diagnostic of a variety of conditions when they can be reviewed post hoc after being stored digitally.

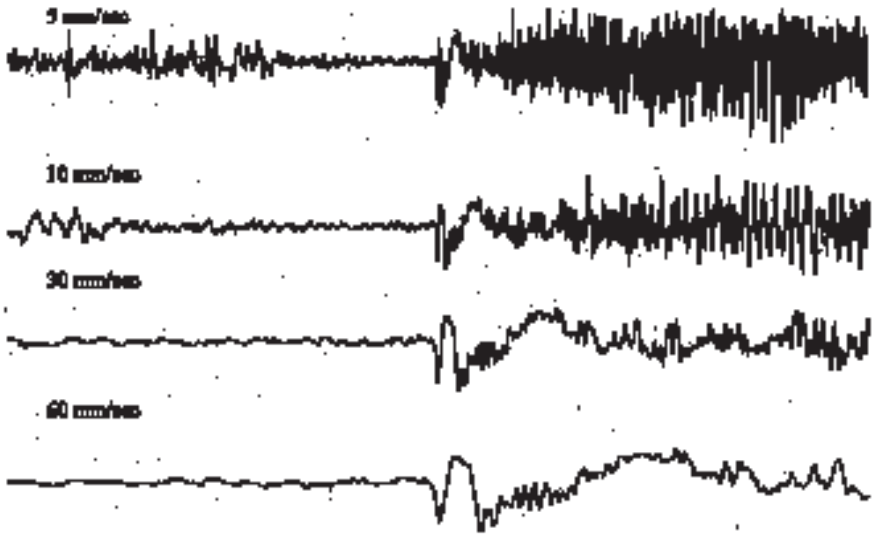

FIG. 3.26. Electroencephalogram from a single channel at the start of a complex partial seizure recorded at several paper speeds. This recording was obtained digitally. At slower paper speeds, more of the event, including its evolution, can be discerned. At faster speeds, more detail over shorter periods of time becomes apparent.

Processing During and After Data Acquisition

Because digitally acquired EEGs are stored as numerical data, a wide variety of computer programs and algorithms can be used to analyze, extract features from, and display data in many different forms. These methods have utility in both clinical and research applications. Examples of clinical uses include compressed spectral array displays of long-term EEG data, such as for intraoperative, intensive care unit or anesthesia monitoring; seizure detection algorithms used for inpatient epilepsy monitoring (27); and automated sleep staging systems. Research applications include such investigations as functional brain mapping with the use of

focal cortical desynchronization in electrocorticographic recordings during cognitive tasks (7,8) and investigation into seizure precursors and prediction (20,22). Details related to this topic are covered in other sections of this book.

Networking, Data Storage, and Report Generation

As mentioned earlier, one of the most useful aspects of digital EEG technology is the ability to connect acquisition machines, which collect data from the patient, to computer networks. This allows for transmission, interpretation, and archival of recordings to remote sites and availability for review at many locations at one time. With the development of broader band networks (e.g., those capable of carrying more data per unit time), typical 16-bit records 20 to 40 Mb in length can be transferred in minutes to locations that are sometimes miles away from the patient. Urgent studies can be read rapidly in these systems and, with appropriate bandwidth access at home (e.g., cable modem or DSL line), after a transfer time of just a few minutes. Transmission of such large files over more standard modems on telephone lines (e.g., 56 K baud) remains impractical for this purpose for now, requiring up to 3 hours to transfer a typical digital EEG record.

Figure 3.27 depicts a typical "high end" network system for a comprehensive center performing routine EEG, epilepsy monitoring, and EEG during Wada testing, positron emission tomographic scanning, intraoperative monitoring, and record review in multiple locations. In this scheme, the EEG machines, also called "collectors," are placed in a variety of inpatient and outpatient locations. At each site, the machine is plugged into a network jack, and studies are transmitted to the hospital server. Epilepsy monitoring unit (EMU) data are kept locally for review and clipping before transfer to the hospital server, because of the large volume of EEG and digital video data that are continuously collected. Data on the server can then be reviewed, and reports can be generated and sent to remote archives on CD, DVD, or other media. In the authors' laboratory, it is protocol never to delete a study from the collector unless a report has been generated and the data are verified to be intact in the archive. Remote sites can be monitored in real time, such as in the operating room, intensive care unit, or elsewhere, although at present, this usually requires the use of third-party software (e.g., PC Anywhere, NetMeeting) for network communication. Home access provides its own challenges, particularly with regard to patient confidentiality and adherence to Health Care Finance Administration and other federal and local standards, which are being considered and put into place at this

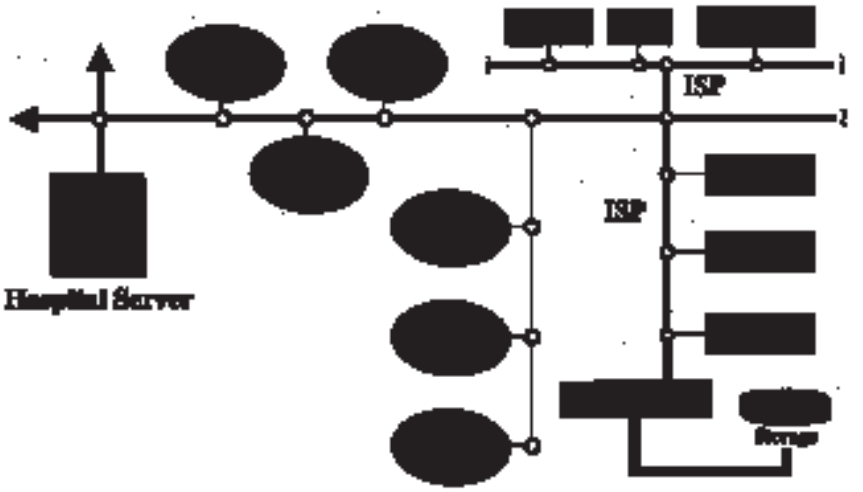

FIG. 3.27. Schematic of computerized electroencephalographic (EEG) network in a tertiary hospital. "Collectors" are digital EEG recording units, with or without digital video; "Central, Fellows and Attending" are reading station areas; "OR" stands for operating room, "ICU" for intensive care unit, and "EMU" for epilepsy monitoring unit. "Research, Home and Remote site" are areas away from the central hospital where data may be reviewed or copied. "ISP" stands for Internet service provider, which provides the link for Internet access to remote locations outside the hospital network.

time. Most comprehensive EEG systems contain both local area networks (LANs), such as in the EMU and outpatient EEG laboratories, and wide area networks (WANs), which cover entire medical centers. The network architecture that makes the most sense for a particular laboratory is a complex issue, often best left to professional designers. It is a function of institutional resources, hardware, usage, and policy and regulations.

Data Storage, Media, Universal Readers, and Report Generation

EEG data, whether paper or digital, have an associated cost of acquisition and storage, in view of regulations that require, in most states, keeping documentation of medical studies for at least 7 years. Table 3.5 lists media and storage costs per year for paper and several types of digital media. Because there are no microfilm, clipping, or remote storage costs for digital media, in addition to environmental considerations, the cost savings of digital stud-

TABLE 3.5. *Cost of storage media per electroencephalographic study*

Paper and microfilm*	$10.54
Optical (1GB)	$4.50
CD-ROM (700MB)	$0.03
DAT (7GB)	$0.12
DLT (15GB)	$0.12
Video tape	$0.31
Jaz Drive (1GB)	$6.00
DVD (4.7GB)†	$0.13

*Does not include off-site storage costs.
†May increase to 20 GB.
CD-ROM, compact disk, read-only memory; DAT, digital audio tape; DLT, digital linear tape; DVD, digital video disk.

ies are easy to see. Of importance is that the costs of digital media continue to drop; for example, a CD at the time of writing this chapter cost about $1.00 and as low as $0.75 when purchased in bulk.

One issue of importance to digital electroencephalographers is having the ability to read data from EEG machines manufactured by different companies on a single platform (e.g., a universal reading station). This is important in cases in which patients are referred for evaluation and bring digital records from other laboratories. The American Society for Testing and Materials is composed of representatives from the EEG community and industry dedicated to working out a universal storage format to enable this type of record exchange. Several software manufacturers also provide universal reading platforms that accept data from *most* manufacturers. Both of these efforts are works in progress but show promise of success in accomplishing this task in the long run.

An added benefit of using digital EEG machines is the ability to read records on a personal computer, which can also be loaded with data base and word-processing software to enable rapid generation of reports and searchable archives for clinical, research, and continuous quality assessment purposes. In such systems, as the authors and others have implemented them, technologists input data that they would normally write on a cover sheet, such as the patient's identifying information, conditions of the record, and medical history, into fields in a data base record residing on the laboratory server. The recording is performed and sent to the server for remote review, and the reading physician inputs features of the record and impressions into the same data base record. In addition to quality information, the need to review the record at conference and technical issues are flagged in the appropriate fields. Finally, when completed, the reader generates a report through a mail-merge program, which takes fields from the data base and inserts them into the body of a report form that has been previously constructed. The process is quite streamlined, except for very difficult records, and is usually time and cost efficient. Reports are then uploaded to the laboratory server, where they can be accessed throughout the hospital through the EEG laboratory's web site. Some manufacturers are currently including data base and report generation software as part of their digital EEG software. Other third-party programs to accomplish this task are becoming available for use, as the popularity of digital systems continues to rise.

EVOKED POTENTIALS

Routine EEG investigates spontaneous electrical activity of the brain. A relatively new and growing area involves study of EEG potentials evoked by sensory signals (visual, auditory, or somatosensory evoked potentials) or by motor tasks (motor evoked potentials). Electrical principles and technological requirements underlying recording of evoked potentials are similar to those underlying recording of the spontaneous EEG, with a few exceptions. Evoked potentials recorded are usually very brief and occur at short latencies, after the evoking stimuli. Rapid data acquisition and storage are thus needed. Evoked EEG signals are sampled at very fast acquisition rates and digitized to facilitate mathematical manipulation. Evoked potentials are small and are subject to poor signal-to-noise ratios. This is overcome by averaging several responses. With such averaging, random noise and other signals that are uncorrelated with the stimulus cancel, leaving only an evoked response (or correlated artifact) related to the stimulus. If N is the number of trials averaged, then the signal-to-noise ratio of an evoked potential is improved by a factor of $\sqrt{N}$. Figure 3.28 shows a typical brainstem auditory evoked potential with 1, 100, 500, and 2,000 averaged trials. The pen-ink-paper method is not conducive to signal averaging; therefore, virtually every modern evoked potential machine entails the use of oscilloscope or computer screen outputs, with the capacity to print studies to a laser or similar printer.

Evoked potential amplifier and filter settings differ substantially from parameters used for routine EEG. In the recording of brainstem auditory evoked potentials gain is set to 200,000 to 500,000. Low-frequency filter cutoffs are usually set at 50 to 150 Hz, high-frequency cutoffs are usually set at 3,000 Hz, and the minimum sampling rate is 10,000 samples per second. Detailed discussions of technique and interpretation of evoked potentials can be found in later chapters in this book, as well as in other standard texts (3).

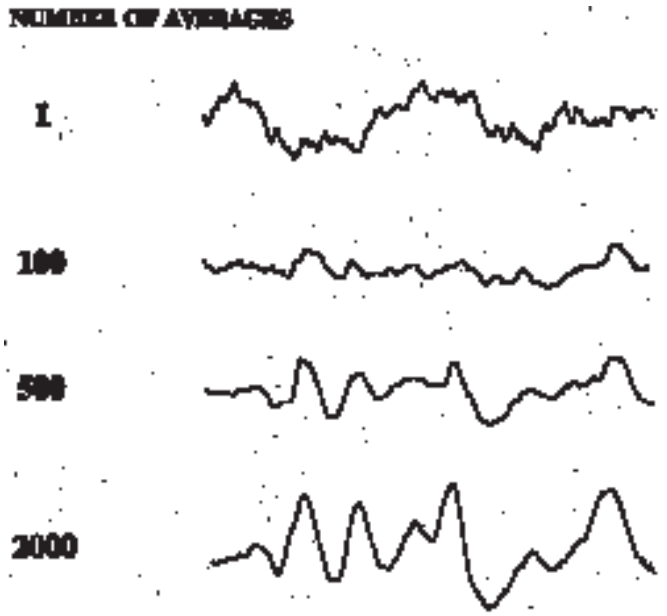

FIG. 3.28. Record of brainstem auditory evoked potential with 1, 100, 500, and 2,000 signal averages. As number of averages is increased, the resolution of the normal waveform increases. Time displayed is 10 milliseconds. The gain of the first tracing is half that of the lower three tracings, to prevent saturation of amplifier by noise.

ELECTRICAL SAFETY

EEG is an extremely safe procedure, but a small possibility of injury does exist. It is imperative that the technologist and electroencephalographer understand how to minimize this risk. Current is the most important predictor of electrical injury. It can cause pain and burns if applied to the skin. Seizures can result from certain types of current applied directly to the brain or to the scalp. Current can electroplate irritating metals from intracranial electrodes into brain tissue. Current can even kill, by inducing ventricular fibrillation. Injury risk can be discussed in terms of three groups with different types of relationships to EEG equipment. The safest group comprises persons who are simply near and possibly touching an electrical device but not intentionally connected to it. The second group comprises people with electrodes attached to skin, in the absence of other medical instrumentation.

TABLE 3.6. *Effects of various currents at 60 Hz*

Current for 1 second	Effect
0.1 mA	Ventricular fibrillation if applied to the heart
0.3 mA	Sensory threshold
1.0 mA	Pain threshold
5 mA	Maximal harmless level
15 mA	Muscle tetany
50 mA	Tissue injury
100 mA	Fibrillation or death

Adapted from Tyner F, Knott J, Mayer WJ. *Fundamentals of EEG technology.* New York: Raven Press, 1983.

The third group contains patients at higher risk, such as neonates and patients with intravascular catheters or other medical instrumentation.

Table 3.6, adapted from Tyner et al. (32), summarizes effects of various currents at 60 Hz on normal persons (group I described earlier).

There are several potential sources of dangerous currents that may flow through patients connected to EEG machines and cause them harm. These sources are described as follows.

Improper grounding

Improper grounding can result from a disruption of the ground circuit inside the EEG machine or from use of a two-prong socket. The cylindrical contact (green wire) on the three-prong plug is the ground contact. Should a short circuit occur in the machine and a current-bearing element make contact with the chassis of the machine, this current should immediately be shunted to the ground contact, because this is the path of lowest resistance. This would quickly blow a fuse or circuit breaker in the EEG machine, which would sense the abnormally high current flow through the now very low resistance of the short circuit. This would not happen immediately, and some current might flow through the patient even if the proper safety mechanisms were intact during a short circuit. If the machine ground contact is not intact, substantial current (possibly life-threatening) may pass through the patient.

EEG machines should never be powered by an inadequately grounded circuit: Three-prong to two-prong adapters should not be used. Machines must always be protected with regulation fuses. Fuses should not be defeated: There is always a reason when a fuse stops working, and it is important to discover that reason rather than subject the patient to an electrical hazard. Hospital-grade power outlets should be used whenever possible for EEG machines (or for any other machines that are to be connected to patients).

These outlets are labeled with a green dot and indicate a higher standard of safety and quality of construction than do other outlets (32). A schedule of preventive maintenance on the EEG machine and outlets should be enacted.

Leakage currents

Leakage currents arise from two main sources: stray capacitance and stray inductance. Stray capacitance usually arises from wires connected to a wall socket or to the EEG machine power supply. Capacitance is a function of the construction of the power cords and of their length. Nearby wires in a power cord are insulated from each other and therefore can function as a capacitor. AC current flows through the "hot" (black) wire in the cord and induces small capacitive currents in the neutral (white) and ground (green) wires as they alternately charge and discharge with the AC current. This leakage current is usually shunted directly to the ground contact; however, if the ground connection is not properly made, this current may flow through the patient. Extension cords should not be used with EEG machines, because they increase the capacitive current to a potentially dangerous amount. Because wires are inefficient capacitors, capacitive currents from an EEG machine are generally far less than 0.1 mA and may be only a few microamperes. Nevertheless, if applied directly to the heart, 0.1 mA could cause ventricular fibrillation.

Each wire carrying current to and through the EEG machine induces a magnetic field that, in turn, creates currents in other wires, including neutral and ground wires. These currents are usually shunted directly to the ground contact, but, again, they may be conducted through the patient should some ground malfunction (ground fault) occur. Stray inductances generally are of less magnitude than stray capacitances.

According to Hill and Dolan (cited in Cooper et al. [6]), maximum leakage currents allowed for the three groups defined earlier are 500 μA for those having casual contact with a medical device; 100 μA for those connected to electrical devices; and 10 μA for the group at high risk.

Double-grounding

If a patient is connected to an EEG machine and to another electrical instrument, there is probably be more than one ground connection. This creates a situation referred to as double-grounding or a ground loop. Because no two ground connections are at identical potential, current may flow from one ground connection to the other through the patient. There are several potential sources of ground-loop currents. Short circuits in the machine or other circuit faults can deliver massive current to a ground loop. Less dangerous but more common are currents in the ground circuit as a result of stray capacitance and stray inductance. Additional currents may be induced in the ground wires by nearby magnetic fields. In this case, the induced potentials in question are small, but the resistances of the ground paths are also small. By Ohm's law, large currents could flow from one ground circuit to another through the patient.

Double-grounding is of particular concern in areas where patients are connected to multiple devices, such as intensive care units and operating rooms. It is not unusual to observe patients connected to EEG machines, electrocardiographic monitors, temperature monitors, electric blood pressure cuffs, ventilators, pulse oximeters, warming or cooling blankets, electric beds, arterial and venous catheters, intracranial pressure monitors, and a variety of other hardware. In such circumstances, the presence of a ground loop is virtually guaranteed. The solution is to connect all devices attached to the patient to a common ground connection plugged into the same wall outlet. If necessary, a grounding bar can be used to gang together the various ground connections. This provides only one low-resistance ground path (not through the patient) for stray currents.

The EEG technologist must remember the principle of single-grounding when an accessory ground connection is necessary to eliminate 60-Hz interference. All ground connections should travel to one point. If the patient is already grounded by another device, it is not necessary (and is potentially dangerous) to attach another ground connection to the patient. Avoidance of multiple ground connections, in addition to being a requirement for patient safety, improves recording quality.

In high-risk circumstances, such as when patients have intravenous catheters, special isolation jackboxes should be employed. These boxes use optical isolation or solid-state variable resistors to separate the patient from any currents generated in the EEG machine (12,32).

Switch sparking

Whenever the power switch on the EEG machine or on the pens is enabled, a small spark occurs inside the machine. This was an explosive and shock hazard in the past (when volatile anesthetics such as ether were in common use) but is not a major concern in most modem recording environments.

Exacerbating Factors

Predicting the consequences of an electric shock is difficult, because several factors influence the biological response. In the clinical setting, the

TABLE 3.7. *Safety rules for performing electroencephalography (EEG)*

Maintain machinery to avoid faulty circuits
Always use a grounded (three-prong) plug to power
Properly fuse the EEG machine
Use one ground connection to patient or ground to a common point
Use an isolation jackbox in high-risk situations

most important factor is instrumentation. A transvenous pacemaker or a central venous pressure catheter provides a low-resistance route for stray currents to travel directly to the heart. Ventricular fibrillation can result from currents that would not even be perceived through intact skin. Skin wounds or excessive abrasion with cleaning paste may increase the risk for injury by a given current at those sites. Good general health may be a factor in resisting effects of electric shock, but many hospitalized patients are ill (6,32). Table 3.7 summarizes important safety rules in EEG recording.

CONCLUSIONS

It is easy to see how the engineering and electronics technology behind EEG continue to evolve as fast digital computers free electroencephalographers and technologists from paper and ink and provide opportunities for quantitative analysis of neurally generated signals. Nonetheless, the basic core technology remains the same as it was when discovered during the 1930s. Postsynaptic potentials generated by large functional masses of neuronal tissue, filtered by and conducted through the cerebrospinal fluid, dura, skull, scalp, and skin are transduced by surface electrodes, amplified, and filtered for review. Unfortunately, as the understanding of brain function and dysfunction increases, the limitations of this empirically discovered technology become more apparent. Functional activity generated by deep structures central to clinical epilepsy, such as the mesial temporal lobe and deep frontal lobe, remain inaccessible for EEG recording. Patterns generated by metabolic encephalopathies are often indistinguishable from those of subtle or nonconvulsive status epilepticus. Seizures that are not directly on the brain surface are often obscured, poorly localized, or even invisible on surface EEGs, sometimes even after placement of intracranial electrodes. These common problems highlight the need for a new type of EEG technology, designed specifically for modern clinical epileptology and neuroscience research, to replace what has been the gold standard for assessing electrophysiologic function in the central nervous system since the early twentieth century. Just as potent "designer" compounds have replaced the less effective naturally occurring substances, which spawned their development in the pharmaceutical armamentarium, so may a new technology devoted to real-time assessment of brain function supplant the current form of EEG. This may well be a long time in coming, because it will be hard to improve upon the immediate accessibility, portability, relatively low cost, and excellent reliability of current EEG technology.

ACKNOWLEDGMENTS

The authors are greatly indebted to Robert Fisher, M.D., Ph.D., for his wonderful and witty input to this chapter in the previous edition. We are also grateful to the late Dr. Sumio Uematsu for the intraoperative photographs reproduced in this chapter. He continues to be missed by the many of us who worked with him. The thoughts expressed in this chapter reflect past experiences and continued learning with many wonderful electroencephalographers throughout training and practice, such as Bob Fisher, Alan Krumholz, Tom Henry, Chip Epstein, Jacqueline French, John Ebersole, Bob Webber, and others too many to be named. Finally, a large measure of gratitude is due Ernst Niedermeyer for providing teaching and mentoring over the years about the importance of a meticulously recorded and judiciously interpreted EEG.

ELECTROENCEPHALOGRAPHIC TECHNOLOGY KEY POINTS

1. EEG current is approximately 1 μA, voltage is approximately 2 to 300 μV.
2. $V = IR$ (volts, amperes, ohms)
3. Voltage law:
   Total of all voltages around a closed circuit is zero
   OR
   V input = total of voltage drops in circuit
   OR
   V input − total of voltage drops in circuit = 0.
4. Current law:
   Total current into a node equals total current out of a node
   OR
   Total current at any junction is zero.
5. For capacitors:

$$Q = CV \qquad \text{(coulombs, farads, volts)}$$

$$I = C\,dV/dt$$

Current = capacitance (a constant) · change in voltage over time.

6. Capacitive reactance (like resistance, but frequency dependent):

$$X_c = 1/(2\pi fC)$$

where f is frequency in cycles per second, or hertz, and C is capacitance, in farads.

NOTE: Capacitors resist current flow more at lower frequencies.

7. Inductance (L, measured in henrys) (not very important to EEG).

$$\text{Inductive reactance} = X_L = 2\pi fL.$$

8. Power $= I^2R = \dfrac{V^2}{R}$ (measured in watts).

9. Alternating current (AC) comes out of wall socket:

$$V(t) = V_p \cdot \sin(\omega t + \tau)$$

where ω is angular frequency (in radians per second) and τ is phase angle (in radians).

radians per second $= 2\pi f$ (frequency in Hz).

10. Direct current (DC) comes out of a battery and has no frequency content.

11. Root mean square (RMS) is equivalent DC voltage of an AC voltage:

$$\text{RMS (sine wave)} = \frac{\text{peak voltage}}{\sqrt{2}}$$

Wall socket delivers 110 V RMS = $110 \cdot \sqrt{2} = 156$ V amplitude.

12. Resistances in series: $ADD = R1 + R2 + R3 \ldots$
Resistances in parallel: reciprocal of sum of reciprocals = $1/(1R1 + 1/R2 + 1/R3 \ldots)$.

13. Capacitances in series: reciprocal of sum of reciprocals = $1/(1C1 + 1/C2 + 1/C3 \ldots)$

Capacitances in parallel: $ADD = C1 + C2 + C3 \ldots$.

14. Time constant $= \tau = R \cdot C$

τ = time it takes for voltage across resistor to fall to approximately 37% $(1/e)$ of initial value, or for a capacitor to charge to 63% $(1 - 1/e)$ of maximum value in an RC circuit.

NOTE: e is approximately 2.718.

NOTE: Avoid confusion: percentage is major change in direction of charge or discharge (up to 63% charging, or down to 37% discharging).

15. Cutoff frequency of a filter (frequency at which $1/\sqrt{2}$ or approximately 70% of signal is passed) is related to the time constant τ by the formula

$$f_{\text{cutoff}} = 1/(2\pi\tau) = 1/(2\pi RC) = 0.16/\tau$$

16. In low-frequency filters, the voltage across the resistor is

$$V(t) = Ae^{-t/\tau}$$

17. Time constants are related to cutoff frequency:

$$\tau = 1/(2\pi f_{\text{cutoff}})$$

Time constant is in seconds, cutoff frequency is in Hz. The cutoff frequency is the frequency at which $1/\sqrt{2}$ of signal is passed (approximately 70%).

18. Low-frequency filtering advances the timing of voltage peaks for the sinusoidal signal. High-frequency filtering delays the timing of voltage peaks. At the cutoff frequency timing, the change is a phase shift of 45° = $\pi/4$ radians = one-eight of the cycle.

19. Ohm's law for *AC:*

$$V = I \cdot Z \qquad \text{where } Z \text{ is impedance}$$

$$Z = \sqrt{(R^2 + (X_C - X_L)^2}$$

20. Reversible electrodes do not easily become polarized, which means they have low electrode potentials, which in turn means they produce signals better.

21. Decibels (dB):

$$\text{dB} = 20 \cdot \log(V_{out}/V_{in})$$

22. Frequency response of a filter: how the signal is altered as a function of frequency. Rolloff is how steep slope of curve is when amplitude plotted against log (frequency). Measured in decibels/(factor of 10 in frequency) = decibels/octave.

23. Common-mode rejection ratio (CMRR): a measure of how well a differential amplifier filters out signals common to both inputs:

$$CMRR = \frac{\text{voltage when input 1 = V and input 2 = ground}}{\text{input 1 = V and input 2 = V}}$$

24. Electrode impedance: 30-Hz sine wave is sent by machine through elec-

trodes. Impedance = 1 or 2 k Ω (machine dependent) per 1 mm of pen deflection.

25. Pen frequency response is limited to about 90 Hz before there is significant arcing.
26. Paper speed is commonly 30 mm per second in the United States; elsewhere, 15 mm per second is used. Slower paper speeds for operative monitoring (and usually for sleep) are sometimes used. Faster speeds help analyze fast events.
27. Analog signal: no spaces between data points, a continuous waveform (e.g., electrical current).
28. Digital signal: An analog signal is sampled at intervals measured in samples per second (= sample rate).
29. Nyquist's law: in order to resolve a waveform of frequency X cycles per second (= X Hz), the signal must be sampled at more than $2 \cdot X$/second (= Nyquist frequency).
30. Aliasing: If a signal of frequency X is sampled at the Nyquist frequency or lower, it can look like a signal of a lower frequency, corrupting the data. This process is called *aliasing*. The signal is said to be aliased.
31. To prevent aliasing, all frequencies that are higher than the band of interest should be filtered out, and sampling at slightly higher than the Nyquist frequency (called oversampling) should be performed just to be sure of accuracy. It should be remembered that filters have a frequency response curve, not just a vertical cutoff (infinite slope).
32. Digital storage: Resolution of a digital signal is a function of the voltage range being sampled (typically ±10 V), the sample rate, number of bits in ADC, the number of bits used for storage, and the resolution of the computer screen used for display.
33. The number of bits (n) used to store digital data divides the voltage range into 2^n increments. The more bits used, the better the resolution of the data. For example:
    1 bit allows data to be 0 or 1
    2 bits allows $2^2 = 4$ increments
    3 bits allows $2^3 = 8$ increments
    4 bits allows $2^4 = 16$ increments
    8 bits allows $2^8 = 256$ increments
    12 bits allows $2^{12} = 4{,}096$ increments
34. Safety:
    I. Three risk groups
        A. Bystanders
        B. Subjects connected to machine
        C. High risk: patients connected to intravenous catheters and other devices; neonates
    II. Potential sources of danger
        A. Improper grounding: more than one ground, three prongs converted to two, defeated fuses
        B. Leakage currents: capacitance of long wires (no extension cords) or nearby cords
        C. Switch sparking (not a "turn on")
        D. Working in puddles (e.g., in the operating room)
    III. Rules to follow:
        A. Use green dot outlets (hospital standard)
        B. Regular maintenance
        C. Proper fusing
        D. No extension cords
        E. One common ground
        F. Isolation jackbox for high-risk circumstances
    IV. Injury table: effects of various currents at 60 Hz

Current for 1 second	Effect
0.1 mA	Ventricular fibrillation if applied to the heart
0.3 mA	Sensory threshold
1.0 mA	Pain threshold
5 mA	Maximal harmless level
15 mA	Causes muscle tetany
50 mA	Causes tissue injury
100 mA	Causes fibrillation or death

    V. Leakage current limits

Devices standing alone	500 µA
If patients are connected	100 µA
Patients at high risk (e.g., with intravenous catheters)	10 µA

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Chapter 4

Electrical Fields and Recording Techniques

Mary B. Connolly, Frank W. Sharbrough, and Peter K. H. Wong

Cerebral Generators of Electroencephalographic Potentials
Electrode Placement
Electroencephalographic Derivations, Polarity Conventions, Calibration, Sensitivity, and Filter Settings
Derivations
Polarity Conventions
Calibration and Sensitivity
Filters
Montages
Unpaired, Paired-Group, and Paired-Channel Montages
Display Conventions
Referential, Bipolar, and Laplacian Montages
Referential Montages
Bipolar Montages
Laplacian Montages
Selection of Montages
Inverse or "Backward" Electroencephalographic Projection
Electrocap Systems
Three-Dimensional Devices
References

Electroencephalography (EEG) enables clinicians to study and analyze electrical fields of brain activity by recording amplified voltage differences between electrodes placed on the scalp, directly on the cortex (e.g., with subdural electrodes), or within the brain (with depth electrodes). For each electrical field, the clinician attempts to determine the nature, location, and configuration of the generator of EEG patterns and whether they are normal or abnormal and epileptiform or nonepileptiform. The clinical interpretation of the EEG findings must correspond to the patient's symptoms, findings on physical examination, and results of other investigations, such as brain imaging.

The traditional and universally accepted method of scalp electrode placement is the international 10-20 system (17,18). The spatial distribution of a changing electrical field requires orderly arrangement of multiple channels, termed a *montage*. Within a montage, different derivations record activity from different spatial intervals.

CEREBRAL GENERATORS OF ELECTROENCEPHALOGRAPHIC POTENTIALS

EEG signals represent the summated electrical activity generated by large populations of neurons (10^5 or more) (12) (see Chapter 1 for a more detailed

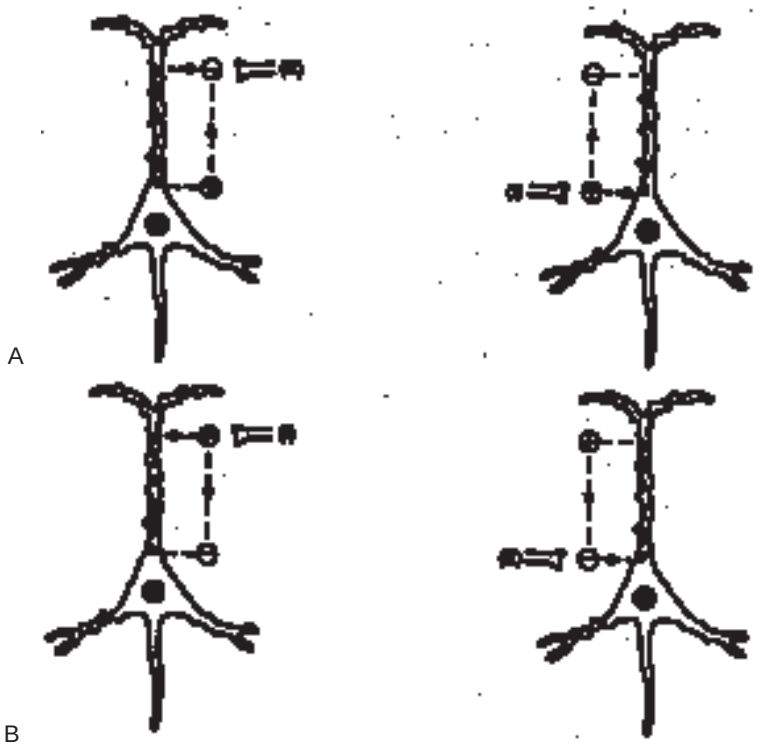


FIG. 4.1. A: A pyramidal cell dipole that is surface negative and depth positive can be produced either by excitatory synaptic input at the surface or by inhibitory synaptic input in the depths. **B:** Conversely, a pyramidal cell dipole that is surface positive and depth negative can be produced by inhibitory activity at the surface-positive end of the pyramidal cell or excitatory activity at the negative end. See also Fig. 4.4.

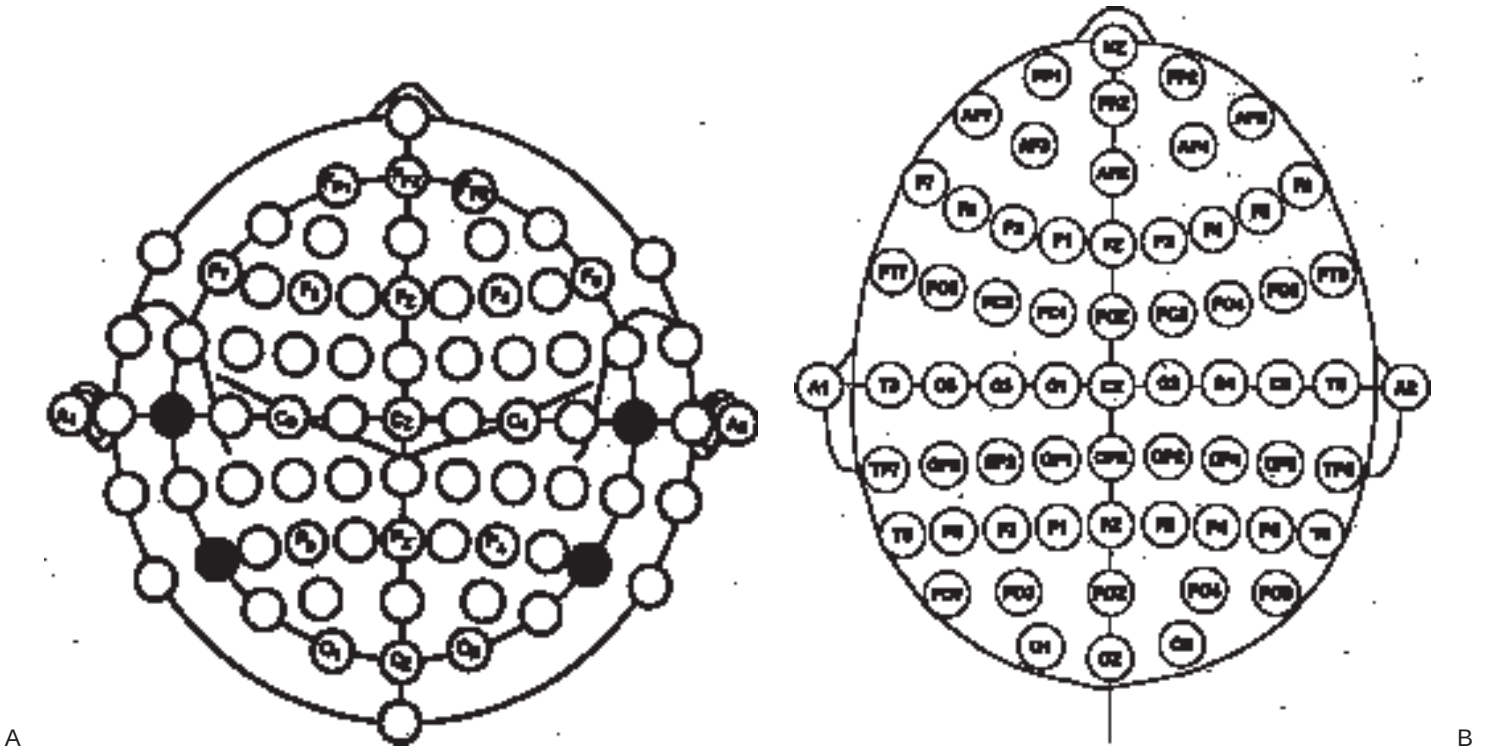
discussion). The main sources of EEG potentials are cortical neurons, which are arranged in layers beneath the cortical surface. Within each layer, neurons are aligned in bundles oriented perpendicular to the cortical surface and activated by synapses on soma-dendritic membranes. EEG signals are continuous variations of summated cellular electrical potentials as a function of time and location. All generators of scalp-recorded electrical activity, whether cerebral or extracerebral in origin, behave like a "dipole": that is, a generator with positive and negative poles. Pyramidal cells are the major source of synaptic potentials and are radially oriented. Synaptic activity at one end of the pyramidal cell produces an active ionic current as a result of changes in membrane permeability. The current loop is completed passively through neuronal membranes at distant, relatively inactive sites. This means that synaptic input at one end of a pyramidal neuron causes current flow through the neural membrane whose direction at the surface is opposite its direction in the depth. This produces polarization shifts in opposite directions at the surface and in the depth; therefore, electrically, the neuron behaves as an extracellular, transcortical, surface-to-depth, radially oriented dipole (see Chapter 2 for detailed discussion).

Although a measurement of polarization extracellularly at the cortical surface predicts opposite extracellular polarization in the depth, it does not permit determination of whether the polarization changes result from excitatory or inhibitory synaptic activity (Fig. 4.1). Thus, it is difficult to determine the three-dimensional intracranial location and configuration of cerebral generators from scalp EEG activity alone (the so-called inverse problem). However, by using intracellular recordings from experimental animals or tissue slices, it is theoretically possible to predict the two-dimensional location and configuration of the scalp potential field for any type of activity. This is the *forward EEG projection* or problem (24,26,27). It is more common in clinical practice to try to determine the (unknown) EEG generators on the basis of the pattern of activity recorded at the surface; thus, the inverse problem is of clinical interest.

ELECTRODE PLACEMENT

Since EEG was first recorded from humans by Hans Berger, who used two electrodes applied on the front and back of the head, various systems have been used over the years (2,21). The Committee of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) recommended a specific system of electrode placement under standard conditions for use in all laboratories (Fig. 4.2*A*) (17). This is the system now known as the international 10-20 system. Specific measurements from bony landmarks are used to determine the placement of electrodes. From these anatomical landmarks, specific measurements are made, and then 10% to 20% of a specified distance is used as the electrode interval. This enables replication consistently over time and between laboratories. The American Clinical Neurophysiology Society (formerly the American Electroencephalographic Society) has recommended using a minimum of 21 electrodes in the international 10-20 system. Odd-numbered electrodes are placed on the left side of the head, and even-numbered electrodes, on the right side of the head. Specific letters designate the anatomical area; for example, "F" means frontal.

In 1991, the American Electroencephalographic Society added nomenclature guidelines that designate specific identifications and locations of 75 electrode positions along five anterior-posterior planes, lateral to the mid-



A B

FIG. 4.2. A: Electrode nomenclature of the 19 most commonly used electrodes, according to the International Federation of Clinical Neurophysiology 10-20 system. **B:** Electrode nomenclature in the International Federation of Clinical Neurophysiology 10-20 system with additional electrodes (this is the 10% system).

line chain of 11 specific sites (see Fig. 4.2*B*). In addition, four coronal chains lie anterior, and four posterior, to the chain of 13 electrode sites between the earlobe electrodes along the midline at the Cz electrodes. Several electrodes have different names in the 10-20 system and the extended nomenclature. The electrodes T3 and T4 in the 10-20 system are referred to as T7 and T8 in the expanded system, and T5 and T6 are referred to as P7 and P8 under the new nomenclature. Currently, there is inconsistency among laboratories in identifying these electrodes (6,7,25,26).

For infants, fewer electrodes are used, and the number varies from laboratory to laboratory. For neonates, a 12.5% to 25% system is used in the Children's Hospital of British Columbia (Fig. 4.3). Specific issues related to recording EEG activity in newborns are discussed in Chapter 6.

In certain situations, additional electrodes can be applied to increase the yield from EEG recordings. These include, for example, sphenoidal, T1, and T2 electrodes in patients with known or suspected temporal lobe epilepsy. Sadler and Goodwin (28) recorded simultaneously from nasopharyngeal, sphenoidal, minisphenoidal, mandibular notch, surface, T1, and T2 electrodes. Like Binnie et al. (3), they found that T1 and T2 electrodes were as effective as sphenoidal and minisphenoidal electrodes and were significantly superior to nasopharyngeal electrodes. T1 and T2 are placed according to Silverman's (29) recommendations: 1 cm above one-third of the distance from the external auditory meatus to the external canthus (nearer to the former). If there is a question of a medial frontal focus, additional electrodes can be usefully applied near the midline (F1, F2, FC1, FC2, FCz).

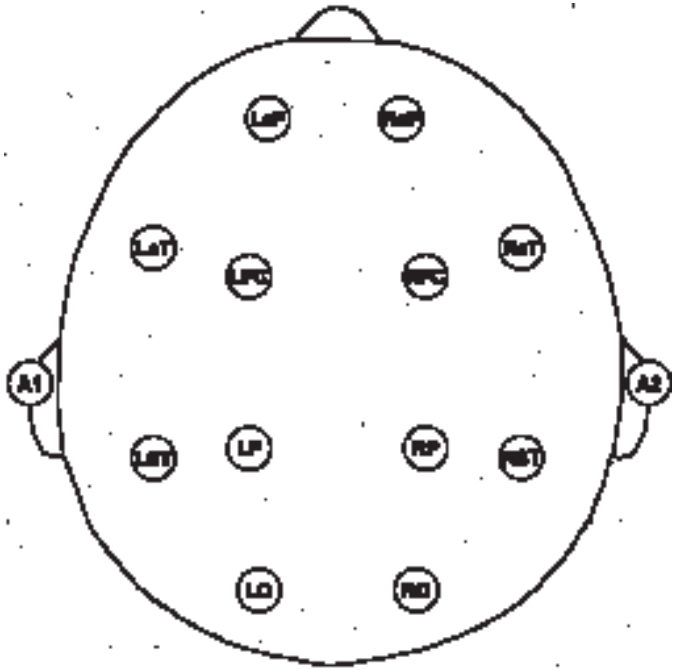


FIG. 4.3. Diagram illustrating the neonatal electrode placements used routinely (12.5% to 25%) at British Columbia Children's Hospital. 1: Measure from nasion to inion and from ear to ear, and mark position one-eighth up from ears, nasion, and inion. 2: Measure head circumference; calculate one-sixteenth, and mark to the left and right of the Fpz position; calculate one-eighth and mark the remainder of the circumference positions. 3: Measure the distance between the anterior temporal electrodes and divide into three parts; repeat for the posterior temporal area. 4: Measure from the frontal-polar to the occipital region, and divide by three.

ELECTROENCEPHALOGRAPHIC DERIVATIONS, POLARITY CONVENTIONS, CALIBRATION, SENSITIVITY, AND FILTER SETTINGS

Derivations

The amplified and filtered output from one recording channel documents the EEG voltage over time across one spatial interval in a relatively undistorted, continuous, and direct display. This appears on paper or video display as a graph of voltage over time. With traditional EEG machines, this potential difference appears in an analog manner as a pen deflection. The direction of the pen, up or down, depends on a polarity convention that is based on whether one input of the amplifier is more positive or negative than the other input.

Polarity Conventions

The two inputs of a differential amplifier are designated *input 1* and *input 2*. In the past, the terms "G1" and "G2" were used, in reference to actual grids in vacuum tubes that were used in the past. The IFSECN has recommended using the terms "input terminal 1" and "input terminal 2" (5). By convention, upward pen deflection occurs either when input 1 is more negative than input 2 or when input 2 is more positive than input 1 (Fig. 4.4). Downward pen deflection occurs if input 1 is more positive than input 2 or if input 2 is more negative than input 1. The polarity convention also specifies that the 10-20 electrode symbols, separated by a dash, designate electrodes connected to the two inputs of an amplifier (e.g., F3-C3 or F4-A2) and that the electrode whose symbol lies to the left of the dash (F3 or F4 in the example) connects to input 1; the amplifier input is indicated by the sign at the top of the calibration signal. Similarly, the electrodes whose symbol lies to the right of the dash (C3

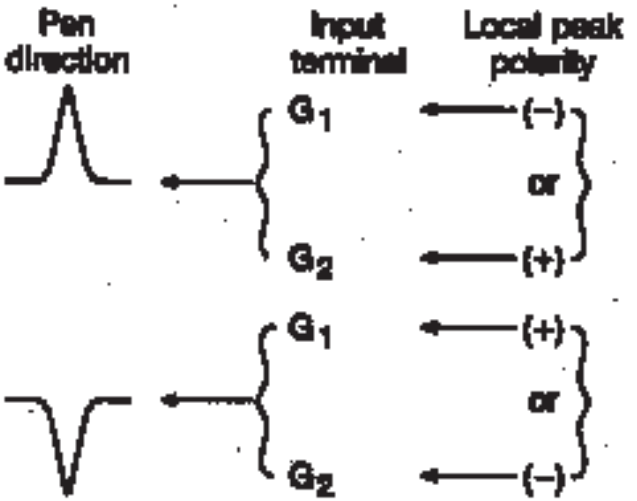


FIG. 4.4. According to the standard polarity convention, an upward signal deflection results if input 1 is more negative than input 2 or if input 2 is more positive than input 1. Conversely, a downward signal deflection results if input 1 is more positive than input 2 or if input 2 is more negative than input 1.

and A2 in the example) are connected to input 2. A single differential amplifier cannot determine absolute polarity. Recording with multiple electrode pairs and displaying EEG activity in several montages enables delineation of the field and determination of the polarity of a given potential.

Calibration and Sensitivity

Individual EEG channels have adjustable controls that allow variation of sensitivity and frequency response. An amplifier's sensitivity (or gain) control changes output voltage; that is, it attenuates the output voltage equally for all input frequencies. Sensitivity is expressed in microvolts per millimeter, which is the input voltage necessary to produce a given amount of vertical deflection and is indicated by a voltage specification placed beside a vertical calibration mark. The EEG instrument's dynamic range specifies the range of input voltages that can be measured accurately from the least to the maximum. The dynamic range is affected not only by the sensitivity setting used but also by the mechanical properties of the display system. During recordings, the technologist should adjust the sensitivity setting as necessary to maintain EEG activity within the system's dynamic range (Fig. 4.5). For ink-writing analog EEG machines, the most important part of calibration is that deflections are measured and carefully observed in all channels, before the start of the EEG recording. For traditional analog paper EEG recordings, the calibration signal also checks pen alignment and time axis. When pen alignment has been adequately adjusted, a sharp signal change applied to every channel should produce a tracing on paper that is exactly synchronized in all channels and of identical deflection amplitude. Obviously, video displays do not use pens and have no alignment problems. In this sense, as in many others, digital EEG systems are considerably more convenient, flexible, and accurate.

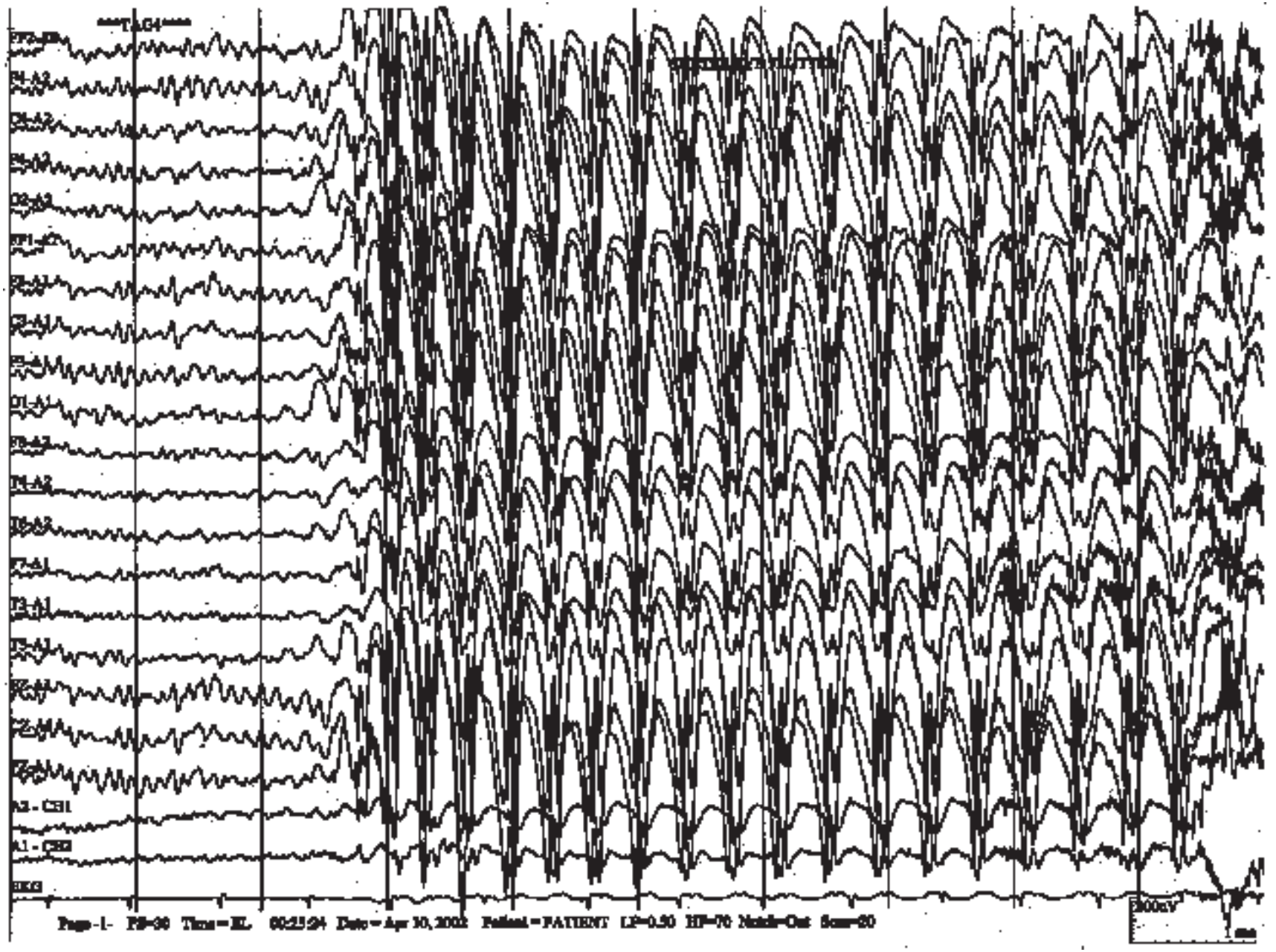
A small calibrating voltage, such as a 5-μV input, displayed with a sensitivity of 7 or 7.5 μV per millimeter, produces a very small deflection, less than 1 mm. This should be assessed to determine whether the onset of the wave is rounded or whether the deflection is absent in any channel. An additional biological calibration is essential to ensure that all the amplifiers respond equally and correctly to a variety of frequencies and not just to a direct current signal. This form of calibration is more sensitive to amplifier malfunction. It is also recommended that a second calibration be performed at the end of the EEG recording, with all of the sensitivities and filter settings that were employed during the recording (American Electroencephalographic Society recommendation, 1986). In the particular setting of electrocerebral inactivity, there is a requirement to calibrate with a 1- or 2-μV calibration signal.

With digital technology, calibration need be performed only once, and amplifier gain and direct current offset can be corrected automatically by the system's software to yield the same gain across channels. Calibration at different frequencies can be a built-in automatic function, and this eliminates the need for manual biocalibration (32).

Filters

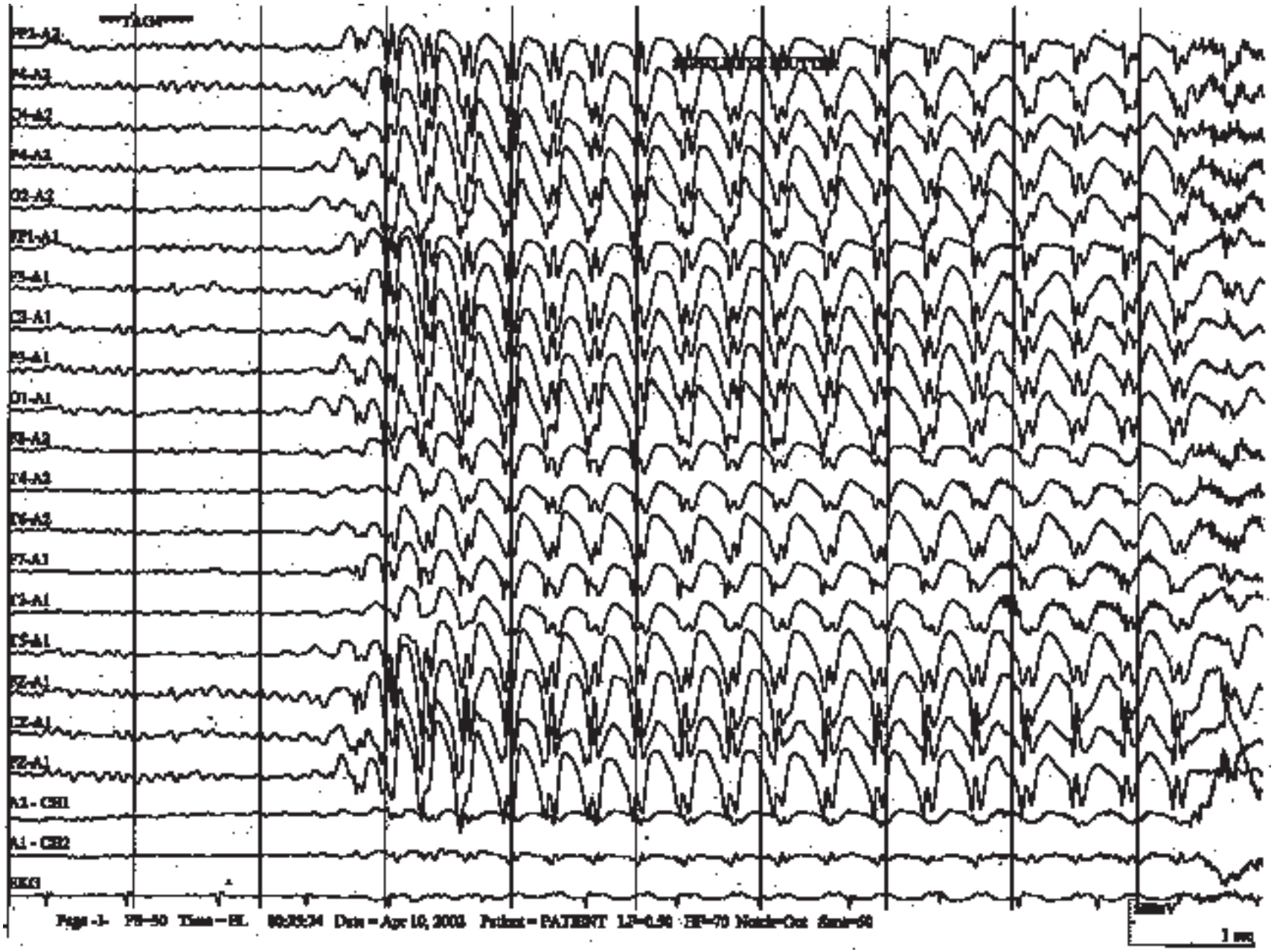
The range of neurophysiological activity within the brain ranges from between 0.25 and 0.3 Hz to as high as 2,000 Hz (in the cerebellum). Under certain circumstances, as in studies of the contingent negative variation or negative direct current shift and pre-ictal activity, frequencies even slower than 0.25 Hz may be recorded. In studies of evoked potentials, a very broad frequency band is required. The broader the frequency band of the recording is, the greater the fidelity with which the actual neurophysiological activity is reproduced. However, a wide frequency band increases the amount of outside interference and unwanted noise. For this reason, filters are used to preserve, to the greatest extent possible, brain wave activity of interest while minimizing extraneous signals. For routine clinical use, it is usually not necessary to record activity greater than 50 Hz; this is in sharp contrast to evoked potentials, whose signal components reach as high as 5,000 Hz. Filters are components in the amplifier that eliminate unwanted frequencies. A filter is described by the frequency range in which signals are amplified without significant distortion. For EEG activity, more than 70% attenuation of a particular frequency component by a filter results in significant distortion. In addition, conventional pen writing mechanisms are incapable of recording activity above 100 Hz accurately.

The instrument's frequency response capabilities are adjustable (19,30). The high-frequency filter, also referred to as the low-pass filter, affects high-frequency activity. A commonly used high-frequency filter setting is 70 Hz; on occasion, 35 Hz is used. The number refers to the particular frequency that has been reduced or attenuated in amplitude. The percentage attenuation varies with the filter characteristic called "rolloff." Thus, a 70-Hz filter affects the designated 70-Hz frequency by 20% to 60% (depending on roll-off) but has much less effect on lower frequencies. In contrast, frequencies above 70 Hz are attenuated to a much greater degree. In the context of epileptiform activity, it is critical that the filters be set so that fast components represented in spikes are not attenuated or distorted. For example, too low a high-frequency filter setting results in spikes that have the appearance of beta activity (Fig. 4.6).



A

FIG. 4.5. A: Generalized 3-Hz spike-wave recorded at a sensitivity of 20 μV/mm; this setting results in clipping of the wave component. **B:** Similar burst of a 3-Hz spike-wave activity as in part *A* but displayed with a sensitivity of 50 μV/mm. (*Figure continues.)*



B

FIG. 4.5. *Continued*.

A

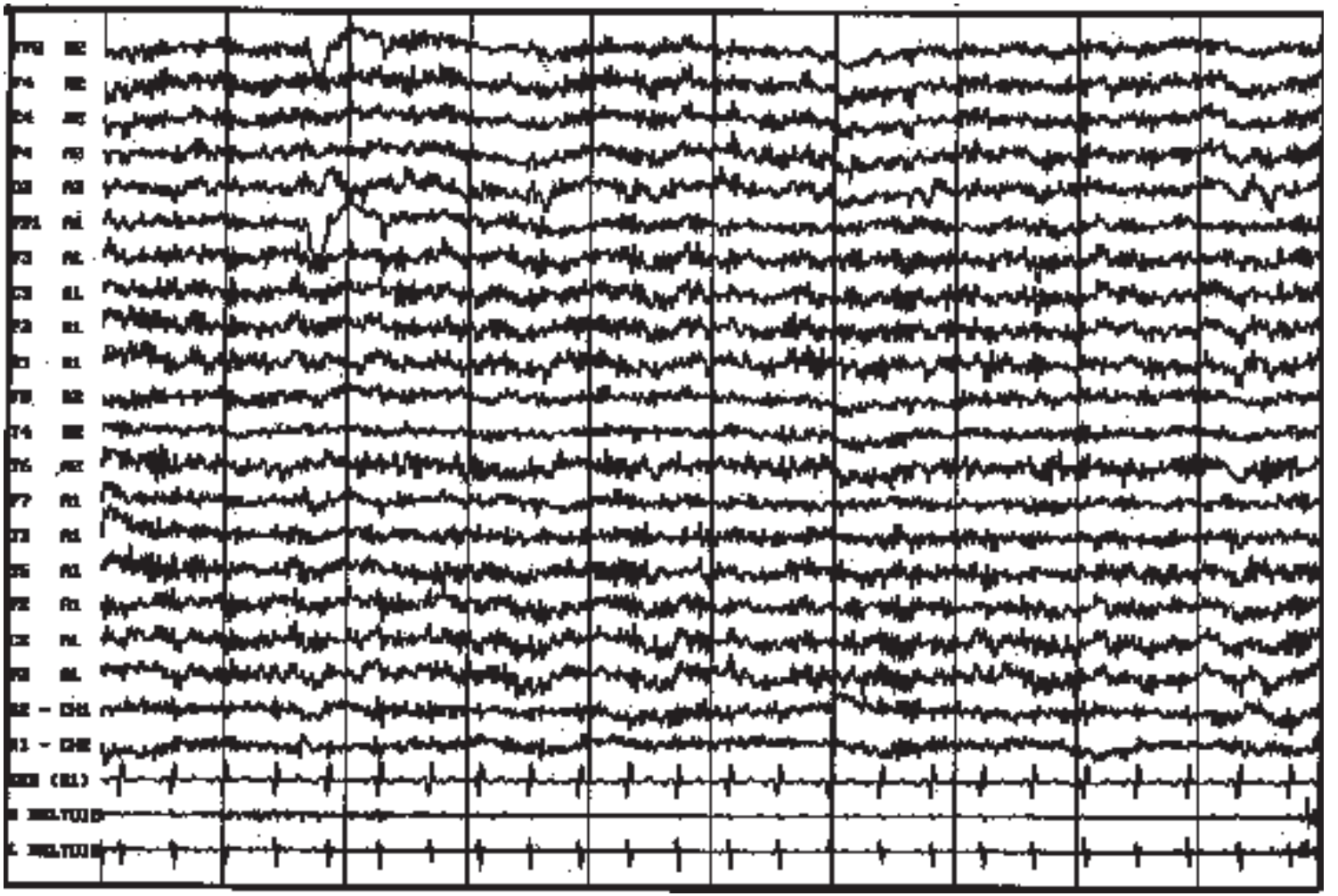
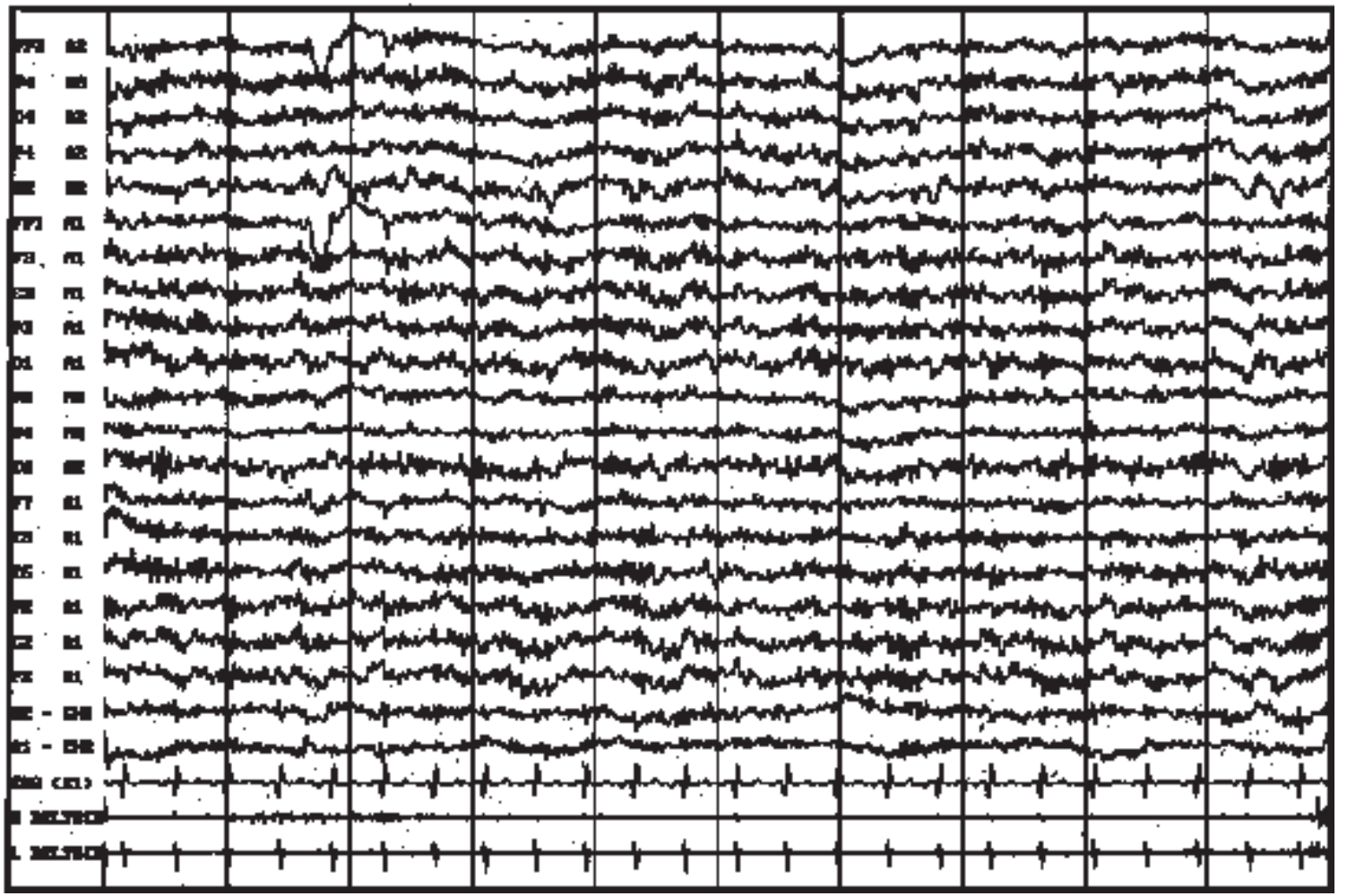


FIG. 4.6. A: Generalized beta activity recorded with sensitivity of 15 μV/mm, a high-frequency filter setting of 70 Hz, and a low-frequency filter setting of 0.5 Hz. **B:** Generalized beta activity displayed with sensitivity and low-frequency filter settings the same as in part *A* but with a high-frequency filter setting of 35 Hz. This results in attenuation of some beta activity. **C:** Generalized beta activity displayed with sensitivity and low-frequency filter settings as in part *A* but with a high-frequency filter setting of 15 Hz. There is even more marked attenuation of beta activity and distortion, resulting in spike-like transients. (*Figure continues.*)



B

FIG. 4.6. *Continued*.

Low-frequency filter settings identify the lower frequency limits below which the amplifier progressively attenuates and distorts physiological signals. Above this limit, the amplifier does not distort signals to a significant degree. Low-frequency filters are also referred to as high-pass filters because they allow higher frequencies above the specified frequencies to pass largely unchanged. The effect of a low-frequency filter is determined by its time constant. In the simple traditional amplifier, one time constant (TC) is calculated by multiplying resistance by capacitance. Time constant can also be defined as the time it takes for a square-wave deflection to decline 63% from its peak or as the time it takes for a square-wave signal deflection to drop within 37% of the baseline. The terms *time constant* and *low frequency* are used interchangeably in practice to describe a low filter's

C

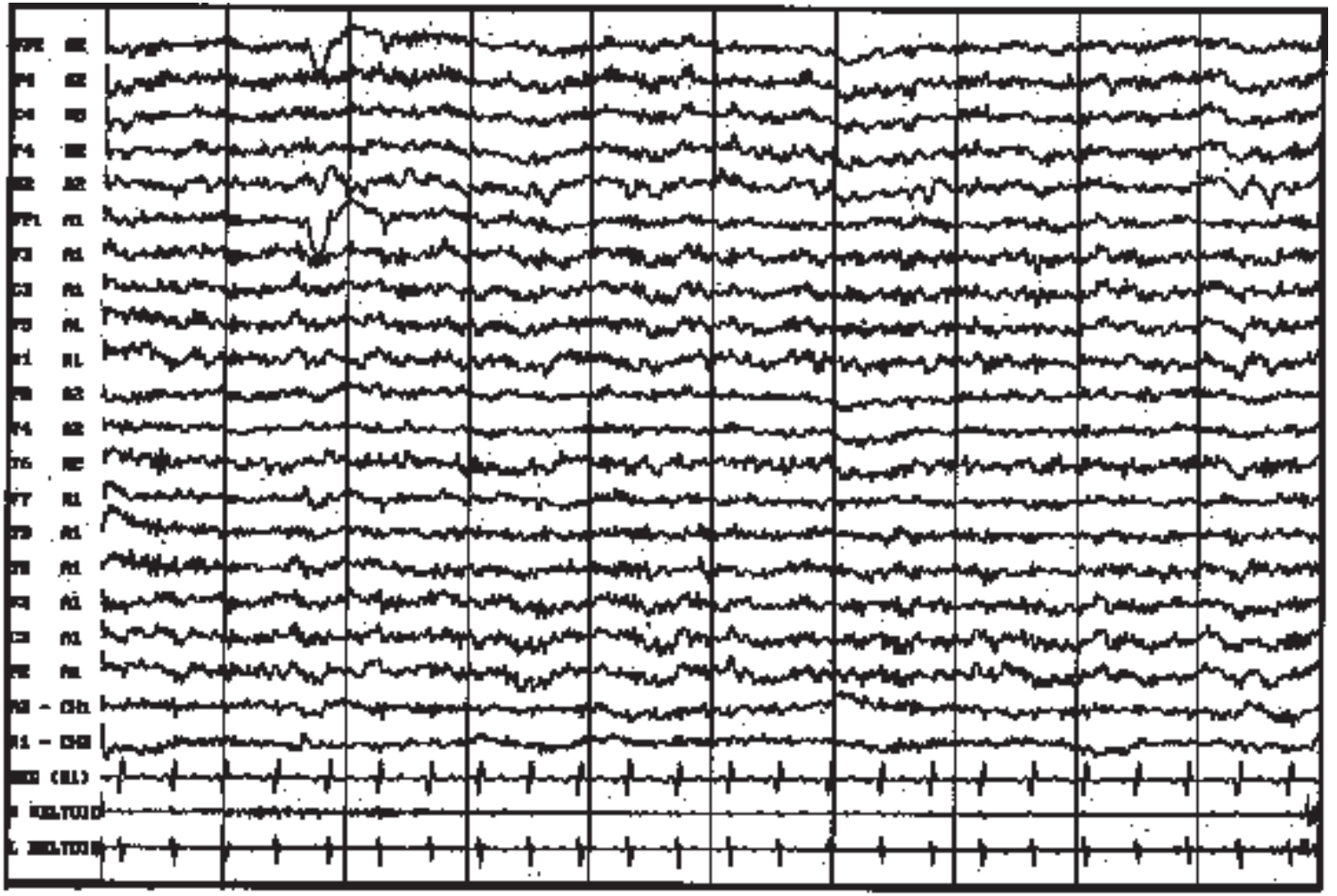
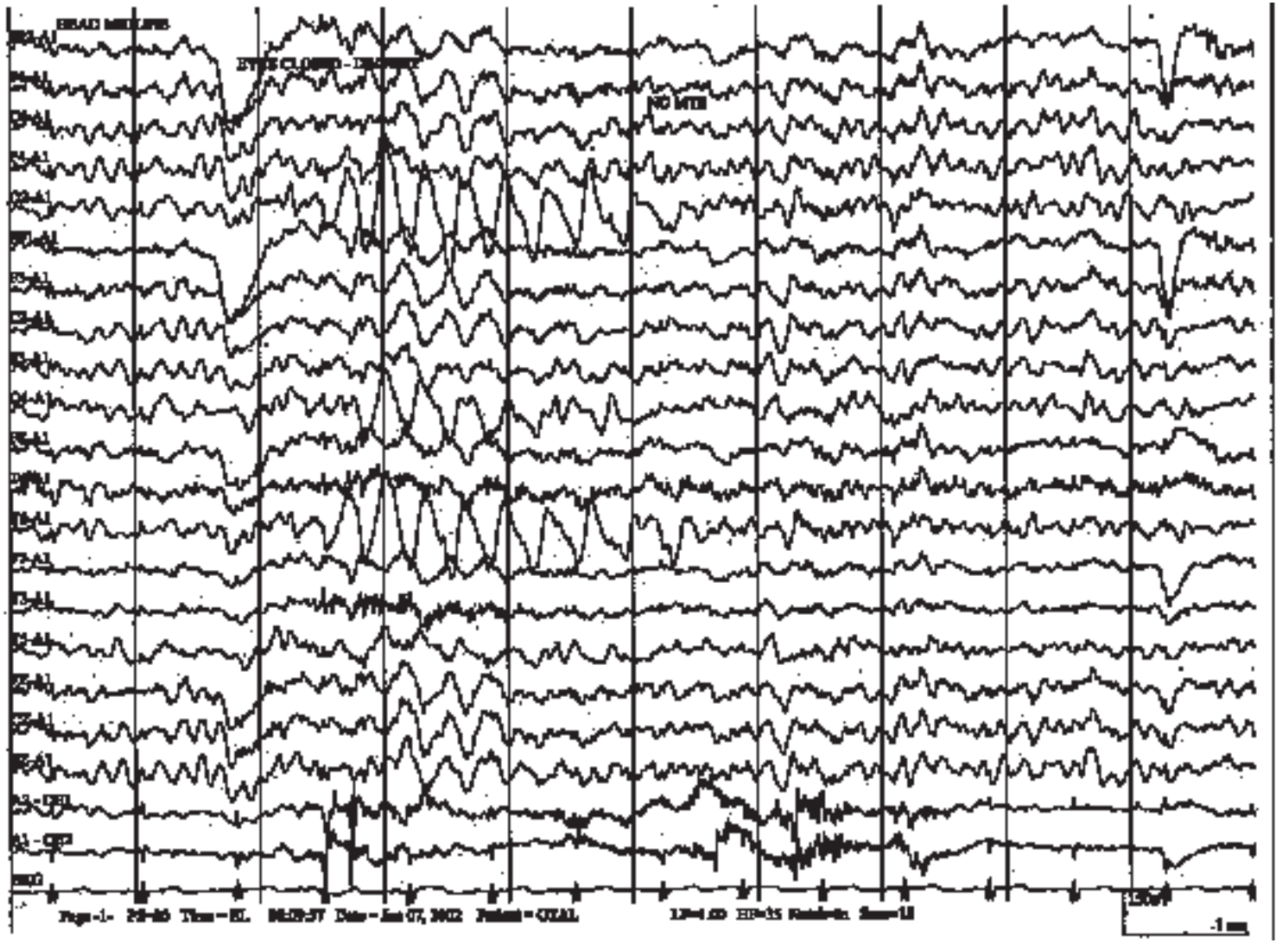


FIG. 4.6. *Continued*.

effect on slower activity, but they are distinct terms and are specified differently. For example, a time constant of 1 second represents a low-frequency filter of 0.1 or 0.16 Hz, depending on the filter roll-off involved; a time constant of 0.3 seconds represents a low-frequency filter of 0.5 Hz. Knowledgeable use of the low-frequency filter increases the yield of important clinical information. For example, in a record dominated by slow activity, short time constants or narrow low-frequency filters attenuate most delta activity (Fig. 4.7) but allow faster frequencies to be displayed more clearly. This may facilitate recognition of asymmetries of faster frequency patterns, such as sleep spindles or beta activity.



A

FIG. 4.7. A: Right posterior temporal-occipital delta activity displayed with sensitivity of 15 μV/mm, low-frequency filter setting of 1 Hz, and high-frequency filter setting of 35 Hz. **B:** Same delta activity displayed with low-frequency filter setting of 3 Hz and with sensitivity and high-frequency filter settings as in part *A.* Note mild attenuation of right posterior delta activity. **C:** Same EEG sample but with low-frequency filter setting of 10 Hz and high-frequency filter and sensitivity settings as in part *A.* There is now marked attenuation of right posterior delta activity. **D:** The right posterior delta activity is enhanced with a display speed of 15mm/sec (sensitivity of 20 μV/mm in this example). (*Figure continues.*)

B

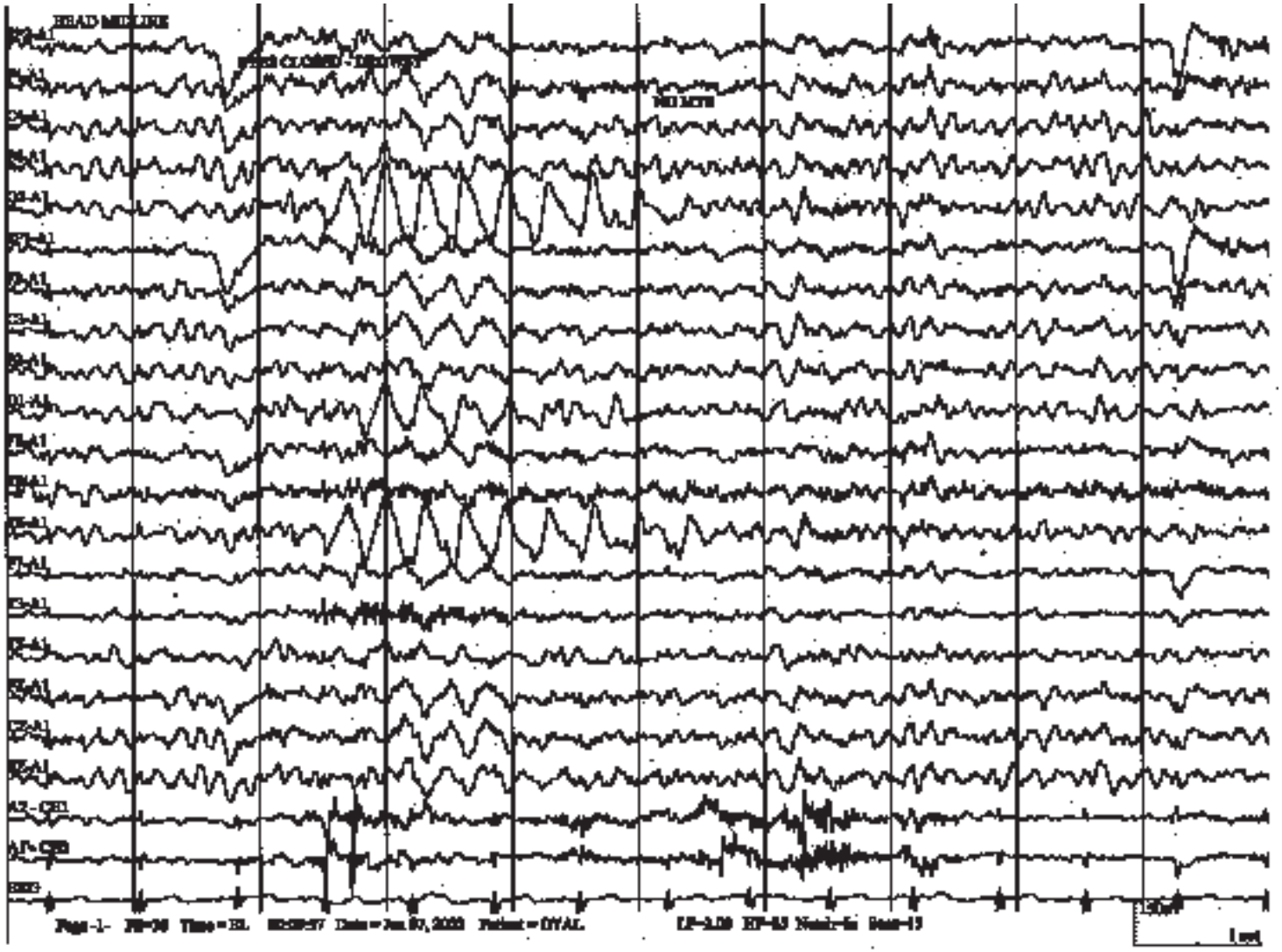


FIG. 4.7. *Continued.*

C

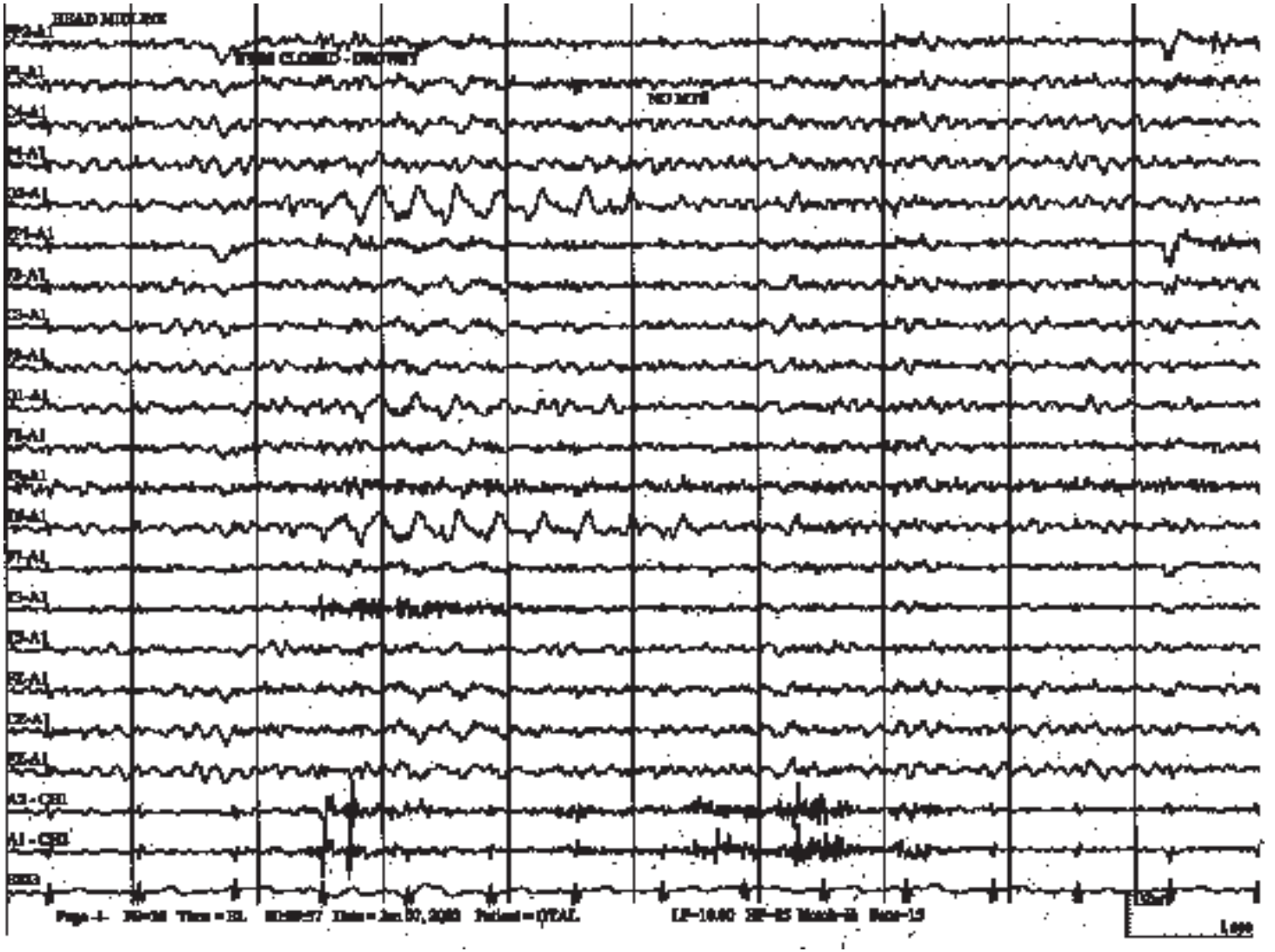


FIG. 4.7. *Continued.*

D

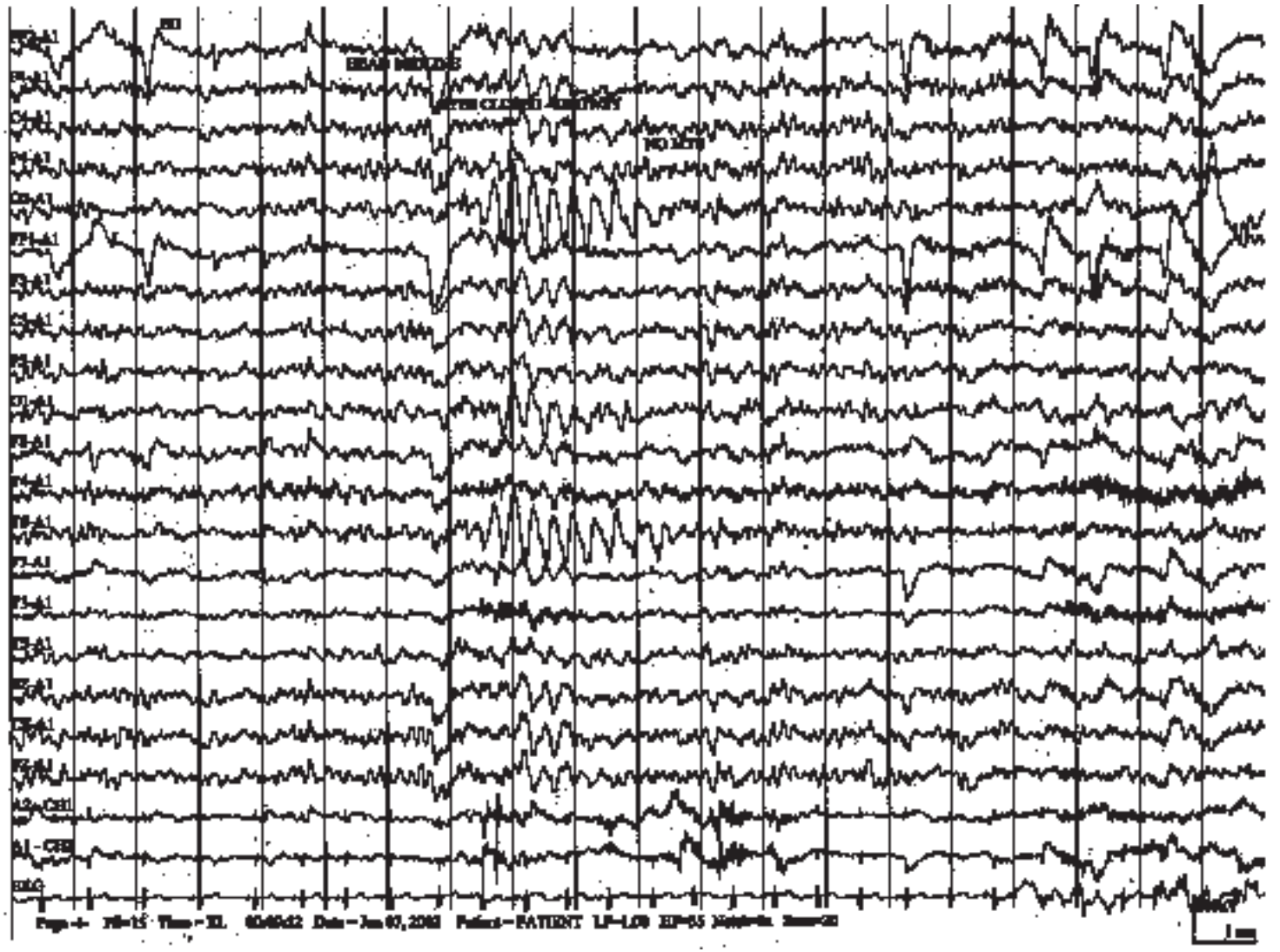


FIG. 4.7. *Continued.*

MONTAGES

Common conventional montages, even with logically organized series of channels, distort spatial information by converting complex patterns of EEG activity originating in three dimensions to a series of channels whose output displays are horizontal, spatially discontinuous, and variable. Spatial delineation of fields has improved steadily as advances in technology have led to a steady increase in the number of recording channels available, but spatial sampling, although vastly improved, is still fraught with problems even today. In addition, the electroencephalographer infers the spatial distribution of EEG activity only indirectly, by cross-comparing activity from different channels. Even this presentation is distorted, however, because a grid of electrodes, each with up to four neighbors (anterior and posterior sagittally and left and right coronally), appears as a series of channels with only two vertical (upper and lower) neighbors on a typical EEG display. Thus, EEG montages unavoidably distort spatial relations among electrodes, because the visual presentation has fewer dimensions that the reality that it depicts (consider the analogous distortions that occur in maps based on Mercator projections of the earth).

Like other inherent mapping distortions, a given EEG montage tends to preserve spatial relationships of electrodes in one direction better than in others. Therefore, a montage is classified as longitudinal if it preserves spatial relations best between electrodes in the sagittal direction and as transverse if it better preserves spatial relations in the coronal direction.

Montages may be classified as unpaired, electroanatomical paired-group, or paired-channel and as referential, bipolar, or laplacian (source derivation). In longitudinal montages, channels are arranged along sagittal lines. Adjacent channels within a sagittal line may either link in bipolar chains or connect to a reference. In transverse montages, channels are arranged in coronal lines.

Unpaired, Paired-Group, and Paired-Channel Montages

In unpaired longitudinal or transverse montages, channels are arranged in anatomical neighboring sequences: for example, sequentially from front to back or from left to right. These are often referred to as *electroanatomical* groupings (19). In paired-group montages, electrodes are arranged from homologous areas of the scalp by placing together left and right temporal, or left and right parasagittal, linkages. Paired-group arrangements apply only to longitudinal montages because the brain does not have functional or anatomical symmetry in the coronal direction. In paired-channel montages, channels from homologous brain areas are paired. Left and right pairs are then subgrouped together in longitudinal lines (e.g, a line of temporal pairs and a line of parasagittal pairs). Midline electrodes cannot be paired.

The characteristics of these montage arrangements are different in terms of the accuracy of voltage representation (distortion) and display of any asymmetry:

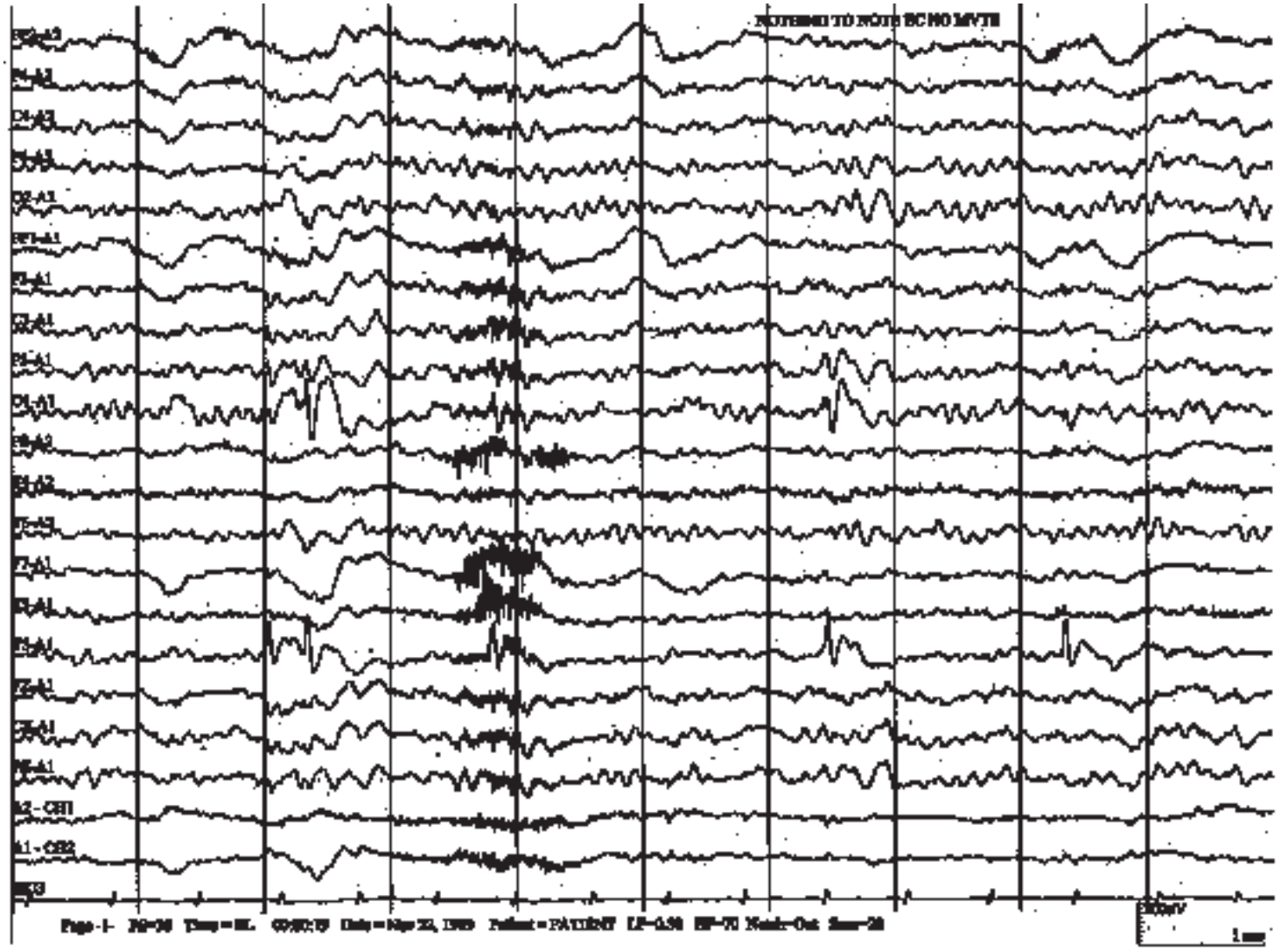
Unpaired	Least distortion, worst display of symmetry
Paired-group	Fair distortion, fair display of symmetry
Paired-channel	Most distortion, best display of symmetry

Display Conventions

In montages, electrodes are arranged in anterior-posterior sequences. For longitudinal montages, this means that frontal electrodes precede central, parietal, and occipital electrodes; anterior temporal electrodes precede midtemporal and posterior temporal electrodes. For transverse montages, electrodes are also displayed in a front-to-back sequence. The left-right convention dictates that for unpaired longitudinal montages, left-sided channels are placed above right-sided channels. In transverse montages, each line of channels proceeds from left to right. For paired longitudinal montages, left-sided channels appear above the homologous grouping of right-sided channels. These left-right displays are used widely throughout North America and conform to the guidelines of the American Electroencephalographic Society (1). However, the reverse convention of "right over left" is used routinely in Europe and is recommended by the IFSECN (18).

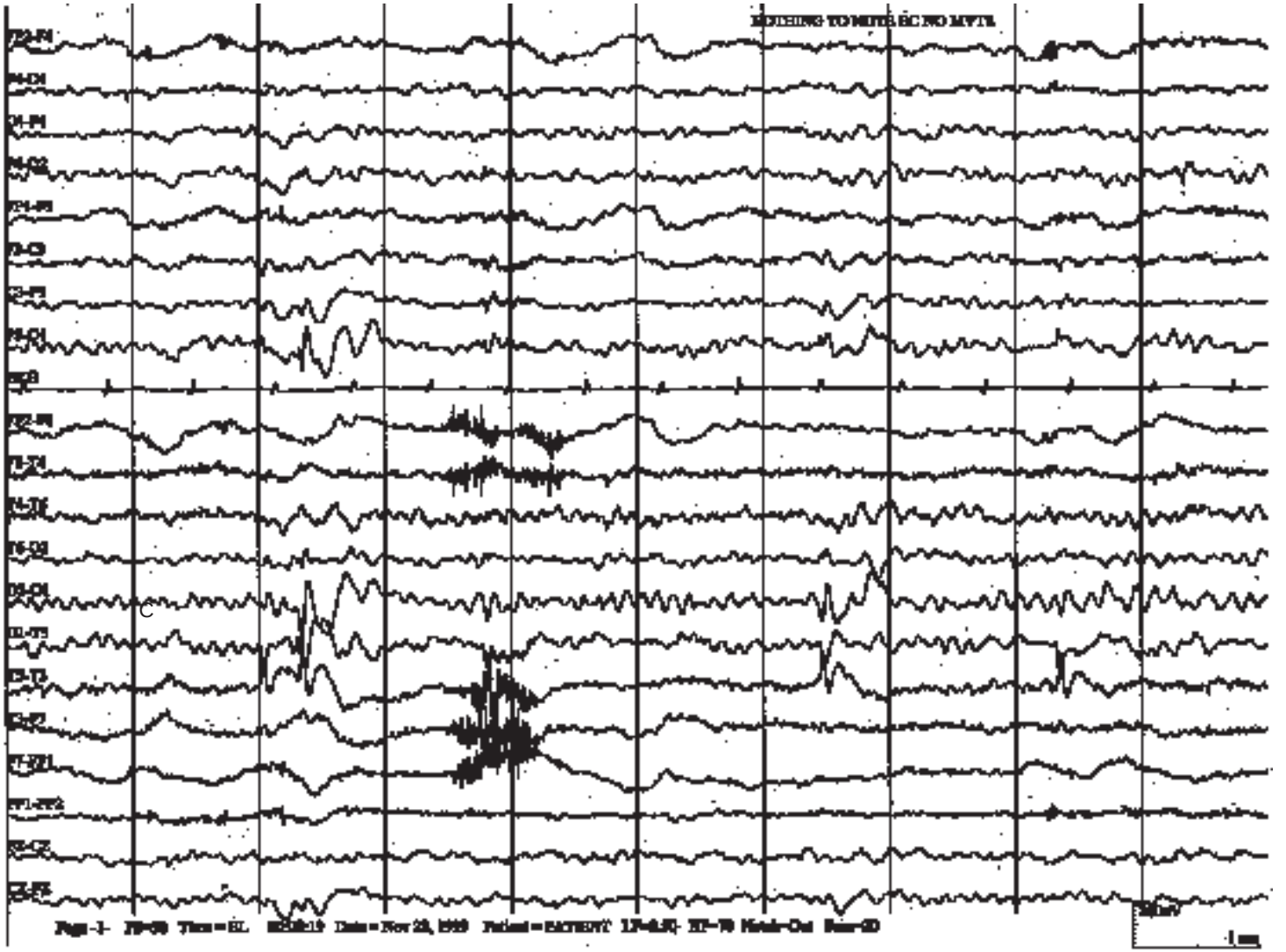
Referential, Bipolar, and Laplacian Montages

Localizing voltage peaks within a potential field requires a line of electrodes crossing the field's maximal potential. For longitudinal or transverse linkages, the clinician attempts to identify one or more electrodes that register the peak potential more than other electrodes within the field. More precise localization requires identifying the maximally involved electrode or electrodes in both sagittal and coronal directions. Such multiple direction readings give information about the topography of the peak. This means that for any voltage peak, the potential recorded by that electrode is greater than the potentials seen simultaneously by its four immediate neighbors. For example, a right frontal potential field can be localized to F4 if the voltage peak at F4 is larger than the voltage change seen simultaneously at FP2, C4, FZ, and F8. Problems in localization arise if peaks lie at the perimeter of an electrode grid (end of the chain) (Fig. 4.8). Localization is commonly achieved with appropriate combinations of referential and bipolar montages (Fig. 4.9). The laplacian source derivation method may also be helpful (9,14,15,23,24,27,28).



A

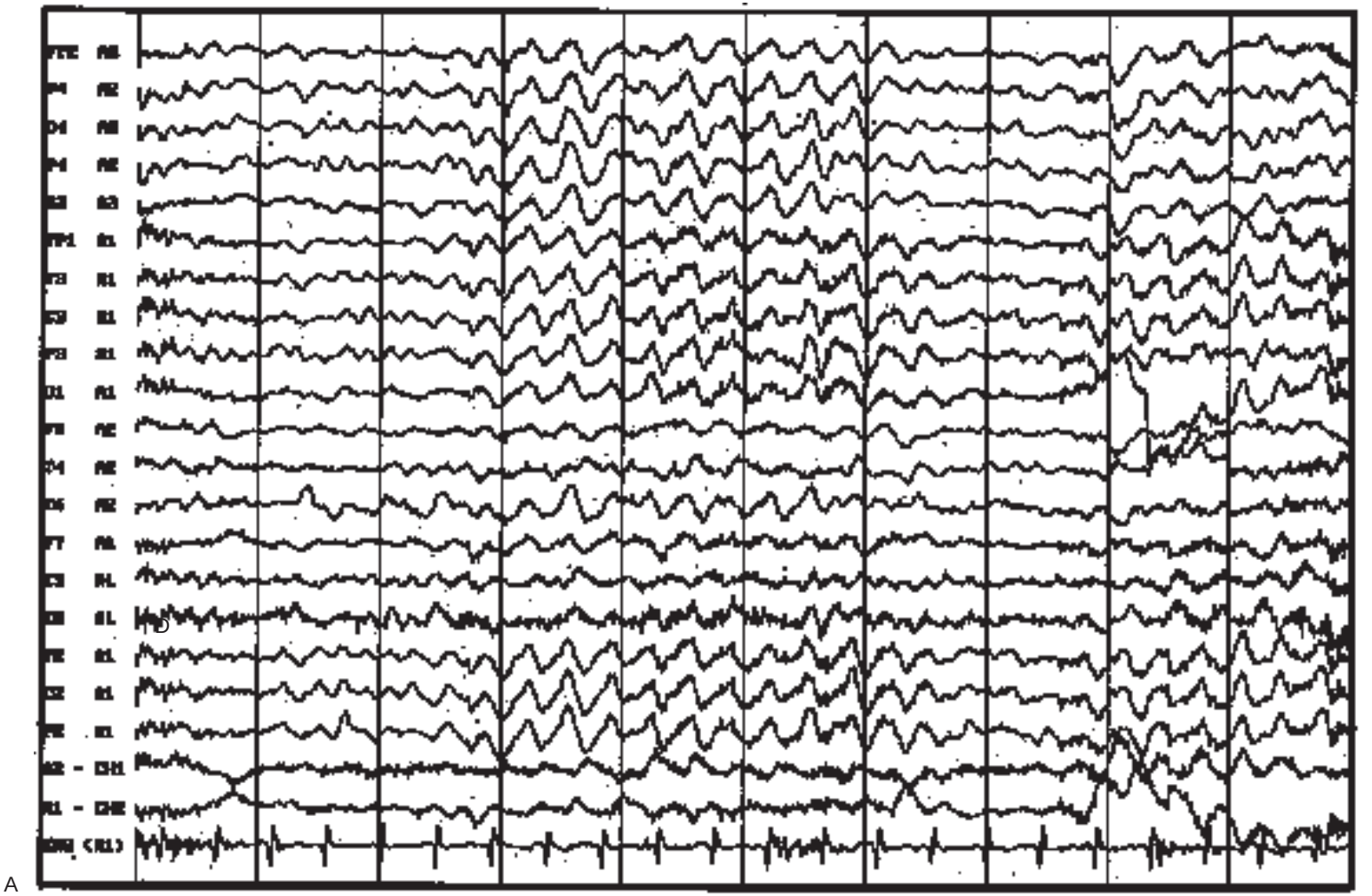
FIG. 4.8. A: Left occipito-temporal spikes displayed with sensitivity of 15 μV/mm, low-frequency filter setting of 1 Hz, and high-frequency filter setting of 70 Hz. **B:** Same spikes as in part *A,* displayed in a bipolar longitudinal montage, which enables accurate localization to the T5 and O1 electrodes. (*Figure continues*.)



B

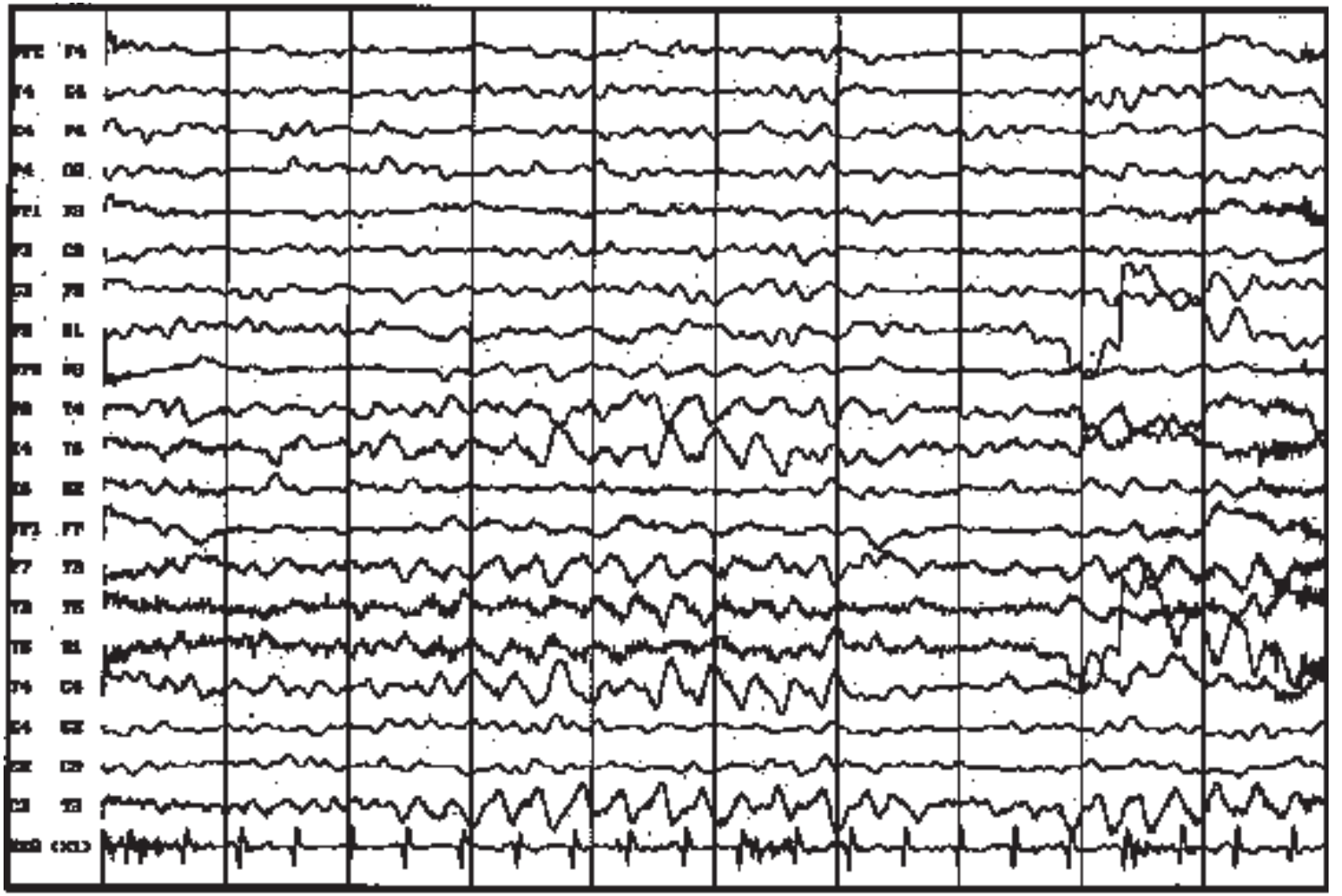
C

FIG. 4.8. *Continued.*



A

FIG. 4.9. A: Temporal delta activity recorded with an ipsilateral ear reference montage, a sensitivity of 50 μV/mm, a low-frequency filter setting of 0.5 Hz, and a high-frequency filter setting of 70 Hz. Delta activity in both temporal regions makes A1 and A2 active and thus poor references. **B:** Temporal delta activity in part *A* displayed on a bipolar montage, which permits accurate localization. (*Figure continues.*)



B

FIG. 4.9. *Continued.*

Referential Montages

In referential montages, a common reference electrode is connected to input 2 of each amplifier. Ideally, for each pair of electrodes in a channel, only one (input 1) is active. This situation is never achieved in real life, because the common reference site is always active to some degree and therefore invariably contributes to the output signal (19). In the past, referential recording was also referred to as *monopolar* recording. The types of reference electrodes used include A1 and A2 ("ipsilateral ears"); A1 plus A2 ("linked ears") (28); Cz, a balanced noncephalic reference such as the neck-chest region; and the average reference ("Goldman-Offner"). The average reference is traditionally derived electronically by interconnecting all active scalp electrodes (all those

of input 1) (13). The clinician can delete selectively from the average one or more electrodes that may contribute disproportionately high voltage activity to the reference, such as frontal leads showing prominent eye movements or electrodes over an area of focal slowing or epileptiform activity.

With digital recordings, a true average reference can be created with any combination of two or more electrodes. As long as electrodes connected to input 1 are more active than the input 2 common reference, a referential montage clearly displays a potential's polarity and voltage field. Selection of a reference site is important. If the selected reference site lies within the field of interest, it is "active"; this makes it difficult or impossible to determine polarity and spatial distribution of the field. A major advantage of digital recording techniques is that they allow reformatting of the EEG with different montages, including those uniquely created for individual patients. The following are examples:

1. A left temporal discharge contaminating the left ear reference and reformatted with the contralateral ear as a reference. The field and amplitude of the discharge can be more readily determined (Figs. 4.10*A* and *B*).
2. A left temporal spike contaminating an ear reference. This can be eliminated by changing the reference to bipolar (see Fig. 4.10*C*) and enhanced by increasing the paper speed (see Fig. 4.10*D*).

Bipolar Montages

In bipolar recordings, both input 1 and input 2 are connected to active recording electrodes. No single electrode is common to input 1 or input 2. Bipolar montages link sequential pairs of electrodes in longitudinal or coronal lines. In linked chains, a single electrode becomes common to two adjacent channels, but it is connected to input 2 in the first channel and to input 1 in the second channel. The site of maximal voltage within a field appears as a phase reversal; that is, simultaneous deflections in two channels sharing a common electrode occur in opposite directions. The direction of the phase reversal (deflections coming together for local negative peaks or diverging for local positive peaks) assists in determining polarity. If the voltage peaks involve two adjacent electrodes equally—for example, F4 and C4—they are equipotential. If equipotential electrodes connect to input 1 and input 2, there is *in-phase* cancellation, and no output appears in that channel. Localizing by phase reversal is possible only if bipolar montages fully encompass the site of maximal voltage in both longitudinal and transverse directions. A phase reversal does not occur unless the electrode chain fully encompasses a local voltage peak. For example, a negative voltage gradient increasing from C3 to P3 to O1 (as with an occipital spike) does not show a phase reversal, and only a downward deflection is seen. Addition of a suboccipital electrode may reveal a phase reversal if the discharge is maximal at O1.

Bipolar montages are most useful in defining localized potential gradients. Of importance, however, is that the deflection in a particular channel is greatest when the voltage gradient between the two electrodes is steepest, *not* necessarily when the absolute voltage is largest. This is an important distinction between bipolar and referential recordings. Other advantages of bipolar montages include (a) eliminating the effect of contaminated references (see Fig. 4.10); (b) easy localization of relatively discrete focal abnormalities by phase reversal; and (c) avoiding problems that can arise from unbalanced amplifier inputs with a common reference. On the other hand, it is possible only to infer (and not compare directly) activity from individual electrodes, and voltage and polarity determinations are always positive. Referential recordings allow clear characterization of widespread or complex potential fields, unambiguous determinations of voltage polarity, and less distortion of EEG patterns exhibiting time lags across the scalp. The major disadvantage of referential recording is that no single reference electrode or method is optimal for all situations, inasmuch as no reference is truly inactive; thus, it is crucial to select an appropriate reference for a particular situation (34). Using the same reference routinely and without thought largely invalidates the advantages offered by a referential recording. With regard to the relation between bipolar and referential montages, it is helpful to remember that they are simply mathematical transformations of one another. For example, converting absolute voltage-to-voltage difference is only a matter of computing the voltage gradient of spatially continuous voltage fields (the first spatial derivative) inferred from longitudinal and transverse electrode arrays displaying discrete fields. Bipolar-to-referential transformation is analogous to integrating an electrical field's voltage gradient in relation to a fixed site to obtain the voltages at individual electrodes. This conceptual parallel between manipulations of spatially discontinuous EEG data and spatially continuous electrical field data assists in understanding laplacian source derivations.

Laplacian Montages

In the laplacian source derivation, voltages at each electrode site are compared with a local average of voltages at immediately surrounding electrodes. Operationally, this means that each channel measures the voltage difference between the electrode of interest (input 1) and a reference (input 2) derived from the average voltage of its nearest neighbor. For example, for F4, the simplest value of the local average would consist of

$$(FP2 + C4 + FZ + F8)/4$$

A

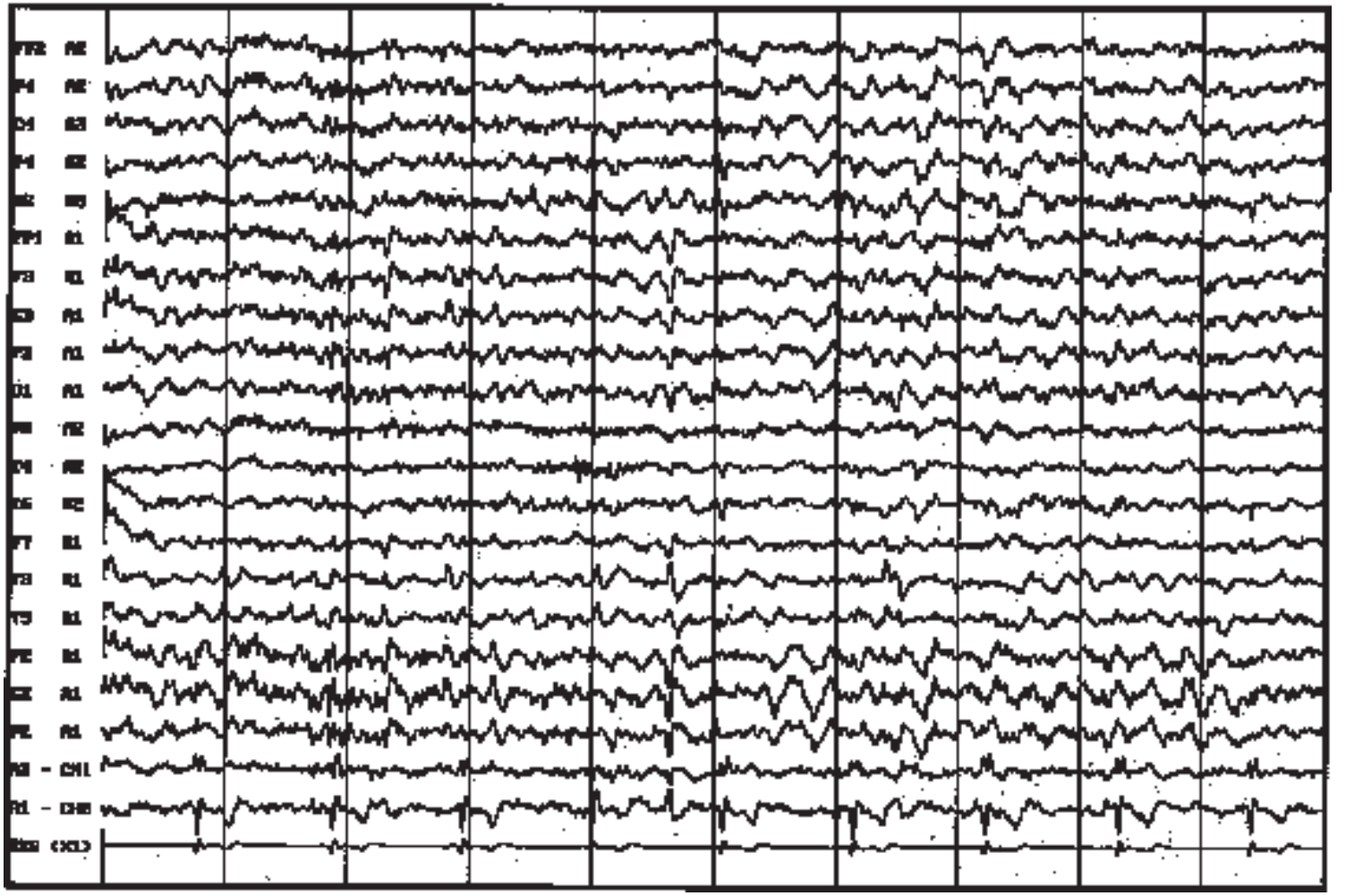


FIG. 4.10. A: Left mid-temporal spike makes A1 active when used as a reference. **B:** Left mid-temporal spike displayed with A2 as the reference. **C:** Same left mid-temporal spike displayed on a bipolar montage allows localization by phase reversal. **D:** Same left mid-temporal spike as in B displayed with paper speed of 60mm/sec. (*Figure continues.*)

B

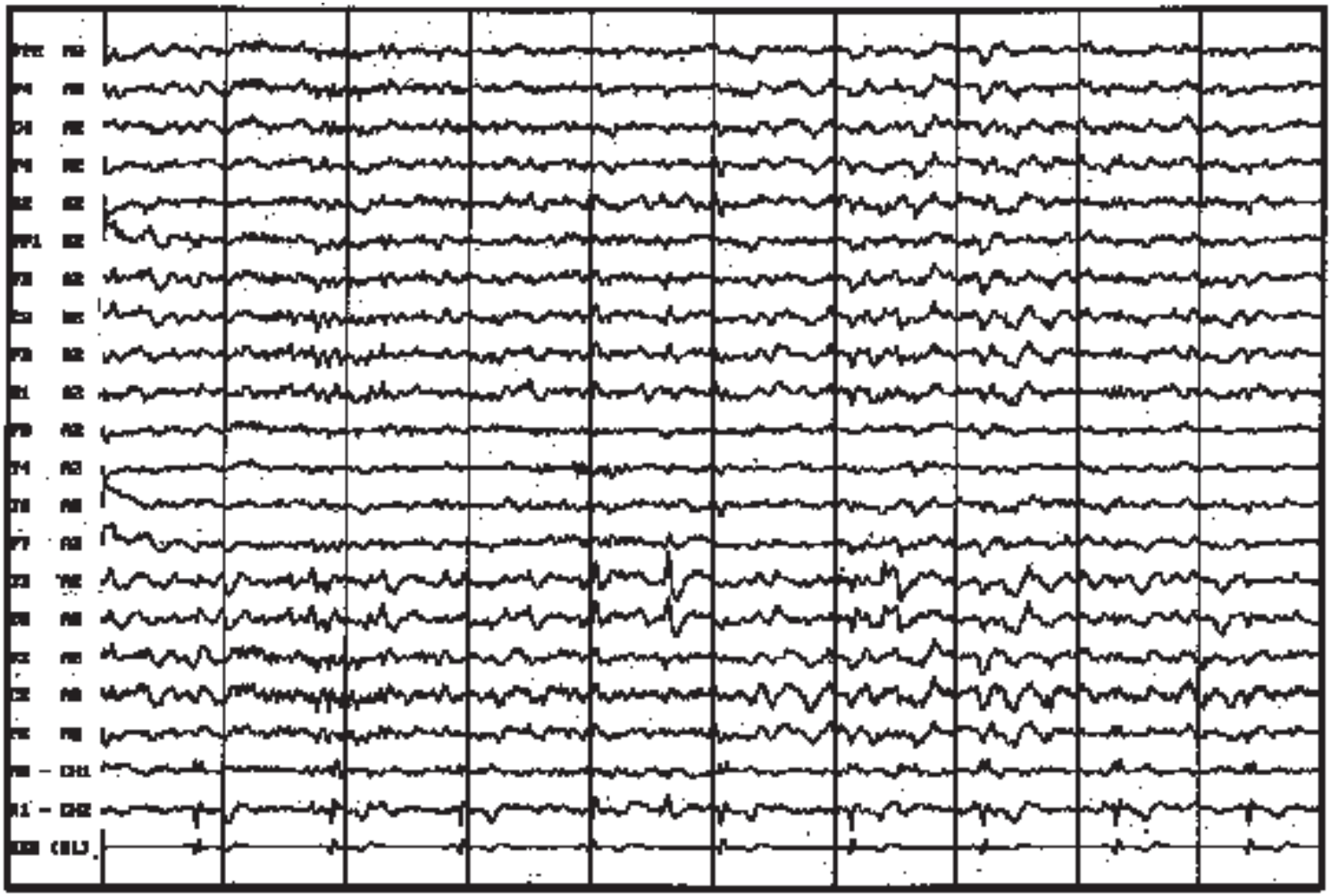


FIG. 4.10. *Continued.*

C

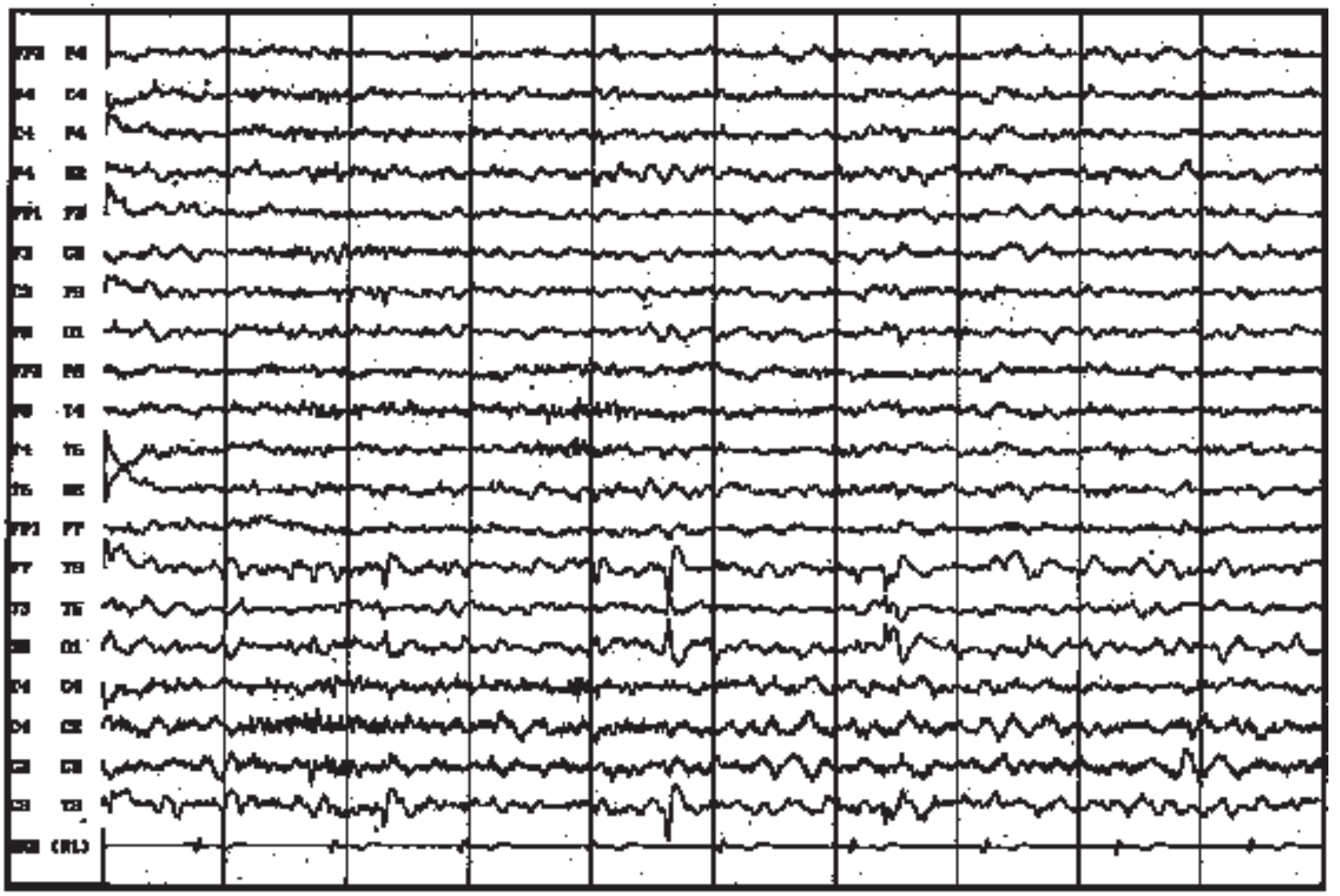


FIG. 4.10. *Continued.*

D

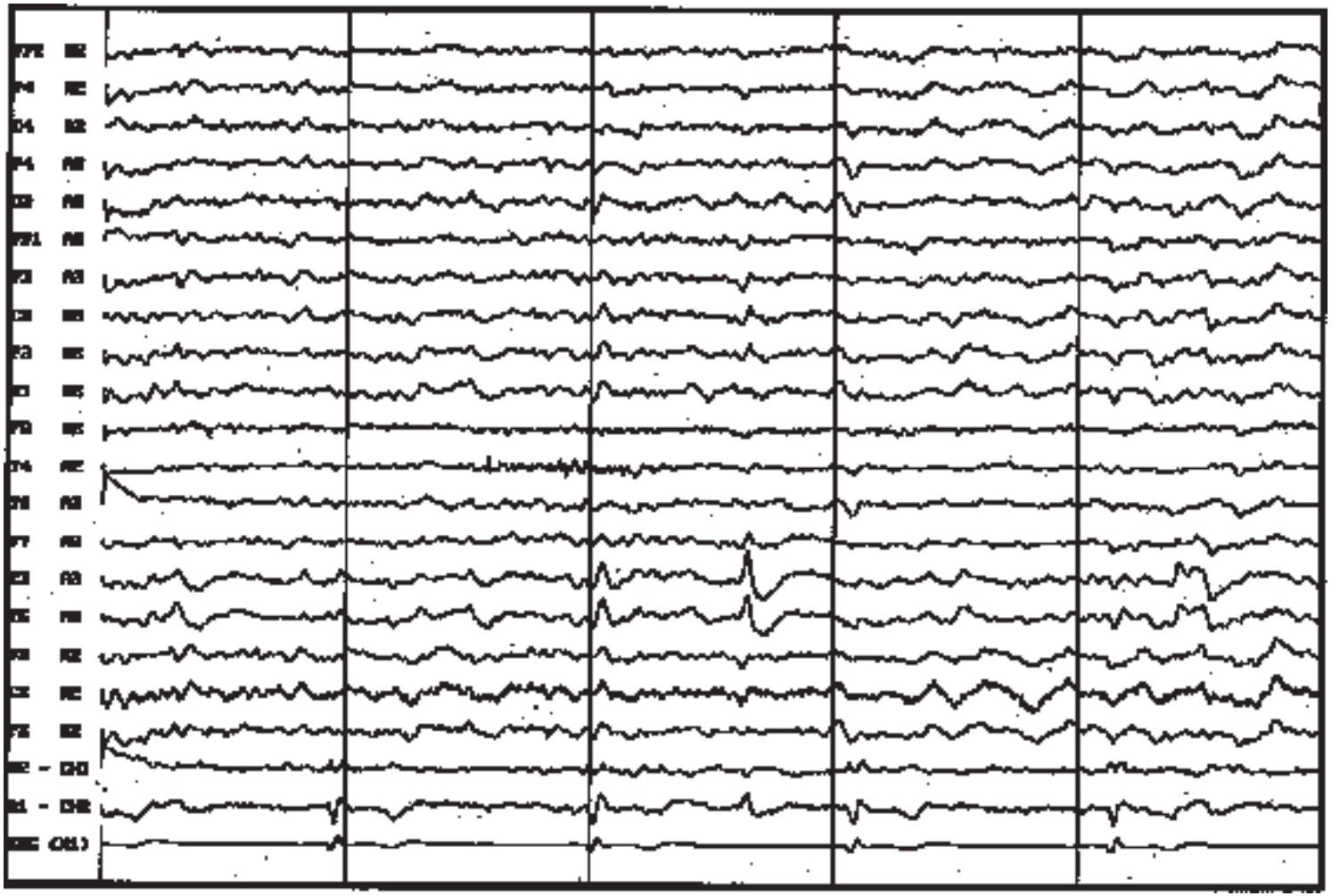


FIG. 4.10. *Continued.*

Because it involves discontinuous measurements from closely spaced electrodes, the source derivation only *approximates* the true mathematical laplacian display of the electrical field, which is a continuous mathematical function representing the second spatial derivative of the field. The output of any channel is proportional to the intensity of local current sources or sinks. Consequently, source derivation combines attributes of both bipolar and referential recording methods. Source derivation montages emphasize regions of local voltage peaks and deemphasize widely distributed activity, much as do bipolar derivations. Voltage peaks are localized to the channel of maximal deflection, and polarity is accurately indicated by direction of signal movement, as with common reference recording. True laplacian source derivations eliminate concern for an active reference. In practice, however, neighborhood average approximations

with large interelectrode distances (approximately 5 cm, as seen with 21 scalp channels) and without symmetry among nearest neighbors (as with edge electrodes such as Fp1/2, F7/8, and O1/2) cause spatial aliasing, the equivalent of an active reference (9,14,15,24,26). This may result in falsely localized voltage peaks, spurious phase reversals, and inaccurate inferences about field distribution. These limitations are lessened, although not eliminated, by the use of more electrodes to provide a denser array (e.g., 128 scalp electrodes).

Hjorth (14,15) addressed the interelectrode distance problem by including in the local average some additional electrodes lying on lines diagonal to the electrode of interest and weighting their contribution as a function of distance. For electrodes of a grid (e.g., Fp1/2, F7/8) with only three neighbors, adding inferior electrodes minimizes spatial aliasing in the laplacian estimate. The mathematical basis of the laplacian transform, as well as the derivation of the laplacian operator, is quite complex and beyond the scope of this discussion. Nunez (23) discussed this quantitatively. The practical use of laplacian derivations has been limited because of difficulty in applying them to conventional EEG hardware. However, with the computer-based EEG machines now widely available, coupled with denser electrode arrays, laplacian derivations are easier to apply.

Selection of Montages

The three types of montages just described can be viewed as three types of input to input 2: (a) Input 2 is the nearest neighboring electrode and changes from channel to channel (bipolar derivation); (b) input 2 is a distant electrode common to all channels (common reference); or (c) input 2 is computed (A1 plus A2 average, common average, and laplacian reference). The "averaged ears" reference and common average reference remain the same in all channels; the laplacian reference differs from channel to channel. Each type of montage has advantages and disadvantages. Optimal EEG recording combines referential and bipolar methods. Comprehensive and accurate assessment of potential fields requires combining all methods intelligently (16,19,22).

Table 4.1 lists eight logical arrangements for referential and bipolar montages. The American Electroencephalographic Society recommended that each laboratory routinely use one of several alternatives from each major group: longitudinal referential, longitudinal bipolar, and transverse bipolar montages. This recommendation does not, of course, preclude using other montages required by individual laboratories, for special purposes, or in particular recording circumstances, but it does establish standards (1). For the standard longitudinal referential montage, the American Encephalographic Society Guidelines proposed choosing among unpaired, paired-group, and paired-channel options. For the longitudinal bipolar montage, the Guidelines recommended using either unpaired or paired-group arrangements as the interlaboratory standard. A paired-channel longitudinal bipolar montage was not recommended, because phase reversals localizing a voltage maximum occur in alternate, not adjacent, channels. The Guidelines recommended only bipolar options for the transverse montage. This reflects difficulty in choosing a suitable, unbiased reference for transverse arrays. Source derivations, with their inherent advantage of less biased reference, may well increase in popularity with the availability of digital EEG and an increased number of scalp channels.

TABLE 4.1. *Montage arrangements*

Montage arrangement	Longitudinal	Transverse
Unpaired	Referential and bipolar	Bipolar and referential
Paired-group	Referential and bipolar	
Paired-channel	Referential and bipolar	

INVERSE OR "BACKWARD" ELECTROENCEPHALOGRAPHIC PROJECTION

Two questions frequently arise:

1. What are the shape and location of the potential field on the surface (which is curved and two-dimensional) of the cerebral cortex?
2. What are the shape and location of the cerebral generator within the three-dimensional volume of the cerebral cortex?

These questions form the so-called inverse, or "backward," EEG projection problem.

The first question has a unique answer if information about electrical properties of tissues intervening between scalp and cortex is sufficient. Spatial deconvolution (24) is the general method of predicting cortical electrical fields (which can later be validated by corticography) from scalp-recorded EEG. However, these predicted cortical fields are simpler than those actually recorded from the brain's surface, because many low-voltage and fast-frequency components of the corticogram attenuate so markedly that they do not appear at the scalp and therefore cannot be reconstructed.

5. Merging the MRI data set with the plot of the electrode positions by using the three common fiduciary points as locking markers (this can be done with a suitable graphical software program).

This results in a coregistered plot of the patient's head and applied electrode positions, which can be rotated and sized at will in order to clarify the relationship of each scalp electrode to underlying brain anatomy. By further graphical manipulation (a process called *segmentation*), software can remove unwanted layers of tissue, revealing the structures beneath (virtual reality craniotomy). For example, selective removal of scalp, skull, and meningeal tissues can create a window to reveal the underlying cortical anatomy and gyral markings (10).

Figure 4.11 shows an epileptogenic focus, displayed as an EEG tracing, a scalp topographic map of the negative spike peak, and superimposed brain anatomy. Although the raw and deblurred maps represent the same negative spike peak, their topographies are different: the cortical peak location is displaced more laterally than might be suggested in the scalp map.

Measurements of individual electrode positions can be made simply by using three-dimensional electromagnetic devices that are based on magnetic coils and sensors, if the instrument is kept away from large ferrous metal structures, which tend to distort magnetic measurements. An alternative with electrode caps is to use caliper measurements to estimate the locations of each of the electrodes in relation to the fiduciary points.

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Chapter 5

Orderly Approach to Visual Analysis: Elements of the Normal EEG and Their Characteristics in Children and Adults

Peter Kellaway

Introduction to the Visual Analysis of the Electroencephalogram
Features of the Normal Electroencephalogram
- Reactivity
- Alpha Rhythm
- Mu Rhythm
- Beta Activity
- Theta Activity
- Posterior Slow Waves
- Anterior Slow Activity in Children
- Lambda Waves
- Temporal Slow Activity: A Normal Finding in the Elderly?
- Hyperventilation Response
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The Clinical Report
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Acknowledgment
References

INTRODUCTION TO THE VISUAL ANALYSIS OF THE ELECTROENCEPHALOGRAM

Analysis of the electroencephalogram (EEG) is a rational and systematic process requiring a series of orderly steps characterizing the recorded electrical activity in terms of specific descriptors and measurements. The elements of this analysis are listed in Table 5.1. For example, in the hypothetical case of an 8-year-old child, some 2-Hz waves are identified in the awake EEG. This activity must then be characterized according to their location, voltage, waveform, manner of occurrence (random or rhythmic, intermittent or continuous), frequency, amplitude modulation (smooth, variable, unchanging, paroxysmal), synchrony and symmetry in homologous derivations on the two sides, and reactivity (e.g., to eye opening). A sustained occipital alpha rhythm of 8.5 Hz is present. The maximum voltage of the 2-Hz waves varies from 40 to 70 μV, approximating the voltage of the occipital alpha rhythm. The slow waves occur randomly and block with the alpha waves when the eyes are open; they tend to occur synchronously and fairly symmetrically on the two sides.

Taken as a whole, these descriptors fit those of a normal EEG slow pattern that occurs commonly in this age group: namely, "posterior slow waves of youth" (2,165). A variance in any of these descriptors might entirely change the significance of the 2-Hz waves; a different locus, a much higher voltage, a more complex waveform, a failure to block with eye opening, or any combination of these may render the findings abnormal. For instance, 2-Hz, 40- to 76- μV random waves in the frontal, rather than occipital, derivations in an awake 8-year-old child is an abnormal finding, the significance of which may be entirely different if the slow waves are rhythmic rather than random, if the waveform are complex, and if the voltage regulation are paroxysmal rather than variable within a narrow range.

TABLE 5.1. *Essential characteristics of electroencephalographic analysis*

1. Frequency or wavelength
2. Voltage
3. Waveform
4. Regulation
   a. Frequency
   b. Voltage
5. Manner of occurrence (random, serial, continuous)
6. Locus
7. Reactivity (eye opening, mental calculation, acapnia, sensory stimulation, movement, affective state)
8. Interhemispheric coherence (homologous areas)
   a. Symmetry
      i. Voltage
      ii. Frequency
   b. Synchrony
      i. Wave
      ii. Burst

The only clinical information required before the EEG analysis is begun is the patient's *age and state.* The age is listed on the patient's data sheet, which should be part of the EEG record.[1] The younger the patient, the more critical it is that age information be precise. In the newborn, age should be specified in days since delivery (chronological age); in infants aged 1 to 3 months, it should be specified in weeks; and in those aged 3 to 36 months, it should be specified in months. This progressively decreasing degree of precision reflects the fact that the landmarks of ontogenetic development of the EEG in the newborn are clearly differentiated in weekly or biweekly epochs but become progressively less sharply delineated with increasing age; for example, there are clearly defined differences between the EEG of a premature infant with a conceptional age of 35 weeks and that of an infant with a conceptional age of 36 weeks, but there are no important or sharply delineated differences between the EEG of a 3-year-old child and that of a 4-year-old child.

The "state" of the patient refers to the clinical assessment of the patient's general state of consciousness; this should be specified in such terms as "alert," "lethargic," "stuporous," and "semicomatose" on the clinical data sheet that accompanies the record. The patient's state also refers to the physiological variations of alertness and levels of sleep that occur during the recording, which are noted by the technologist.

Although these two items of information (the patient's age and state of consciousness) are essential for an accurate interpretation of the EEG, it is a good teaching exercise and a test of analytic acumen to read a record occasionally when only one or neither of these two items is known. Attempting to determine the patient's age or, more easily, physiological state according to the characteristics of the EEG activity sharpens analytic technique and subjective criteria.

That *age* is an important determinant of the characteristics of the EEG has been known since Hans Berger's early studies in 1932. The electrical activity of the brain—awake, asleep, and in response to stimuli—varies considerably with age; a particular activity or pattern that is normal at one age may be quite abnormal at another.

In the premature infant, the age factor is critical. In reading the records of such infants, the initial step is to determine whether the conceptional age

[1]Both age and birth date should be recorded.

(gestational age plus time since delivery) can be determined from the characteristics of the EEG. Absence or distortion of features that normally make this possible is evidence of abnormality, as are differences between the maturational characteristics of the various stages of the awake/sleep cycle in the same infant (dyschronism). At the other end of the age spectrum, EEG features such as focal, episodic, temporal theta activity may be within the normal range for an elderly person but are outside the normal range for a young adult.

The *state of alertness* or of altered levels of consciousness (physiological and pathological) is also a critical factor in EEG interpretation. The obvious situations are the well-known alpha-type record and the spindle sleep-like patterns that may be seen in comatose patients, which, in spite of their "normal" appearance, have precise pathological significance in the altered states of consciousness in which they may be found. Less well recognized are the dramatic EEG changes sometimes seen in young children in association with changes in affective state and with subtle physiological alterations of cerebral state that are antecedent to the onset of clinically evident sleep.

FEATURES OF THE NORMAL ELECTROENCEPHALOGRAM

Reactivity

Before the various features of the normal EEG of adults and children are described and discussed, it is important to recognize that the identification of a particular activity or phenomenon may depend on its "reactivity" (see Table 5.1). An important element of the recording and its analysis is the testing of the reactions, or responses, of the various components of the EEG to certain physiological changes or provocations. These include eye opening and closing, repetitive movements of the extremities, visual scanning, sensory stimulation, and hypocapnia produced by hyperventilation.

Specification of the reactivity of a given activity, rhythm, or pattern is essential for the identification and subsequent analysis of the activity and may clearly differentiate it from another activity with similar characteristics. For example, occipital slow waves intermixed with the alpha rhythm, which block with the alpha rhythm when the eyes are opened, may be a normal finding in a child, but similar slow waves that do not block may be pathological. Similarly, a series of rhythmic, high-voltage, monomorphic 3- to 4-Hz waves in the frontal leads occurring in association with arousal in a young child may be normal, but a similar burst occurring spontaneously and not associated with arousal may be abnormal.

Alpha Rhythm

The occipital alpha rhythm should be the starting point for visual analysis. The initial questions should be the following: Is an occipital alpha rhythm present, and are its characteristics appropriate for age? If there is little or no occipital alpha rhythm, is it because the patient's eyes are open (reactivity) or because the patient is drowsy or asleep (state)? Is it an idiosyncrasy of a normal adult (genetic)? Or is it an abnormal finding?

Some persons (adults; rarely children) who are apparently normal show no alpha activity, at least under the conditions of a routine clinical recording. Other persons, also apparently normal, may show brief episodes of occipital alpha activity only during hyperventilation or, transiently, on arousal from sleep.

In addition to providing clues concerning the patient's affective state (e.g., anxiety) or level of arousal, the presence and character of the occipital alpha rhythm are critical determinants in evaluating the significance of other activities present. Thus, the presence of some low-voltage, 5- to 6-Hz rhythmic frontocentral activity in an adult may, in the transient absence of an occipital alpha rhythm, merely signify the patient's drowsiness; in the total absence of an occipital alpha rhythm, however, such activity may have pathological significance. Similarly, the presence of the frontocentral theta activity would be more ominous if the occipital alpha rhythm itself were slow (e.g., 7 Hz). It is important to remember that the occipital alpha rhythm may be preserved in conditions that produce marked slowing of the activity in anterior derivations. Thus, a slow occipital alpha rhythm usually denotes a more serious change than if its frequency were maintained.[2] Conversely, preservation of the occipital alpha rhythm despite marked slowing elsewhere is a favorable finding.

Normal Characteristics

The normal range for the frequency of the occipital alpha rhythm in adults is usually given as 8 to 13 Hz. The distribution curve for the mean alpha rhythm frequency in a series of 200 selected men (141) is shown in Fig. 5.1. Note that the incidence of an occipital alpha rhythm as slow as 8 Hz is less than 1%. Although population studies indicate that an 8-Hz alpha rhythm may be found in normal asymptomatic young adults, in clinical practice this should always raise the suspicion that the alpha rhythm has slowed, which, statisti-

[2]There are exceptions: A notable example is the slowing of the occipital alpha rhythm that may be an early sign of intoxication with phenytoin.

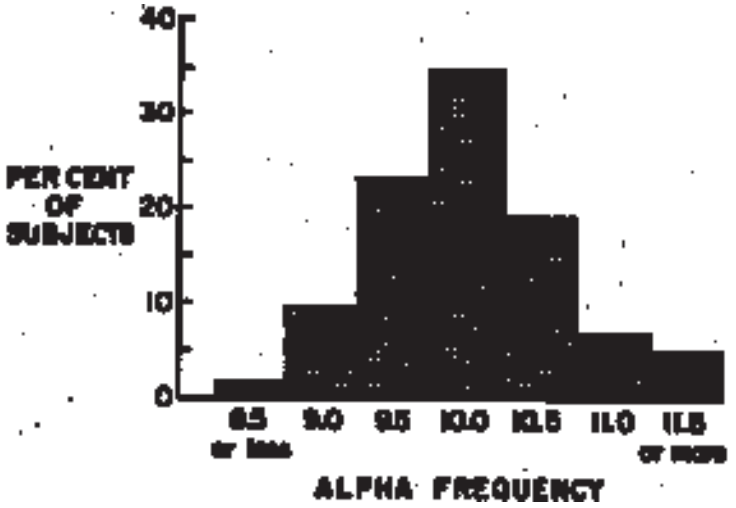


FIG. 5.1. Distribution of the mean alpha frequency in a series of 200 volunteer flight personnel, aged 24 to 35 years, on active duty in the United States Air Force (144 pilots and 56 navigators).

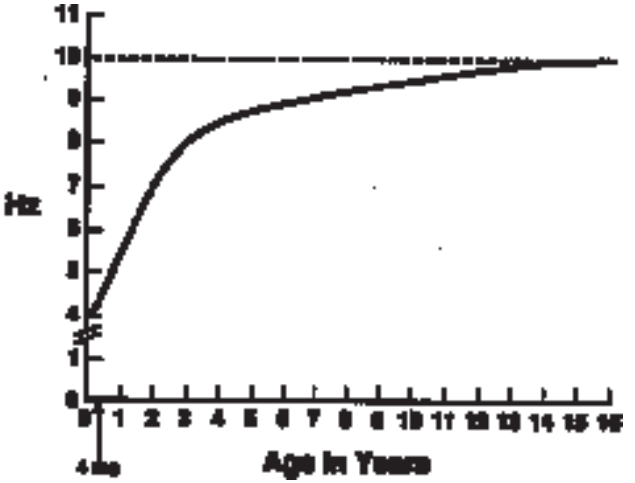


FIG. 5.2. Curve showing the development of the occipital alpha rhythm between the ages of 4 months and 16 years. Some rhythmic 3- to 4-Hz activity is present in the electroencephalograms of awake infants aged 2 to 4 months, but it is not reactive to eye opening. From the time rhythmic activity that is reactive to eye opening first appears, the frequency increases rapidly, reaching 5 to 6 Hz by 12 months and 8 Hz by 36 months. At that age, there is a sharp inflection in the rate curve, and the frequency increases only 2 Hz over the next 6 years. (From Kellaway P, Noebels JL, eds. *Problems and concepts in developmental neurophysiology.* Baltimore: The Johns Hopkins University Press, 1989.)

cally, is more likely. The maturational curve for occipital alpha rhythm frequency (Fig. 5.2) shows that the lower limit of the adult range is usually reached by the age of 3 years. The curve has an overall parabolic course, with the rate of change diminishing after late adolescence. In late life, the frequency of the occipital alpha rhythm tends to decrease, and this change appears to be related to changes in cerebral metabolic rate (57,84,154–157,182).

It has been shown that the frequency of the occipital alpha rhythm is closely related to cerebral blood flow; it has also been shown that if cerebral perfusion falls below a certain critical level, the occipital alpha rhythm slows. This relationship of alpha rhythm frequency to the adequacy of cerebral perfusion has been demonstrated repeatedly in patients with cardiac failure: Pacemaker or cardiac implants may result in an increase of as much as 2 Hz in alpha rhythm frequency (188).

When certain drugs (particularly phenytoin) approach toxic levels, the alpha rhythm slows without other changes in the EEG (175a). Consequently, if alpha rhythm frequencies are at the low end of the normal spectrum for age in patients who are taking such drugs, the possibility of toxic effects should be considered. Carbamazepine, at therapeutic levels, may slow the alpha rhythm in children (59).

Frequency in Children

The relationship of the occipital alpha rhythm frequency to age in normal control subjects is shown in Fig. 5.2. Occipital rhythmic activity that is responsive to eye opening appears in approximately 75% of normal infants between the third and fourth months after (full-term) birth. Initially, this activity is not well sustained and has a frequency of approximately 3.5 to 4.5 Hz. The frequency increases rapidly, reaching 5 to 6 Hz in approximately 70% of children by 12 months of age. At age 36 months, 82% of normal children born at full term show a mean occipital alpha rhythm frequency of 8 Hz (range, 7.5 to 9.5 Hz). By the age of 9 years, the mean alpha rhythm frequency is 9 Hz in 65% of controls; in the same percentage of persons, the mean is 10 Hz by the age of 15 (48,165).

In infants and young children, the occipital alpha rhythm may totally block with the eyes open, and slower activity may be mistaken for the occipital alpha rhythm. For this reason, a portion of the awake EEG

should be recorded during passive eye closure. Infants and very young children usually do not close their eyes until they become drowsy and are ready to fall asleep; at that time, the occipital rhythm may slow before disappearing.

Frequency in the Elderly

For many years, it was commonly thought that the frequency of the dominant posterior rhythm decreased, with normal aging, to the lower end of the alpha activity range or even below it. Extrapolation from the parabolic curve describing the age–alpha frequency relation indicates that a decline in frequency might be expected at about age 58 years (48,165). The weight of the evidence derived from studies of healthy elderly persons indicates that although there may be a decrease in alpha frequency in some normal persons in later life, the mean frequency is maintained at or above 9 Hz (57,84,100,154–157,168,182,191). In another study of selected healthy subjects with a mean age of 68 years, the mean alpha frequency was 9.7 Hz, and only two subjects had an alpha rhythm as slow as 8 Hz (3).

Voltage

Absence of an alpha rhythm (or even a very-low-voltage alpha rhythm) is not encountered when recordings are made directly from appropriate regions of the brain in unanesthetized persons. Indeed, a number of alpha rhythm generators exist in the cortex and the depths of the brain, and they produce remarkably high voltage rhythms (181). On the other hand, the voltage of the alpha rhythm as recorded at the scalp in apparently healthy persons (73) may barely exceed the noise level of the amplifiers.

Normative studies have shown that 6% to 7% of healthy adults have alpha rhythm voltages of less than 15 μV at the scalp (141). It must be kept in mind, however, in considering the voltage characteristics of a given activity, that interelectrode distance is a factor that influences the actual voltage measured, depending on the size of the potential field and the position of the electrodes in relation to that field (Fig. 5.3). In discussing voltage, the electrode placements used in measuring the voltage should be specified. In one series in which the P4-O2 derivation was used, 75% of normal adults were found to have alpha rhythm voltages of 15 to 45 μV (141). The relationship between interelectrode distance and the amplitude of activity recorded in the

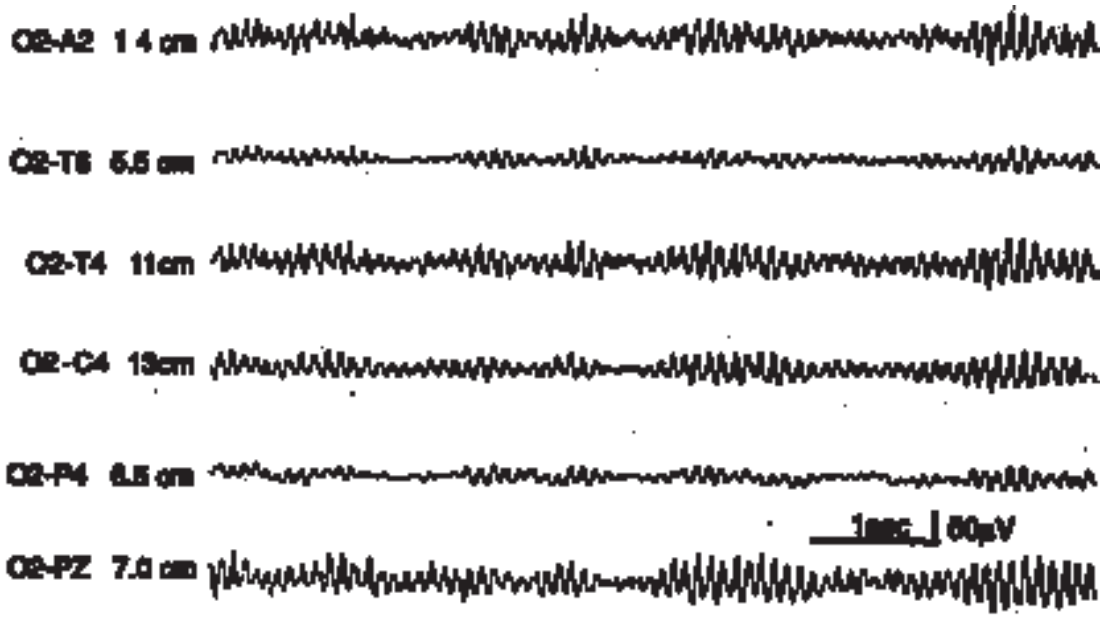


FIG. 5.3. Effect of interelectrode distance on recorded amplitude of alpha rhythm. Note that this is not the only factor determining amplitude; the geometry of the potential field is also a factor. For example, although the interelectrode distance between O2 and PZ is half that between O2 and A2, the recorded amplitude is actually somewhat greater.

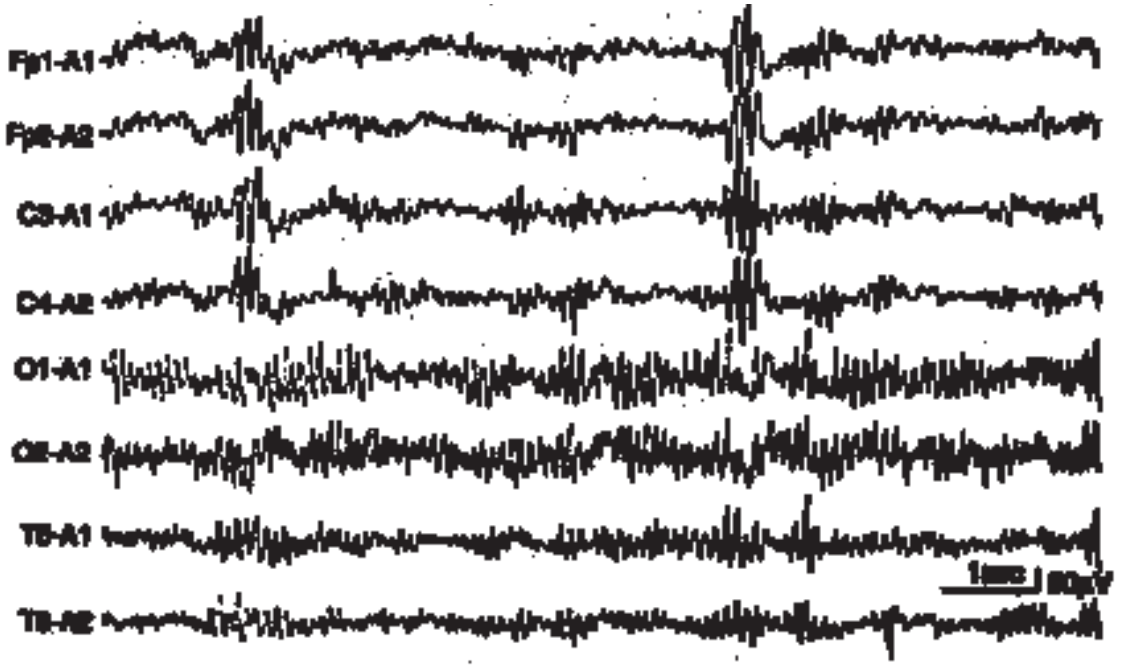


FIG. 5.4. Paroxysmal generalized 8-Hz rhythmic activity in a 21-year-old man with an initial buildup of rhythmic, frontal-dominant but generalized high-voltage 8- to 10-Hz activity.

scalp EEG can be accurately characterized by an exponential function (52); the increase in potential difference is proportional to the square of the distance up to about 10 cm.

Children rarely show low-voltage (less than 30 μV) alpha rhythms. In their control group, Petersén and Eeg-Olofsson (165), using the T5-O1 derivation, found no children with voltages less than 20 μV; only 1.3% of the children had voltages of 20 to 30 μV, and all of those were older than 12 years.

In this same series, the average alpha rhythm voltage in children aged 3 to 15 years was 50 to 60 μV. Approximately 9% of the children of this age group (predominantly those aged 6 to 9 years) showed alpha rhythm voltages of 100 μV or more. High voltage should never, in itself, be considered an abnormal finding; however, paroxysmal bursts of 9- to 12-Hz activity having a wider area distribution than the occipital alpha rhythm (Fig. 5.4) are abnormal (63). This pattern, associated with epilepsy, can be clearly differentiated from a normal alpha rhythm on the basis of its distribution, paroxysmal features, and lack of reactivity to eye opening.

The voltage of the occipital alpha rhythm diminishes with increasing age; this probably, in large part, reflects (a) changes in the density of the bone and (b) increased electrical impedance of the intervening tissue, rather than a decrease in the voltage of the electrical activity of the brain. This impression is based on the observation that during electrocorticography, the voltage is not appreciably reduced in older patients who showed low-voltage alpha rhythms at the scalp. The relation between EEG voltage and the impedance of the intervening tissues is discussed in more detail in the later section on bilateral voltage symmetry.

Regulation

Good regulation of frequency[3] and voltage[4] of the occipital alpha rhythm is characteristic of the EEGs of approximately 80% of young adults (48,165). With increasing age, there is a tendency for alpha activity to become less well regulated.

[3]"Good regulation" of frequency is defined as follows: a sustained rhythm in which the mean frequency does not vary more than ±0.5 Hz (as measured during any 2-second epoch in which the activity is sustained).

[4]Regulation in terms of voltage refers to the smoothness of the envelope of the waxing and waning of voltage that the alpha rhythm typically shows.

As mentioned earlier, the peak frequency of the occipital alpha rhythm is remarkably constant and, in healthy persons, shows virtually no variation throughout the day or over long periods (37,51,177,193). Precise computer analytic techniques have demonstrated that the peak alpha rhythm frequency may increase in women during the initial phase of the menstrual cycle, but the change is so small (0.3 Hz) that it escapes notice in routine visual analysis (37,51,177,193). The *stability* of frequency regulation of the alpha rhythm does fluctuate somewhat throughout the day and in relation to certain physiological changes (e.g., the menstrual cycle). Regulation is also affected in some persons by mental activity and anxiety. Thus the general comments concerning "regulation" of the alpha rhythm refer to conditions of recording that approach the optimal conditions for "good" regulation: a quiet, nonstressful environment; eyes closed; the subject at rest but still alert.

Both voltage regulation and frequency regulation of the occipital alpha rhythm are "good" from the ages of approximately 6 months through 3 years. During this period, the occipital activity may be almost monorhythmic, and the voltage variation on the EEG is usually smoothly contoured (Fig. 5.5). From the ages of 3 to 14 years, poor regulation (particularly of voltage) is common in normal subjects, and the regulation in approximately 33% of children in this age group is poorer on the low-voltage side (48,165).

Distribution

The occipital region is the site of maximal alpha rhythm voltage in 65% of adults and 95% of children. However, in some normal persons, the amplitude of the alpha activity in the central and temporal regions is equal to or greater than that in the occipital derivations. In about 32% of normal young adults, the alpha activity is widely distributed; it may be predominantly central or temporal, or it may be essentially equal in both areas (141). Studies with implanted electrodes have shown that multiple alpha generators exist in the human brain, not only in the occipital region but also in central and temporal regions (163). These generators overlap and influence each other; therefore, what is recorded at the scalp at any locus reflects an "averaged" field pattern.

Bilateral Symmetry

Asymmetry of the occipital alpha rhythm voltage on the two sides occurs in 60% of adults; in 50%, the right side shows the higher voltage (without

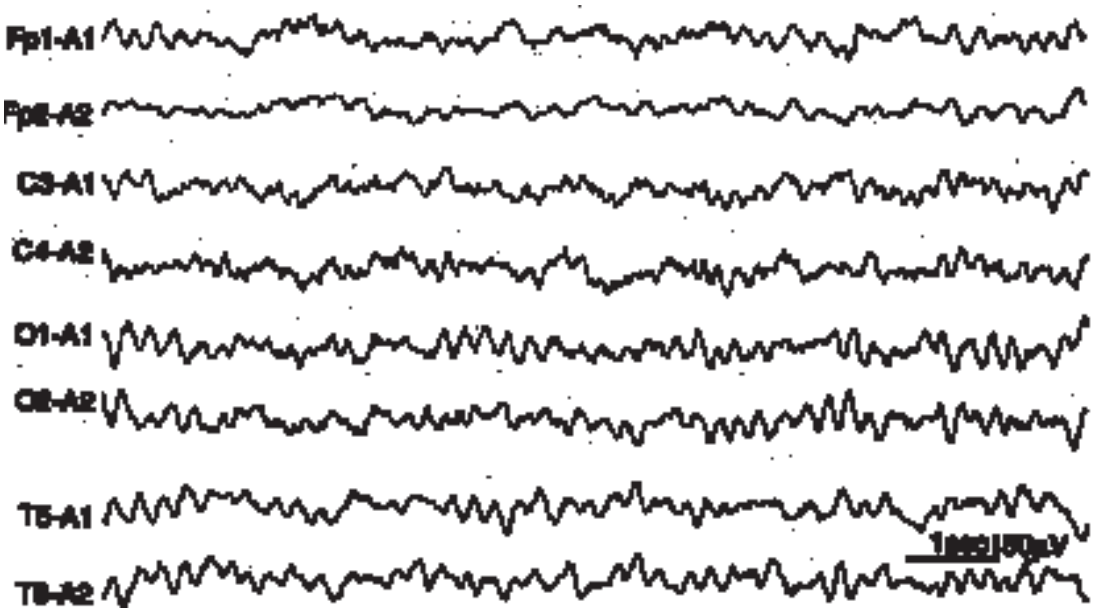


FIG. 5.5. Normal electroencephalogram of an awake, asymptomatic 9-month-old infant, eyes closed. The almost monorhythmic occipital activity with little or smoothly contoured amplitude modulation is typical of the 4- to 24-month age group.

consistent correlation with handedness). The asymmetry between sides is generally less than 20% [5]; only 17% of normal adults show differences greater than this. In only 1.5% is the asymmetry more than 50% (141).

In practice, an asymmetry of 50% or more should be regarded as clinically significant until proved otherwise. An additional consideration is the side of the low voltage. Because there is a statistical probability that the alpha rhythm has a higher voltage on the right side in a given individual, asymmetries of 35% to 50% should be considered suspect if the right side has the low voltage.

In 95% of normal children, the alpha rhythm voltage has an asymmetry between sides of up to 20%. In 98% of these children, the lower voltage is on the left side, and there is no relationship to handedness. In the 5% of children with asymmetries of more than 20%, none showed a difference of more than 50%. The same rule mentioned above for adults should be used in the assessment of asymmetries in children when the low voltage appears on the right side, because the likelihood that the right side should be the high-voltage side is 98:2 (48,165).

A difference in skull thickness on the two sides may be a major factor in determining the presence of voltage asymmetry. Through the use of an ultrasonic-pulse technique, it was shown that a difference in skull thickness of more than 33% in homologous regions of the two sides may be present in normal persons; the left is more commonly the thicker side (approximately 72% of cases). Differences in skull thickness of this degree can account for voltage asymmetries of 20% to 70% (129). Thus, a difference in bone thickness on the two sides not only may account for asymmetries seen in normal subjects but also may mask or simulate abnormality. In the absence of actual measurements of bone thickness, asymmetries of less than 50% probably are diagnostically insignificant. The clinician should be especially attentive to the presence of subgaleal swelling caused by hematoma and for leakage during an infusion into a scalp vein, because these also greatly reduce the apparent voltage of the EEG activity recorded by overlying electrodes.

Asymmetry of the mu rhythm (a central rhythm of alpha activity frequency, discussed in detail later in this chapter) and of temporal alpha activity is the rule rather than the exception, and predominance of the activity on one side is not uncommon in asymptomatic persons. For these reasons, asymmetry of the mu and temporal alpha activity should be interpreted with caution, especially in children. In prolonged (36-hour) and serial studies in children, the mu rhythm sometimes showed higher voltage on one side (even to the point that it appears unilateral) for prolonged periods and then showed predominance on the opposite side (34,67). Such findings may well be significant in terms of subtle brain functions, but the clinical electroencephalographer should not conjecture about the presence of focal cortical lesions. Admittedly, there appear to be cases, such as those that Gastaut et al. (67) originally described, in which the mu rhythm appears to be enhanced at or near the site of a craniocerebral injury, but the greatest percentage of unilaterally predominant mu rhythms are not associated with evident cortical lesions. It must also be remembered that high voltage of the mu rhythm on one side may result from an underlying or subjacent skull defect (e.g., burr hole) that provides a low-resistance pathway for activity in the cortex underlying the region of absence of bone. Mu rhythms are often enhanced during and after hyperventilation, and this may further mislead the inexperienced electroencephalographer to an assumption of abnormality.

Temporal alpha activity in young adults is usually fairly symmetrical on the two sides. However, elderly persons, in whom the voltage of this temporal activity may be greater than that of the occipital alpha rhythm, may show alternating voltage lateralization; in 80%, the left side shows higher voltage. (This is discussed further later in this chapter in relation to temporal slow activity in the elderly.)

Reactivity

The reactivity (i.e., blocking) of the alpha rhythm to conditions other than eye opening is variable. Hans Berger found early on that an individual's alpha rhythm diminished in amplitude or "blocked" during periods of concentrated mental effort, such as making calculations. However, in 24% of the normal young adults studied by Maulsby et al. (141), no alpha blocking was detected in a controlled test situation. Failure of the alpha activity on one side to attenuate during concentrated mental effort is evidence of cerebral dysfunction or lesion of the nonreactive side (212). In some apparently healthy persons, the alpha rhythm seems to be blocked almost continuously, appearing only very briefly (1 second or less) in certain situations (e.g., upon arousal or starting hyperventilation). It has been suggested, although not proved, that in some subjects the alpha rhythm may be "blocked" or diminished in amplitude by "anxiety."

Alpha Variants

A characteristic of the occipital alpha rhythm is that it may show what seem to be abrupt phase reversals, so that the resultant wave or waves have

[5]The asymmetry is the difference between the two sides, expressed as the percentage of the high-voltage side.

a frequency of half that of the ongoing alpha activity and in some instances have a greater amplitude. This phenomenon was first described by Goodwin in 1947 (76). He also described a "bifurcation" in the individual alpha waves, so that a superimposed harmonic rhythm of twice the basic frequency was produced. He noted that both the subharmonic and harmonic patterns blocked with eye opening, along with the alpha rhythm. He referred to the two patterns, respectively, as "slow" and "fast" alpha variants. In different people, these two patterns vary in their degree of expression, from a random, sporadic occurrence to a predominant feature of the occipital activity. All degrees occur in apparently normal persons. The current concept of alpha variants is that they are a "physiological variation of the basic cortical rhythm" and that they "have no correlation with any clinical entity or with increased convulsive susceptibility" (2).

An early report indicated that the slow alpha variant pattern is much more common in persons with "symptoms usually associated with emotional instability" (2) or with "psychoneurosis" (76) than in normal persons. However, more rigorous investigation is needed before this can be established as fact, and even if such a correlation were established, its meaning would have to be determined before the findings had any clinical utility.

Several other rare occipital slow patterns of unknown significance have been seen in adults referred for EEG studies. One of these patterns may be related to the slow alpha variant, because it seems to evolve from it. The typical slow alpha variant configuration progressively changes to a simple monomorphic wave with a frequency of half that of the alpha rhythm. The new rhythm may persist for several seconds and then be replaced by a return of the alpha rhythm. This sequence of events may occur several times over a period of several minutes. Aird and Gastaut (2) found only one case that approached this type of pattern in their study of 500 "normal" young adults aged 19 to 22 years, and Maulsby et al. (141) found three cases in their study of 200 highly selected male subjects aged 24 to 36 years.

Mu Rhythm

The mu rhythm,[6] a central rhythm of alpha activity frequency (usually 8 to 10 Hz) (Fig. 5.6) in which the individual waves have an arch-like shape, is present as a visually detectable rhythm in 17% to 19% of young adults (65,141,167). It is less common in the elderly and in children. A clearly defined mu rhythm occurs in only 5% of normal children younger than 4 years, and the incidence increases little up to the age of 8 years. Between 8 and 16 years, the incidence increases from about 7% to the adult figure of 18%. It is more common in girls than in boys throughout childhood and adolescence; the incidence is approximately twice as high in girls at age 14 (48,165).

The voltage characteristics of the mu rhythm resemble those of the occipital alpha rhythm. The mu rhythm does not block with eye opening but blocks unilaterally with movement of the opposite extremity. Its presence relates to the level of attention and is enhanced by immobility (28).

The mu rhythm is particularly labile (26–28): It is suppressed by fatigue, by somatosensory and sensorimotor stimulation (26,27,118), and, to some degree, by mental arithmetic (25,27) and problem solving (36). However, because it commonly occurs when an alpha rhythm is present in the central region, it may be difficult to differentiate by visual inspection (119).

The mu rhythm may be present one day and undetectable the next (personal observations from prolonged monitoring studies; see also Schoppenhorst et al. [179]). Its degree of expression may also vary from time to time during the same day (20). The true incidence of the mu rhythm in normal persons is obscured by all these factors, which would tend to produce significant sampling errors in any study group.

According to established facts and personal experience in recording electrocorticograms from the sensorimotor cortex of unanesthetized patients during surgery, the mu pattern is a *ubiquitous rhythm of the sensorimotor cortex at rest,* a concept first enunciated by Shoppenhorst et al. (179). However, it is the central beta rhythm recorded directly from the prerolandic region that shows a strong blocking response to movement of the extremities on the opposite side (95).

Routine clinical studies have shown that the mu rhythm may be quite asymmetrical and asynchronous on the two sides, even though the subject is motionless and at rest (119). It may be present on only one side in persons with no clinical or other laboratory evidence of organic brain disease. Very-high-voltage mu activity may be recorded in the central region over a bone defect (e.g., bur hole), and its sharp configuration, mixed with slower frequency activities that may be present, may mislead the clinician to a presumption of a potentially epileptogenic focal process (32,119).

In infants whose occipital alpha rhythm is still less than 6 Hz, a well-organized and fairly well-sustained 8- to 10-Hz activity may be present in the

[6]Synonymous with wicket, comb, and arcade rhythms and *rythme en arceaux,* these names were derived from the distinctive waveform of this activity. The Greek letter mu (μ) now designates this rhythm because the symbol resembles the waveform and conforms with the practice of using Greek letters to name specific EEG activities.

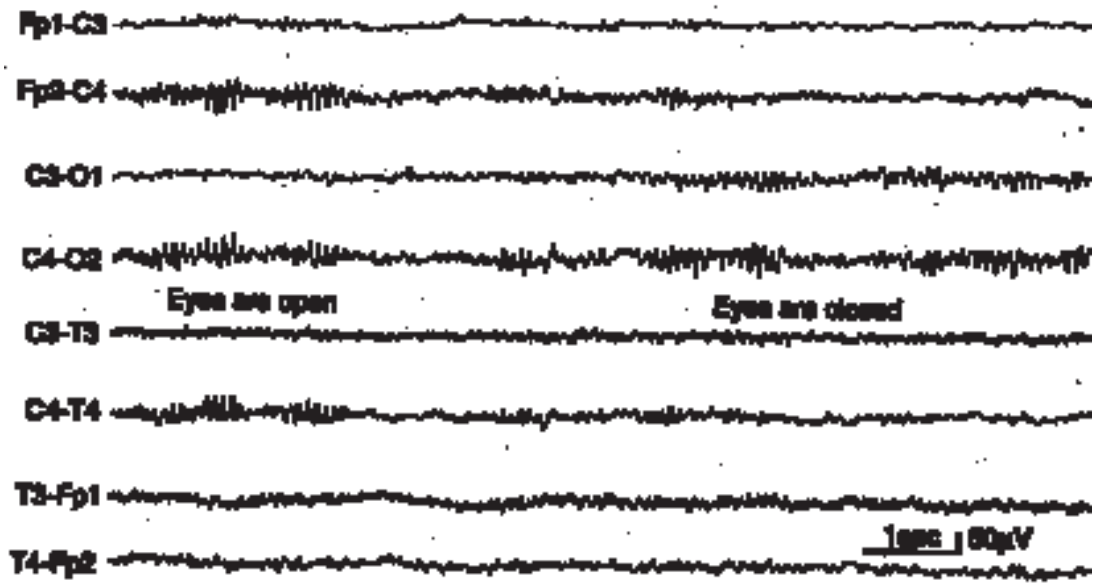


FIG. 5.6. Episode of mu rhythm occurring during a period when the eyes are open and the occipital alpha rhythm is blocked. Electroencephalogram of asymptomatic 25-year-old woman. Mu-rhythm asymmetries of this degree are not uncommon in normal subjects.

central regions bilaterally. It lacks the characteristic waveform of the mu rhythm but may be ontogenetically related to it. This activity was originally described by Pampiglione in 1977 (158):

> "In the rolandic area of each hemisphere and at the vertex some rhythmic activity kept on appearing in most infants, at somewhat irregular intervals, in the form of 8–10 per sec waves of the order of 20–40 microvolts, with variable lateralization, often occurring independently over the right or the left side. . . . This activity would often diminish or disappear altogether when the baby used his hands or played with toys, but it would increase when the baby was at rest with his arms and hands relaxed. . . . Distribution, frequency and behavior were similar to those of the mu rhythm in older children and adults."

Beta Activity

Activities with frequencies higher than 13 Hz are commonly present in the EEGs of normal adults and children. Three distinct frequency bands in the beta activity range may be distinguished: a common 18- to 25-Hz band, a less common 14- to 16-Hz band, and a rare 35- to 40-Hz band. High-voltage activity in the first two frequency bands is present at the cortex in unanesthetized humans, particularly in the prerolandic and postrolandic cortex. This fast activity is greatly attenuated in the scalp EEG. In 97% to 98% of normal awake adults and children, the voltage in the EEG is less than 20 μV; in 70%, it is 10 μV or less (recorded between closely spaced scalp electrodes) (48,141,165).

Beta activity with a voltage of 25 μV or more in the clinical EEG has been considered abnormal. Although such findings are statistically outside the range of normal variation, little is known about the significance of beta activity. The early literature documents a significantly higher percentage of "fast" EEGs in epileptic patients than in normal controls and implies that a fast EEG (a record with much beta activity with a voltage of 25 μV or more) may be considered supportive evidence for a diagnosis of epilepsy. However, "fast" EEGs also occur with a greater incidence than in normal controls in a number of other, nonepileptic conditions (89,201,204), and fast EEGs have no correlation with epilepsy in children (46,61,62,88,185).

The presence of beta activity at amplitudes of 25 μV or more is currently of little or no diagnostic utility (except when drug ingestion is suspected). Thus, if a patient with a differential diagnosis of syncope versus epilepsy is referred for EEG studies, the finding of excessive voltage and a prevalence

of beta activity in no way clarifies the diagnosis. Similarly, the impression that high-voltage beta activity may have some specific significance for the diagnosis of minimal brain dysfunction, dyslexia, behavior disorder, or hyperactivity (attention deficit hyperactivity disorder) has no established basis; the finding neither proves nor illuminates the diagnosis.

There is evidence that beta activity is a multifactorial genetic trait and that an age factor is responsible for its penetrance (203); however, the relationship to age is complicated. For example, whereas beta activity is a predominant feature of the EEG of premature and full-term infants, it is barely evident in the EEGs of young children. It may be increased in voltage and persistent in the precentral region in middle-aged and elderly women, but it tends to have a low voltage during old age, especially in men (57,84,154–157,182).

In evaluating beta activity, it should be kept in mind that many commonly used drugs (e.g., barbiturates, benzodiazepines, chloral hydrate) increase the amplitude, and thus apparently the amount, of beta activity (58). Because the incidence of beta rhythms with amplitudes much above 20 μV is statistically low in normal persons, the presence of such activity suggests the possibility of drug ingestion. Although the 18- to 25-Hz band is the one most generally affected, some drugs also increase the 14- to 16-Hz activity.

In the presence of skull defects, beta activity in the area of the defect or adjacent to it may be enhanced as a consequence of the low-impedance pathway. Defects of dura, bone, and scalp enhance beta activity more than other, lower frequency activity (99), which has led to erroneous identification of so-called foci of fast activity in patients with surgical or traumatic skull defects.

Beta activity of 18 to 25 Hz usually increases in amplitude during drowsiness, light sleep, and rapid-eye-movement (REM) sleep, and it usually decreases during deep sleep. When a barbiturate or other beta-enhancing drug is administered to promote sleep during the EEG examination, the resultant fast activity increases with the onset of light sleep, decreases markedly during deep sleep, and then remains prominent after the patient is aroused. This effect of sedation is particularly pronounced in children.

Beta activity should have the same frequency on both sides. However, even in normal persons, there may be a voltage asymmetry, with the activity being as much as 35% lower on one side. Such asymmetries may result from differences in skull thickness, as described earlier for the alpha rhythm. On the other hand, a consistently low voltage on one side (greater than 35%), whether focal, regional, or hemispheric, is often a useful diagnostic feature; it indicates cortical injury (e.g., acute contusion, acute ischemia, or the presence of a subdural or epidural fluid collection). Focal, regional, or hemispheric depression of beta activity may also occur transiently after a focal epileptic seizure. Beta activity is generally the first to show diminished voltage in the presence of a cortical injury or subdural or epidural fluid collection; therefore, its presence on the low-voltage side can be helpful in assessing the significance of a voltage asymmetry of other background activity in the same region (if the asymmetry is borderline in degree). In this regard, it must be remembered that beta activity amplitude is particularly susceptible to the presence of subgaleal fluid, and special care should be taken by the technologist to note the presence of scalp swelling: its location, extent, and degree.

Beta activity, especially when frontocentral in origin, is predominantly out of phase in the two hemispheres; consequently, its amplitude is greater in the paired interhemispheric frontal derivation than in either frontal electrode paired with an "indifferent" electrode or with another adjacent scalp electrode (Fig. 5.7).

Beta activity in the 14- to 16-Hz band is usually most marked in the frontocentral region but may show maximum voltage elsewhere, even in the occipital region. The location of the maximum potential field does not appear to have particular physiological or pathophysiological significance. Beta activity in this band, when present, is usually enhanced by hyperventilation and indeed may become clearly evident only during this activity. It may be present during sleep but should be distinguished from sigma activity, which, by definition, occurs only in bursts.

Activity in the 35- to 40-Hz band is rarely seen in clinical EEGs. Only one report has described activity of this frequency; it was seen only in adults and was reported to be associated with "organic psychosis" or "dull psychopathy" (70). Such activity has not been reported in any series of normal adults or children, and the frequency response of some EEG amplifiers precludes the possibility of recording activity of this frequency even if present.

Although frequencies above 25 Hz are rarely seen in scalp recordings, depth electrode studies in humans have revealed cortical activities with frequencies up to 50 Hz and voltages of 15 to 70 μV (163).

The 18- to 25-Hz activity in the EEG during wakefulness is usually enhanced during stages 1 and 2 sleep, and tends to decrease during the deeper sleep stages.[7] In infants older than 6 months, the onset of sleep is

[7]REM sleep is rarely documented in routine clinical EEG recordings of adults and children because time and other factors often do not allow this stage to be reached. However, when REM sleep is recorded, beta activity equal to or greater than that seen in the record during wakefulness is usually present.

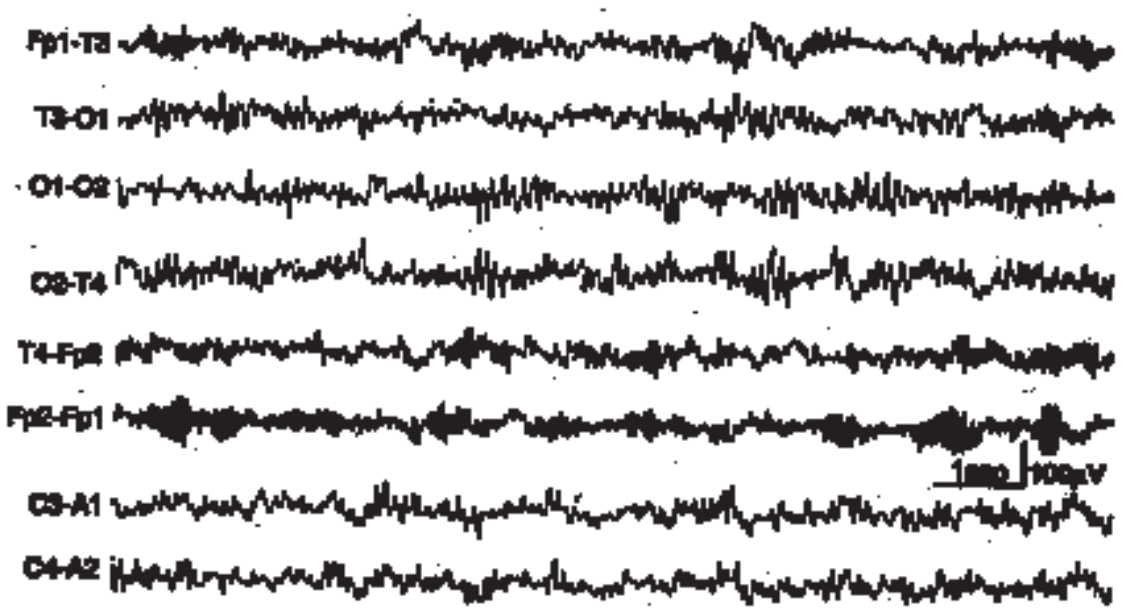


FIG. 5.7. Frontal beta activity in a 12-year-old boy, referred for abdominal pain and receiving diphenoxylate and atropine (Lomotil). Note the high amplitude of the beta activity in paired frontal derivation in comparison with ipsilateral derivations.

marked by increased beta activity in the central and postcentral regions (110). The frequency of this activity is usually 20 to 25 Hz; in infants aged 12 to 18 months (the age at which beta activity is usually maximally expressed), it may have a maximum amplitude of 60 μV (Fig. 5.8). This activity diminishes in both incidence and voltage with increasing age, and beta activity amplitudes exceeding 5 to 10 μV are rare after the age of 6 years. Again, the diagnostic utility of beta activity during sleep is limited.

Focal, regional, or hemispheric depression (defined as being at least 50% lower on one side) of beta activity is a reliable indicator of abnormality, and it is usually accompanied by depression of other background activity on the same side. It is a sign of either cortical depression (contusion, ischemia, atrophy, or cystic defect) or the presence of an intervening fluid collection somewhere between the cortex and the electrode sites. Conversely, high-voltage, generalized but anterior-dominant, fast activity may be a sign of brain damage. In children, a mixture of 18- to 25-Hz and 14- to 16-Hz beta activity with sigma activity of 10 to 14 Hz may occur during sleep in a pattern that has been called "continuous spindling and fast activity" (101). This abnormal finding is seen in certain cases of cerebral palsy and mental retardation. The continuous sigma activity may be the predominant feature of the pattern and has led to the name *extreme spindles,* which has been applied to essentially the same phenomenon (69). The interpretation of pronounced fast rhythms (but not so pronounced as to qualify as "continuous fast activity and spindling") in children during sleep is an unresolved problem. Whatever the voltage and duration of the beta activity, consideration must be given to the effects of any drugs the patient may have been taking; consideration must also be given to the effects of any drugs used to promote sleep for the purpose of the EEG study. The electrographic effects of a given drug dose are different in different persons, even if dose-weight schedules are used. There have been no definitive studies to determine whether these differences are related to the drug level in the blood or to differences in the response of the brain to equivalent levels. In children given sedation for sleep in the EEG laboratory, beta activity may become very pronounced if sleep does not ensue after a reasonable period (approximately 35 minutes). Similarly, beta activity may become greatly enhanced in the postsleep record when the child is awakened.

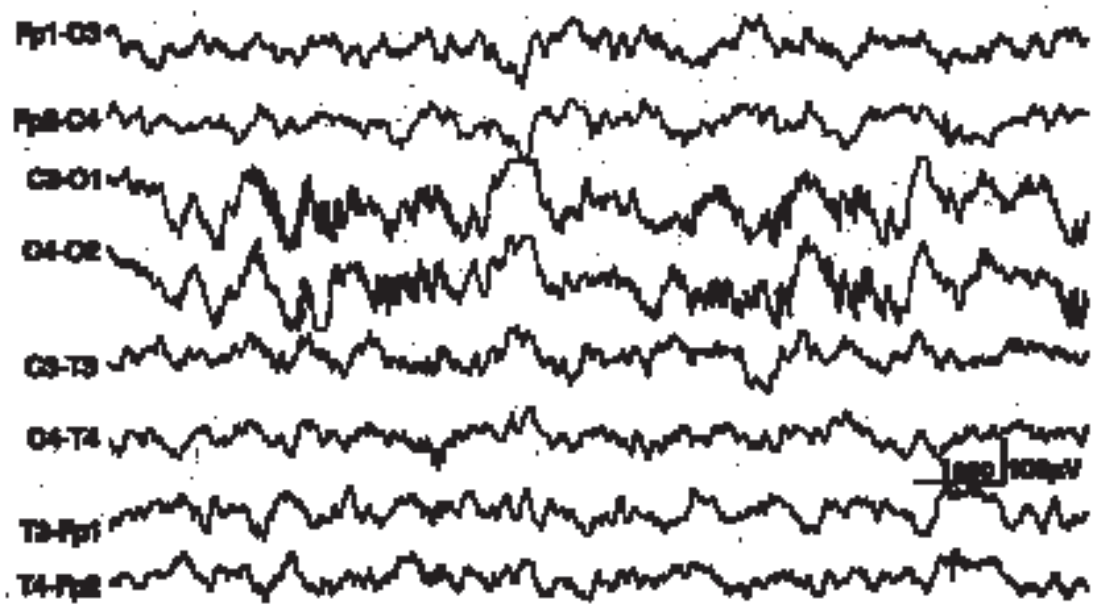


FIG. 5.8. Posterior 20- to 22-Hz activity present almost continuously but tending to show bursts of high voltage, in an asymptomatic 18-month-old girl.

Theta Activity

Frontal and Frontocentral Theta Activity

Most normal young adults show traces of 6- to 7-Hz random activity but show no activity slower than this. In approximately 35%, some low-voltage (less than 15 μV) 6- to 7-Hz waves may be present in the frontal or frontocentral region with the eyes closed and in the presence of a well-sustained occipital alpha rhythm (141,216). The 6- to 7-Hz activity in the frontocentral region tends to become sustained and higher in voltage with the onset of drowsiness, but this effect can usually be recognized because the occipital alpha rhythm concomitantly becomes intermittent or disappears. In patients whose alpha rhythm is low in voltage or poorly sustained, the onset of drowsiness can be determined objectively by using eye electrodes to detect the slow, pendular eye movements that accompany the onset of the drowsy state (141).

In young adults, and particularly in children, heightened emotional states enhance frontal rhythmic theta activity in the 6- to 7-Hz range (24,33,54,60, 93,122,123,150,210). Moreover, some normal persons show marked frontocentral rhythmic theta activity (with the eyes open) while performing certain tasks (218). It has not been established whether this latter effect results from a change in affective state related to the task or is a concomitant of some other aspect of brain function.

Because the routine clinical EEG examination generally does not encompass evaluation of "affective state" or even of "vigilance" during the recording, the presence of some 6- to 7-Hz random or rhythmic activity in the routine EEG cannot be regarded as having pathological significance. As mentioned earlier, approximately 35% of young, nondrowsy, asymptomatic adults show some very-low-voltage (less than 15-μV) 6- to 7-Hz activity in the frontal or frontocentral region in the environment of a quiet, smoothly operating, clinical EEG laboratory. In 10%, the voltage is 15 to 25 μV, and the activity tends to occur in rhythmic serials. The extent to which more sustained, higher voltage (greater than 15-μV), 6- to 7-Hz rhythms reflect the patient's emotional state (24,33,54,60,93,122,123,150,210) or some other physiological condition cannot be assessed properly unless specific procedures are carried out. Hence, there is no clear-cut end point at which frontal theta activity can be specified as abnormal. This problem is particularly important in children, who are especially prone to increased theta activity in highly emotional states and in whom frontal theta activity was once identi-

fied as an abnormality having a specific association with behavior disorders. Indeed, the presence of this "abnormality" in the EEG was originally thought to be "evidence of the organic nature of the behavior disorder present" (96). Clearly, enhanced theta activity in such children might result from emotional upsets engendered by the behavior problem and its consequences rather than from pathologically altered brain function. The clinical interpretation of anterior theta rhythms in the EEGs of children was overly influenced by a series of early reports, beginning with that of Jasper et al. in 1938 (96), who stated that such activity was more pronounced and more prevalent in children with behavior problems than in normal, age-matched controls. It is clear that Jasper et al. and subsequent investigators regarded this theta activity as evidence of fundamental brain pathology. Lindsley and Cutts (133), for example, reported that although occasional brief runs of 5- to 8-Hz waves in the frontal and central regions are not unusual in normal subjects, they should be considered abnormal "if they are present as much as 10% of the time in well-organized `runs' or `bursts.'" This concept has been reiterated ever since (usually without critical reappraisal) as a criterion of abnormality in children. However, the runs of 6-Hz activity shown in Fig. 5.9 are comparable to those that Lindsley and Cutts described as abnormal. The tracing in this figure is from the EEG of an asymptomatic 19-year-old man. Such rhythmic activity appears in approximately 15% to 20% of asymptomatic children and adolescents between the ages of 8 and 16 years; serial studies indicate that the occurrence of such rhythms is age-related, appearing in a given child at a certain age, increasing to a peak voltage at approximately the age of 8 years, and tending to diminish and finally disappear thereafter (48,165). Thus, age and ontogenetic processes are factors in the appearance of this type of anterior theta rhythm. Evidence also indicates that genetic factors may play a role (43). The problem is: At what point do frontal 6- to 7-Hz rhythms—because of high voltage, unusual persistence, or paroxysmal regulation—qualify as evidence of abnormal function?

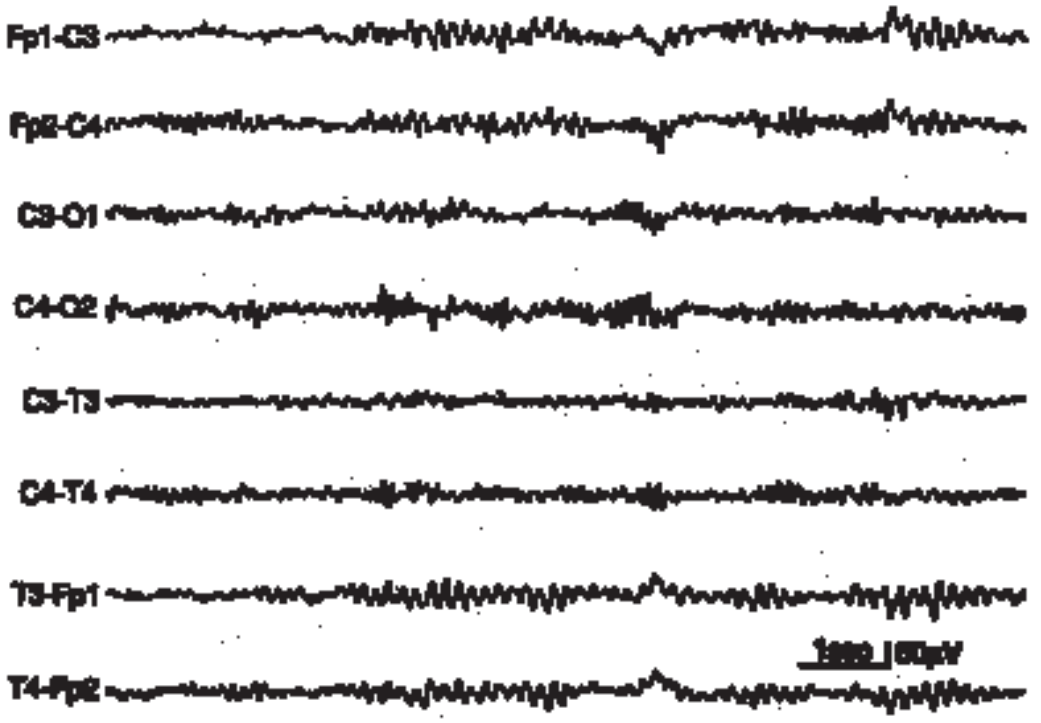


FIG. 5.9. Monomorphic, rhythmic 6- to 7-Hz moderate-voltage activity, occurring in fairly prolonged runs in the frontal leads in an asymptomatic 19-year-old pilot. Theta activity of this degree occurs in asymptomatic young adults but usually not so continuous or so pronounced at this age as in this subject.

Monomorphic, rhythmic 6- to 7-Hz activity occurring in high-voltage (greater than 100-μV) paroxysmal bursts in the frontal or frontocentral region (Fig. 5.10) is not typically seen in normal children (zero incidence in controls). The two extremes of rhythmic theta activity occurrence are shown in Figs. 5.9 and 5.10; however, all degrees of theta activity may be encountered in pediatric practice. At what rate of amplitude change, maximum voltage attained, or degree of persistence, or in what combination of these, does such activity have diagnostic significance? The problem is compounded by the fact that such rhythms are potentiated during drowsiness and by hyperventilation, and what may be a "baseline" rhythm awake and at rest may become paroxysmal during stage I sleep or during overbreathing. Clearly, the true meaning of such rhythms must await development of a more sophisticated knowledge of neuropsychiatry. In clinical practice, the electroencephalographer should not be misled by poorly controlled studies that purport to show that monomorphic frontocentral activity of 4 to 6 Hz (which interrupts and exceeds in peak amplitude the background activity) is correlated with clinical epilepsy. Activity of this description is seen as often in children referred for problems other than epilepsy. Nor should the electroencephalographer be led into false syllogistic thinking—that is, that because a significant incidence of such theta rhythms has been reported in epileptic patients, other disorders that display such rhythms must be epileptic in character.

The problem of interpretation of pronounced theta rhythms in children has been compounded by the reports of Doose et al. (42,43,45,80,81), who equated such rhythms with susceptibility to convulsions and particularly with "clinically manifest epilepsy" (44). They described the pattern as consisting of runs of bilaterally synchronous, monomorphic 4- to 7-Hz rhythmic activity shown most clearly by referential recording from the central regions. The runs

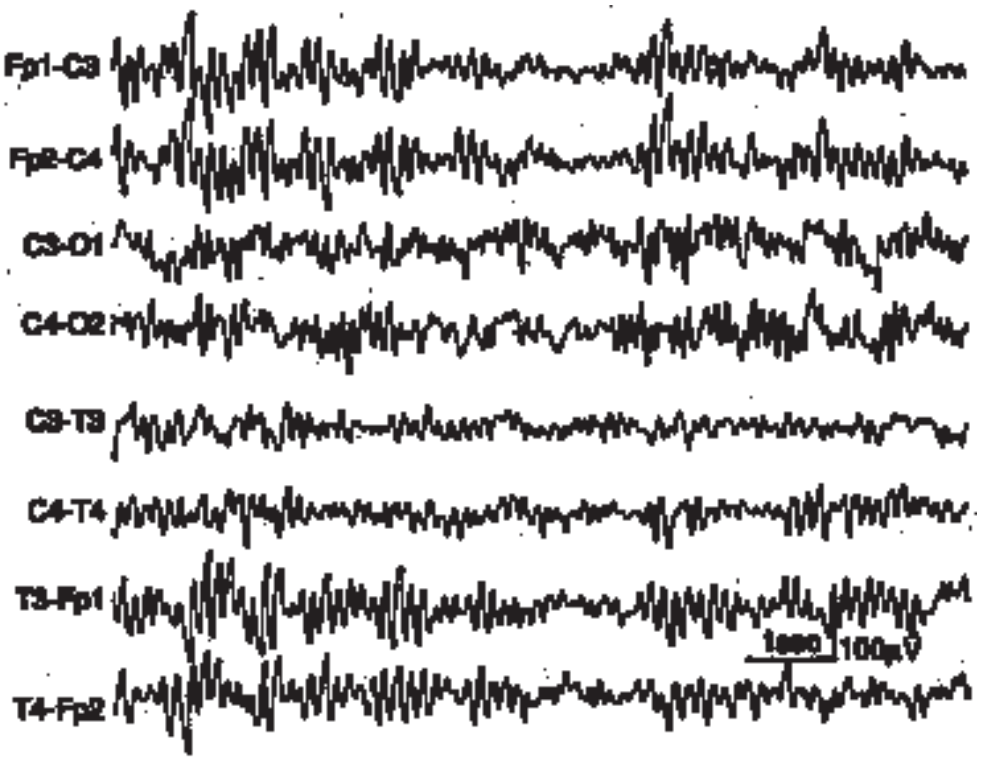


FIG. 5.10. Monomorphic, rhythmic, high-voltage 6- to 7-Hz activity in a 9-year-old boy. Rhythmic 6- to 7-Hz activity, similar to that seen in Fig. 5.9, occurs commonly in this age group but usually not so continuously as in this subject. This high-voltage, frontal theta activity is outside the range of normal variation for any age.

of rhythmic 4- to 7-Hz monomorphic waves often have a spindle shape, tend to spread to the frontal and posterior regions, and tend to dominate the EEG. The rhythm occurs predominantly in children aged 2 to 6 years.

The examples these authors used to illustrate this activity (e.g., Fig. 1 of Doose and Gundel [44]) are typical of what normal children of this age may show in the hypnagogic state. They dismissed this point, however, with the inaccurate assumption that hypnagogic activity occurs "predominantly as a paroxysmal generalized phenomenon," whereas the theta rhythms that they described "are less paroxysmal and tend to be localized in the parietal regions" (see Fig. 1of Doose and Gundel [44]). They also dismissed the hypnagogic state as a possible explanation, because children who show the rhythm "may show no evidence of being sleepy." Yet the term *hypnagogic* was originally used, instead of the term *drowsy waves,* to describe the hypersynchrony prodromal to sleep so as to convey the important fact that the infant or young child showing the pattern *may have the appearance of being fully awake.*

Doose et al. (42,43,45,80,81) presented evidence that the 4- to 7-Hz rhythm that they described "is not only characteristic of primary epilepsies of early childhood but may be found in secondary epilepsies with focal symptomatology" and "in a relatively high percentage of controls" (44). The author's experience with EEGs of many thousands of young children (both normal and with wide-ranging complaints) has led him to believe that the theta pattern as described by Doose et al. is a ubiquitous pattern related to age, not to dysfunction.

Midline Central Theta Activity

A midline central (Cz) theta rhythm has been described in children and adults (31,148,211). As described by Westmoreland and Klass (211), it consists of trains of rhythmic waves of sinusoidal or mu-like form having a consistent frequency within the 4- to 7-Hz range. The rhythm, which is predominantly 6 or 7 Hz, occurs episodically in trains that have a duration of 4 to 20 seconds. It is present only in the awake state, is not related to drowsiness, and is a different rhythm from the bilateral rhythmic central theta activity that is a common finding in sleep. The rhythm has a high correlation with epilepsy but is not related to any particular type (148,211). It is, however, not specifically related to epilepsy, inasmuch as about 25% of the persons who show this pattern have other disorders.

It is not seen in normal subjects at any age, but it is mentioned here so that it may be clearly differentiated from the midline *frontal* theta rhythm that may occur in adults during mental tasks (218), such as reading.

Posterior Slow Waves

Perhaps no EEG finding has been more misunderstood and misevaluated to the detriment of the patient than slow activity in the parieto-occipital and occipitotemporal regions. The interpretation of such activity in children, adolescents, and young adults continues to be fraught with difficulties. Perhaps the problem can be clarified by reviewing how some of the difficulties arose.

In 1938, Jasper et al. (96), beginning with the premise that "the important electrical signs of brain dysfunction given by the electroencephalogram might contribute to our understanding" of certain primary behavior disorders, studied 71 children between the ages of 2 and 16 years who had been admitted to the Bradley Home with a primary diagnosis of behavior problem. For controls, a comparison was made with the EEGs of "40 normal children of comparable age, 70 normal adults, and 219 patients with other nervous or mental disorders." As a pioneer effort, this study was important chiefly in terms of its heuristic value. The authors' conclusion that "abnormal brain function as revealed by the electroencephalogram is an important component in the majority of a group of problem children whose disorder had been considered as primarily psychogenic previous to using this method of diagnosis" was to have a far-reaching influence on future studies, and for a long time no systematic attempt was made to examine this concept or its implications. A long series of papers reported similar findings and reached similar conclusions, each tending to repeat the errors in the research design of the original study without, however, the extenuating circumstance of being the first to deal with the subject.

The errors of experimental design in the original study of Jasper et al. (96) were largely a reflection of the lack of knowledge at this very early point in the history of clinical electroencephalography. Thus, although the authors were concerned about the intelligence of the subjects, they did not control for state (e.g., drowsiness, alertness) and did not appear to make significant adjustments of EEG criteria in terms of age. Consequently, although the study included children as young as 2 years, the authors considered, for the purpose of their study, that the EEG was abnormal if the waves below 7 Hz occurred in more than 10% of at least 100 seconds of record.

The fundamental limitations of this original study (and of many subsequent studies) were the small size of the control group and the basis of the criteria of abnormality. Furthermore, in all the studies, there was the pervading concept that the "abnormalities" are signs of damage. The evidence for this concept was not conclusive (only circumstantial) and included some statistical conceptualizations of questionable validity.

The occipital slow activity seen by Jasper et al. (96), by Lindsley and Cutts (133), and by other early workers who studied children with behavior problems was not well characterized and, in fact, consisted of several types, ranging from continuous delta activity with no alpha rhythm to episodic delta activity with a continuous superimposed alpha rhythm of normal frequency. Clearly, several varieties of occipital or posterior slow activity may be present in children; furthermore, there are numerous permutations of amplitude, waveform, incidence, and posterior areal distribution that cannot be combined into a single category of abnormality without regard for age and state.

The weight of the statistical evidence (33,87,95,133,161) seems to confirm a greater incidence of posterior slow activity in children with behavior disorders than in selected controls of the same age. The character of the deviation and its degree vary considerably, however, and probably do not reflect a unitary pathophysiological mechanism, even in terms of brain damage or lack of it. The evidence of Aird and Gastaut (2), Wiener et al. (216), and Sutter and Harrelson (190) suggests that asymptomatic children with no antecedent history of brain insult may show posterior slow activity, and this slow activity appears to be age-related. It is likely that some of the types of posterior slow activity described in problem children reflect simply that the subjects are children of a certain age.

The interpretation of posterior slow activity can be made coherent only if its characteristics are clearly defined in terms of the analysis schema outlined in the first two sections of this chapter. First, some posterior slow activity, intermixed with the alpha rhythm, is present in the EEGs of 7% to 10% of highly selected normal young adults (18 to 30 years of age). The type of activity present in 90% of these persons consists of moderate-voltage (defined as no more than 120% of the alpha rhythm voltage) fused waves intermixed with the alpha rhythm (which is often superimposed on them). These waves have been called *polyphasic waves* (48,165) or *posterior slow waves of youth* (2). An example of this type of activity in a normal young adult is shown in Fig. 5.11. This type of posterior slow activity is rare

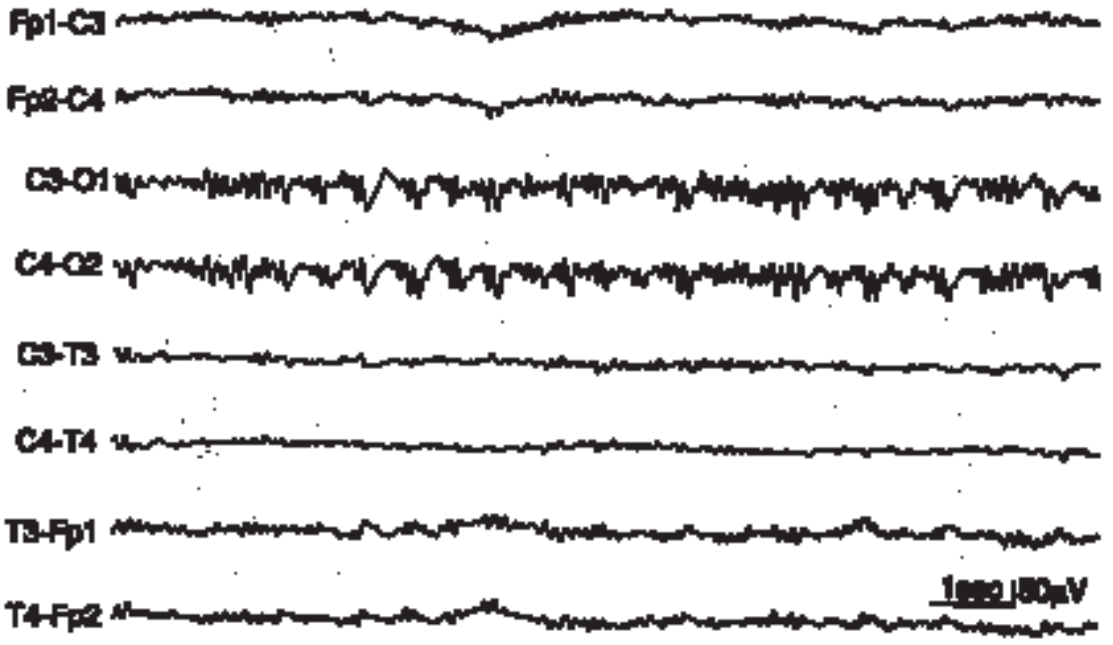


FIG. 5.11. "Posterior slow waves of youth" in an 18-year-old asymptomatic woman. Long interelectrode distances and the central-occipital derivations emphasize this type of slow activity.

in normal adults after age 21 years but has a 15% incidence in persons aged 16 to 20 years (48,165).

Such waves are uncommon in children younger than 2 years, but they are maximally expressed (in amplitude and incidence) in children aged 8 to 14 years (see Fig. 5.16*B*); they occur more often in girls than in boys. It is common for the amplitude and incidence of posterior polyphasic waves in a child to diminish as the recording proceeds. The basis for this change is not clear; it may reflect a change in the anxiety or stress level of the child (24,33,54,60,93,122,123,150,151,210).

A practical point to remember is that the potential field of posterior polyphasic waves is such that they appear to be much more pronounced when recorded from C3–O1 or C4–O2 than from scalp-to-ear derivations (e.g., O2–A2). These waves block with eye opening and disappear with the alpha rhythm during drowsiness and light sleep. They are not always symmetrical or synchronous on the two sides, but the asymmetry should not consistently be more than 50%. They are accentuated by overventilation and, possibly, by stress (24,33,54,60,93,122,123,150,151,210).

If polyphasic or fused waves were the only type of occipital slow activity encountered in children, the difficulty of interpreting children's EEGs would be considerably lessened. However, occipital slow activity may be present in numerous permutations of amplitude, waveform, occurrence, and topography, which renders it difficult to distinguish between normal and abnormal findings.

In terms of manner of occurrence, there is an occipital slow activity that is semirhythmic in character and is a normal finding between the ages of 1 and 15 years (48,165); this is discussed in detail later. Except for this age-related finding, in the awake state there should be no *rhythmic* component in the occipital regions that has a frequency slower than that of the normal range (for age) of the occipital alpha rhythm.

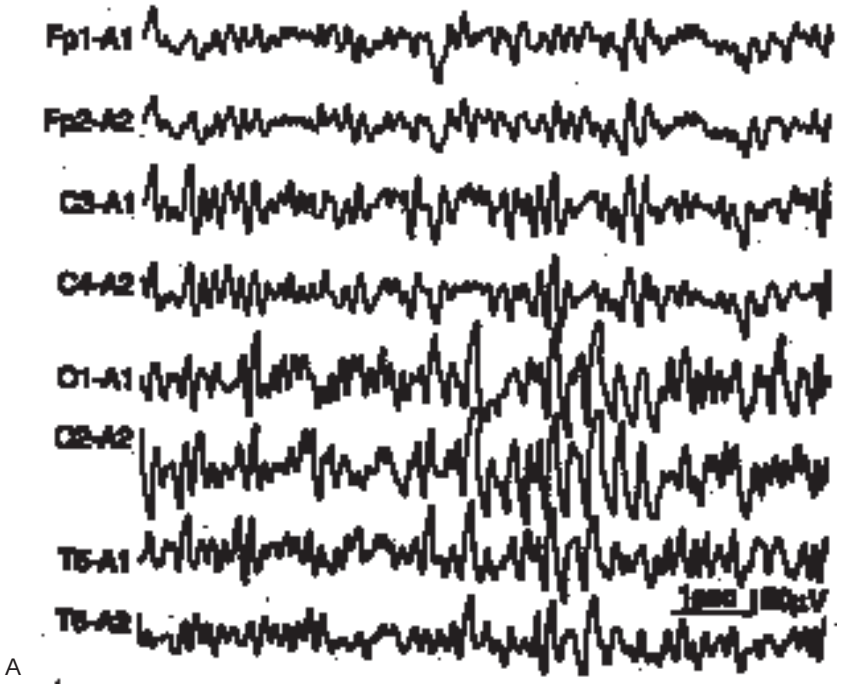
Random, occipital slow activity may be present in normal children in a wide range of waveforms, voltages, and wavelengths, and interpreting the meaning of such activity is complicated by the fact that, in children, the occipital region appears to be a common site for the EEG expression of disordered function. Thus, after closed-head injury or hypoxia or in the various encephalitides, occipital slow activity may be the initial and the last persisting EEG sign of dysfunction resulting from the brain insult. However, because of the wide range of normal variation in the amount and character of occipital slow activity in normal children of various ages and under various conditions, it is often difficult to assess the significance of random occipital slow waves. Nevertheless, it is possible to provide some guidelines for interpretation on the basis of (a) studies of normal children and (b) the experience gained from prospective serial studies of children with various types of brain insult.

Serial observations dating from the time a brain insult is incurred allow definition of certain features of occipital slow activity that are more characteristic of abnormal than of normal function. Thus, when the slow activity deviates from that commonly seen in normal children, the deviation or deviations can be characterized in terms of (a) complexity and variability of waveform, (b) incidence (how often slow waves occur within a given time epoch, such as 10 seconds),[8] (c) voltage ratio (e.g., whether the voltage of the slow activity is greater than 1.5 times the voltage of the occipital alpha rhythm), (d) persistence (whether the occipital slow activity persists with the eyes open), (e) synchrony (whether the occipital slow activity is synchronous on the two sides), and (f) symmetry (whether the occipital slow activity is predominant on one side) (Figs. 5.12 and 5.13).

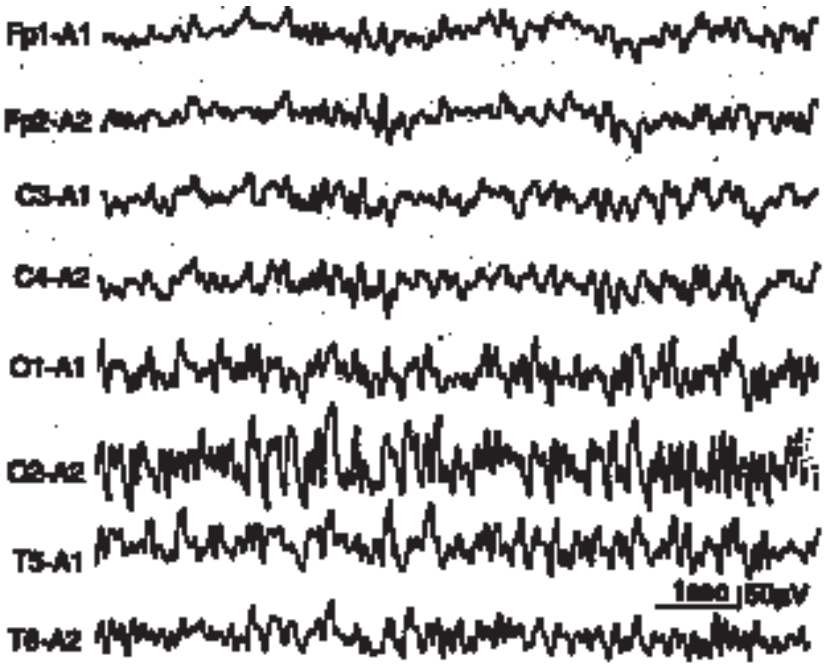
Any or all of these factors and their degree of expression may be used to formulate an index of abnormality. When this index is high, there should be no difficulty with evaluation. A definitive statement of normal or abnormal cannot be made, however, about many EEGs encountered in clinical practice. The term *borderline* is sometimes applied in this situation, but the clinical utility of this designation is doubtful.

When serial EEGs are obtained after brain injury (147) or in patients with various disease states (e.g., encephalitis), this index of abnormality can be employed effectively. It is much less useful if the EEG is an isolated diagnostic study. In the latter circumstance, even if the electroencephalographer can conclude with confidence that occipital slow activity present on an EEG is outside the range of normal variation, the diagnostic significance (or clinical meaning) of such a finding is not clearly evident *ipso facto.* If, for example, the patient is referred to the EEG laboratory because of "possible seizures," does the presence of an occipital dysrhythmia—or, for that matter, any nonspecific dysrhythmia—help establish a diagnosis of epilepsy? Occipital slow dysrhythmia, as an isolated finding, occurs as often in children who are referred for behavior disorder or learning disability and who

[8]In children aged 6 to 24 months, awake, occipital activity is monorhythmic, and with the eyes closed, there should be no random slow waves with a duration exceeding 0.25 second aftnd an amplitude more than 1.5 times that of the alpha rhythm. This is not true of light sleep, in which random delta waves characterize the occipital derivations (110).



A



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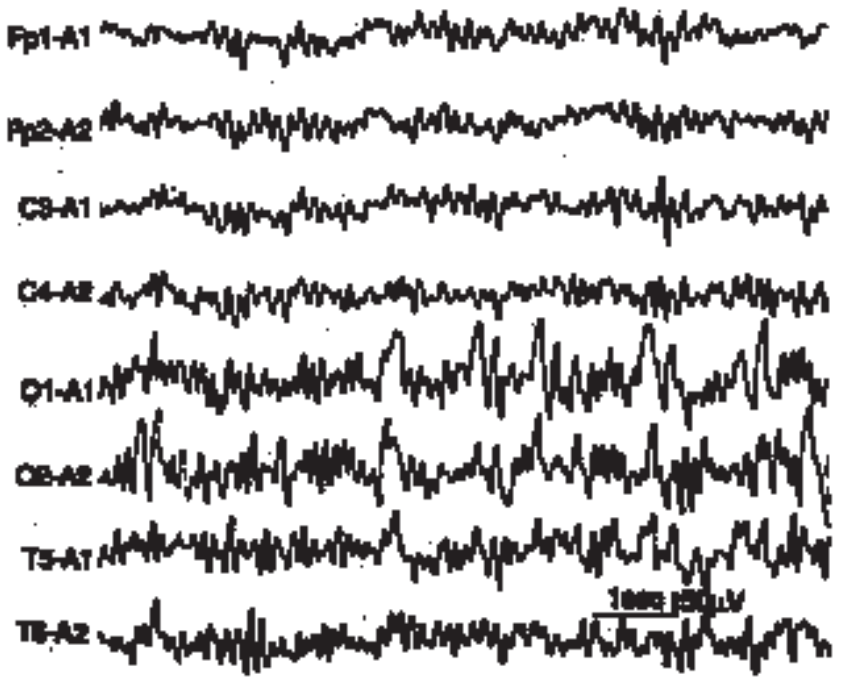
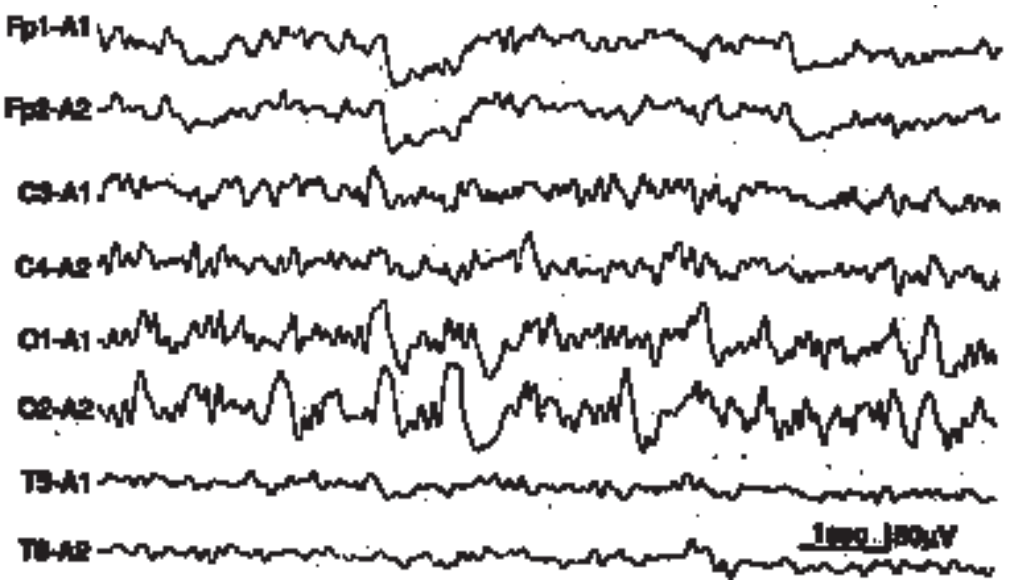


C

FIG. 5.12. A: This EEG is outside the range of normal variation for age (8 years, 1 month) because of high-voltage (three times that of the alpha rhythm), rhythmic 4-Hz waves, which are not seen in normal children. **B:** This occipital slow activity is chiefly 5 to 6 Hz; although it sometimes exceeds the voltage of the occipital alpha rhythm, it is within the range of normal variation for age (8.5 years). Occipital slow activity is usually of higher voltage on the right side; this degree of asymmetry causes no concern. In view of the amount, frequency, and voltage of the occipital activity, this EEG is slightly slow. **C:** The occipital slow activity (3 to 4 Hz) is polymorphic, asynchronous, and over 300 μV. These features are outside the range of normal variation for age (8 years); however, the slow activity in anterior derivations is well within the range of normal. (*Figure continues.*)

D



E

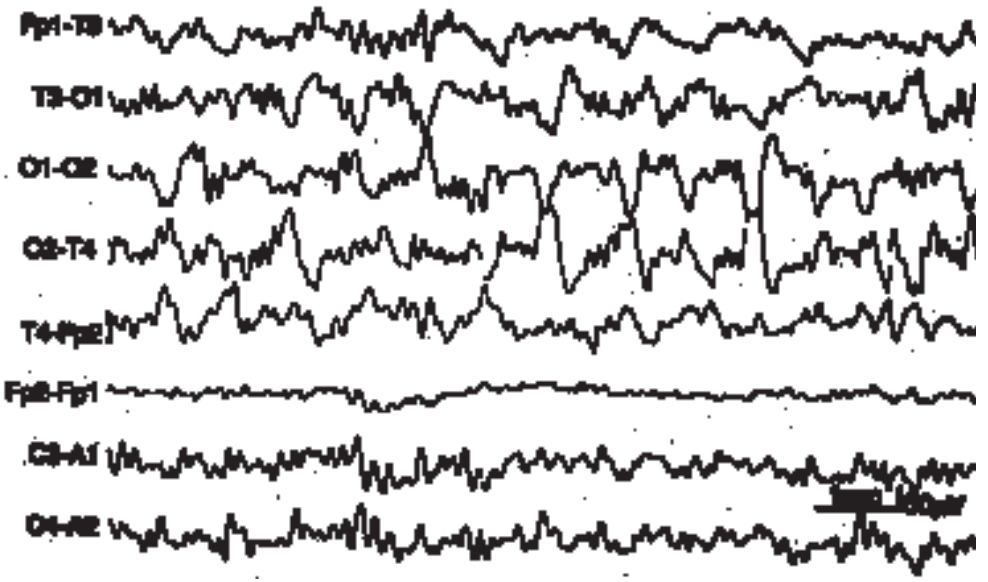
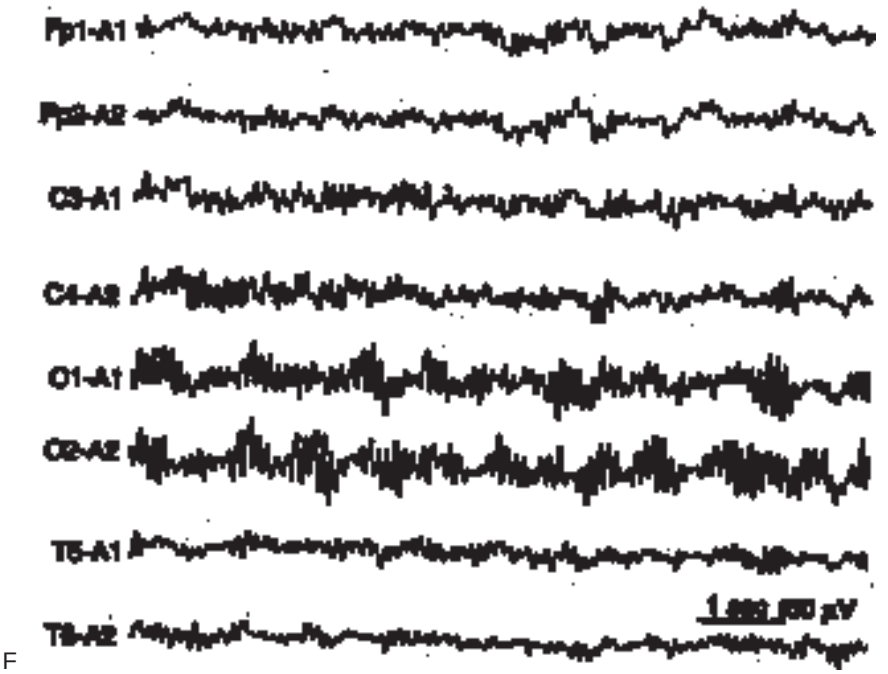


FIG. 5.12. *Continued.* **D:** In an 8-year-old child with meningitis, these high-voltage, random, 2.5- to 3.0-Hz asynchronous waves in the occipital derivations are abnormal, even though the slow activity in anterior derivations is within the range of normal variation. **E:** From the same patient as in part *D.* In scalp-to-scalp derivations, the amount and degree of occipital slow activity are obvious. Note that the duration of some waves exceeds 0.75 seconds. (*Figure continues.*)



F

FIG. 5.12. *Continued.* **F:** For comparison, a "supernormal" electroencephalogram in a boy aged 7 years, 9 months. Occipital slow activity is minimal and masked by a continuous alpha rhythm. The amount of slow activity seen in anterior derivations is within the range of normal variation up to age 16 years.

do not have seizures as it does in epileptic children (Table 5.2). Even in instances of known epilepsy, the finding of an occipital slow dysrhythmia does little to illuminate the diagnosis. The occipital dysrhythmia may be bilateral, but even this does not establish that the patient has a "generalized" epilepsy. The patient may also have an occult focus not revealed in the EEG. In such a case, it is possible that the occipital dysrhythmia does not relate directly to the patient's epilepsy, but instead occurs as a result of some other intercurrent factor (e.g., phenytoin intoxication).

The foregoing is prelude to a plea: The criteria for what is considered abnormal in children and indicative of disease or disorder must be improved. Also, more caution must be exercised in assigning significance to such findings. Examples of various degrees and types of slow activity encountered in children of a given age are shown in Fig. 5.12. The samples illustrate the range from supernormal to clearly abnormal. It would be more useful if the various types of occipital slow activity could be illustrated for each age. In addition to *random* slow waves, occipital or "posterior" *rhythmic* slow waves are seen in normal children (48,165). Episodic rhythmic, 2.5- to 4.5-Hz, monomorphic and polymorphic low- to moderate-voltage waves (<100 μV) occur in the parieto-occipitotemporal region (usually maximal at O1 and O2) in approximately 25% of normal awake children aged 1 to 15 years. Such activity is most prominent in those 5 to 7 years of age. Runs of this activity rarely last more than 3 seconds and are present only 2% of the time (48,165). Hyperventilation generally causes this activity to become more continuous and higher in voltage.

Rhythmic occipital slow activity of various types and frequencies that does not seem to reflect an insult or to have an established genetic origin has been reported in the EEGs of adults (2,6,120,166). These rhythms are perhaps of some interest as EEG anomalies, but they are important in the discussion of the characteristics of the normal EEG only in that they can be recognized as being outside the range of normal variation but having no known pathophysiological significance.

Posterior Slow-Wave Transients Associated with Eye Movements. In some young children (aged 6 months to about 10 years), some eye blinks or eye movements are associated with a single monophasic or diphasic slow transient that has a duration of 200 to 400 milliseconds and an amplitude of

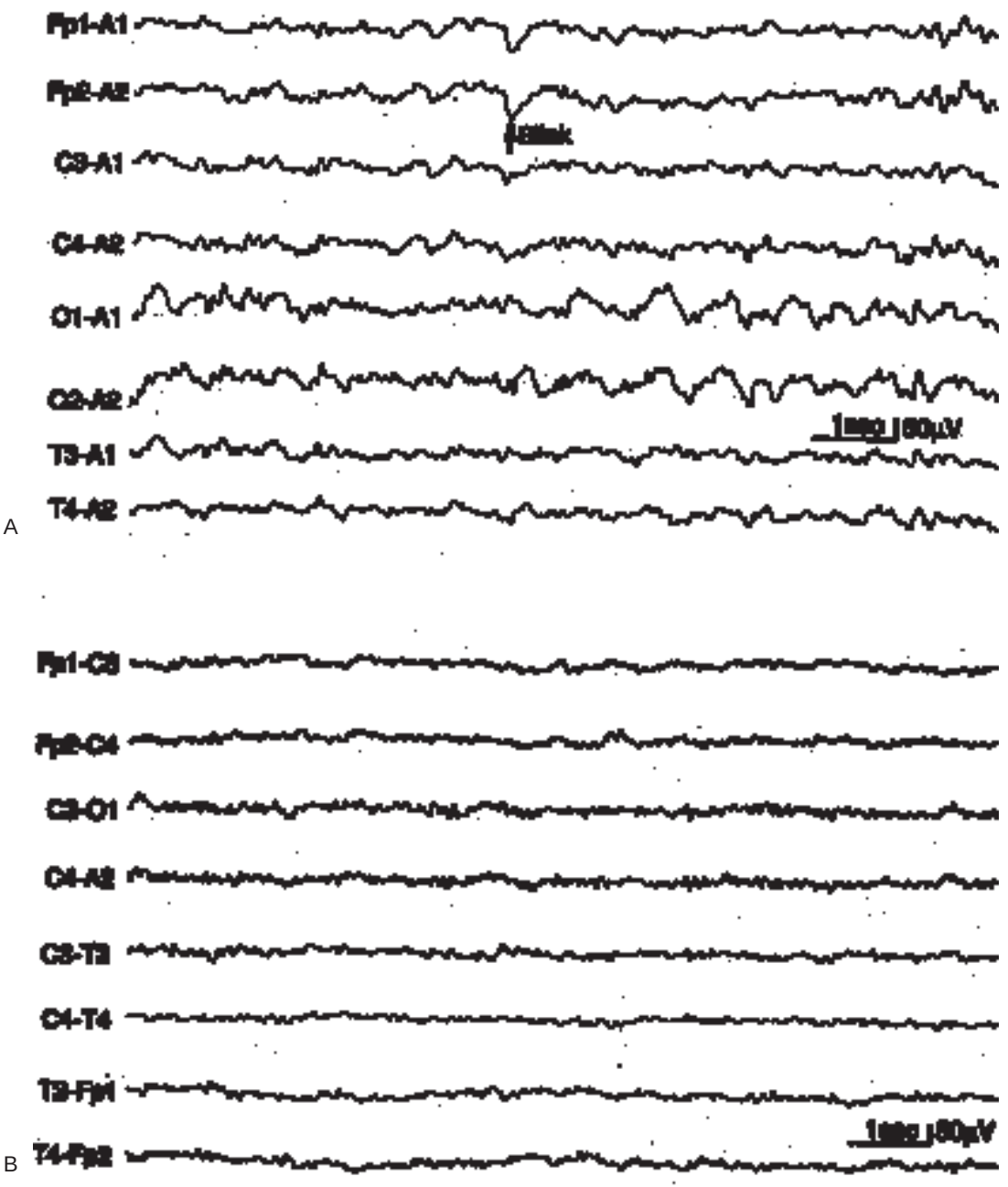


FIG. 5.13. A: Polymorphic slow activity in the occipital leads is often difficult to evaluate if low in voltage and random in occurrence, as in a 14-year-old boy. The slow activity is different from that shown in Fig. 5.11 (normal for the age of 18 years) and from that in Fig. 5.16*B* (normal for the age of 10 years). The occipital slow activity in this tracing, made 6 hours after injury, typifies that seen soon after closed-head injury (concussion) occurring in late childhood or adolescence. This slow activity usually resolves within 10 days. **B:** From the same patient as in part *A,* 7 days after injury. Note that the occipital slow waves have disappeared. The alpha rhythm is somewhat slow, poorly sustained, and poorly organized, but it is "normal" for age.

TABLE 5.2. *Electroencephalographic (EEG) findings in children with known seizures compared with other children commonly referred for EEG studies (age group: 3–16 years)**

EEG findings	Epilepsy (%) (*N* = 3,046)	Primary behavior disorders (%) (*N* = 2,626)	Learning and communication disorders (%) (*N* = 3,148)	Questionable seizures (%) (*N* = 1,163)
Normal	39.6	66.9	65.8	64.0
Nonspecific dysrhythmias	19.0	19.9	21.0	24.0
Foci	29.8	7.5	8.0	8.7
Spike-and-wave	4.8	1.8	1.9	3.0
Other	7.8	0	0	0.3

*Note that the incidence of nonspecific dysrhythmias is approximately the same for all groups and is similar to the incidence (16%) given by Wiener et al. (216) for normal children.

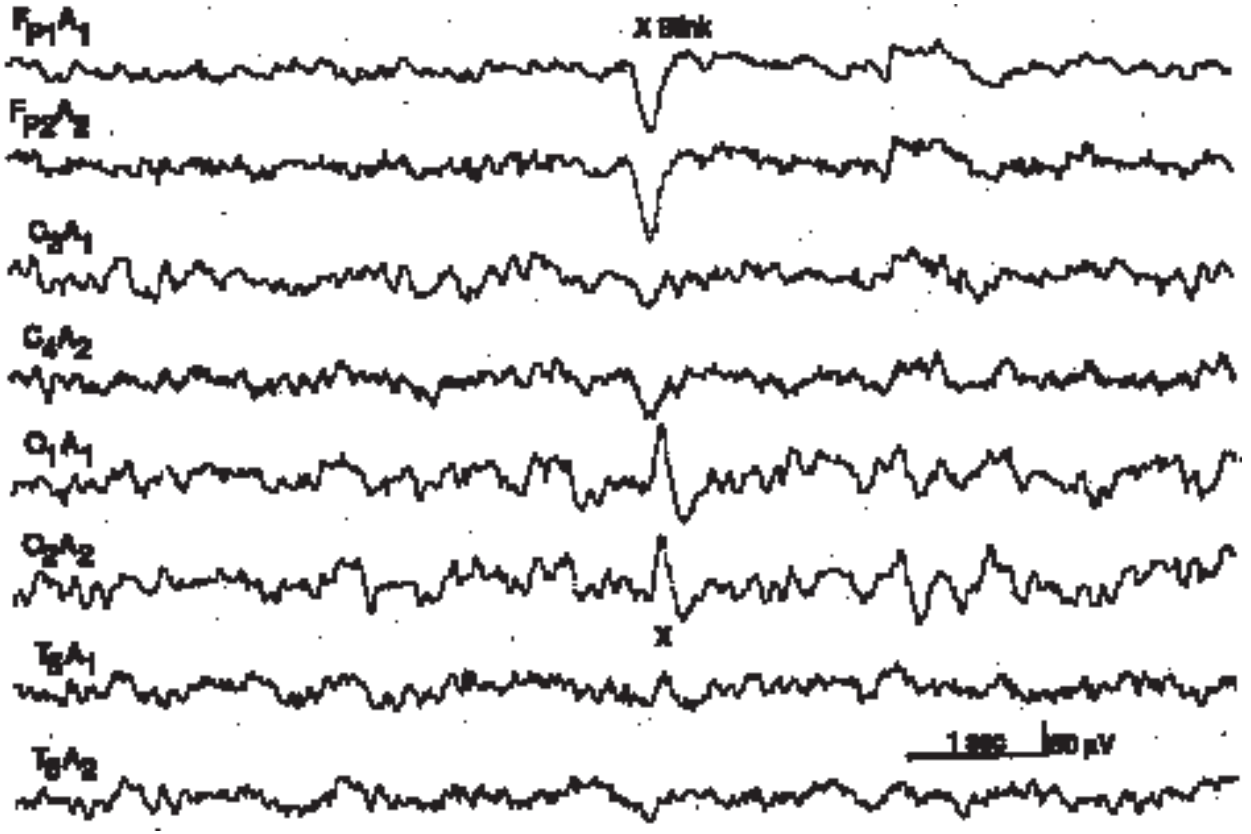


FIG. 5.14. Occipital sharp transient associated with eye blink in a 13-month-old boy, awake.

up to 200 μV. These transients are usually confined to the occipital region and occur with a latency of 100 to 500 milliseconds after the blink or eye movement (Fig. 5.14).

The initial component of these transients is surface positive, and it and the ascending phase of the next surface-negative component have a steep wave front. The descending phase of the second component is much less steep. These transients are often asymmetrical on two sides and do not occur with every eye movement or blink. They are seen most frequently in children aged 2 to 3 years (213).

These posterior slow-wave transients that follow an eye movement or blink are normal phenomena but may be mistaken for abnormal activity, particularly if they seem to occur in the absence of eye movements or blinks. To establish an association between these events, it may be necessary to record horizontal and oblique as well as vertical eye movements, because the former may not be detected easily in frontal EEG derivations.

Anterior Slow Activity in Children

It has long been known that the amount of slow activity in the EEGs of children decreases with increasing age and that the persistence and frequency of the slow activity vary in different areas. Both of these facts are clearly illustrated in Fig. 5.15, a graphic representation of the findings of an

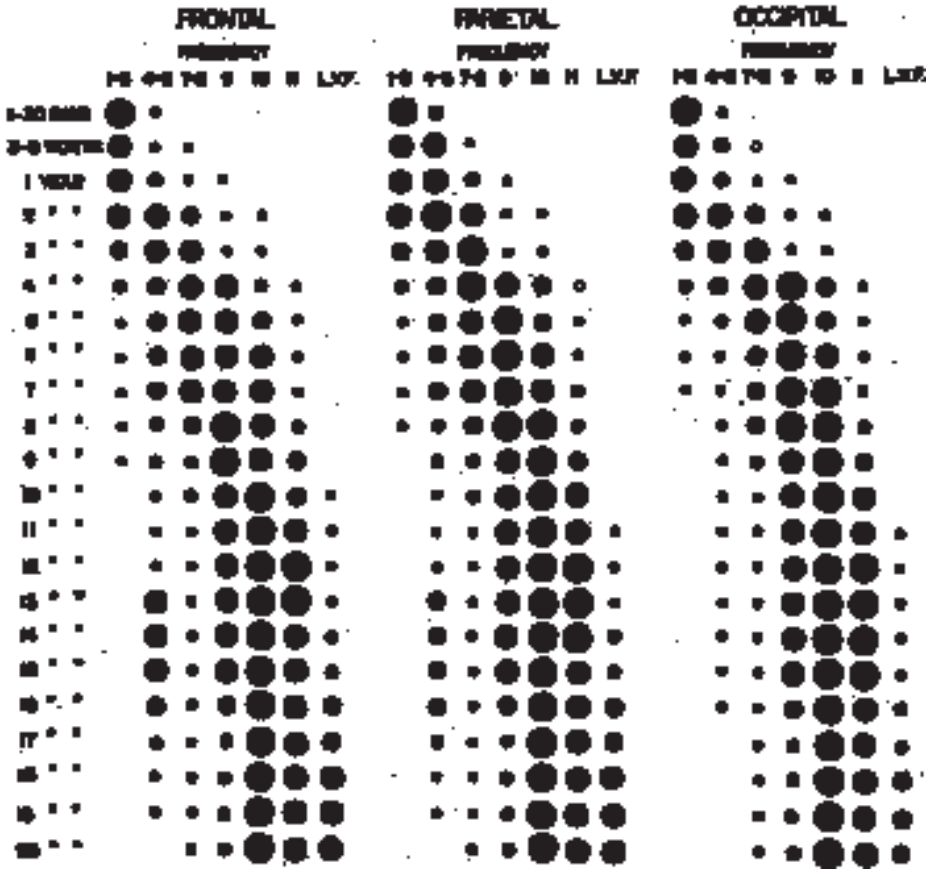


FIG. 5.15. Graphic summary of early frequency-analysis study of Gibbs and Knot (75). The designation of "Parietal" refers to the parietal bone of the skull. Actual electrode locations are approximately those of the C3 and C4 positions. At the time this study was made, temporal derivations were not used routinely by this group. L.V.F., low-voltage fast activity.

early frequency-analysis study by Gibbs and Knott (75). This figure may be regarded as a fairly good approximation of the frequencies present and their degree of expression in various regions at different ages. It does not, however, provide information concerning the waveform of the activity, its voltage, or the manner of its occurrence (e.g., random, continuous runs), all of which are critical elements of visual analysis and are essential to clinical evaluation of the EEG.

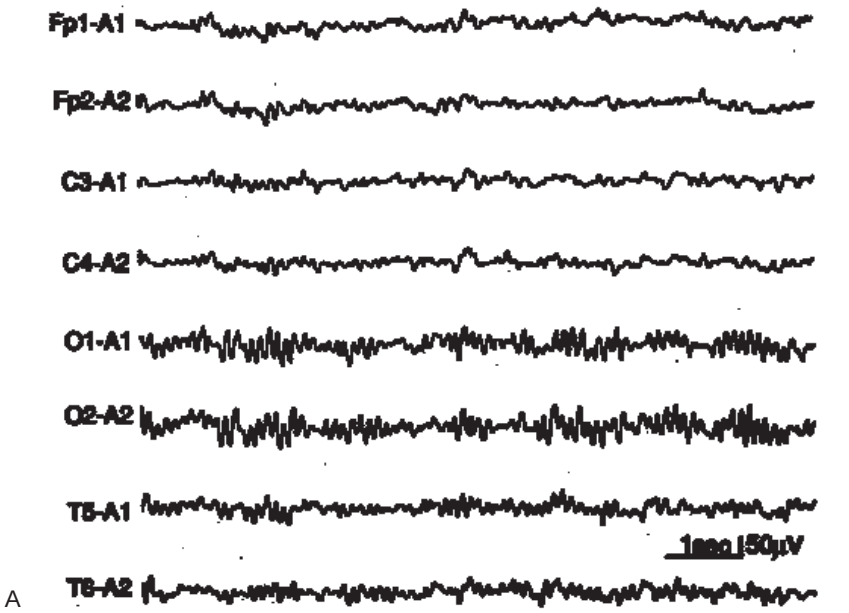
Another important aspect of assessing the amount of slow activity in the EEG is the frequency:voltage ratio. It has become the practice for clinical electroencephalographers to rate an activity as having high or low voltage in relation to its frequency. Thus, at the two ends of the EEG frequency spectrum, a 25-Hz activity is regarded as being high in voltage if its amplitude is 30 μV, but a 1- to 2-Hz wave of similar amplitude is considered low in voltage. This convention grew out of the everyday experience of recording the EEGs of human subjects: Beta activity is generally much lower than 25 μV in amplitude; hence, anything higher is "high voltage." On the other hand, 1- to 2-Hz waves of over 800 μV are common during physiological (sleep) and in abnormal conditions in humans. The convention has significance in terms of the power-spectral characteristics of the EEG. The clinical electroencephalographer assesses the significance of slow activity in relation to its voltage; this frequency:voltage ratio is an important component of the set of mental templates (one for each age range) that must be developed in order to have a consistent basis for evaluation. The age range to which each such template can be applied varies with age, because the *range* of normal variation is different at different age levels.

In evaluating the amount and duration of slow activity present in relation to the age of the patient, it is helpful to use the concept of the "ideal" EEG for each age as a standard of comparison. "Ideal" is not used to convey perfection (particularly in a clinical sense) but is, instead, employed in the platonic sense of "prototype." The "ideal" is based on what 75% of asymptomatic children of a given age show in terms of the slow activity present in the various derivations. Approximately 5% of normal children (same age) show less slow activity than the ideal, and their EEGs more closely approximate the adult pattern (these are sometimes called "super normal" EEGs) (48,165). Another 15% of normal children show slightly greater amounts of slow activity than the ideal, and 5% show moderately increased amounts of slow activity. These general concepts have been adopted, modified, and expanded by the author's colleagues and collaborators in Sweden and underlie their categorizations of "slightly increased slow" and "moderately increased slow" (48,165). These benchmark papers of Eeg-Olofsson and Petersén provide the essential data on which the kind of mental template required for the evaluation of children's EEGs can be developed.

Eeg-Olofsson and Petersén (48,165) rated the amount of nonrhythmic (random) slow activity in the EEGs of children in their normal series as "minute," "normal," "slightly increased (SIL)," and "moderately increased (MIL)" for age. Of their highly selected healthy children, approximately 87% had random slow activity in an amount rated as normal for age. Approximately 8% had lesser amounts of slow activity than this, and 4.3% had slightly greater amounts of nonrhythmic slow activity; in 0.5% of the series, the random slow activity was MIL. This compares with the concept of the "ideal" EEG and the range of normal variation that was developed from studies of asymptomatic but not highly selected children. Eeg-Olofsson and Petersén found that the incidences of SIL and MIL were greatest in children between 6 and 11 years of age and were significantly higher in girls than in boys.[9]

Comparison of Eeg-Olofsson and Petersén's prototypic EEG samples of "normal," "slightly increased," and "moderately increased" slow activity with the author's own prototypes indicates that the highly selected healthy children in the Gothenburg series (48,165) showed lesser amounts of random slow activity than did the author's unselected asymptomatic children. If the criteria offered by the Gothenburg study of highly selected children are used as a basis of interpretation in routine clinical practice, considerable caution must be exercised in categorizing an EEG of a given child as "outside" the range of normal variation; care should be taken here because the "pathological" significance of an abnormal EEG, which is too readily equated with brain "damage" (or, at best, "dysfunction"), is often based on simplistic reasoning. The talent of the clinical electroencephalographer is measured not so much by an ability to make a visual analysis of the tracing but by an ability to determine what the findings mean in a particular patient under particular circumstances in relation to a particular clinical history. The characteristics of the EEG are determined by numerous influences, not the least of which may be the uniqueness of the laboratory environment. Factors that determine the characteristics of an individual's EEG at any time are discussed in the final section of this chapter. It is beyond the scope of this chapter to attempt to convey the "ideal" and the "range of normal variation" for each age. Figure 5.16 illustrates the concept for a single age level.

[9]This finding is in accord with the concept that the *range* of normal variation itself varies with age.



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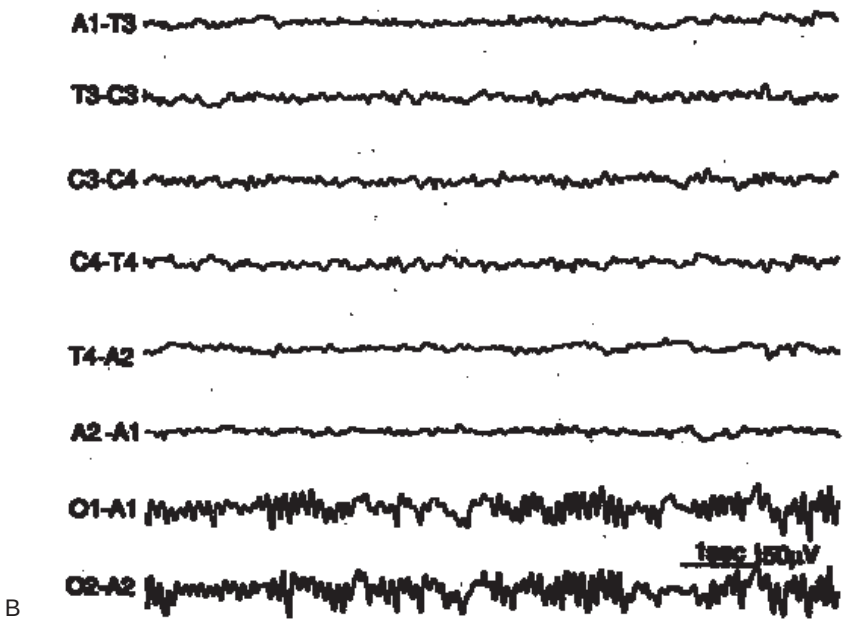

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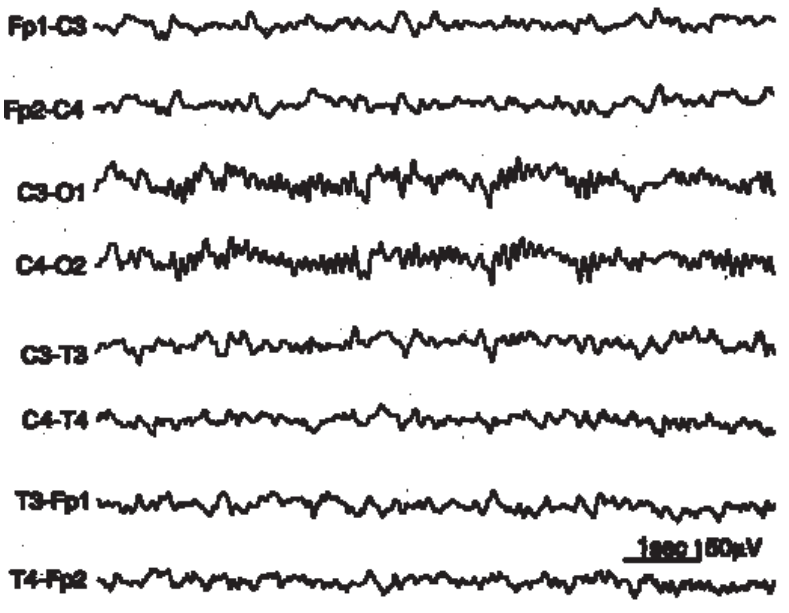


C

FIG. 5.16. A: "Supernormal" electroencephalogram (EEG) for age (10-year-old girl). Greater amounts of slow "fused" (polyphasic) activity could appear in the occipital leads, as in part *B,* or greater amounts on random 4- to 6- Hz moderate-voltage activity could appear in the anterior leads and yet remain within the range of normal for age. **B:** This EEG, from an asymptomatic boy aged 10 years, 2 months, shows greater amounts of "posterior slow waves of youth" than in part *A* but has slightly smaller amounts of anterior slow activity. **C:** Moderately increased slow activity; random moderate-voltage, 4- to 6-Hz activity; and some slower low-voltage fused forms in anterior derivations. Occipital derivations show moderate amounts of polyphasic slow activity. The subject was 9 years, 8 months old.

Lambda Waves

When an individual's eyes are open, especially if the room is well illuminated, sharp waves with a duration of 160 to 250 milliseconds may be recorded in the occipital regions bilaterally. These sharp transients, designated *lambda waves,* are particularly likely to be present if the patient is visually scanning a complex picture. The necessary condition for generation of these waves is saccadic movements of the eyes (4,56). Gastaut (68) initially described them as "biphasic or triphasic potential variations with a small initial positive phase and a prominent subsequent negative phase." More recent studies, involving the use of computer techniques, have shown that the most prominent phase in the occipital region is surface negative (132,174). However, most of the studies concerning lambda waves recorded from the scalp in human subjects (4,53,79,173,176,180,194) describe them as predominantly surface positive at the occipital electrodes (Fig. 5.17). Routine experience indicates that the duration and waveform of lambda waves vary considerably among individuals and that, particularly in children, the highest amplitude and sharpest component are generally surface negative in the occipital derivations. Lambda waves are much more commonly seen in children aged 2 to 15 years than in adults; they are rarely seen in the routine EEGs of elderly people. With long interelectrode distances (e.g., C3 to O1), lambda waves with amplitudes as high as 65 μV may be seen in children (Fig. 5.18).

In a routine clinical EEG, lambda waves may be quite asymmetrical on the two sides and, in fact, may be present on only one side. This asymmetry may lead to the misinterpretation of lambda waves as a focus of abnormal activity. This is especially likely to occur if the technologist or electroencephalographer fails to note that the waves occur only during the eyes-open condition. If there is any doubt concerning the nature of the activity, then eye closure, diminution of illumination, or having the patient stare at a blank white card should eliminate lambda waves but should have no effect on the incidence or amplitude of abnormal occipital sharp waves.

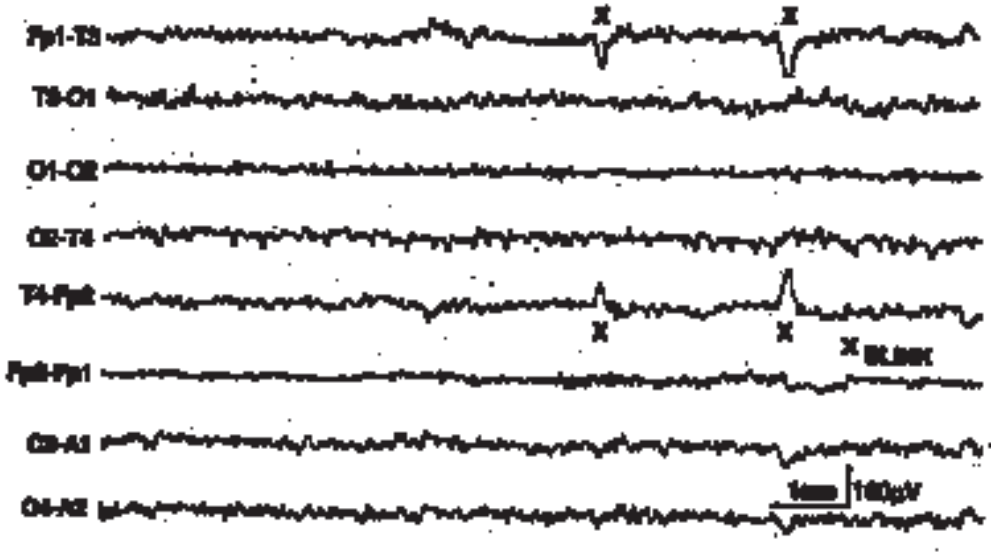
The amplitude of lambda waves, and hence the likelihood that they will be seen in routine EEGs, is greatly influenced by the complexity of the sensory field, by the intensity of illumination of the sensory field, and by its proximity. There are also marked individual differences in the ease with which such waves may be detected (28,56,180).

In children, and less commonly in young adults, scanning of a complex geometric pattern may produce lambda waves, which are predominantly surface negative and have a spike-like configuration (see Figs. 18*A* and *B*). These are a normal finding even when asymmetric on the two sides. When present unilaterally, they may be mistaken for an abnormal focus of spike discharge, but the distinction can easily be made by simply replacing the geometric image with a blank surface. These observations (105) were confirmed by Sunku et al. (189).

Temporal Slow Activity: A Normal Finding in the Elderly?

With increasing age, a significant number of persons show episodic, irregular slow activity in the temporal regions, usually with maximum voltage in the midsylvian region. A 50-year-old subject may typically show a series of EEG changes in the temporal regions during the next 15 years of life. The sequence of changes may be as follows: the first new activity to appear might be episodic, temporal 8- to 10-Hz waves of higher voltage than the occipital alpha rhythm. With time, some episodic activity that is usually a subharmonic frequency (4 to 5 Hz) of the alpha rhythm may then appear. This mixed alpha/theta activity is usually more marked on the left side, is enhanced by overventilation, and may persist when the occipital alpha rhythm blocks with eye opening or with drowsiness. The episodes are usually quite brief, ranging from two to three waves to rarely more than six or seven. Overventilation increases their voltage and persistence. Enhanced temporal alpha activity is not a constant feature. Episodic temporal theta activity of this type, designated *sylvian theta activity* by Gastaut et al. (64), may remain unchanged for many years (up to 20 years in the author's experience), or it may become higher in voltage, more polymorphic, and more persistent.

Because independent temporal focal slow activity may be seen in aged but asymptomatic persons, Obrist et al. (154–156) and Kooi et al. (117) suggested that it is a normal accompaniment of the aging process. Others (21,64,66,112,196), beginning with Gastaut et al. (64), suggested that temporal EEG changes are associated with cerebrovascular insufficiency. A group of persons with evidence of cerebrovascular insufficiency was compared with an age-matched group of controls who had no evidence of such disease; the age incidence of temporal slow activity was shifted to the left in the insufficiency group, and there was a greater overall incidence of this type of activity (Crawley and P. Kellaway, unpublished observations). Furthermore, in a series of subjects aged 50 to 70 years, a comparison of the persons who show temporal slow activity with those who do not revealed a 35% higher incidence of hypertension, coronary insufficiency, peripheral artery occlusion, and other evidence of systemic vascular disease in those



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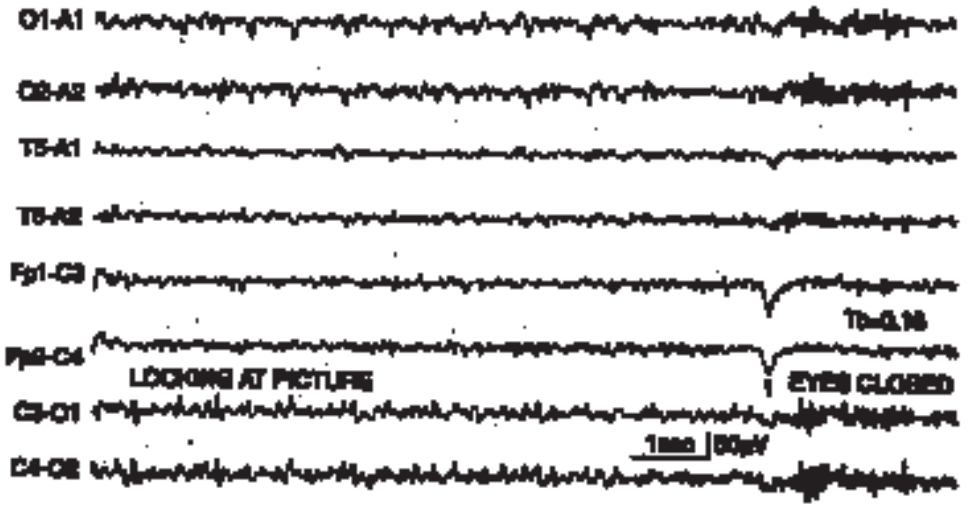


B

FIG. 5.17. A: Lambda waves in an asymptomatic 25-year-old woman looking at a pattern (e.g., ceiling tile). **B:** Recording designed to provide greater definition of lambda waves In an asymptomatic girl, aged 12 years. Note that lambda waves are often polyphasic, and in this child the predominant phase is positive at the occipital electrode.

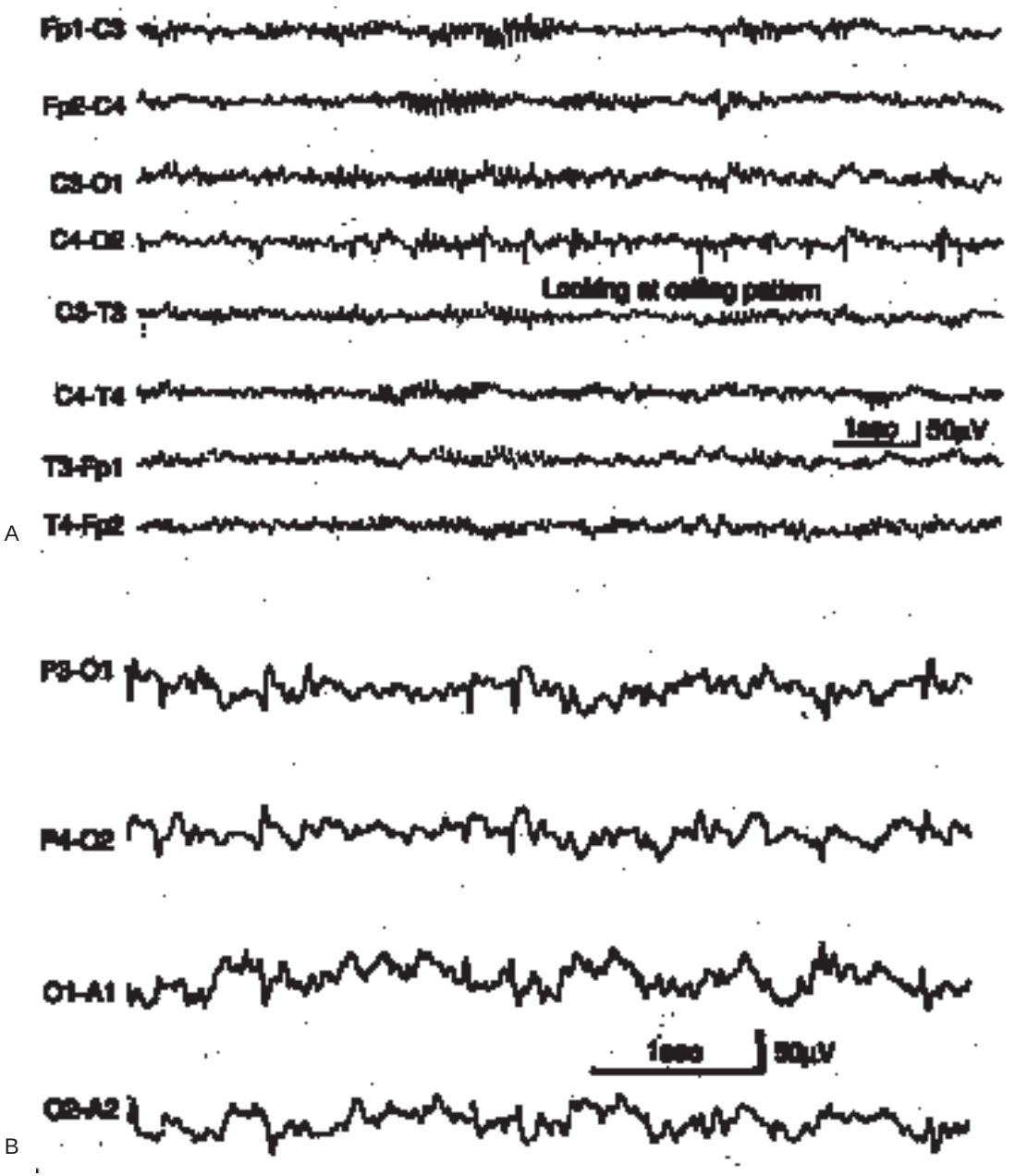


FIG. 5.18. A: High-voltage lambda waves in an asymptomatic 15-year-old, with the maximum amplitude phase negative at the occipital electrode. Note that lambda waves are quite "sharp," are of short duration, and occur almost entirely on the right side. **B:** Lambda waves occurred bilaterally while the subject, a normal child aged 10 years, 7 months, was looking at a pattern in the ceiling tile. Note that the waves have a sharp negative phase.

with the temporal slow activity (Crawley and P. Kellaway, unpublished observations). However, the predominantly left lateralization of the temporal slow activity appeared to have no relationship to the side on which the first or any subsequent transient ischemic attack or completed stroke might occur. These observations, made over a period of 20 years, are based on presurgical and postsurgical EEGs of more than 1,800 patients with insufficiency and on serial EEGs of a group of 200 executives aged 45 to 75 years. However, a well-designed prospective and longitudinal study with quantitative methods has not been performed, and so the descriptive data just mentioned have not been published. To be useful, such a study would have to include measurements of regional blood flow, quantitative EEGs, and neuropsychological evaluations. In the absence of such data, the clinical electroencephalographer faces the problem of interpreting the significance, if any, of various degrees of temporal slow activity seen in a high percentage of middle-aged and elderly patients. It is common practice to report some temporal theta waves and possibly a few temporal delta waves as normal findings in elderly patients. The problems of how much slow activity is allowed and how old the patient must be for the findings to be considered normal are currently being neglected; as a consequence, there is enormous variability in the way individual electroencephalographers evaluate this type of finding.

When episodic 4- to 5-Hz, low- to moderate-voltage waves are present in the temporal leads bilaterally or with a marked predominance on one side (usually the left) in persons aged 50 years or older, it is reasonable to report their presence and to note that such activity may occur in asymptomatic persons in this age group. When the activity is present in younger adults, or if there is episodic temporal delta activity, the suspicion of clinically significant abnormality is increased. It is important also to recognize that, because temporal slow activity occurs in asymptomatic elderly persons, such findings in patients of this age group who are referred because of head injury or possible cerebral metastases are *unlikely* to be related to these etiologies and therefore carry the same meaning here as would a normal EEG.

A case in point concerns a 65-year-old man who was in the hospital for gallbladder surgery. He fell out of bed one morning and bruised his forehead; he was not unconscious but seemed confused for several minutes after getting back into bed. The EEG (made on the afternoon of the same day) showed a well-regulated 9-Hz occipital alpha rhythm, with some episodic, low-voltage 3- to 5-Hz waves in the left temporal region and some rare activity of similar frequency that occurred independently in the right temporal region. Statistically, there is a high likelihood that such EEG findings in a man of this age predated the injury; also, focal episodic left-lateralized temporal theta activity is an unlikely consequence of an acute closed-head injury. Follow-up EEGs 5 and 10 days later showed no change.

Another case concerns a 72-year-old woman with a history of breast cancer and bilateral mastectomy, referred for EEG studies because of attacks of dizziness and headaches. The tentative diagnosis was cerebral metastasis. The EEG showed an 8-Hz alpha rhythm, with some moderate-voltage (85 μV maximum) 4- to 5-Hz waves that appeared episodically in the left and right temporal regions independently but were much more marked on the left side, where there were also occasional low-voltage 3- to 4-Hz waves. The EEG report indicated that these findings were probably not related to the presence of cerebral metastasis but that a follow-up study at 4 weeks might be helpful in this regard. Over a period of 18 months, the patient continued to complain of headache and dizziness, but several EEGs failed to show any change. Over the next 3 years, the patient's symptoms showed some fluctuation but no progression and no evidence of cerebral metastasis. The EEG remained essentially unchanged.

Torres et al. (191) found a significantly higher percentage of focal slow activity in volunteer elderly subjects "who showed no signs or symptoms of central nervous system disease" than in patients with known cardiovascular disease. However, in another series of elderly patients "rigorously selected for neuropsychiatric normality," Katz and Horowitz (100) found a very low incidence of focal temporal slow activity, and one study (200) reported that temporal slowing is correlated with subtle speech problems and computed topographic scan changes.

The more that temporal slow activity differs from the simple prototype shown in Fig. 5.19, the more it should be regarded with suspicion. The slower the activity, the greater the voltage, and the more complex and (particularly) the more continuous the waveform is, the less reasonable it becomes to regard the finding as being within the range of normal variation for age.

The definition of temporal slow activity is critically important. The slow activity must be characterized in terms of frequency, amplitude, mode of occurrence, precise location, and percentage of time during which the subject is awake. All studies of elderly patients have found low-voltage intermittent temporal theta activity in a percentage of asymptomatic elderly persons; an incidence of about 35% has been reported by several different groups (3,23,91,191). Paroxysmal bursts or long trains of rhythmic theta

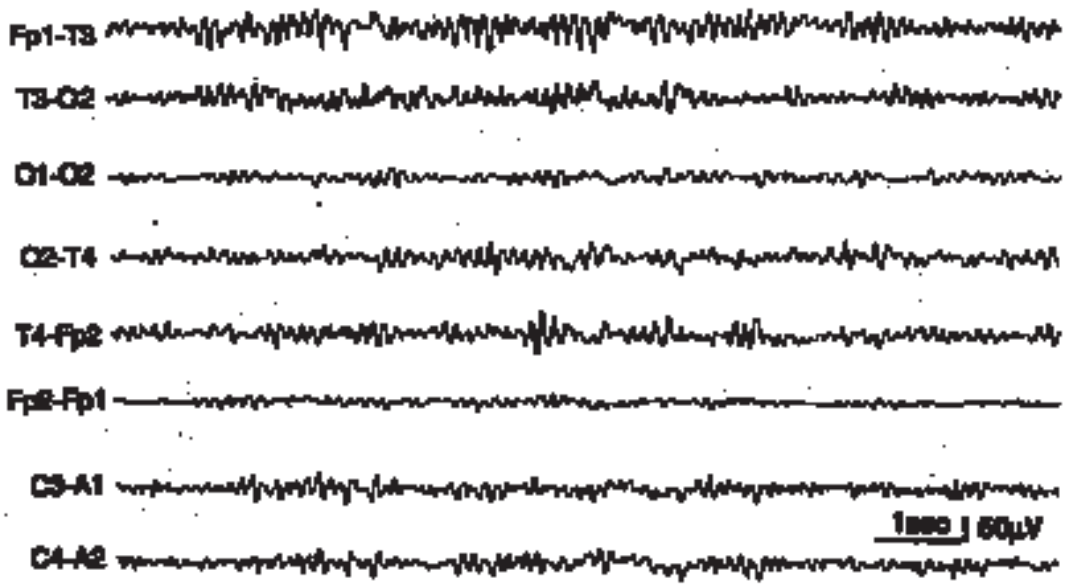


FIG. 5.19. Temporal alpha and fused slow activity on the left side and occasionally independently on the right in a 60-year-old man with occlusive carotid disease, more marked on the right.

activity in the temporal region are not seen in normal elderly persons. Episodic focal temporal delta activity occurs in only 12% to 18% of such persons (3,100,191). The slower the activity, the higher its voltage, the greater its persistence, and the more strongly lateralized it is, the less likely that it will be found in normal elderly subjects.

Episodic delta activity occurring focally in the temporal regions, synchronously or asynchronously on the two sides, is an abnormal finding in elderly persons (162,196); moreover, the correlation with vascular insufficiency, particularly with small-vessel disease, is much greater than it is with temporal theta activity (P. Kellaway and Crawley, unpublished observations).

Hyperventilation Response

Throughout the literature of pediatric electroencephalography, the response to hyperventilation is cited repeatedly as partial or complete supporting evidence of brain abnormality in children. Historically, this concept originated in the early report of Lindsley and Cutts (133):

> Overbreathing in some cases produced what we have called a "hyperventilation effect." This is defined as a distinct change (usually abrupt) in the electroencephalogram, consisting of a sequence of slow waves, ranging in frequency from 2 to 8 per second and usually of a magnitude considerably above anything of similar frequency occurring in the records before hyperventilation. The "hyperventilation effect" may persist as a continuous series of rhythmic slow waves or may consist of repeated bursts of slow waves at irregular intervals. Two measurements were made, one of the duration from the beginning of hyperventilation to the onset of the "effect," the other of the duration from the cessation of hyperventilation to the disappearance of the "effect."

Lindsley and Cutts's subjects spent 1.5 minutes hyperventilating unless a marked effect appeared before that time, in which case subjects were told to stop overbreathing and to remain quiet until the record returned to the original state. Lindsley and Cutts found that children with behavior problems showed a more abrupt and greater buildup of slow activity and more prolonged effects after cessation of hyperventilation than did normal controls. The subjects were instructed "how to hyperventilate or overbreathe at a relatively uniform depth and constant rate," but no measurements were made to determine the blood carbon dioxide tension (PCO_2) or pH changes, nor were the blood-glucose levels measured at the time of the test. It is now known that all of the measures of the "hyperventilation effect" used by Lindsley and Cutts (i.e., abruptness of the change, amplitude and slowness of the

waves produced, and degree of persistence of the effect after overbreathing stopped) are determined by the effectiveness of the overbreathing in producing a change in blood PCO_2 as well as by the level of blood glucose at the time of the test. It is difficult to judge the degree of hypocapnia (blood PCO_2 reduction) produced by a given hyperventilation effort (9), particularly in children; the rate, depth, and consistency of the respiratory effort are extremely difficult to gauge and compare without measuring the respiratory exchange or blood PCO_2 changes. Even if attempts are made to standardize the performance of overbreathing, the effect on blood chemistry is unpredictable (149); furthermore, an uncertain relation exists between the levels of peripheral and cerebral blood gases because of cerebral vasoconstriction and resulting in hypoxia, which, until recently, has been considered the main basis for the effect on the EEG (77,160). A critical review of the world literature on the subject (156) has not yielded unequivocal evidence for the idea that cerebral hypoxia is the critical factor in producing this response. It has been shown that hypocapnia produces decreased activity of the of the mesencephalic reticular formation (10) and that lesions that disconnect the cortex from the anterior part of the reticular ascending activating system abolish the hypersynchronous slowing effect of hyperventilation (10,183).

The blood-glucose level is important in determining the degree of response to hyperventilation (17,18,41). Most routine EEG studies of children do not control for this factor; however, even in adults, a low blood glucose level (<80 mg per 100 mL) favors the appearance of slow waves, and a high level (>120 mg per 100 mL) tends to inhibit or prevent such an effect (41).

If effective overventilation is obtained in children, slow waves appear much more abruptly and are more pronounced than in adults, and the slowing outlasts the overbreathing for a longer time in children (74). The degree and abruptness of the response seem to relate directly to age (19,74,78,206). Indeed, when the blood PCO_2 change produced by overbreathing is measured, there is a linear relationship between age and the effect produced (38,39). Practically speaking, under routine laboratory conditions, in which respiratory effort and effect are not measured, the most pronounced responses to overventilation usually occur in children 8 to 12 years of age (19,55,165) (Fig. 5.20).

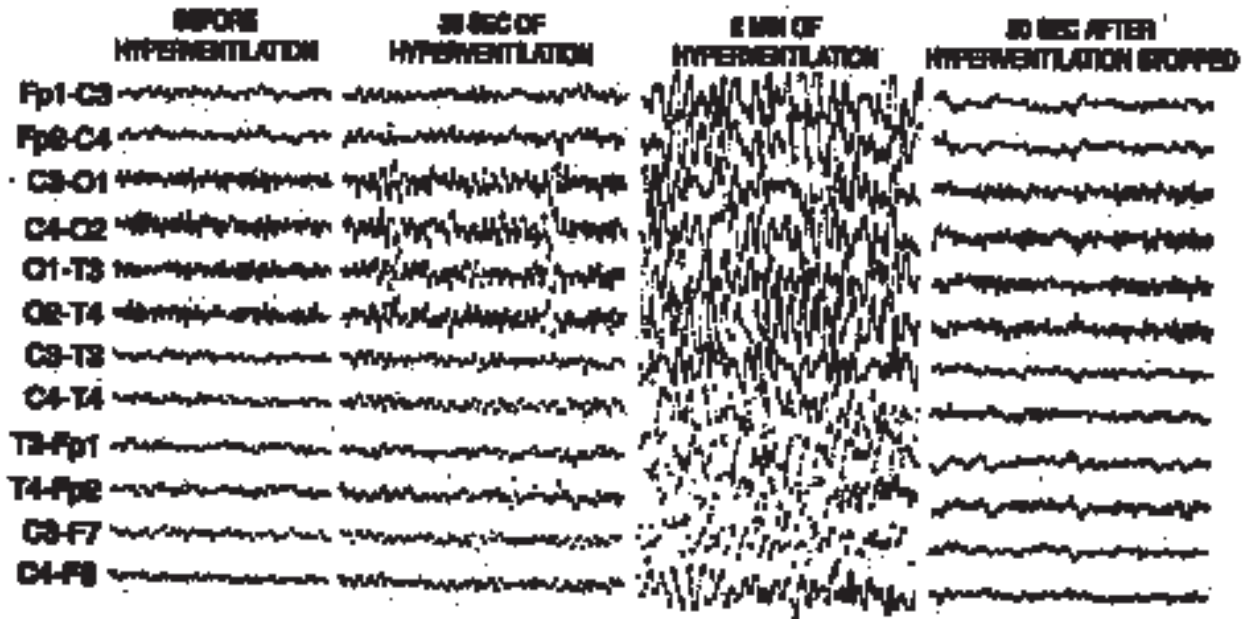


FIG. 5.20. Example of pronounced overventilation response that may occur in children 8 to 12 years of age. The subject was a girl aged 9 years, 6 months, at time of the electroencephalographic study, with serum glucose level of 110 mg/dL. She had no history of seizures or evidence of central nervous system disease. Note that initial posterior slowing, typically seen in children, is quite marked after only 30 seconds of overventilation. Some frontal delta activity continues 50 seconds after overventilation stopped.

Practical experience has shown that in routine diagnostic electroencephalography, interpretation must allow wide latitude for the degree of slowing and for the abruptness and duration of the hyperventilation effect. Only the elicitation of *abnormal wave complexes (spike-and-slow-wave, sharp-and-slow-wave) or clear focal or lateralizing changes* can be considered unequivocal evidence of abnormality. Even paroxysmal slow bursts are not acceptable evidence of abnormality, because these may be elicited in normal children under certain circumstances (48,165). Nonetheless, "susceptibility to hyperventilation" (7) and other characterizations of pronounced overventilation responses have been used as diagnostic measures in the evaluation of children (92).

Although prominent slow activity occurs less commonly in adults than in children, it too should be regarded with the same degree of caution. An abrupt, pronounced, or prolonged buildup of slow waves should never, in itself, be considered a basis for classifying an EEG in an adult as abnormal and certainly should *never* be considered a criterion for the diagnosis of epilepsy. If the blood glucose is near normal and the pronounced or prolonged slowing persists, there may be some reason to suspect abnormal brain function. However, in the absence of direct measurement of the blood PCO_2 level, only elicitation of a focal abnormality or production of an abnormal wave pattern can reliably indicate disordered brain function.

Activity of Drowsiness, Arousal, and Sleep

Activity of Drowsiness (Stage I Sleep)

Monorhythmic Slow Activity. The state termed drowsiness in adults and children—a condition characterized by slow, pendular eye movements—is classically associated with the disappearance of the occipital alpha rhythm and the appearance of some rhythmic and semirhythmic theta activity in the central or frontocentral regions. A comprehensive study of drowsiness has shown that there may be several variations of this pattern, including some persistence of the occipital alpha activity into the drowsy state (178). The various EEG patterns are not detailed here but are well documented in Santamaria and Chiappa's book (178), which is devoted entirely to this subject. Many of the patterns described have been recognized as state-related and not abnormal findings by experienced electroencephalographers, without benefit of the rigorously derived data that this book provides. The findings reported in this book are critical to the interpretation of the EEG and, as the authors stated in their preface, will be of great utility to electroencephalographers, polysomnographers, and investigators involved in psychophysical studies that use EEG and evoked potentials.

Drowsiness is usually defined as a presleep state, or a prodromal or twilight condition between being fully awake and asleep. In infants and young children, overt signs of drowsiness may not be evident even though the EEG shows changes indicating that the child is falling asleep. "Drowsiness" commonly conjures up a certain vision of a "heavy-lidded" appearance and, on the contrary, infants may have their eyes wide open and may be irritable and restless during a variable period before onset of clinical and electrographic sleep. For that reason, the author and colleagues have used the less common term *hypnagogic* to refer to this state (110). A smooth transition from the hypnagogic state to sleep may not occur, especially in the strange environment of the EEG laboratory; instead, the child's condition may fluctuate between sleep, arousal, and transitional states. A steady state of slow-wave sleep (stages II, III, and IV) may not appear under ordinary conditions in the EEG laboratory for intervals ranging from a few minutes to an hour or more.

In order not to be misled by the sometimes dramatic changes in the EEG that occur during the transition between wakefulness and sleep, the clinical electroencephalographer must know the EEG patterns and their variations that may occur during this state in children of various ages. The electroencephalographer can better understand and interpret what transpires if the entire process of falling asleep is recorded. The irrational, if economical, practice of turning off the instrument while waiting for the child to fall asleep may also result in loss of critical data: An important electrographic event may occur only once or only during one stage of the sleep cycle. Furthermore, the child sometimes drops precipitously into deep sleep, with a consequent omission of the productive stages II and III of sleep.

The changes that take place in the transient stage between wakefulness and sleep are best understood in view of the changes with increasing age from birth onward: once a sustained, rhythmic, occipital activity appears at approximately 3 months of age, the onset of the hypnagogic state is marked by sustained, monorhythmic, slow generalized activity. When this activity first appears, the frequency is 3 to 4 Hz, and it increases in older children to 4 or 5 Hz. Approximately 30% of 3-month-old infants show this hypnagogic hypersynchrony; the degree of its expression and duration vary in a single

infant at different times and on different days. It may be seen in normal children up to the age of 12 or 13 years but is increasingly rare after the age of 11 years, when it appears in only 10% of healthy children. Figure 5.21 shows the incidence of this drowsy pattern in the author's own series of 1,000 healthy children. The relation to age resembles that reported by Gibbs and Gibbs in asymptomatic children (71) and by Eeg-Olofsson et al. in highly selected normal subjects (49).

In some children, the occipital alpha rhythm may slow as drowsiness ensues (Fig. 5.22), and at a time when anterior derivations show the more usual 4- to 5-Hz hypnagogic hypersynchrony, the occipital derivations may show some high-voltage, less regulated, slower (3- to 4-Hz) activity. The latter effect occurs in not more than 3% of healthy children before the onset of sleep, but it occurs in approximately 6% after arousal. It commonly occurs during a transient episode of arousal. In the author's series of healthy controls, all children with this pattern were younger than 4 years.

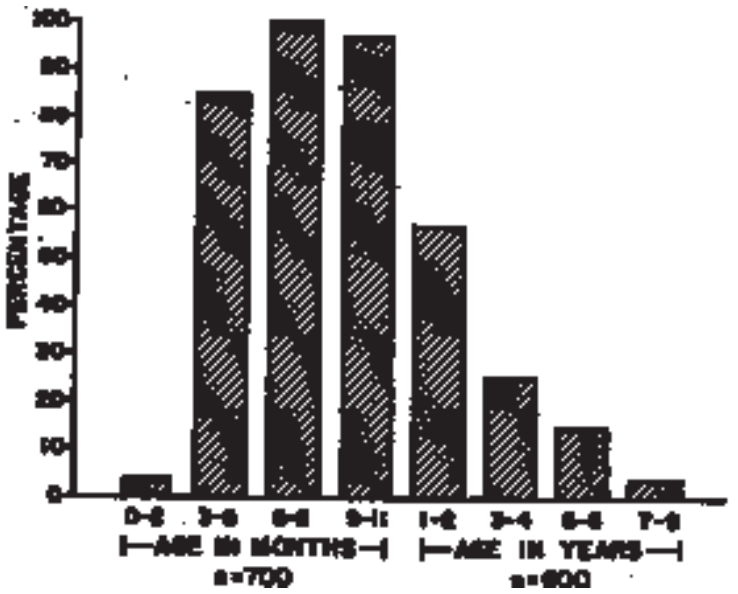


FIG. 5.21. Age distribution and incidence of sustained monorhythmic slow-activity drowsiness in asymptomatic children.

More commonly, as a shift toward sleep takes place, the occipital alpha rhythm becomes less persistent, and a central or frontocentral rhythm of 4-6 Hz develops; this rhythm may have a high voltage (200 μV). Examples of monorhythmic drowsy patterns in children of various ages are shown in Figs. 5.22 and 5.23.

Paroxysmal Slow Activity. Gibbs and Gibbs (71) and Kellaway and Fox (110) were the first to describe paroxysmal slow bursts during drowsiness in normal children. The latter authors described it as follows:

> "The onset of the hypnagogic phase is signaled by a general reduction in the amplitude and rhythmicity of the activity of all areas. This relative `quiet' may then be broken by paroxysmal bursts of high voltage sinusoidal waves which involve all leads but which are greater in amplitude in the precentral or central regions and generally more strongly expressed in the frontal than in the occipital regions."

"These paroxysmal bursts may reach extremely high voltages when maximally expressed (in excess of 350 microvolts) and therefore constitute a possible source of error both for the interpretation of sleep where this is sought and for the interpretation of waking records where the oscitant state may intervene without true sleep ensuing....The appearance of such bursts in the period just preceding true sleep, or at its onset, or at a time when the electrogram shows other evidence of the hypnagogic state, is never considered an epileptiform manifestation unless accompanied by spike discharges in some form. Long experience has shown that if a patient with established petit mal epilepsy shows abnormal paroxysmal activity during sleep the spike component is always strongly in evidence and the epileptiform serials persist into fairly deep levels of sleep. A distinguishing characteristic then of the pre-oscitant paroxysmal episodes is that they make a brief appearance at the onset of sleep and do not persist into deeper stages."

The example of paroxysmal drowsy waves illustrated in the report of Kellaway and Fox (110) is shown in Fig. 5.24. The paroxysmal activity in this sample, which they considered representative for age (35 months), has a frequency of 4.0 to 4.5 Hz, shows maximum voltage in the central regions, and shows a spindle-like waxing and waning of amplitude typical of the drowsy patterns seen in their series of asymptomatic children.

More complex waveforms, slower wave bursts, and a more frontal dominant distribution of the activity may also be seen in normal children. The example of paroxysmal slow activity illustrated by Gibbs and Gibbs (71)

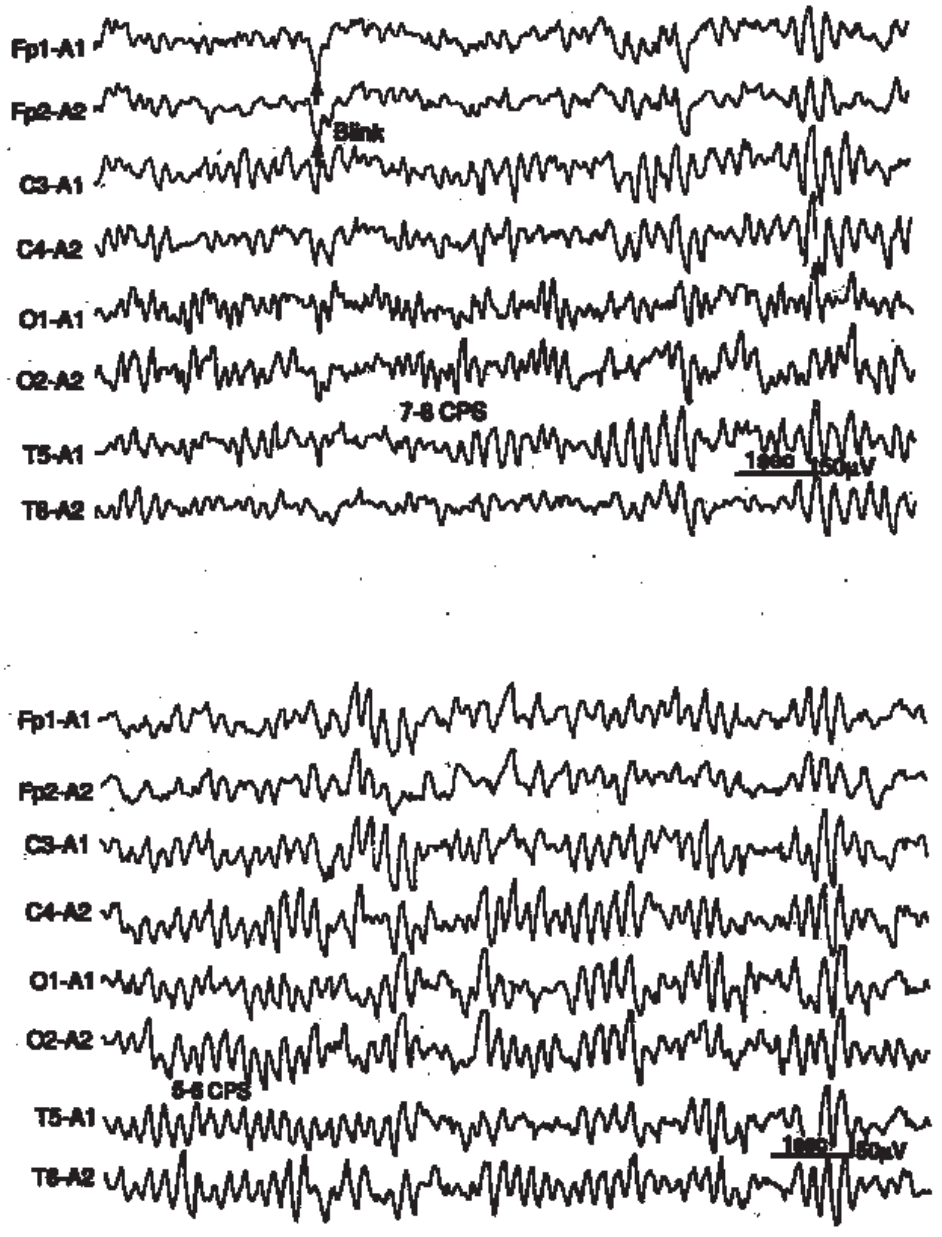
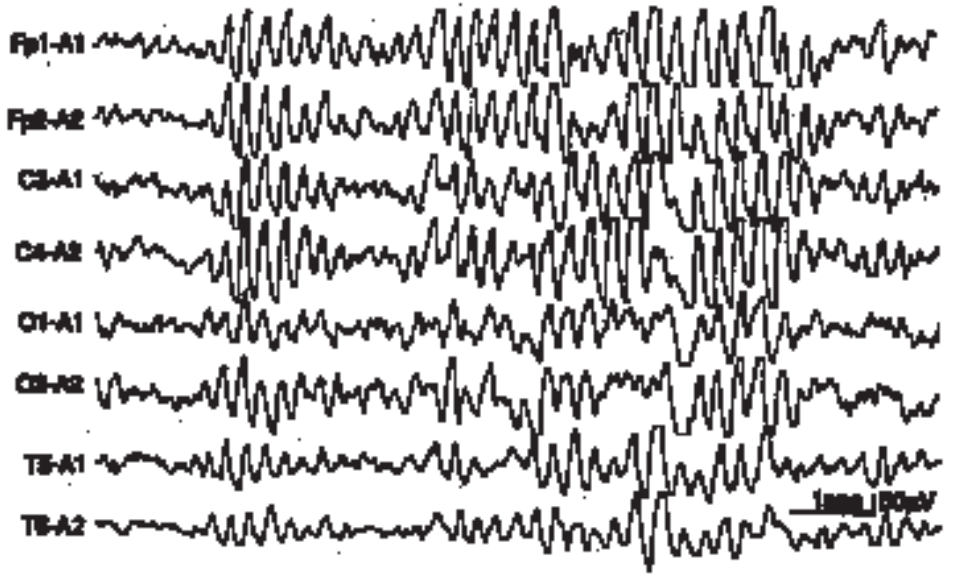


FIG. 5.22. A and **B:** Slowing of the occipital alpha rhythm as the record shifts from the awake state (first two-thirds of part *A*) to the drowsy state (last third of part *A* and all of part *B*) in an asymptomatic girl aged 28 months.



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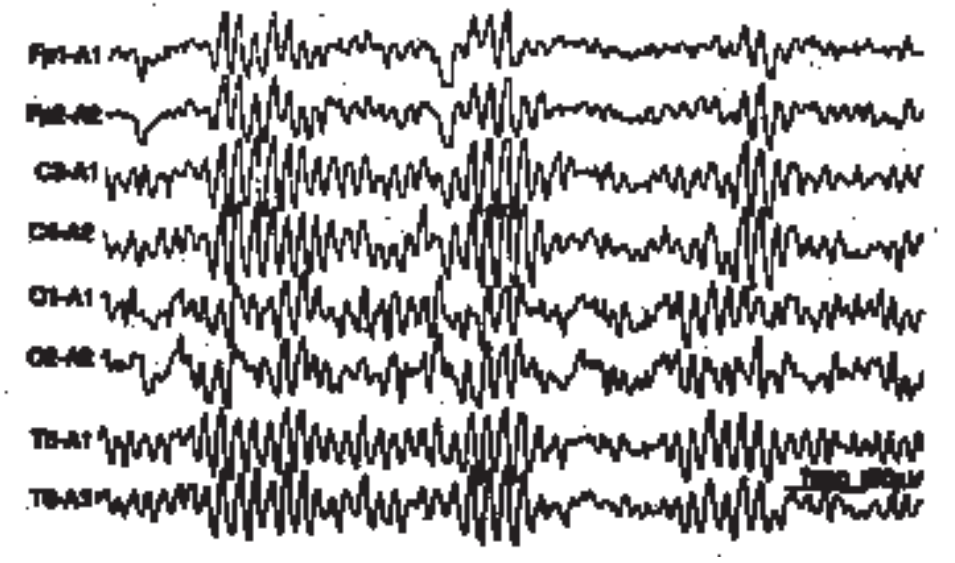


B

FIG. 5.23. A: Almost continuous "hypnagogic hypersynchrony" in an asymptomatic 6-month-old infant. **B:** Continuous "drowsy" pattern in an asymptomatic 12-month-old infant.

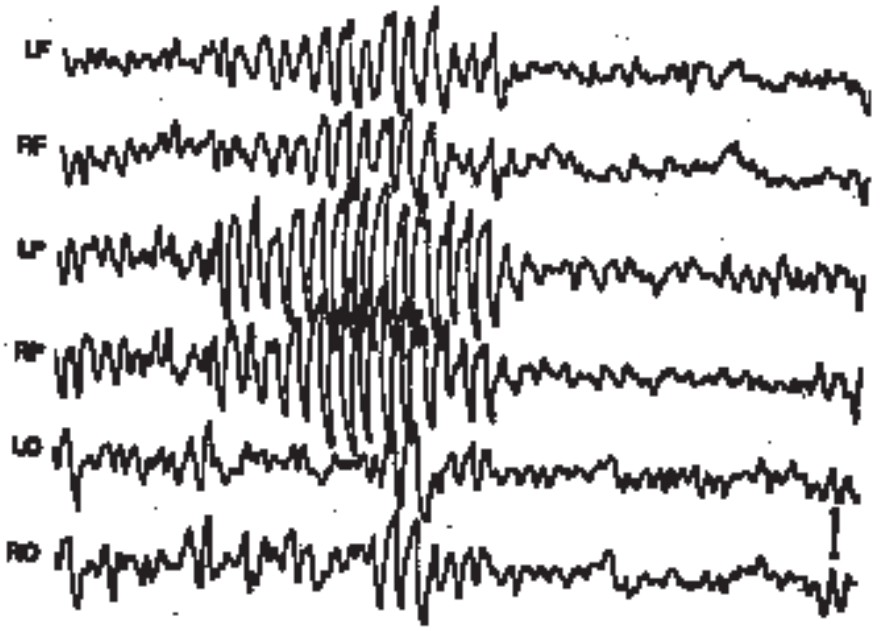


FIG. 5.24. Paroxysmal "hypnagogic hypersynchrony" in an asymptomatic girl aged 35 months. (From Kellaway P, Fox BJ. Electroencephalographic diagnosis of cerebral pathology in infants during sleep. I. Rationale, technique, and the characteristics of normal sleep in infants. *J Pediatr* 1952;41:262–287.)

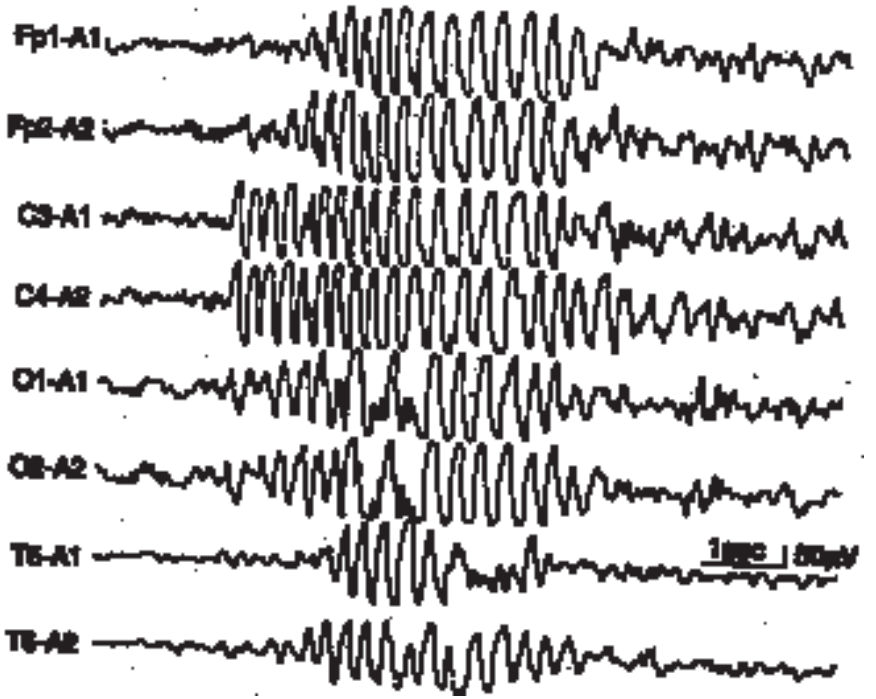


FIG. 5.25. Paroxysmal "hypnagogic hypersynchrony" in a 14-year-old girl, asymptomatic at the time of the electroencephalographic study and during the 20 years after the tracing was made. There was no family history of seizures. Complex, paroxysmal slow bursts of this type, occurring only in drowsiness, are rare at this age (see Fig. 5.27).

shows (a) some waves at the end of the bursts as slow as 2.5-3.0 Hz, and (b) some complex waveforms with faster components superimposed on, or intermixed with, the slow waves. Figures 5.25 and 5.26 show examples of activity of this type in drowsy asymptomatic children. It is difficult to distinguish between such bursts and a pattern described by Gibbs and Gibbs (72) which they designated "pseudo petit mal." They characterized the pattern as "paroxysmal diffuse 3–4 per second slow waves, with a poorly developed spike in the positive trough between the slow waves, occurring in drowsiness only...and most prominent in the parietal [central: C3–C4] areas." Gibbs and Gibbs saw this pattern only in children between the ages of 3 months and 9 years and only in 0.1% of normal children aged 0 to 14 years. Eeg-Olofsson et al. (49), however, found similar activity during drowsiness in 7.9% of 599 highly selected normal children aged 1 to 16 years. The highest incidence (12%) was in children aged 4 to 5 years. Gibbs and Gibbs described this "drowsy" pattern as consisting of bursts of 2- to 4-Hz waves of 100 to 300 μV, with a spike or spike-like component appearing briefly, early or late, in the burst. The pattern disappeared as soon as drowsiness was replaced by deeper sleep. A wide diversity of patterns of paroxysmal drowsy bursts, , ranging from a common type with occasional notching of the slow waves to bursts with polyspike-like components, may occur in normal children (see Fig. 5.26).

Figure 5.27 illustrates the incidence of "paroxysmal hypnagogic hypersynchrony" in asymptomatic children of different ages. The hatched bars

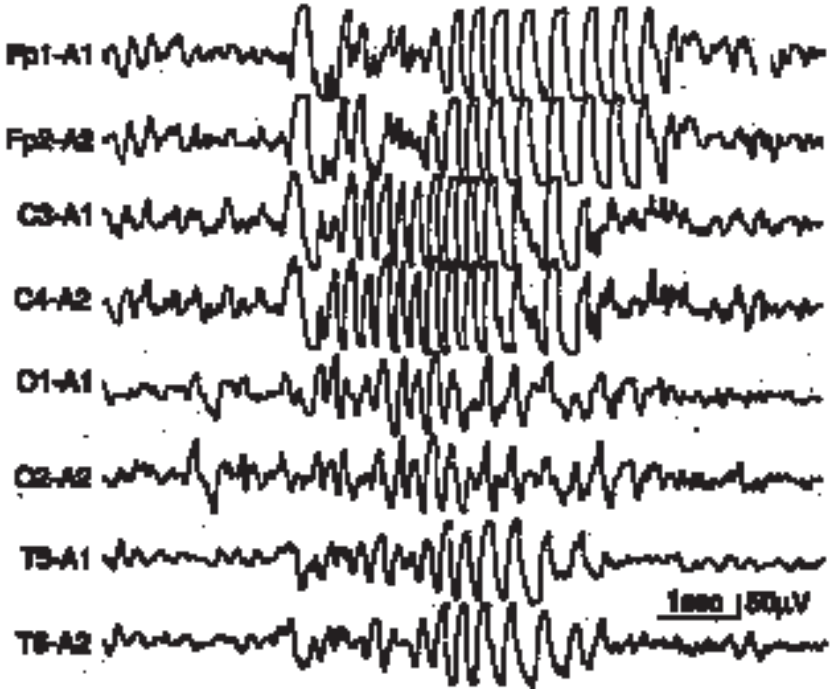


FIG. 5.26. Complex wave configurations such as in O1 and O2, as well as low-voltage, spike-like components seen in other derivations, are most common in drowsy, asymptomatic children between the ages of 4 and 9 years. The subject was an asymptomatic 7-year-old boy.

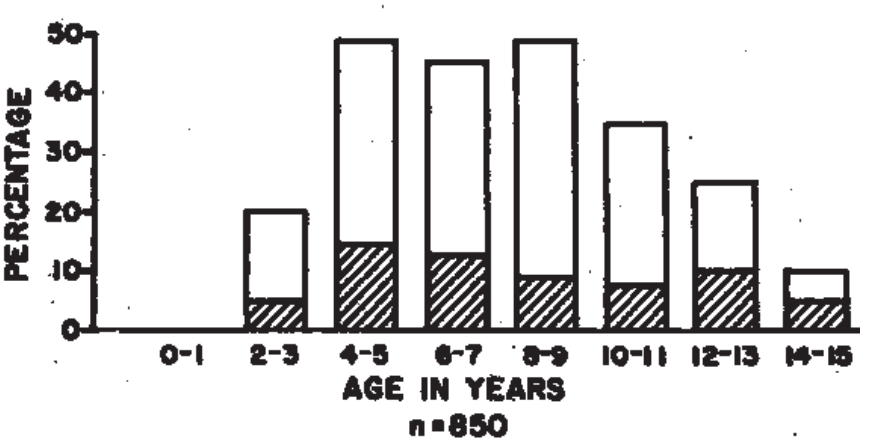


FIG. 5.27. Percentages of asymptomatic children of various ages who show paroxysmal slow bursts in drowsiness. Hatched areas show percentages having sharp or spike-like components intermixed with slow waves, as in Figs. 5.25 and 5.26.

show the incidence of what Brandt and Brandt (12) called the "severe" type (i.e., slow bursts with sharp or "spike-like" components). The percentage approximates that found by Eeg-Olofsson et al. (49) in their highly selected normal children.

In routine clinical practice, if such bursts occur only during drowsiness or at the onset of sleep, they cannot be considered evidence of abnormal function and certainly cannot support a clinical diagnosis of epilepsy. Even bursts with a clearly defined spike component fitting Gibbs and Gibbs's (72) definition of "pseudo petit mal" have only a tenuous association (10%) with febrile convulsions. According to Gibbs and Gibbs, the incidence of epileptic (other than febrile) convulsions is only 7% greater in children with "pseudo petit mal" bursts than in children with normal EEGs, a difference that is not statistically significant.

From the ages of 3 months to 6 years, patterns of drowsiness may vary from time to time in the same child. If sleep begins abruptly, little hypersynchrony of any type may be seen. If there is a delay in the onset of true sleep, continuous, rhythmic, high-voltage slow or paroxysmal slow activity may persist for prolonged periods. Transient arousals (Fig. 5.28) frequently elicit a paroxysmal type of slow pattern; thus, it is important for the technologist to make note of such arousals and for the electroencephalographer to watch for artifacts associated with such a change of state.

Arousal from any level of sleep in infants and children is generally associated with a paroxysmal change. This may be a single, high-voltage, sharp-wave transient similar to that in adults, or it may be a complex three-phase change, which, if unexpected or unrecognized as an arousal event, may be misinterpreted as abnormal.

In general, the ages with pronounced arousal patterns coincide with those for hypersynchronous slow drowsy patterns.

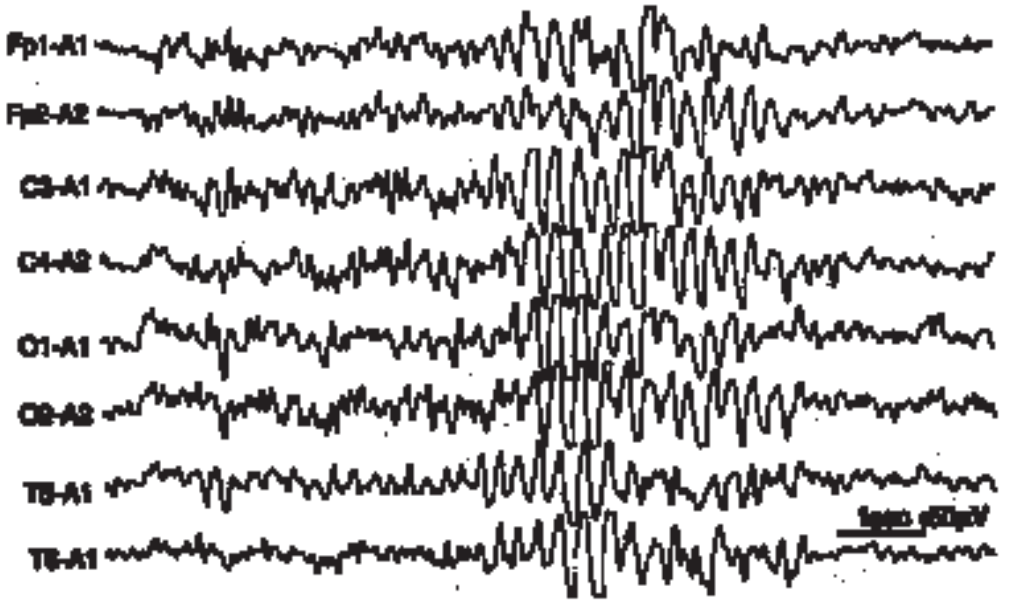


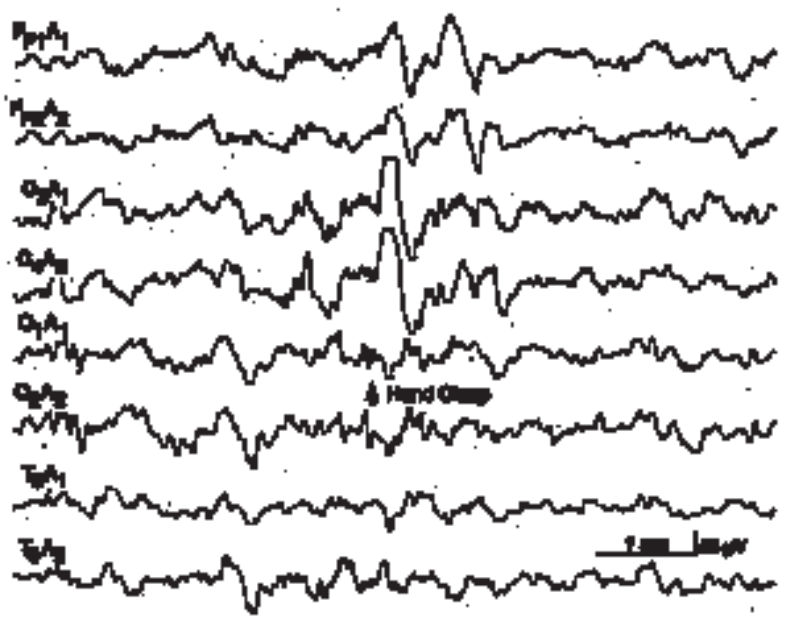
FIG. 5.28. Transient arousal in an asymptomatic boy, aged 7 years. Just before the beginning of the sample, the child had been asleep (stage II). A brief period of desynchronization is followed by some central and occipital alpha activity lasting 2.0 to 2.5 seconds and, in turn, by a high-voltage, central-dominant, "drowsy" burst lasting about 3 seconds; then sleep resumes.

Activity of Arousal

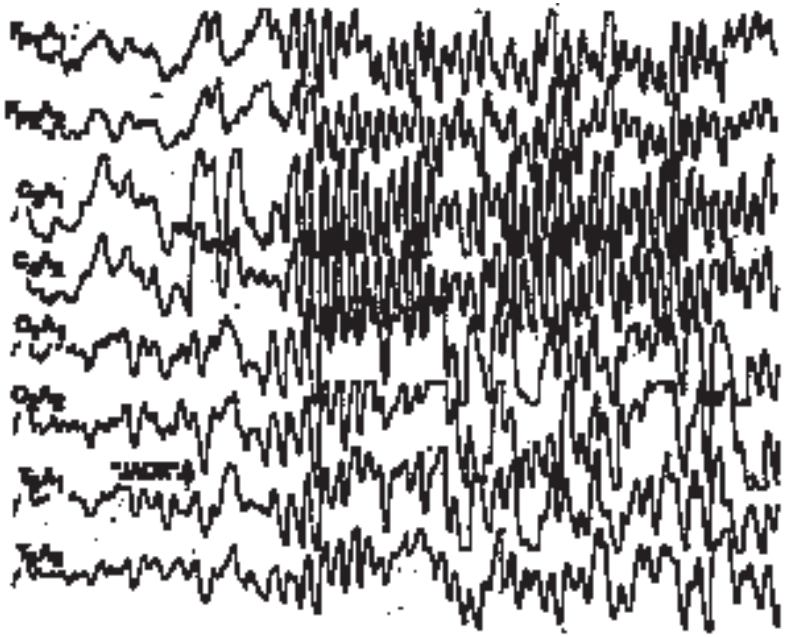
Loomis et al. (135) were the first to show that reactive arousal involved a more or less complex electrographic pattern, rather than a simple and immediate transition from sleep to waking activity. In adults, they observed an initial diphasic slow wave followed by a series of rapid oscillations of about 8 to 14 per second, the total pattern occurring maximally in the central regions "but appearing at lower amplitude in the frontal, occipital, and temporal areas also."

This phenomenon appears prominently in children but varies somewhat in character and degree with age. The initial slow component, sometimes erroneously referred to as the *K complex,* is discussed later in relation to the spontaneous, bilateral central sharp-wave transients seen in light sleep. The fast component represents, as the original workers hinted, a process associated with a greater degree of arousal. Thus, the slow-transient component may represent the only response to a stimulus (e.g., a loud sound), with no clinical signs of arousal and, in fact, no transition to a lighter stage of electrographic sleep (Fig. 5.29*A*). The fast component

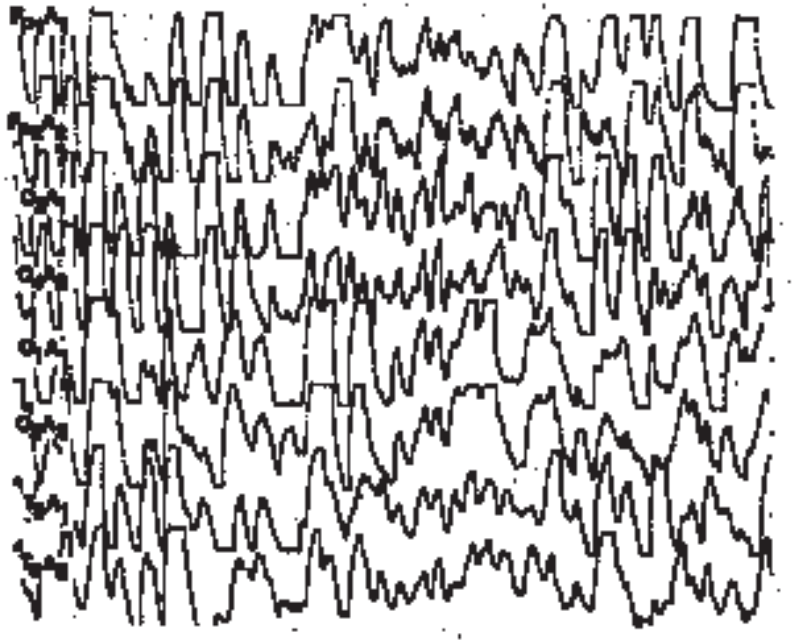
FIG. 5.29. Response to stimulus, and phases of arousal response, in a normal child, aged 6 years. **A:** Handclap elicits only a vertex transient, with no clinical or electroencephalographic evidence of arousal. Calling the child's name results in a full sequence of arousal, as follows: **B:** The first phase is the central dominant fast component. **C:** In the next phase, the central fast component is replaced by generalized slow activity, with rhythmic monomorphic delta activity in the frontal regions and slower, less rhythmic, activity in posterior derivations. **D:** The last phase of the arousal pattern before the normal alpha rhythm reappears consists of posterior rhythmic and semirhythmic delta activity. The child appears to be awake as soon as phase C (frontal delta activity) occurs. The calibration is the same for all four tracings. Arousal in a child may be aborted at any of these phases, with a reversion to sleep. The degree of arousal may alternate between phases two or more times before an awake state is sustained.



A



B



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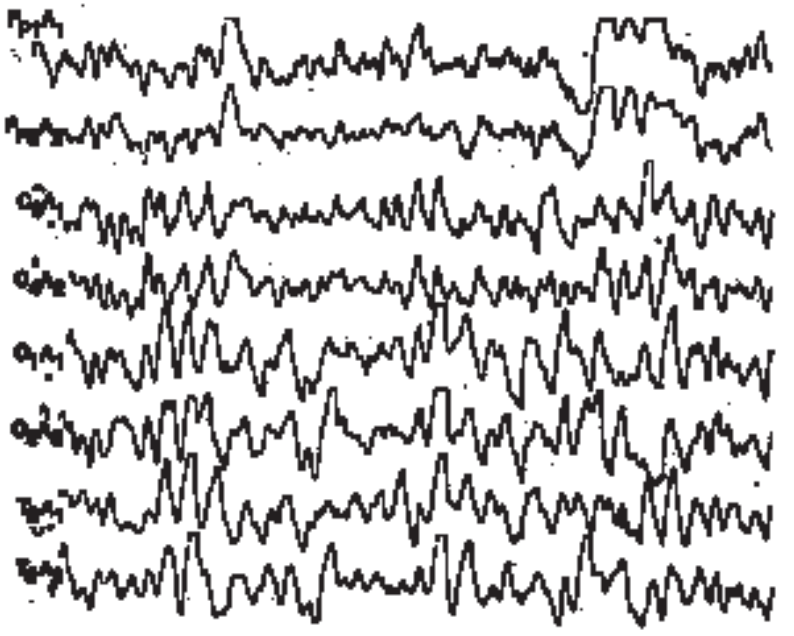

D

(see Fig. 5.29*B*) may also occur without further EEG or clinical evidence of arousal but is often *followed* by such evidence.

Neither component of the electrographic arousal reaction is clearly defined before the age of 2 months. During the first 8 weeks after birth, and especially during the first 6 weeks, the transition from sleep to waking is characterized only by a degree of desynchronization. Sometime between the eight and twelfth week, rudimentary diphasic slow-wave responses to applied stimuli may occur; also, at about this time, the first signs of a definite rhythmic hypersynchrony, similar to that of the drowsy state, appear in the immediate postarousal state. However, the slow component of the arousal reaction is rarely well defined before the age of 3 months.

The faster component of the arousal reaction usually does not appear before the age of 7 months. Initially rudimentary, it consists of a few moderately high voltage sinusoidal waves of 4.0 to 4.5 Hz in the frontocentral region, superimposed on a slower, irregular background activity.

With increasing age, this fast component of arousal increases in frequency until it reaches the adult rate of 8 to 10 Hz. In children, it is maximal in the central region (C3 to C4), and its field is such that its voltage is higher at F3 and F4 than at P3 and P4. Its appearance is transitory, and its duration is usually no more than 4 to 5 seconds. Occasionally, runs of this activity may last as long as 30 seconds (110).[10]

Postarousal Hypersynchrony

In children, the fast component of the arousal pattern is quickly followed by what in adults would be called a "paradoxical arousal response." Thus, as the child awakens, a high-voltage, monomorphic, quite slow rhythm (2.5 to 3.5 Hz) appears in the frontal regions (see Fig. 5.29*C*); and as further arousal ensues, the rhythmic slow activity becomes less slow and moves posteriorly, with the voltage and persistence of the rhythm progressively diminishing in anterior derivations (see Fig. 5.29*D*). In infants and children in whom continuous "monorhythmic slow" or "paroxysmal slow" activity occurs during drowsiness, there may be similar episodes of postarousal hypersynchronous slow activity of similar frequency (110).[11]

The various components of arousal and awakening patterns in children shown in Fig. 5.29 may be aborted at any point in the process. If an external stimulus triggers the arousal (if there is a sudden sound, if the child's name is called, or if the child is touched), a diphasic sharp-wave transient appears in the region of the vertex; if no arousal effect is produced, the background EEG activity reverts immediately to its prestimulation character (as in Fig. 5.29*A*). Presumably, a further degree of arousal is signaled by the appearance of the fast central component (as in Fig. 5.29*B*), and overt signs of arousal (e.g., movement or eye opening) do not occur until the hypersynchronous slow activity appears (see Fig. 29*C*). *Spontaneous* arousal may occur without the appearance of the diphasic central (vertex) sharp-wave transient.

In adults, the arousal pattern depends on the level of sleep that preceded the arousal. Arousal from stage I (drowsiness) is not associated with any change other than a reversion to the awake alpha rhythm pattern (Fig. 5.30). Once the spindle stage has been reached, an attenuated form of the arousal patterns seen in children may occur: There may be an initial diphasic central sharp-wave transient, followed by a brief train of waves of alpha activity frequency that occur *in the frontocentral region,* and there may be one or two high-voltage, frontal slow waves (1.5 to 3.0 Hz). Examples of adult arousal patterns are illustrated in Figs. 5.30 and 5.31.

A postarousal, frontocentral burst of 4- to 5-Hz waves of brief duration may occur in young adults and is fairly common in adolescents. The only data on the incidence of this type of postarousal burst in asymptomatic subjects are those of Gibbs and Gibbs (71), who found the bursts in at least 40% of subjects 10 to 14 years of age.

Perspective on Patterns of Drowsiness and Arousal

Episodes of drowsiness and arousal are common in routine EEG studies and are expected aspects of prolonged EEG monitoring. For the clinical neurophysiologist, they constitute a paradox: Their occurrence is to be sought because they may reveal abnormal rhythms or discharges not otherwise manifest; however, transient episodes of drowsiness, particularly if recurrent throughout the record, are a common hazard for misinterpretation. Similarly, transient episodes of arousal or semiarousal may be mistaken for paroxysmal abnormalities. Santamaria and Chiappa, in their monograph on the subject (178), made an excellent case for using eye-movement monitoring for the detection of drowsiness and arousal. They showed that, in addition to the better known slow, pendular movements that signal the oscitant state, there occur more rapid phasic movements of the eyes and eyelids that may facilitate recognition of the drowsy state.

[10]This is probably the same arousal rhythm that White and Tharp (214) reported in a series of children with "minimal brain dysfunction"; they did not study its incidence in a matched control group.

[11]In infants, when this phase of postarousal slow activity is over, passive eye closure should be done in order to determine the frequency of the occipital alpha rhythm.

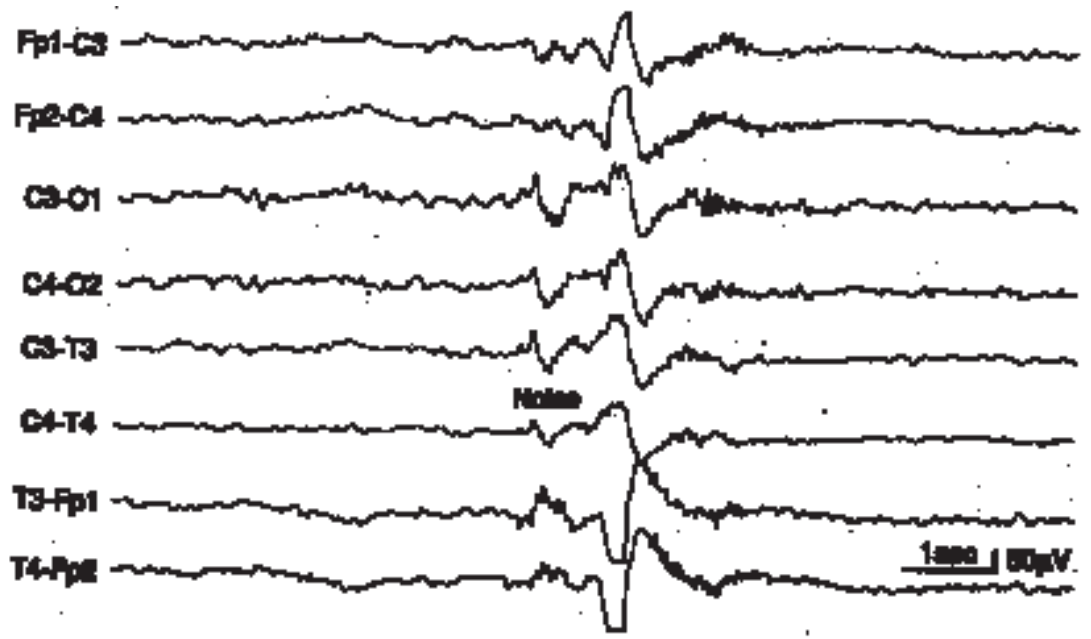

FIG. 5.30. In stage I sleep, arousal is associated with an immediate return of the waking pattern without an initial high-voltage, slow-wave transient.

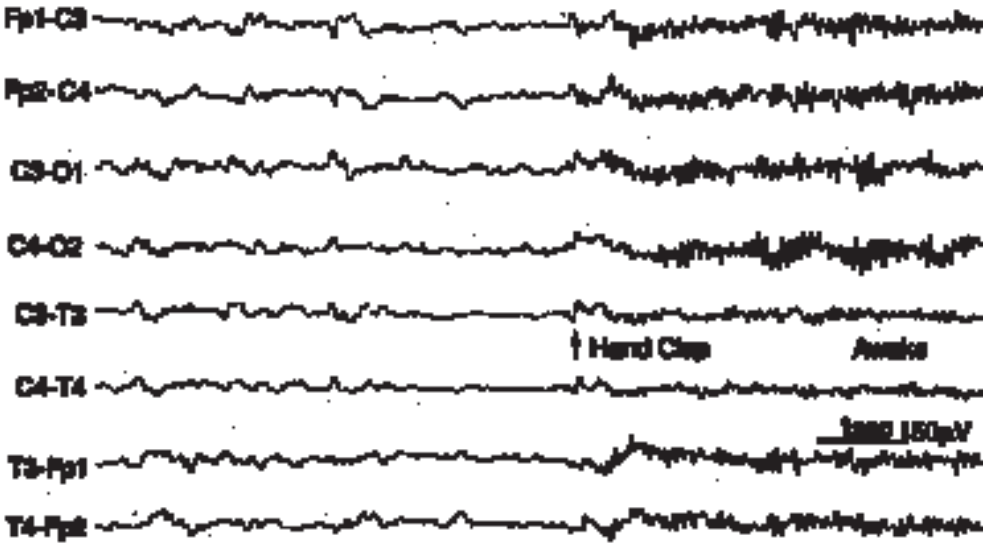

FIG. 5.31. Abortive-arousal response consisting of a slow-wave transient, maximum in voltage in the frontal leads, followed by a train of 9- to 14-Hz waves; the subject was a normal adult. Vertex transient and low-voltage spindle (sigma) activity occur before the abortive-arousal response. Such arousal patterns may occur spontaneously.

A wide range of patterns associated with drowsiness and arousal were seen in a small sample of normal subjects (55 adults, aged 22 to 79 years). These patterns differed from those generally recognized by electroencephalographers as being characteristic of normal drowsiness or arousal (178). In routine practice, whether frontocentral or central 3- to 5-Hz activity seen in an adult's EEG is related to drowsiness can be determined with the aid of hyperventilation. The constant urging to greater or sustained effort has the effect of keeping the subject alert and thus decreasing slow activity that is associated with drowsiness; at the same time, abnormal slow activity is accentuated as a result of hypocapnia produced by the hyperventilation.

The complex and varied EEG patterns of sleep and arousal are not well understood. Transitions through the various stages of sleep and from sleep to arousal involve changes in the activity and interaction of brainstem systems and in the noradrenergic and cholinergic modulation of cortical activity (187,198). The diverse EEG patterns that reflect these complex functional changes may therefore contain important information concerning physiological and pathophysiological processes. They have already yielded useful insights concerning pathophysiological mechanisms in epilepsy (108). As Santamaria and Chiappa (178) suggested, the less common patterns of drowsiness (and, perhaps, of arousal) and their relationship to eye movements and other behavioral phenomena may have significance in dysfunctional terms for disorders of sleep and cognition and for aberrations of the aging process.

It is regrettable that in this new era of diagnostic imaging, interest in electroencephalographic phenomena should be waning long before the significance of the many varied electrical patterns associated with sleep has been explored, much less determined.

Activity of Sleep

Vertex Sharp-Wave Transients. The onset of stage II sleep is signaled by the appearance of bilaterally synchronous sharp-wave transients in the central region (Fig. 5.32). Although maximal in voltage in the C3 and C4 electrode positions, when they are of high voltage, as they sometimes are in young children, they may be evident over a wide area of the frontocentral region. These sharp waves are usually diphasic, with an initial surface-negative deflection followed by a low-voltage, surface-positive phase. The sharp wave may be followed by a slow, surface-negative wave and/or a sleep spindle.

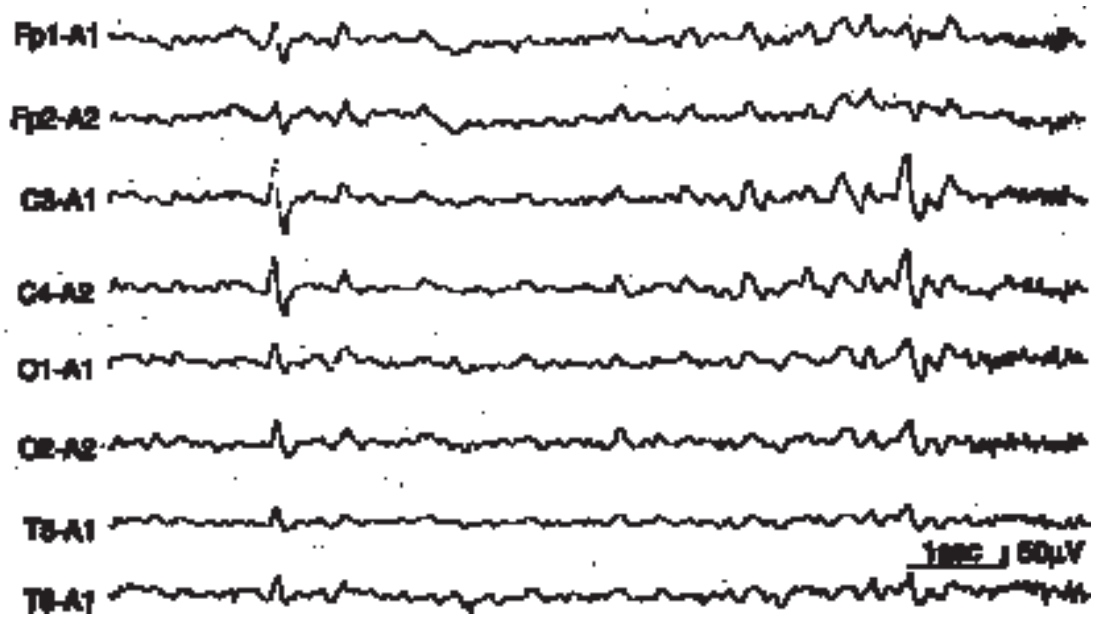

FIG. 5.32. Example of bilateral vertex transients in an asymptomatic 12-year-old girl. Note the diphasic waveform in central derivations.

From the time these waves first appear (at approximately 8 weeks post term), they are bilaterally synchronous and essentially symmetrical on the two sides. With persistent asymmetry of more than 20%, a lesion on the low side should be suspected. Some variable voltage difference between the two sides is not uncommon in young children, but if the low voltage always appears on the same side, it should be regarded as significant. Unlike other sleep activity (e.g., spindles), vertex transients are always bilaterally synchronous in normal persons. A breakdown of this synchrony is usually a sign of increased intraventricular pressure (obstructive hydrocephalus). Asynchrony should be distinguished from the situation not uncommonly seen in children in which the vertex transients do not occur on both sides each time. In this situation, one or the other side may show more vertex transients (and spindles), but whenever they occur bilaterally, they are symmetrical on the two sides. Although this phenomenon—in which an occasional vertex transient (and spindle) may be missing on one side—occurs in apparently healthy children, it is comparatively rare (<3%) and may indeed be pathophysiologically significant.

The very high voltage that vertex transients may attain in children aged 2 to 4 years may come as a surprise to the electroencephalographer not accustomed to children's records. The high voltage and sharply peaked waveform must not lead to an incorrect interpretation of abnormality. Similarly, these vertex transients in children, in contrast to the situation in adults, may occur in quick succession (every 1 to 2 seconds), and an "interference pattern" may result, giving these waves a complex configuration that seems abnormal (Fig. 5.33).

The voltage and, to some degree, the configuration of successive vertex transients in any series may fluctuate considerably, and in a given montage, it may be difficult to distinguish the vertex transients (Fig. 5.34) from abnormal sharp-wave discharges arising unilaterally or bilaterally from foci in this region (rolandic spikes). The problem often can be solved by mapping the fields of the various sharp waves present.

K Complexes and Vertex Transients. The term K complex was originally used by Loomis et al. (134,135) to denote a series of waves that could be detected in the EEG during sleep in response to an auditory stimulus (see Fig. 5.31). As the word "complex" implies, the term was not meant to describe a single transient or sharp wave, although the term K complex has often been applied to the spontaneous vertex transients of sleep. The electrical field of the slow component of the K complex at the scalp is essentially similar to that of the vertex transient, and the initial component may have a similar waveform. It has, in fact, been suggested that vertex transients constitute EEG responses to afferent stimuli arising from interoceptors.

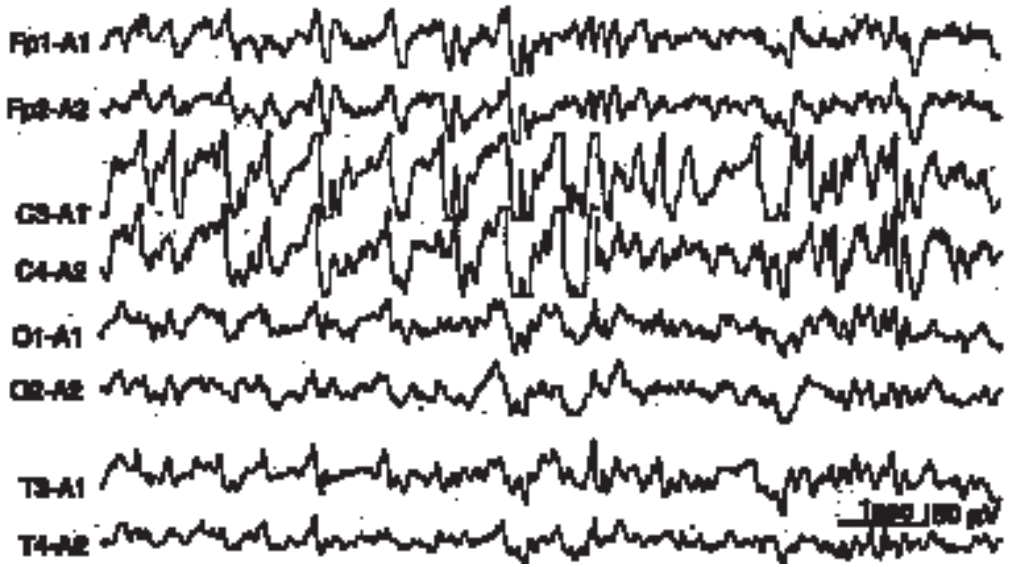

FIG. 5.33. Vertex transients occurring in repetitive sequence in an asymptomatic 11-year-old boy. Note the variable and often sharp waveform. The higher-voltage transients cause blocking at normal gain.

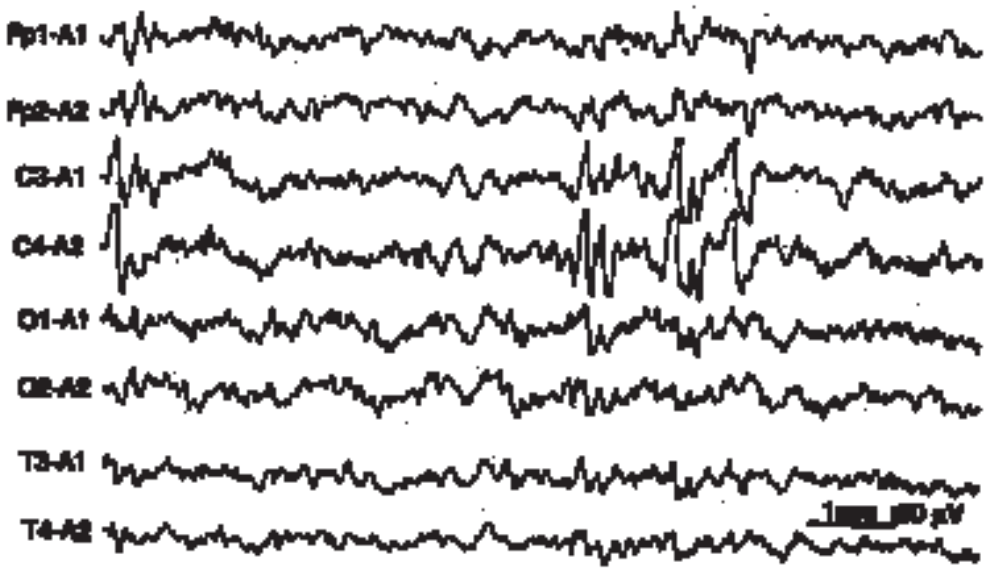

FIG. 5.34. Characteristically "sharp" appearance of some vertex transients in children is increased in this montage by the admixture of electrocardiographic artifact and fast activity. The sample is from an asymptomatic girl aged 9 years 6 months with no evidence of central nervous system disease.

Once stage II sleep has been reached, a single "click" stimulus will elicit a sharp, diphasic wave in the central region bilaterally that is indistinguishable in waveform, amplitude, and field from the spontaneously occurring vertex transient in the same individual. The spontaneous vertex transients may occur in relatively quick succession, as shown in Fig. 5.33, and appear in quick succession (every 1 to 2 seconds) throughout stages 2 to 4 of non—rapid-eye-movement (NREM) sleep; however, the central sharp-wave transients elicited by a stimulus show a relatively long refractory period and may disappear if the stimulus is repeated at short intervals over a period of 30 seconds or more. This accommodation effect can be overcome simply by changing to a novel stimulus: for example, by substituting the calling of the child's name for one of the clicks (personal observations). The duration of the refractory period in which a second stimulus (e.g., a click) is not effective has not been measured precisely, but it is estimated to be at least 5 seconds.

Spindles. Sleep spindles are bilaterally asynchronous at the time of their first appearance at 6 to 8 weeks post term (110) (Fig. 5.35), and they become increasingly more synchronous during the first year of life; thus by the eighteenth month, most spindles are bilaterally synchronous. Before the age of 2 years, asynchrony of sleep spindles cannot be considered evidence of abnormality. The waveform and duration of sleep spindles in infants differ from those in adults: The spindles may be 2 to 4 seconds in duration and lack the typical fusiform amplitude modulation that gives the adult type of sleep spindle its name. The individual waves of the spindle may be sharply peaked (reminiscent of the mu rhythm) in the surface-negative phase (110) (see Fig. 5.35).

Three types of spindles may be distinguished by their frequency characteristics and potential field. The most common, and usually the only type seen in adults, has a frequency of approximately 14 Hz, and the center of the field coincides closely with the C3 and C4 electrode placements. The spindles are characteristic of stages II and III sleep, but they are also the distinguishing characteristic of "spindle coma" or "coma sleep" (29). Unilateral slowing of spindle frequency may occur in the presence of lesions of the ipsilateral hemisphere (172).

Spindles that have a fundamental frequency of approximately 10 to 12 Hz and a more anterior locus of origin occur in 5% of normal children aged 3 to 12 years (Fig. 5.36). These "frontal" spindles, which are seldom more than 3 seconds in duration, should be clearly differentiated from "continuous spindling" or "exaggerated" spindles, which are an abnormal finding seen in children with certain types of cerebral palsy and mental retardation. Frontal 10-Hz spindling that is almost continuous can result from drug

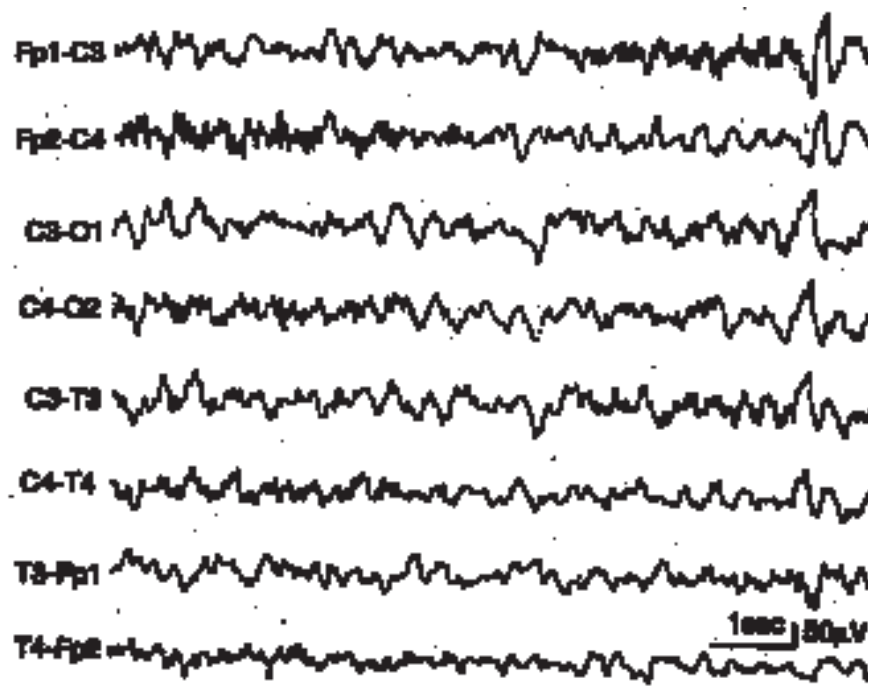

FIG. 5.35. Typical infant sleep spindles. Note the asynchrony (attenuation) between the two sides, prolonged duration (>4 seconds), lack of fusiform amplitude modulation, and mu-like waveform.

action (e.g., morphine and halothane anesthesia), but the unremitting character of the activity and the lack of reactivity to intense stimuli clearly distinguish it from the frontal dominant 10-Hz spindles of sleep (Fig. 5.37).

Fusiform bursts of 18- to 22-Hz activity in sleep should not be confused with sleep spindles (sigma activity). Most commonly, these bursts are effects of medication, particularly the phenothiazines and barbiturates (Fig. 5.38), but they are also associated with certain pathological conditions in the absence of drugs.

Fast Activity. Sometime between the fifth and sixth month, many infants begin to show low-voltage fast activity during the early stages of sleep. This activity occurs in all derivations but is most pronounced in the central or postcentral region (see Fig. 5.8). The frequency averages approximately 28 Hz, but it varies as much as ±6 Hz in different subjects. When the fast activity first occurs, its amplitude is very low (5 µV or less), but relatively high amplitudes (30 µV maximum) may be seen by the twelfth to eighteenth month, when it seems to reach its maximum expression. After the age of 30 to 36 months, pronounced fast activity during early sleep is less common, and in general, the amplitudes seen are not as great as in children aged 12 to 18 months. Older children are much less likely to show fast activity during early sleep, and after the age of 7, it is relatively uncommon (110).

When sedation with a barbiturate or other fast activity–inducing drug is used to promote sleep, fast activity is increased in the awake and asleep EEG. This fast activity has a frequency chiefly in the range of 18 to 22 Hz and a predominantly anterior distribution. When sedatives are administered at some point just before or during the recording, the fast activity induced displays maximum voltage during light sleep (stages 1 and 2) and is greatly diminished during deeper sleep. Upon arousal, the fast activity increases again and becomes much more pronounced than in the presleep record—unless there was an inordinate delay in the onset of sleep. Fast activity induced by chronic medication, or by a drug administered a long time before the recording, shows the same diminution during the deep sleep stages but is *equal* during the pre-sleep and post-sleep *awake* tracings.

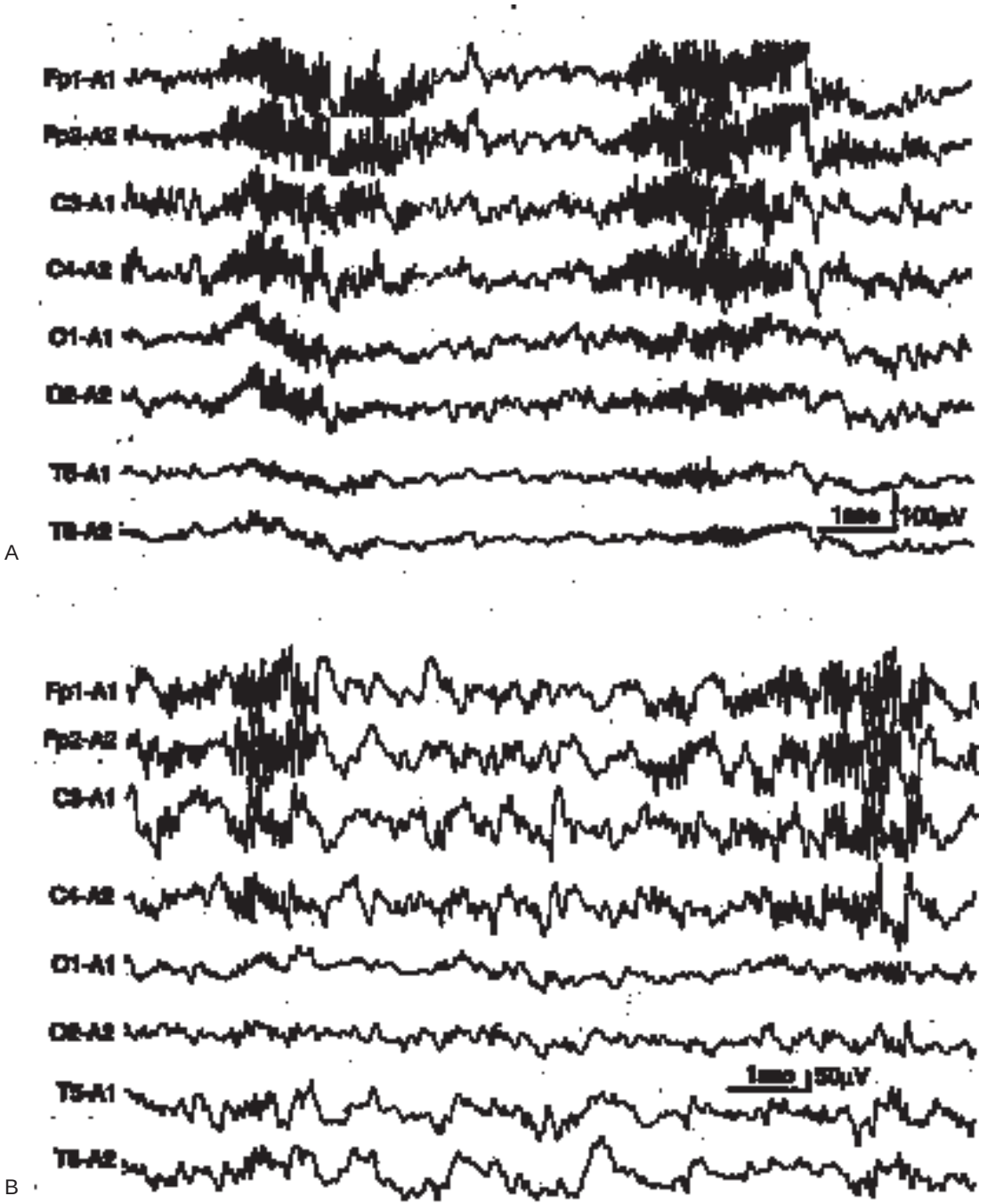

FIG. 5.36. A: Example of 12-Hz frontal-dominant spindles in stage II sleep in an asymptomatic male, aged 10 years, 10 months. These spindles are often high in voltage in comparison with 14-Hz central spindles and have a larger potential field. **B:** Example of 10-Hz frontal-dominant spindles in an asymptomatic 6-year-old boy.

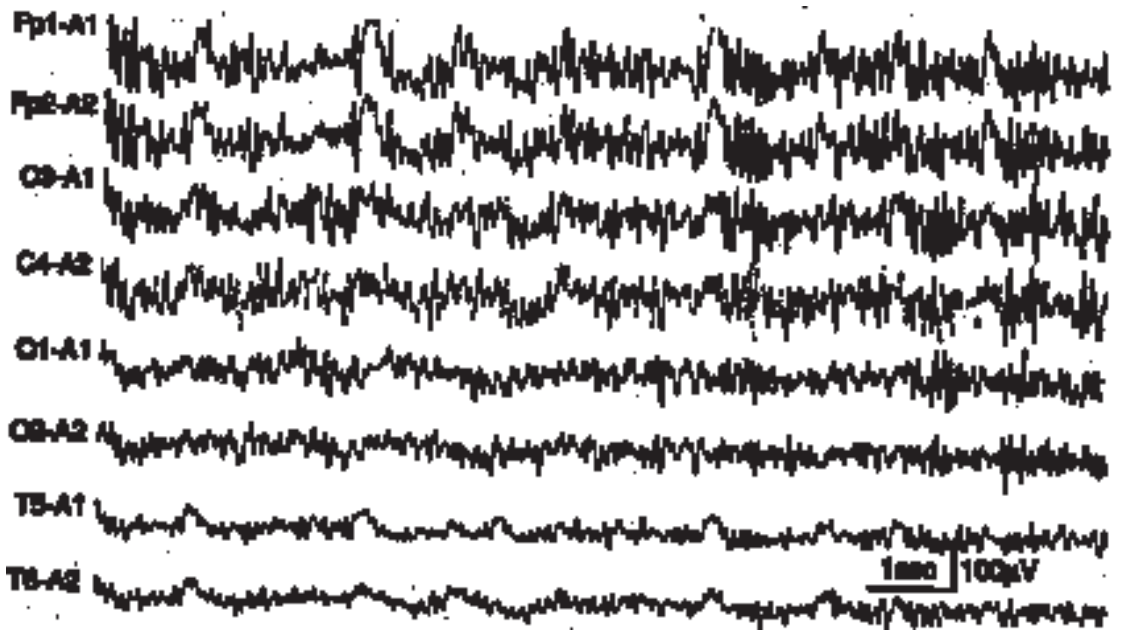

FIG. 5.37. Almost continuous 10- to 12-Hz, moderately high voltage, frontal-dominant activity showing a spindle-like amplitude modulation in a woman aged 52 years who was stuporous from a diazepam overdose.

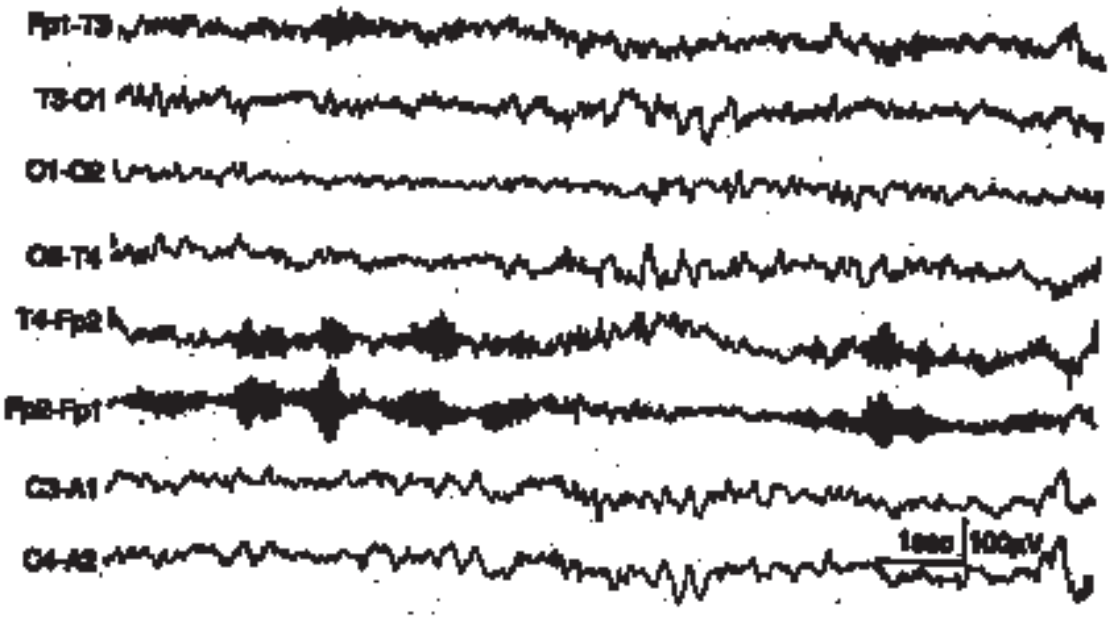

FIG. 5.38. Barbiturate "spindles" such as those in this figure are sometimes confused with physiological sleep spindles. Note the greater amplitude of paired frontal derivation in comparison to homolateral frontal derivations; this is a common finding with barbiturate spindles but is not characteristic of sleep spindles. The subject was a boy aged 13 years, 4 months, with generalized seizures and taking phenobarbital (150 mg per day). Fast activity was not present before treatment. The sample is from stage I sleep.

The voltage of both natural and induced fast activity should be essentially the same bilaterally. With a consistent difference of more than 30%, an abnormality on the low-voltage side should be suspected, except when the fast activity is confined to a circumscribed focal area, in which case it may be associated with a focal lesion in that region (94). (Beware, however, of the pitfall mentioned elsewhere: the low-resistance pathway provided by a bone defect in the skull.)

Fast activity of cortical origin is particularly susceptible to the effects of ischemia, hypoxia, contusion, and the presence of subdural fluid. Thus, its depression or absence focally or unilaterally may be a useful sign on the EEG, particularly in relation to other findings (e.g., the presence of a slow-wave focus).

Positive Occipital Sharp Transients. Surface-positive sharp transients, occurring singly or, more commonly, in runs of 4 to 5 Hz, are often seen in routine EEG sleep recordings (Fig. 5.39). These interesting waves are commonly seen in the EEG laboratory because they are prone to occur during daytime naps and particularly if the patient has been partially aroused and quickly returns to sleep. The pattern occurs in persons aged 4 to 50 years and is most common and best expressed in those aged 15 to 35 years. The individual waves show a sharp, surface-positive peak, followed in some instances by a low-voltage, surface-negative peak. The initial deflection of each wave has a somewhat slower time course than the ascending phase, and so the resultant waveform may have a checkmark-like shape; some authors refer to them as occipital V waves of sleep.

Positive occipital sharp transients of sleep (POSTs) (199) are always bilaterally synchronous but are commonly asymmetrical on the two sides (Fig. 5.40); voltage differences as great as 60% are seen in normal persons. This may lead to misinterpretation of POSTs as abnormal sharp-wave activity in one or the other occipital region. In this regard, it is important to remember that POSTs may occur at a time when the background activity has an amorphous character that might be thought to represent drowsiness or a slightly slow awake pattern (Fig. 5.41).

The helpful distinguishing characteristics of POSTs are (a) their surface positivity (abnormal surface-positive cerebral spikes are rare), (b) the fact that they tend to occur in trains with a repetition rate of 4 to 5 Hz, and (c) their predominantly monophasic checkmark-like waveform.

Occipital Slow Transients. In children, the transition from light to deep sleep may be associated with the bilateral appearance of high-voltage slow transients in the occipital regions (110). These waves vary from a cone-shaped configuration (Fig. 5.42) to a diphasic slow transient (Fig. 5.43) rem-

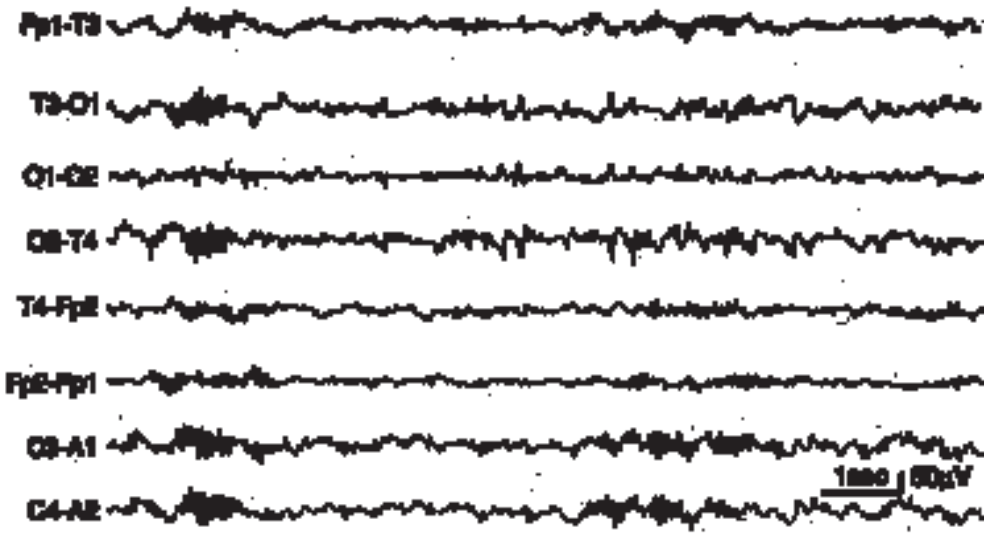

FIG. 5.39. Positive occipital sharp transients of sleep (POSTs) during stage II sleep (note presence of 14-Hz spindles) in an asymptomatic 14-year-old boy.

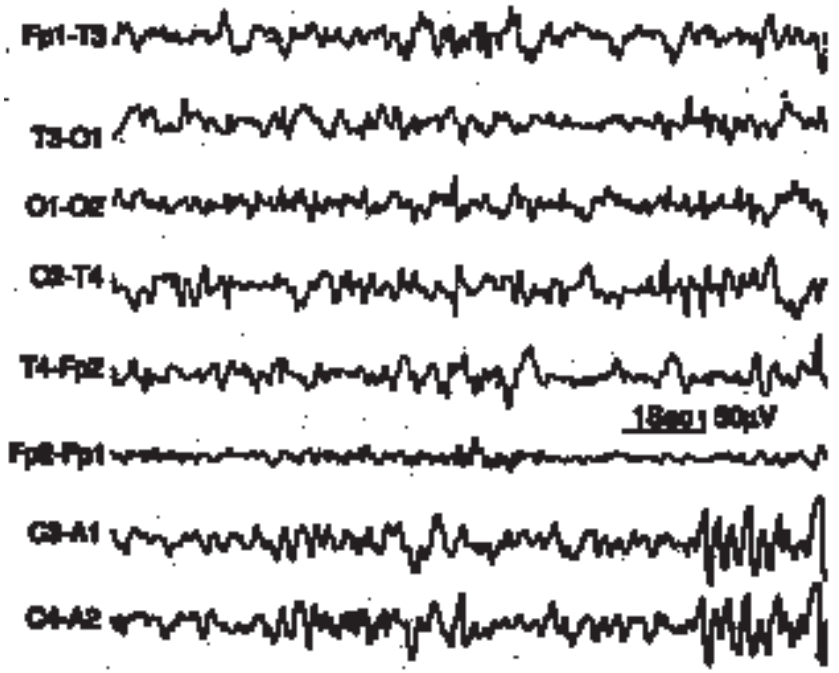

FIG. 5.40. Asymmetrical positive occipital sharp transients of sleep (POSTs) in a healthy girl aged 11 years. Note considerable voltage difference between sides, especially of the isolated sharp wave (POST) near the center of the sample. The facts that the series shows a repetition rate of about 5 Hz at the right side of sample and that the sharp waves are positive at O2 provide clues to their identity. However, although positive sharp waves or spikes rarely signify abnormal activity, electrodes near the midline (e.g., O1 or O2) may reveal only the positive end of a dipole, presumably because the negative end lies on the mesial surface of the hemisphere.

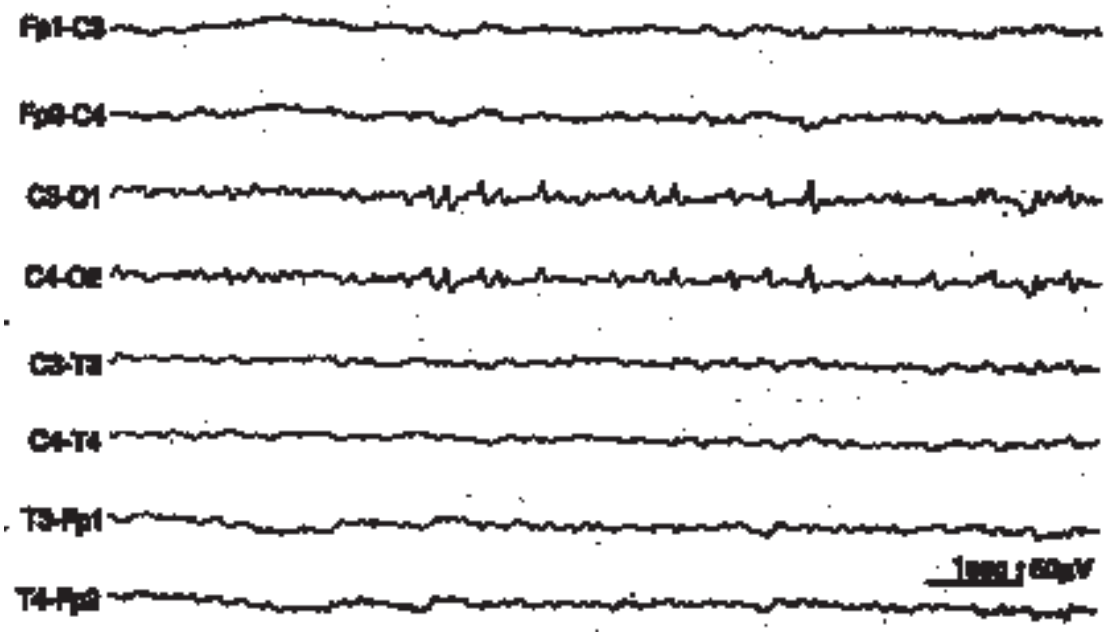

FIG. 5.41. Positive occipital sharp transients of sleep (POSTs), occurring after drowsiness but before spindle sleep had been reached, in an asymptomatic 17-year-old girl. Note the low-voltage, slightly slow or "drowsy" appearance of the record. POSTs are often seen during daytime naps that may occur during routine studies in the typical electroencephalograph laboratory.

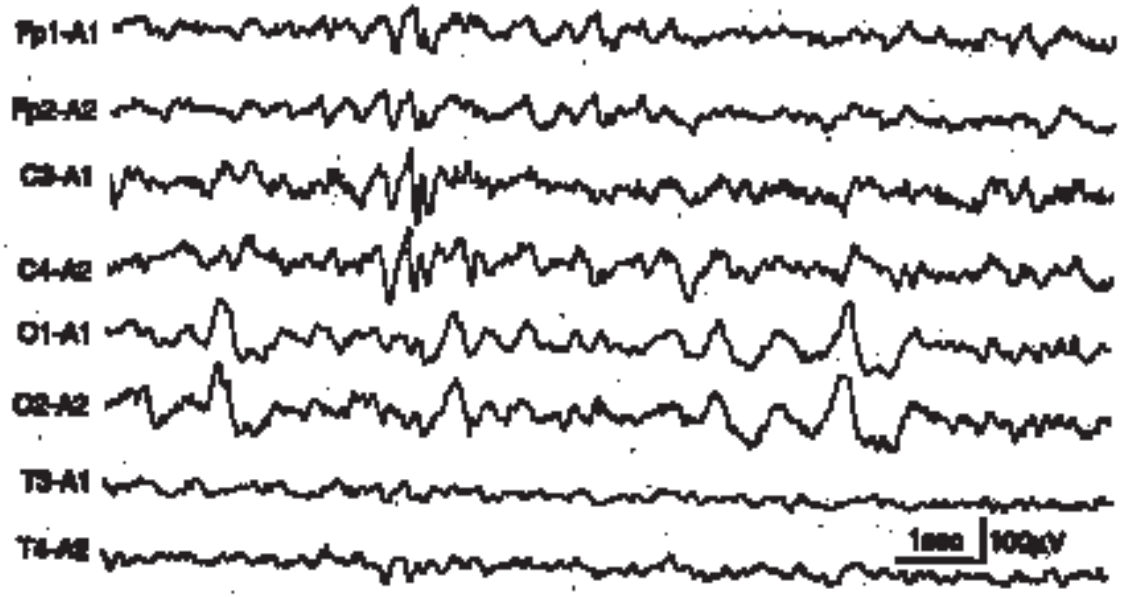

FIG. 5.42. Cone-shaped, posterior slow transients during light sleep in an asymptomatic 35-month-old boy.

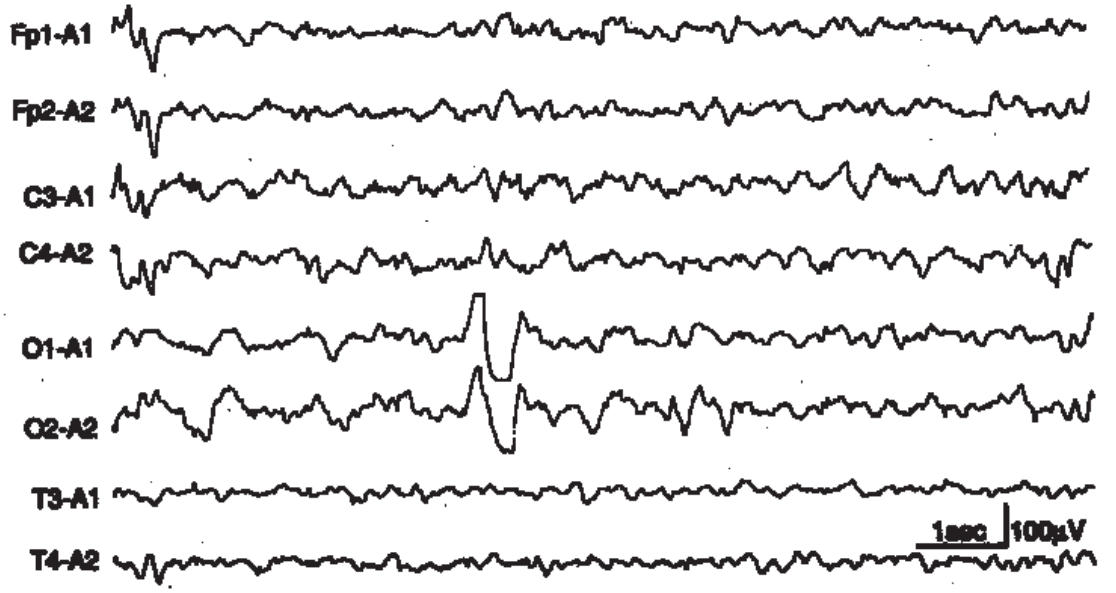

FIG. 5.43. Diphasic slow-wave transients in the occipital derivations in light sleep in the same subject as in Fig. 5.42.

iniscent of a prolonged v ertex transient. At first, during light sleep, these transients occur e very 3 to 6 seconds; with deepening sleep, the y appear more frequently and seem to meld into the continuous, occipital-dominant, random, very slow delta waves of stage IV sleep.

THE CLINICAL REPORT

Visual analysis in terms of the specific descriptors as set forth in Table 5.1 provides the basis for the initial par t of the for mal EEG report, namely the *technical description.* The next aspect of the repor t, the *technical impression,* comprises a summary statement of the o verall analysis (e.g., paroxysmal generalized 3-Hz spike and wave dysrhythmia with normal background activity for age). F inally, an assessment is made of the signif icance of the EEG findings in relation to the clinical histor y and the patient' s clinical state: the *clinical impression.*

THE MEANING OF "NORMAL" AND THE SIGNIFICANCE OF DEVIATIONS FROM THE NORM

The purposes of this chapter are to delineate the processes in volved in an orderly approach to visual analysis and to provide information concerning the elements of the "nor mal" EEG in adults and children. The latter endeavor, if it is to be an ything more than a pedago gical exercise, requires some discussion of the meaning of "nomal." Perhaps more important is that some thought should be directed toward the meaning of deviations from normative data. Do such deviations always imply *abnormality?* Do they imply that the brain has suffered some sort of insult? Does their presence necessaril y mean that the y have a causative relationship with the symptoms or signs for which the patient was referred? The history of clinical electroencephalography has certainly not been distinguished by thoughtful analysis of these problems or even by a critical sense of their signif icance. Perhaps this has been the natural outcome of the quest for laborator y techniques that can pro vide "penny in the slot" diagnoses: the kind of explicit certainty that computed tomography and magnetic resonance imaging are apparently now providing, at a somewhat higher price, for diseases with a mor phological signature.

From its inception, there has been a tendenc y in electroencephalography to view minor deviations from the norm as objective evidence of disordered brain function,[12] the result of some past or ongoing pathological process. To some electroencephalographers, many EEG f indings automatically mean epilepsy; to others, cer tain findings (e.g., a spik e focus) al ways imply the presence of a palpable brain lesion. Such concepts are now undergoing reappraisal (106,107). It is gradually becoming recognized that the EEG characteristics of a gi ven individual are the product of di verse internal and external influences, acting on a geneticall y determined substrate. These influences may be conceptualized diag rammatically in ter ms of their interactions. Figure 5.44 represents an attempt to specify the f actors that determine the characteristics of the EEG and to illustrate their inter play (109).

Many years ago, Kennard (113,114) suggested that the total EEG patter n may ultimately result from all the stabilizing and disr uptive influences brought to bear on cerebral function. The validity of this concept is being clarified only now.

The Individuality and Stability of the Human EEG

Fortunately for clinical electroencephalography, the EEG of an adult shows remarkable stability over time. This was originally noted by Travis (192,193)

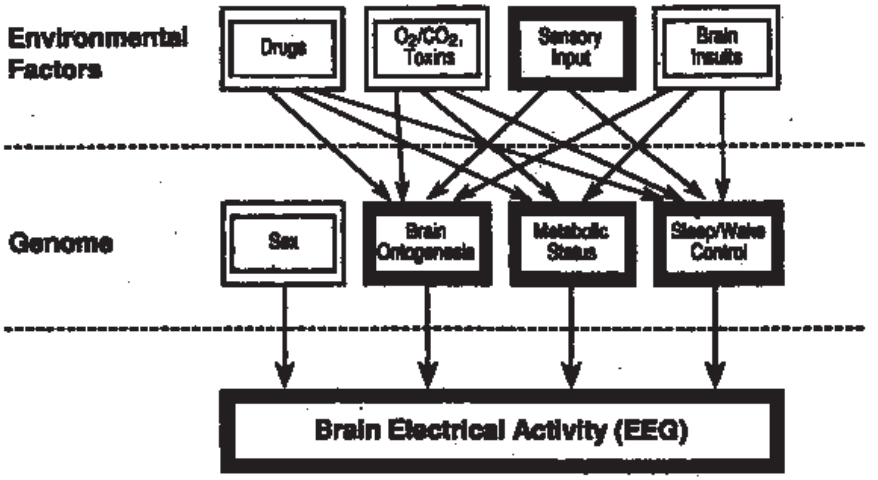

FIG. 5.44. Schematic representation of the factors and their interactions that determine the characteristics of brain electrical activity. (From Kellaway P. Introduction to plasticity and sensitive periods. In: Kellaway P, Noebels JL, eds. *Problems and concepts in developmental neurophysiology.* Baltimore: The Johns Hopkins University Press, 1989:3–28.)

[12]Minor dysrhythmias have been used to "pro ve" the already tenuous clinical diagnosis of minimal brain damage.

in the very early days of electroencephalography and has been confirmed by several more recent studies (8,116,139,197). With the application of modified techniques of communication theory with multivariate statistical analysis, it has been shown that an individual can be recognized by his EEG spectral pattern with a confidence probability of about 90%. The stability of the individual's spectral pattern holds for different conditions such as eyes open, eyes closed, auditory stimulation, and task performance. This specific individuality of the human EEG provides strong presumptive evidence that the characteristics of the EEG are determined primarily by genetic factors.

The Genetic Substrate

After the individuality and stability of the EEG had been established, there was an effort to determine EEG similarity within pairs of monozygotic and dizygotic twins (40,85,130,131,171,201,203). Analysis of the EEGs of 110 pairs of monozygotic twins of various ages revealed only one pair with dissimilar awake EEGs and four pairs with dissimilar sleep EEGs. Of 98 dizygotic pairs, in contrast, only 17 were found to be similar. The rate of maturation of the EEG was similar for the monozygotic twins but different for the dizygotic ones (201,203). Striking similarities in the spectral features of the resting EEGs of monozygotic twins have been found by several different groups (47,136,137,219). The similarity of the EEGs of monozygotic twins has been shown in such twins who were reared apart in different environments (97,98,184).

A finding with dual significance in this regard is that alcohol has similar effects on the EEGs of monozygotic twins, but the EEGs of fraternal twins become more dissimilar after alcohol ingestion (169,170). This indicates that the effect of alcohol on the EEG is under genetic control and reflects genetic differences in the sensitivity of the target organ. A common observation in routine clinical electroencephalography is the very great difference in the amount and amplitude of beta activity that may be seen in persons of similar ages and with similar blood levels of barbiturates, benzodiazepines, and other drugs that increase fast activity. Thus, the findings of the alcohol study may, as the authors suggest, be generalized to all centrally acting substances.

The possibility that each of the spontaneous rhythms of the human brain might constitute heritable traits now seems fully confirmed. However, although there is strong evidence for apparent polygenic transmission of some spectral frequency patterns, no specific gene locus for a specific EEG rhythm has yet been identified in humans. Researchers have obtained unambiguous evidence in mice that a spontaneous and predominant EEG rhythm can be expressed as a hereditary trait under the control of a single recessive locus (124,152).

Kennard (113,114) was the first to suggest the possibility that familial or inherited tendencies may be important in the genesis of some of the deviations from normal (e.g., nonspecific dysrhythmias) seen in children. A significant familial factor has been established for certain abnormal or specific patterns of the child's EEG: 3-Hz spike-and-wave activity (83,143–146), rolandic spikes (13–16,151a), and 14- and 6-Hz positive spikes (164,175, 202). The most provocative and surprising finding is the genetic or familial factor associated with focal EEG abnormality (5,14). Clearly, it appears that deviations from "normal" may be the "neurophysiological consequence of a genetically controlled biosynthetic pathway" (145).

Ontogenetic Plasticity

Although the emergence and differentiation of the electrical activity of the brain are initially dependent on the genetic substrate, the character of the activity is also vitally influenced by environmental factors. For example, the maturational evolution of the brain, which continues for some time after birth, is currently conceived as an orderly sequence of interactions between the genome and the milieu. The fine-tuning of cortical properties is governed to a certain extent by the external environment so as to adapt the organism to the characteristics of that environment. If these requirements exceed the limits set by genetic rules, the respective functional characteristics are eliminated (for review, see Kellaway and Noebels [111]).

This plasticity is possible only when processes of organization are taking place. In general, the period of life in which the organism is maximally susceptible to lasting structural and functional changes coincides with the period of fastest neuronal growth (35). However, there is evidence that some modification of structure and function by subtle environmental factors may be possible, at least in the visual system, up to the age of 2 to 3 years (86,205).

Afferent input (in terms of the entire sensory environment) is a critical factor in the ontogenesis of the electrical activity of the brain; aberrations of sensory input early in life may profoundly alter the character of the EEG. Thus, persons deprived of visual input from birth have no occipital alpha activity, and deprivation or incongruity of input from the two eyes occurring within a very early epoch after birth may result in the development of occipital spikes (109).

As stated previously, age is a primary factor in determining the characteristics of the EEG: The younger the individual, the more critical the age factor.

In premature infants, an age difference of a week may be associated with markedly different EEG characteristics, but there is little difference between the EEG characteristics of an infant at term and those of one aged 4 to 5 weeks. The EEG of an 8-year-old child may be indistinguishable from that of an 11-year-old. The ontogenetic evolution of the EEG throughout infancy, childhood, and adolescence has been well documented (48,103,165).

Less clearly understood is the role played by age—degree of cerebral development—in determining the characteristics of the EEG in response to a brain insult or injury, particularly during very early life. For example, it has been shown repeatedly that when a significant injury is sustained during the perinatal period, the EEG initially may manifest abnormality, become normal and remain so throughout early childhood, and then become abnormal again during middle or late childhood. Thus, brain damage may not be revealed in the EEG recorded at a given age even though it is in fact present (104,109).

The effect of a given insult or injury on the immature brain may be determined in part by the stage of development at the time of the injury. For example, hypsarrhythmia, and the characteristic infantile spasms that accompany it, may be a manifestation of a wide variety of diffuse cerebral insults operant during the perinatal period and early infancy (90,102,121). If the same degrees and types of insult are sustained later in the course of cerebral maturation, they do not produce the same types of EEG changes or the same types of clinical seizures. Hypsarrhythmia and infantile spasms constitute the response of the brain to a nonspecific insult at a certain critical stage of development.

The rate of maturation set by genetic instruction may be retarded or arrested by the effects of various brain insults, and the timing of such an insult determines the characteristics of the EEG both acutely and in the long term. Walter (208,209) suggested that many of the lesser dysrhythmias of childhood may simply reflect delayed cerebral maturation. He hypothesized that such a delay might occur, even in the absence of a causative brain insult, as a result of "less than optimal trophic influences or systemic growth promoting endocrine and chemical influences" (209).

The suggestion has been made, and evidence adduced to support it, that differences in the EEGs of control children and, for example, children of a similar age with behavior problems may reflect maturational differences rather than damage or dysfunction (11,115,140). Common experience also suggests that maturational factors are significantly related to minor dysrhythmias, but the nature of this relationship remains obscure. Thus, the slow rhythms (e.g., frontal theta activity and posterior slow waves) tend to disappear with increasing age. This was documented in serial studies (P. Kellaway, unpublished observations) and can be inferred from samplings of different age groups (48,165). In practical terms, if minor dysrhythmias are important for the diagnosis and evaluation of behavior disorders, learning disabilities, and so forth (as has been suggested), they must then be progressively less so with increasing age.

Epidemiological studies (125–128) of behavior disorders in children yielded some interesting findings that have a bearing on this point. In a study of 482 children selected randomly from households systematically sampled in Buffalo, New York, Lapouse (126) found "a strikingly high prevalence of so-called symptomatic behavior" and pointed out that its "excessive presence in younger as contrasted with older children, and the weak association between those behaviors and adjustment, give rise to the question *whether behavior deviations are truly indicative of psychiatric or organic brain disorder or whether they occur as transient developmental phenomena* in essentially normal children" (emphasis added). It seems likely that parallel deviations may occur in the behavior and EEG patterns at a certain time in the life of a young child as coincident manifestations of a transient, ontogenetically determined influence.

Gender

The normative studies of Eeg-Olofsson and Petersén (48,165) showed statistically significant sex differences in the incidence of certain EEG patterns or in their characteristics (e.g., a much higher incidence of mu rhythms and a significantly higher frequency of the occipital alpha rhythms in girls and women). Some of these are mentioned elsewhere in this chapter.

Metabolic and Homeostatic Factors

The influences of homeostatic and metabolic factors have been well documented and have been discussed in several reviews (e.g., Harding and Thompson [82]). These factors become more important when deranged, and it is essential that the electroencephalographer recognize that disease states may affect the EEG secondarily through these factors rather than directly. For example, the frequency of the occipital alpha rhythm may be decreased by any condition that impairs cerebral metabolism. Thus, slowing of the alpha rhythm may result from chronic pulmonary insufficiency, chronically diminished cardiac output, or profound hypothyroidism. It was enlightening, in the early days of heart transplantation and implantation of cardiac pace-

makers, to observe increases in alpha frequency of up to 2 Hz after normal cardiac output was restored, with the brain no longer subjected to chronic hypoperfusion.

Sleep and Wakefulness

The characteristics of the EEG, in subjects awake and asleep, are considered briefly in terms of their interpretation in clinical EEG practice. More extensive treatment of the transformations of the EEG that occur during normal sleep is available in several monographs (159,217).

Psychoaffective State

Kennard (113,114) suggested that anxiety or tension states might influence the EEG characteristics of a child in important ways. This possibility has been espoused most persistently by Lairy (122,123) and Igert and Lairy (93). They drew attention to the fact that occipital slow activity (or "posterior slow activity of youth") appears responsive to psychological factors, and Cohn and Nardini (33) speculated that posterior slow waves constitute "a conditioned response of a disordered brain to the exigencies of interpersonal experiences." Werre (210) reported evidence that, even in adults, posterior slow waves are sensitive to frustration; and Garcia-Badaracco (60) adduced circumstantial evidence to support his view that posterior slow waves are the consequence of frustration as well as evidence of what he called a "quasi-constitutional sensitivity to frustrations." Speculations aside, it is a common observation that the amount and amplitude of this slow activity may vary throughout a recording, generally being more pronounced at the beginning of the recording period and diminishing with time. Many factors could account for this phenomenon; there have been no controlled studies in this area, but the obvious suggestion is that the slow activity diminishes as the child becomes more accustomed to the unique and unfamiliar circumstances of the laboratory procedure. Carels (24) reported an increase in posterior slow waves in a young adult neurotic patient with each "social encounter," the EEG becoming more normal in a hospital (protective) environment.

Lairy (123) maintained that posterior slow activity in children with behavior disorders and learning disturbances may reflect adaptation to stress and that certain EEG abnormalities may be interpreted as a sign of impaired adaptation. The prognostic significance of the findings "depends upon the degree of impaired control and the possibilities of recovering equilibrium." In her view, the presence of posterior slow activity implies a more favorable prognosis for therapy than does a "normal" EEG, inasmuch as she believed that the latter is a sign of "hyperadaptation, which leaves little hope for functional secondary readaptation." Lairy's hypothesis appears to be based largely on intuitional or circumstantial evidence and on inferences drawn from her own and others' clinical observations. In spite of the fact that these concepts have yet to be proved by systematic research, they are of heuristic importance and should not be dismissed lightly.

Of all areas of the brain sampled during scalp electroencephalography, the occipitotemporal regions in the child are the most sensitive to hyperventilation (38,39; P. Kellaway, unpublished data); after hypoxia, head injury, or encephalitis in children, the slowing effect persists longest in the occipital region (147). Similarly, in children with leukemia, posterior or occipital slowing of undetermined origin occurs during the acute phase and with exacerbation (138). Each of these findings indicates a sensitivity or high reactivity of this part of the brain in children. A similar high reactivity to emotional factors may also be present, as suggested by the findings of Werre (210) in a single subject.

Several investigators have reported an association between emotional state and theta activity. Walter (208), for example, reported that he induced bursts of this activity by depriving young children of pleasurable stimuli. Similarly, frustration, annoyance, and embarrassment have been reported to cause enhancement of theta activity (54), even in adult subjects (150). Adey et al. (1) and Burch et al. (22) reported increased theta activity in the EEG of an astronaut during launch and the initial hours of space flight, and similar findings have been reported during space flights conducted by the Russians (186). The Russian scientists (207) interpreted the findings as a reflection of a "high level" of psychoemotional reactions during the early phases of the flight. Adey et al. (1) believed that more fundamental physiological substrates—concerned primarily with alerting and orientation—were involved. Whether the anterior theta rhythms in humans are responsive simply as part of an alerting or orienting mechanism or are elements of a psychoaffective response has not been clearly established by experimental studies such as those of Walter (208,209) or Melin (142), who exposed young adults to shocking and horrifying movies and found increases in the theta and occasionally the delta components of the subjects' EEGs.

That EEG patterns are indeed plastic and responsive to functional factors appears to be established; it has yet to be proved, however, that persistent aberrations of the EEG of the child may be a consequence of prolonged emotional stress (e.g., chronic anxiety or frustration). Nordland (153) attempted to answer the question by comparing the EEGs of maladjusted

children who had histories of chronic psychological stress (e.g., conflict, insecurity, or anxiety) with a group in whom these factors were not significant. Her results indicated that "an abnormal EEG may be a symptom of protracted states of psychological tension"; but, as Nordland herself pointed out, the study does not provide conclusive answers to the question. Nevertheless, the evidence is sufficient (50) to give pause to those who maintain the view that the dysrhythmic EEG is always evidence of organic dysfunction acquired through infection, injury, or other organic insult (30,215).

Extrinsic Factors

Extrinsic factors (e.g., drugs, trauma, infection) are considered in various other chapters of this book.

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Chapter 6

Neonatal Electroencephalography

Robert R. Clancy, A.G. Christina Bergqvist, and Dennis J. Dlugos

Technical Aspects of Neonatal Electroencephalographic Recording and Interpretation
Recording Artifacts
Visual Analysis of the Normal Neonatal Electroencephalographic Background
Conceptional Age, State, and Medical Status
Timing of Electroencephalographic Examinations
General Properties of the Electroencephalographic Background
Overview of Electroencephalographic Ontogeny
Composition of Electroencephalographic Background Activity (Named Patterns)
Specific Neonatal Electroencephalographic Background Patterns and State
Types and Significance of Abnormal Electroencephalographic Backgrounds
Excessive Discontinuity
Burst-Suppression Pattern
Abnormal Voltage
Abnormal Asymmetry
Classification of the Electroencephalographic Background and Its Implications
Sharp Electroencephalographic Transients
Frontal Sharp Electroencephalographic Transients
Temporal and Central Negative Sharp Electroencephalographic Transients
Negative Sharp EEG Transients in Other Locations
Positive Sharp Waves (Rolandic, Vertex, and Temporal)
Electroencephalographic Neonatal Seizures and Clinical Correlations
An Organized Approach to Visual Analysis of the Neonatal Electroencephalogram and Common Interpretation Pitfalls
References

Unaided clinical neurological examination of the healthy or sick newborn has severe, inherent limitations. The natural functional repertoire of the immature central nervous system (CNS) is modest. The bedside neurological examination is performed to assess the state of consciousness or arousal, to judge the amount and quality of motor activity, to evaluate active and passive tone, and to observe primitive and postural reflexes. The clinical examination, per se, does not directly measure higher cortical function, preservation of which is key to a healthy neurological future.

Although the actual generators of the neonatal electroencephalogram (EEG) are not specifically known, they are presumed to arise directly from neurons in the cerebral cortex, under the modulation of critical "deep gray" structures such as the thalami. The neonatal EEG is one of the few objective methods of measuring the functional integrity of the immature cortex and its connections. Empirically, it is most commonly used to measure the impact of a known medical or neurological insult on the brain and to detect or confirm the presence of seizures (17). Neonatal EEG is best employed as a supplement to a comprehensive evaluation of the patient that assimilates the clinical, neuroimaging, and electrophysiological viewpoints. EEG is rarely used to determine precisely the cause of an encephalopathy. Rather, it is performed to determine the severity of the brain injury and the likelihood that a permanent neurological condition will persist. As such, neonatal EEG is a premier prognostic tool when performed by an experienced electroencephalographer.

Although the basic electrophysiological principles that underlie neonatal EEG interpretation are similar to those used to read EEGs of older children, there is a different approach to interpreting and understanding tracings recorded in the very young infants. During infancy, brain maturation occurs at a rapid pace, accompanied by parallel changes in the appearance of the neonatal EEG. This is a challenge to the interpreter, who must be knowledgeable about the normal appearances of the EEG for a variety of ages, behavioral states, and medical conditions of the patients.

Routine bedside EEG examinations are sometimes supplemented or supplanted by the use of cerebral functional monitors, intended for long-term detection of electrographic seizure activity or to record global, simple measures of EEG trends over time (such as "amplitude integrated EEG") (1,5,9,26,39,40,66,94). The intention of this chapter is to provide a useful, broad perspective on conventional neonatal EEG examinations so that meaningful interpretations may be made even by those who are not highly experienced in reading newborns' records. Although there are abundant publications of highly detailed descriptions of the subtle nuances of neonatal EEG interpretation (19,56), the focus of this chapter is to provide a pragmatic, orderly approach to visual EEG analysis.

TECHNICAL ASPECTS OF NEONATAL ELECTROENCEPHALOGRAPHIC RECORDING AND INTERPRETATION

The international 10-20 system of electrode placement has been modified for neonatal EEG recording because of infants' small head size and the relative lack of EEG activity in the extreme frontopolar regions (Fig. 6.1). The standard neonatal montage includes electrodes Fp3 (halfway between Fp1 and F3), Fp4 (halfway between Fp2 and F4), C3, C4, T3, T4, 01, 02, Fz, Cz, Pz, A1, and A2 (19). If the earlobes are too small, mastoid leads (M1 and M2) may be substituted. Fp3 and Fp4 electrodes are used because electrographic background activity and frontal physiological sharp waves are better visualized there than at the usual frontopolar locations (Fp1 and Fp2) (88).

A single montage, which includes both anterior-posterior and transverse arrays with coverage across the central vertex (Cz), is acceptable for most neonatal recordings (Fig. 6.2). Recording montages that include vertex

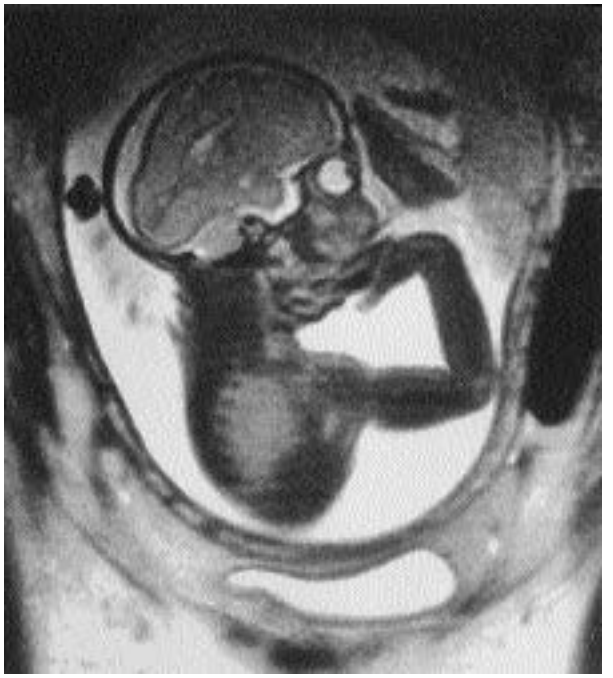


FIG. 6.1. Intrauterine magnetic resonance imaging examination of fetus 30 weeks of estimated gestational age. Notice the relatively simple convolutional markings of the frontal lobes in comparison with the occipital cortices.

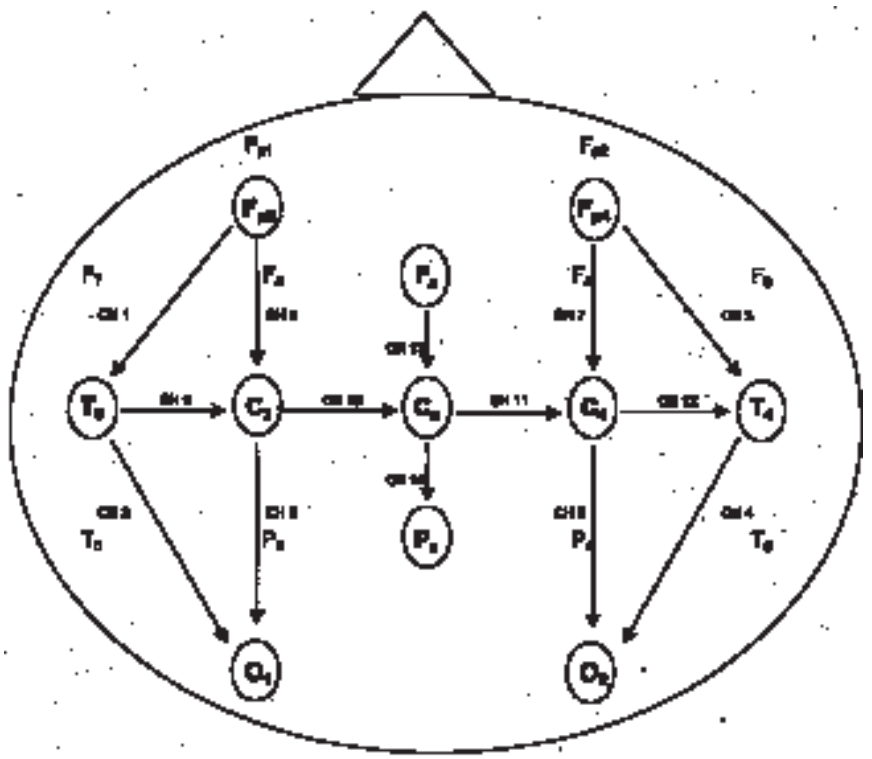


FIG. 6.2. Modification of the international 10-20 system commonly used in neonates. A single montage includes anteroposterior, transverse, and midline arrays. Fp3 and Fp4 replace the usual Fp1 and Fp2 electrode locations.

regions are highly recommended. Some important EEG transients such as positive vertex sharp waves, negative vertex sharp waves, and electrographic patterns of seizures may be confined to those regions and missed if midline electrodes are not included in the recording montage (79). Extra recording electrodes or other montages may be employed to clarify localized abnormalities if necessary. Eighteen EEG channels are typically needed to allow for the standard neonatal montage and noncerebral electrodes. Thus, eight-channel recording machines are inadequate for a comprehensive evaluation of simultaneous EEG and physiological variables such as heart rate and respiration. The presence of scalp intravenous catheters in neonates may disrupt the usual placement of EEG electrodes. The electrode should be placed adjacent to the catheter site, as close as possible to the usual scalp location. The corresponding contralateral electrode should be placed in a symmetrical scalp location.

Noncerebral electrodes provide crucial information about the behavioral state of the infant and assist in the recognition of artifacts. In neonates, at least two channels must be devoted to noncerebral electrodes (2). The following noncerebral electrodes are commonly employed:

1. A respiratory monitor is usually placed on the abdomen or chest to detect respiratory motion. The sensitivity should be adjusted to yield a clearly visible vertical deflection when a low-frequency filter setting of 0.3 to 0.6 Hz is used. These monitors help identify the deep, slow, and regular respiratory pattern of quiet sleep, the more rapid and irregular pattern of wakefulness and active sleep, periodic breathing and apneas.
2. Eye monitors are used so that both vertical and horizontal eye movements (including eye blinks, nystagmus, and rapid eye movements [REMs]) can be identified and distinguished from cerebral electrical activity in the frontal regions. Two electrodes are placed obliquely across either eye: one on the nasion and the other inferior to the outer canthus. The sensitivity setting in the eye channels should be the same as the cerebral electrodes.
3. The electrocardiogram (ECG) monitor detects electrocardiographic activity and assists in identification of movement artifacts. Pulse artifact may be seen over the anterior fontanel in electrodes Fz, Cz, or Pz and can be temporally correlated with the QRS complexes.
4. An optional electromyogram (EMG) electrode may be placed under the chin to monitor submental muscle tone. If recorded, the ECG channel may be omitted because the R wave is usually visible in the submental channel. A sensitivity of 3 mV per millimeter, a low-frequency filter setting of 5 Hz, and a high-frequency filter setting of 70 Hz are often optimal for this channel. Although submental EMG activity per se is unreliable in identifying sleep states in neonates, the channel can be helpful in confirming the extracerebral nature of movement artifacts. In patients being supported with extracorporeal membrane oxygenation (ECMO), the EMG channel can be attached to the ECMO pump to time pump cycles and monitor pump flow artifact. Surface electrodes may also be placed on involved limbs if tremors or clinical seizure manifestations are present.

Paper speed may be set at the standard speed of 30 mm per second or at the "slow paper speed" of 15 mm per second. Recording at 15 mm per second may be advantageous because it *compresses* the recording and facilitates visual recognition of delta activity, the dominant frequency in neonatal EEG. This principle is also used to optimize the recognition of slow activity in tracings of older persons. Slow paper speed also helps to visually assess the degree of discontinuity and interhemispheric synchrony in discontinuous recordings. All EEG samples illustrated in this chapter were recorded at a paper speed of 15 mm per second.

Electrode impedance less than 5 k Ω can be obtained regularly, although higher impedances may be allowed to avoid excessive abrasion of delicate infant skin. Marked differences in impedance between electrodes should be avoided. Sensitivity for cerebral electrodes is initially set at 7 μV per millimeter and adjusted as needed to visualize low-voltage fast activity. Higher sensitivity may also be helpful in patients with apparent low-voltage records from scalp edema. The low-frequency filter is usually set at 0.3 to 1.0 Hz to capture the full complement of delta activity in the neonatal EEG. The high-frequency filter is set at 50 to 70 Hz.

Accurate, abundant clinical data and behavioral notations by the EEG technologist are critical for adequately interpreting the neonatal EEG. Estimated gestational age (EGA), legal age, conceptional age, medical status, medications, mechanical ventilation or ECMO, and other relevant observations should be recorded. During the recording, frequent notations of eye opening and closing are necessary to recognize state changes. Notations regarding head position, scalp edema, small and large body movements, breathing patterns, apnea, hiccups, sucking, and "patting" by caregivers also provide information about the context of the recording session and help to identify artifacts. Clinical descriptions of the presence of unusual behavior such as tonic posturing, sustained eye deviation, nystagmus, clonic jerking, myoclonic activity, apnea, color changes, and vital sign fluctuations allow for clinical correlation with electrographic seizure activity.

At the end of the recording, the technologist should stimulate the infant vigorously and long enough to demonstrate the presence or absence of EEG reactivity. Stimulation is especially important in patients with a depressed mental status; in patients with an invariant, excessively discontinuous EEG; and in those who are therapeutically paralyzed. Auditory and somatosensory stimuli should be applied and notations made regarding behavioral or electrographic changes. Photic stimulation is rarely clinically useful in neonates and is not strongly recommended (2).

The length of a neonatal EEG varies with the clinical situation. Ideally, the full gamut of wakefulness, active sleep, transitional sleep, quiet sleep, and arousal are all recorded (31). Thirty minutes is the minimum duration for a record, but records often extend for 60 minutes or more if there is a strong clinical suspicion for seizures that have not been recorded.

Recording Artifacts

Various extracerebral artifacts complicate the interpretation of neonatal EEGs. Many artifacts can be identified in accordance with the same principles applied to adult EEG interpretation. For example, the simultaneous presence of unusual-appearing activity in extracerebral electrodes (e.g., the ECG or respiratory channel) or an activity of peculiar morphology (e.g., electrode pops) suggest artifact. Genuine electrographic seizures typically evolve in morphology, frequency, and amplitude. Some sustained rhythmic artifacts superficially mimic electrographic seizures (e.g., ECG, pulse, and respiratory artifacts) but do not show the physiological progression of ictal waveforms. In older patients, identifying a plausible "potential field" of an event may help distinguish genuine cerebral activity from some extracerebral activity, but this principle is less helpful in some neonates. Some normal and abnormal EEG transients in neonates have restricted electrical fields. For example, abnormal positive vertex sharp waves may be exquisitely confined to a single electrode without "physiological spread" to neighboring regions.

Muscle artifact may be prominent in the temporal bipolar derivations, but it is typically too fast to be confused with cerebral activity. EMG artifact reduces when the infant calms down or falls asleep. Sucking artifact, a unique form of neonatal muscle activity (Fig. 6.3), typically results in high-amplitude, very sharp potentials in both temporal regions, without spread to adjacent scalp regions. Notations by the technologist should clarify the situation. Hiccups produce movement artifact occasionally with striking regularity in both cerebral and extracerebral electrodes (Fig. 6.4).

Eye movement artifact may be confused with frontal EEG activity, and eye monitor electrodes aid in their recognition. Eye movements generate deflections that are "out of phase" between the eye channels (Fig. 6.5), whereas frontal cerebral activity is "in phase" between the eye channels.

ECG, pulse, ballistocardiographic, and respiratory artifacts are also identified with the aid of extracerebral electrodes. ECG artifact (Fig. 6.6) can dominate the tracing in a low-voltage recording and is especially prominent as a cardiac "dipole" across the temporal regions. The ECG potentials reflected over the scalp surface are coincident with the QRS complexes in the ECG channel. Pulse artifact may occur at any location, but it is often prominent over the anterior fontanel, especially in the Cz electrode. Intermittent pulsations of the fontanel are transmitted to cerebral EEG electrodes, causing rhythmic deflections that may mimic focal rhythmic delta activity or an electrographic seizure. There is a slight but consistent delay between a QRS complex and its coupled pulse artifact. In some infants, cardiac motion causes recoil of the infant's entire body, leading to ballistocardiographic artifact (Fig. 6.7), which may be present in all electrodes or limited to the dependent (e.g., occipital) leads. Respiratory artifact (Fig. 6.8) may also occur at any location. Mechanical ventilation with high-frequency jet ventilators (which generate respiratory rates up to 400 breaths per

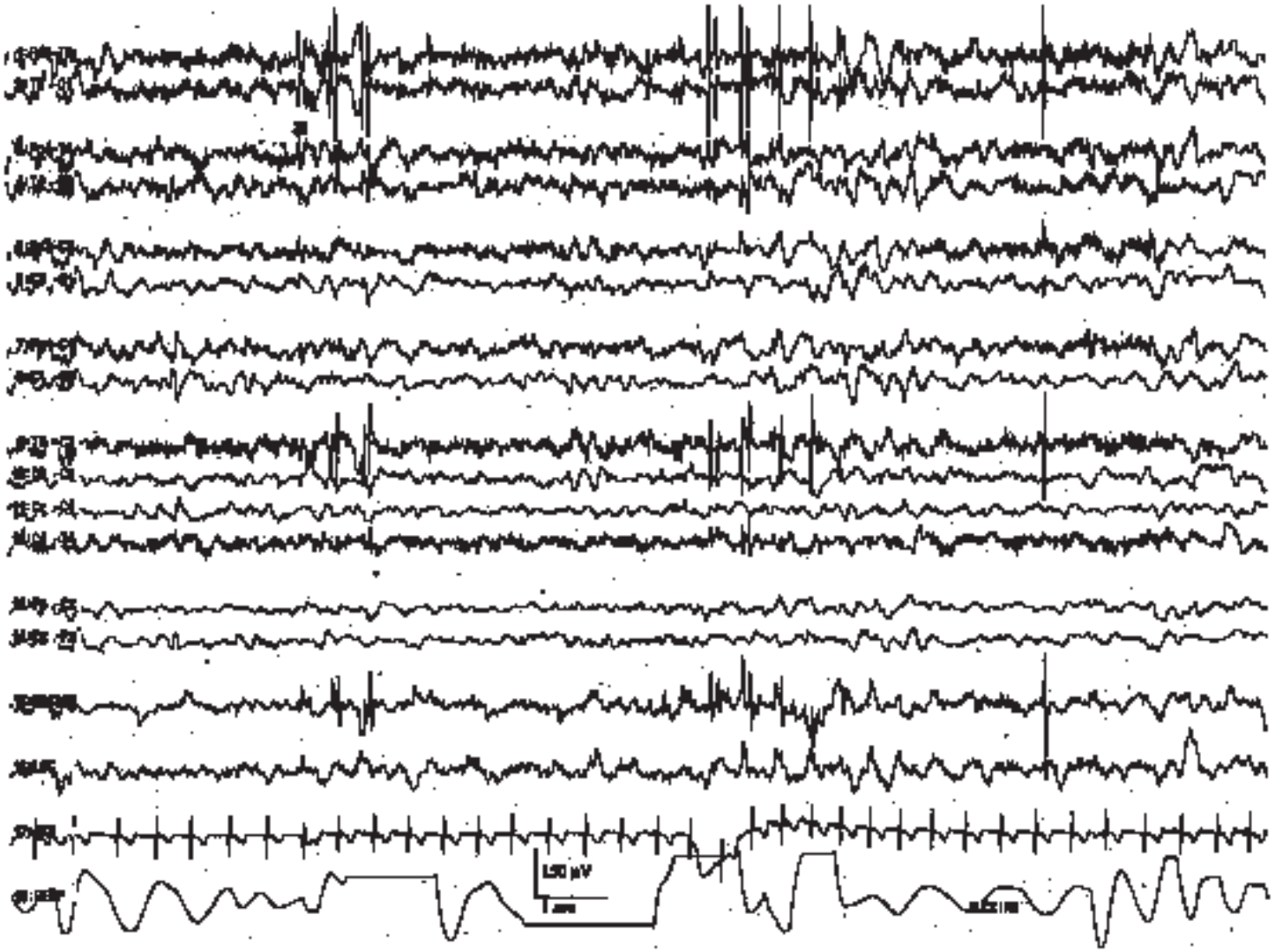


FIG. 6.3. Sucking artifact in an infant 46 weeks of conceptional age with a history of hypoxic ischemic encephalopathy (HIE) and seizures. Sucking artifact (*arrow*) is clearly evident over both temporal regions, the left more than the right.

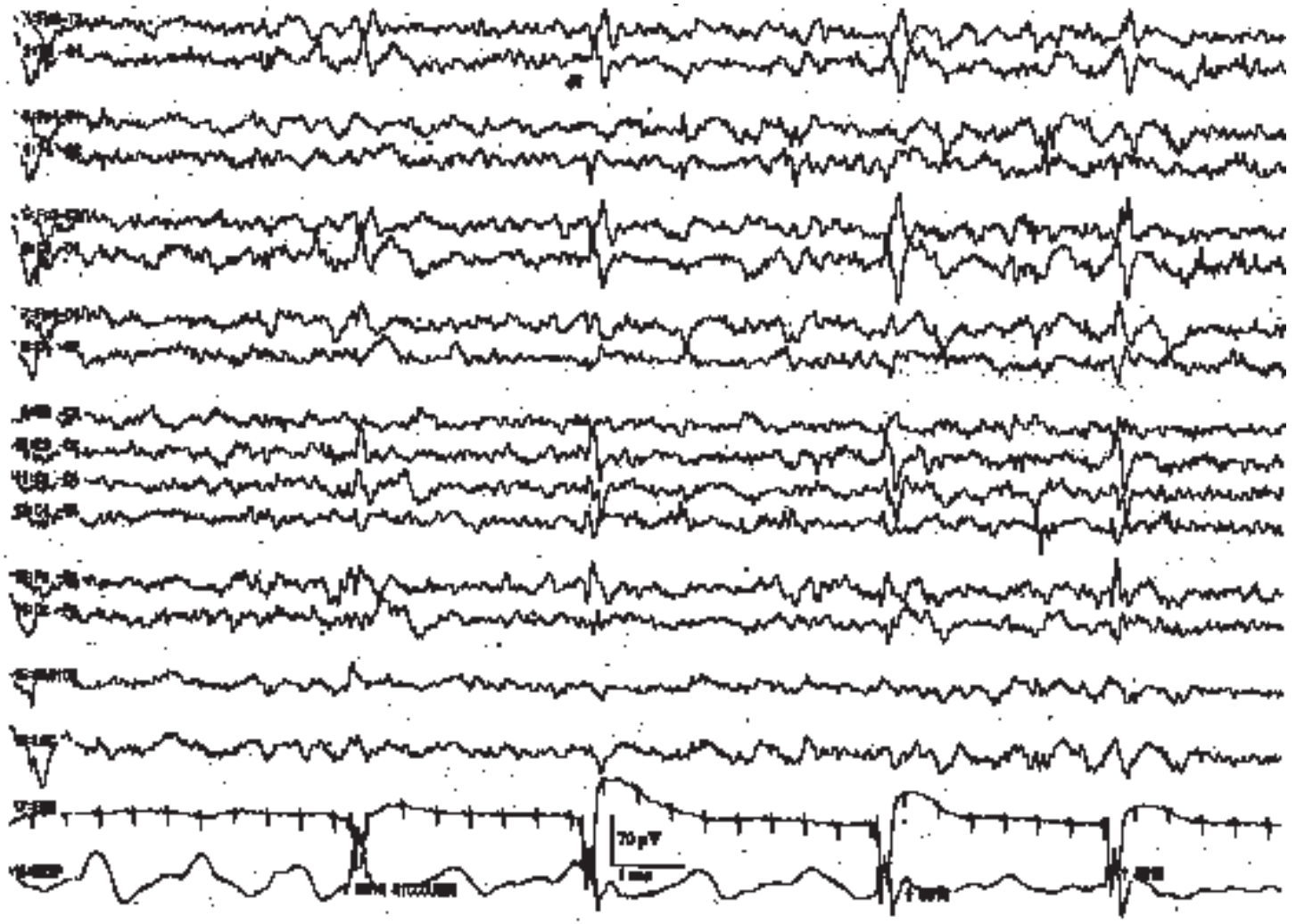


FIG. 6.4. Hiccup artifact in an infant 41 weeks of conceptional age with meningitis. Typical hiccup artifacts (*arrow*) are present, which impart a "periodic" appearance to the record. Note the prominent movement artifact contaminating the electrocardiogram and respiratory channels, which confirms its extracerebral origin.

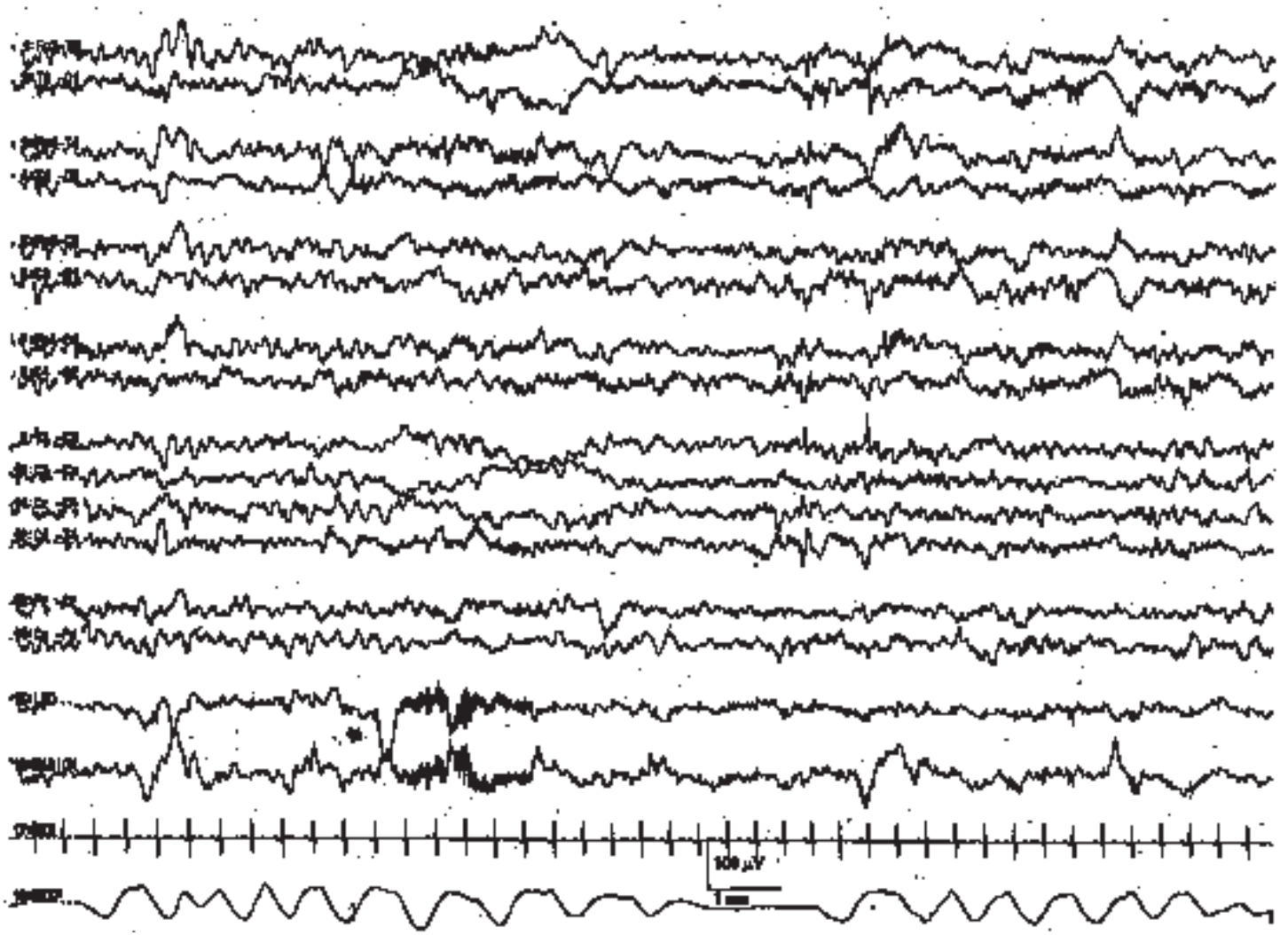


FIG. 6.5. Eye movements in an infant 40 weeks of conceptional age with gastroesophageal reflux. Out-of-phase activity is present in the two eye channels (*arrow*), which confirms extraocular movement activity.

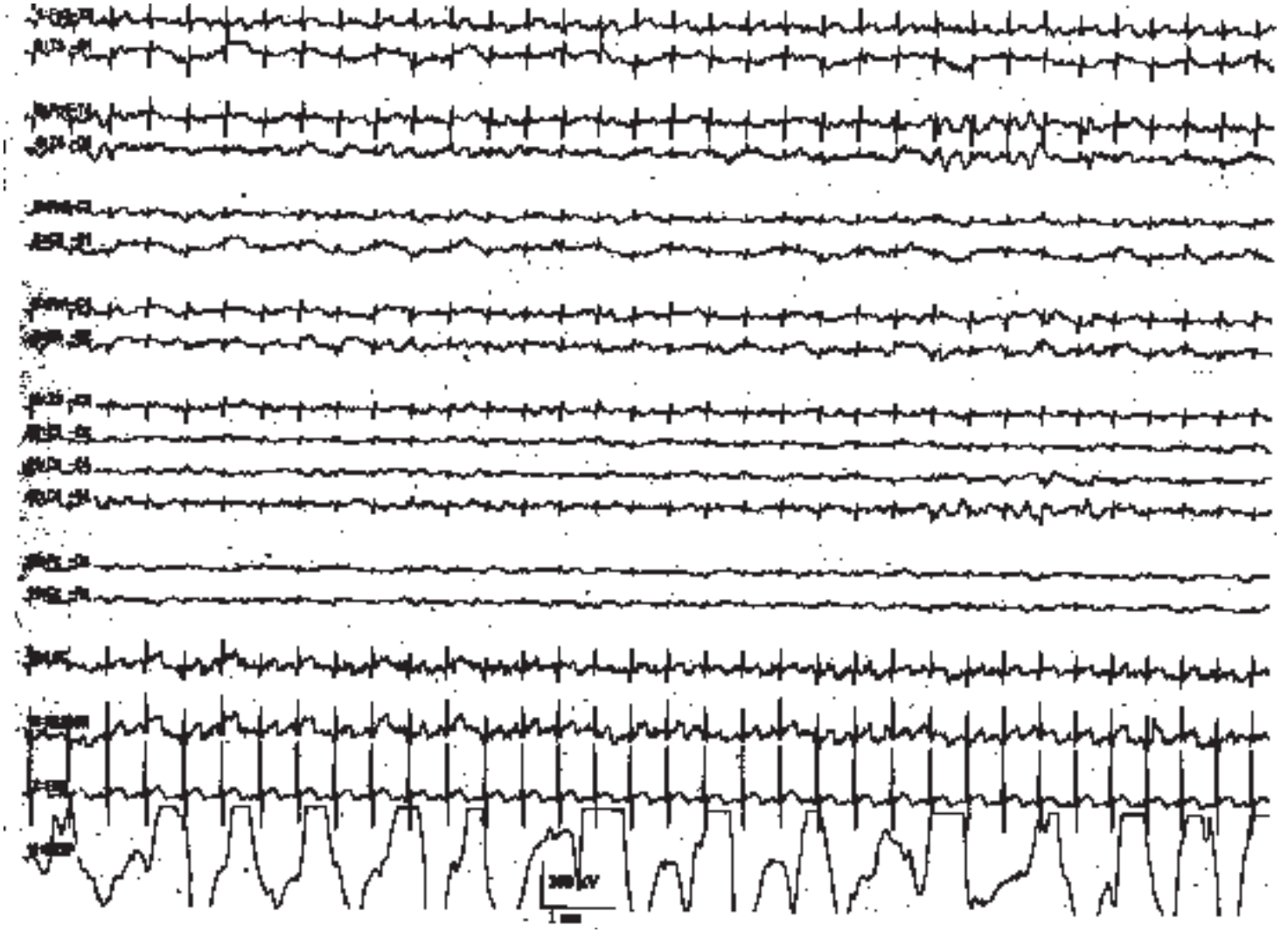


FIG. 6.6. Electrocardiogram (ECG) artifact in an infant 46 weeks of conceptional age with Klippel-Trenaunay-Weber syndrome and seizures. ECG artifact is present throughout the electroencephalographic background. Note the positive T3 and negative T4 dipole of the QRS complex.

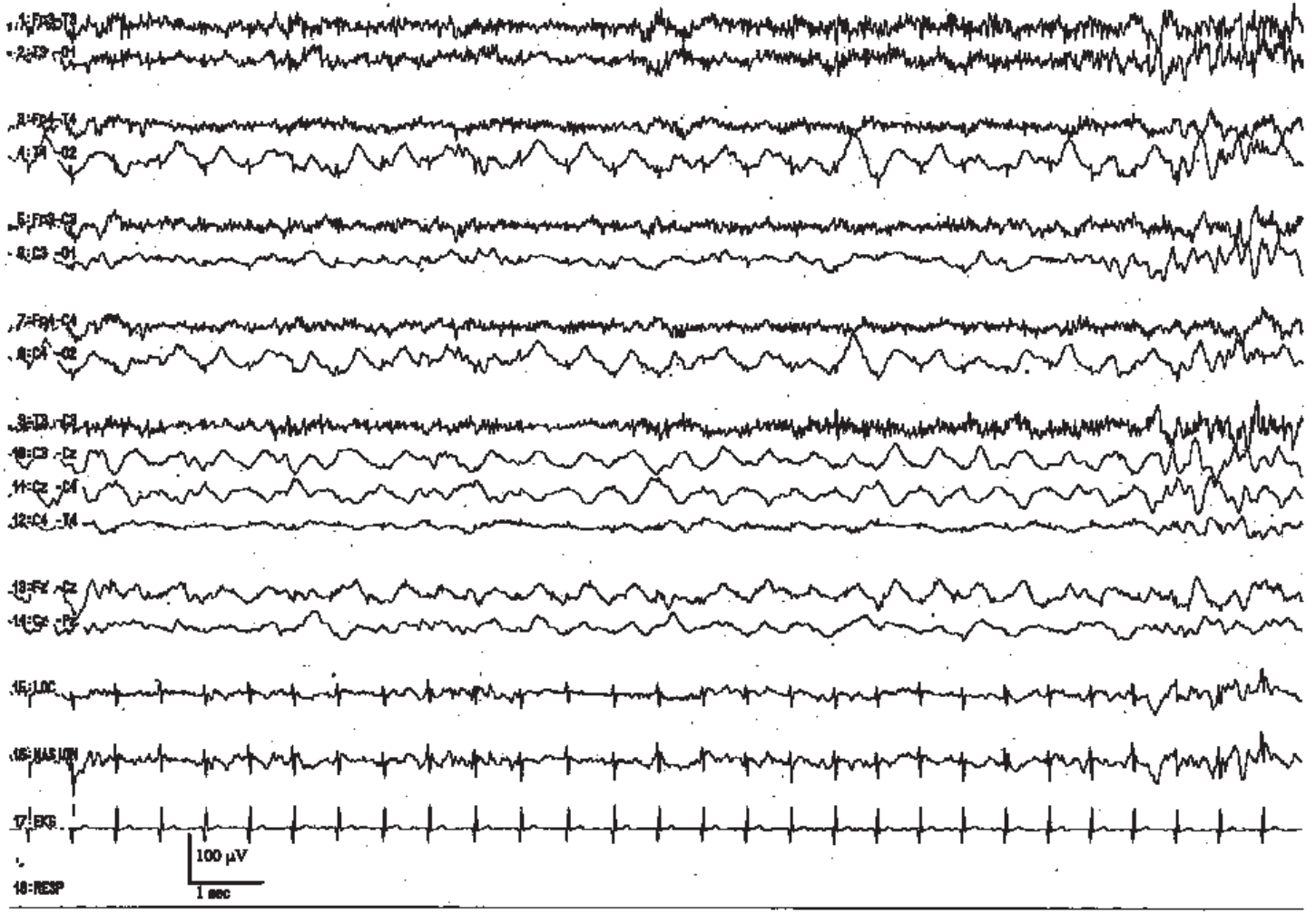


FIG. 6.7. Ballistocardiographic artifact in an infant 44 weeks of conceptional age with left ventricular hypertrophy. The head was turned to the right. Cardiac recoil motion resulted in rhythmic movement artifact at O2 and Cz.

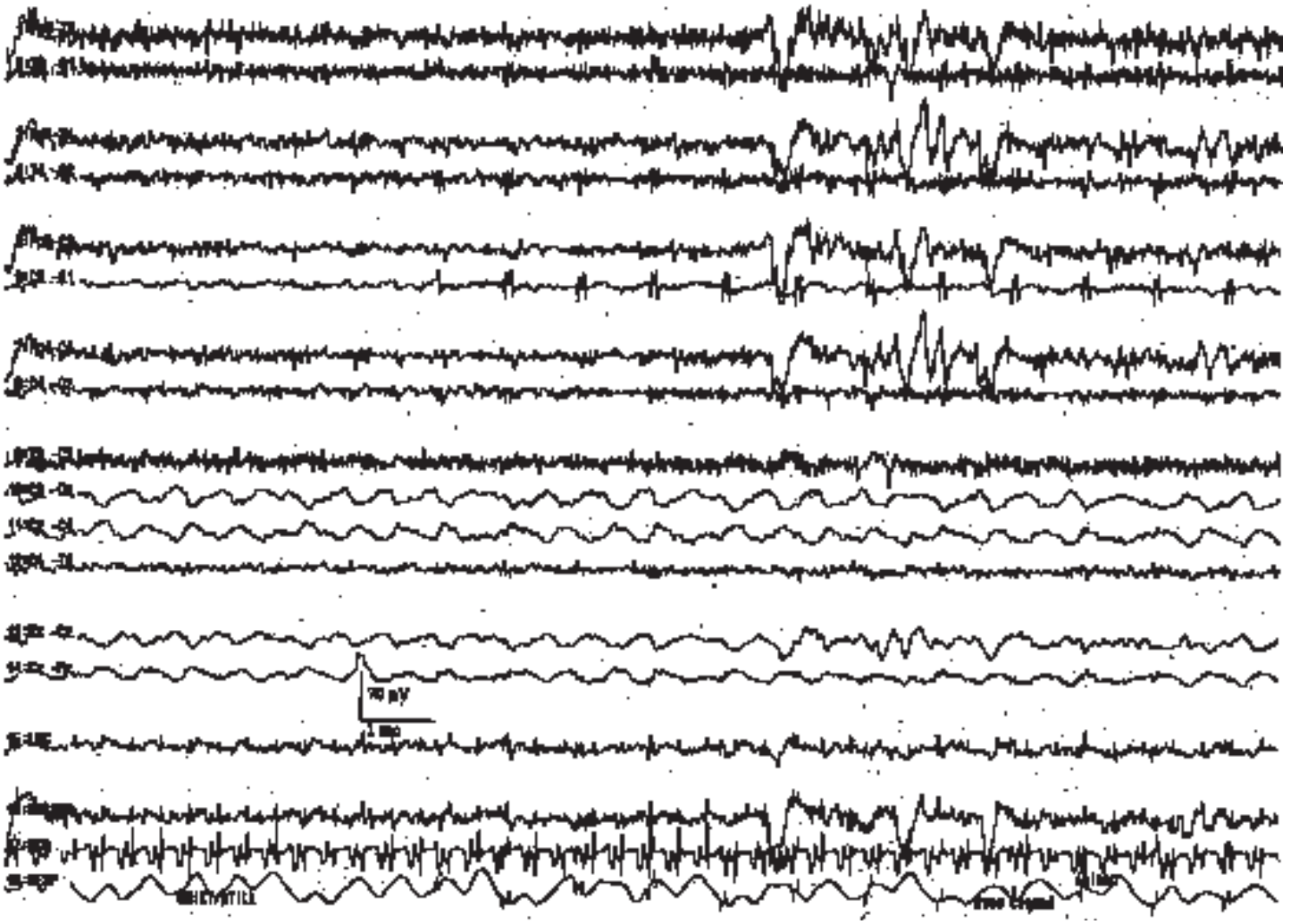


FIG. 6.8. Respiratory artifact in an infant 41 weeks of conceptional age with head trauma. Rhythmic activity at Cz correlated with respirations.

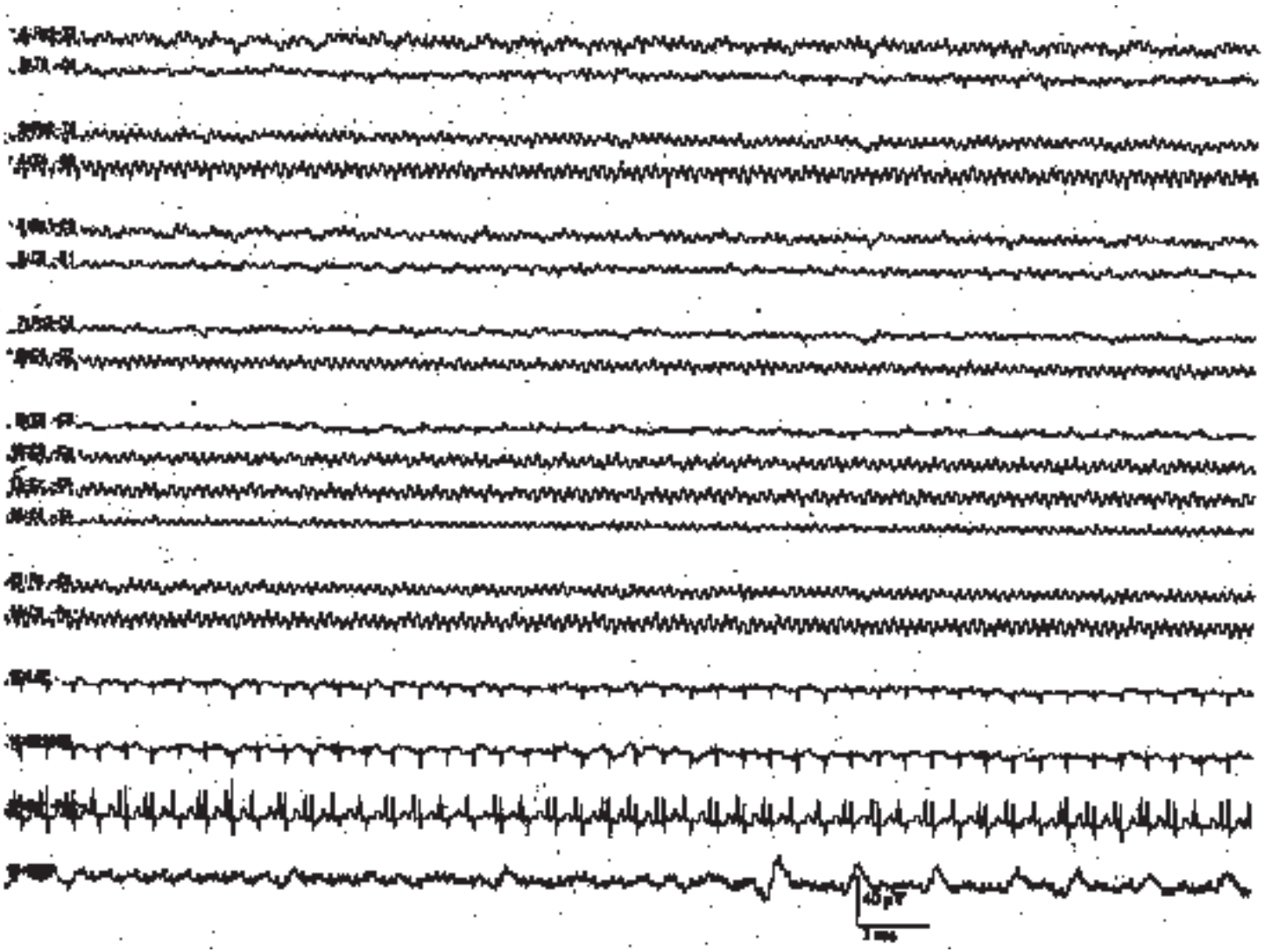


FIG. 6.9. High-frequency ventilator artifact in an infant 40 weeks of conceptional age with persistent pulmonary hypertension. Invariant, rhythmic, sinusoidal artifact from the ventilator is widely reflected throughout the tracing.

minute) and oscillating ventilators cause the infant's entire body to vibrate, which results in focal or diffuse rhythmic artifact (Fig. 6.9). Correlation of the rhythmic EEG activity with the respiratory monitor allows for identification. ECMO pump artifact is usually conspicuously constant and invariant throughout the record.

"Patting the baby" artifact may mimic electrographic seizure activity (Fig. 6.10), and the technologist's notations are critical for correct interpretation. Crescendo clonic limb movements in a jittery baby (Fig. 6.11) may generate rhythmic movement artifact that is transmitted to cerebral electrodes, causing deflections that sometimes mimic focal electrographic

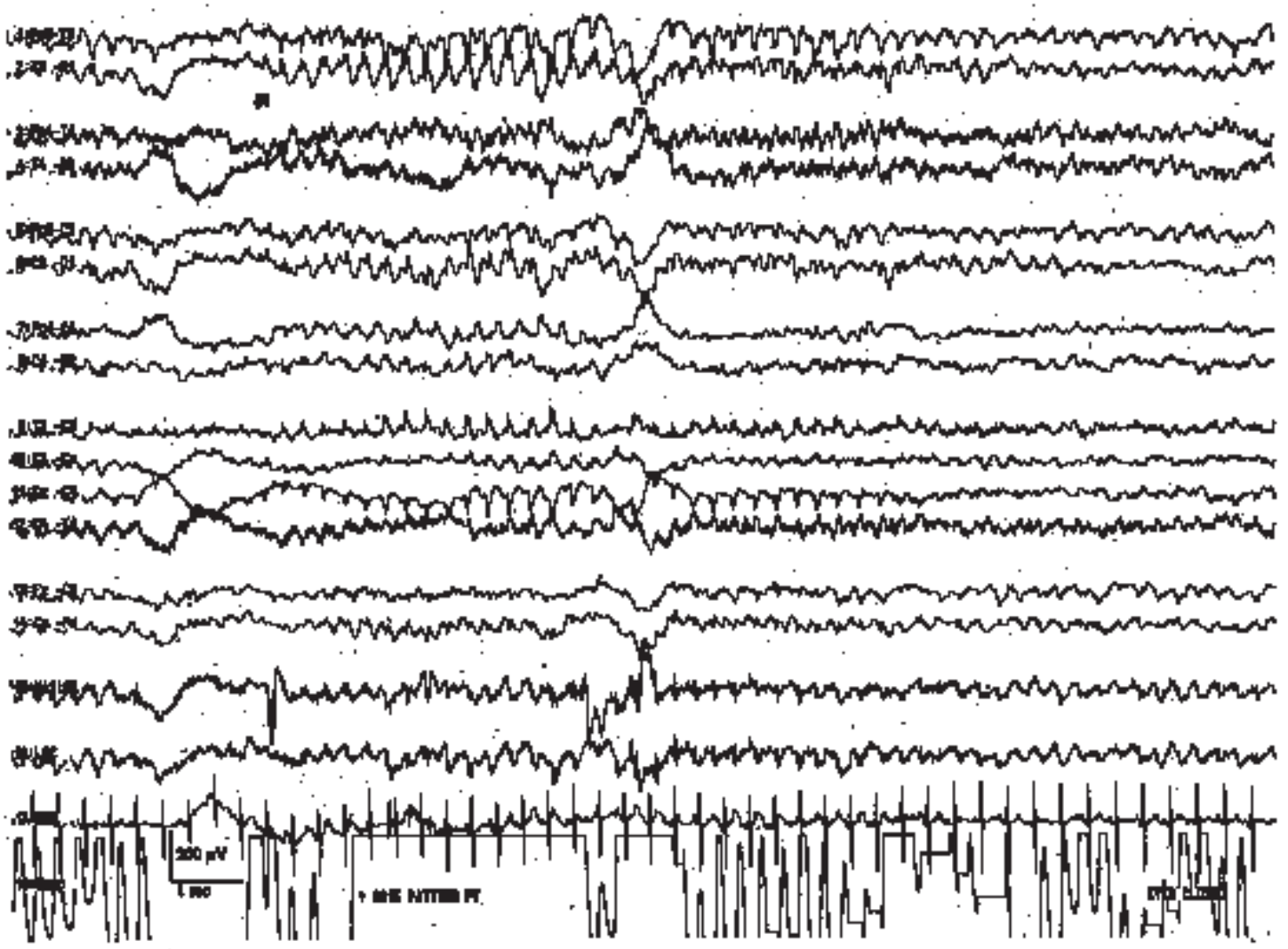


FIG. 6.10. Patting artifact in an infant 44 weeks of conceptional age with sepsis, apnea, and seizures. Patting artifact (*arrow*) can mimic an electrographic seizure.

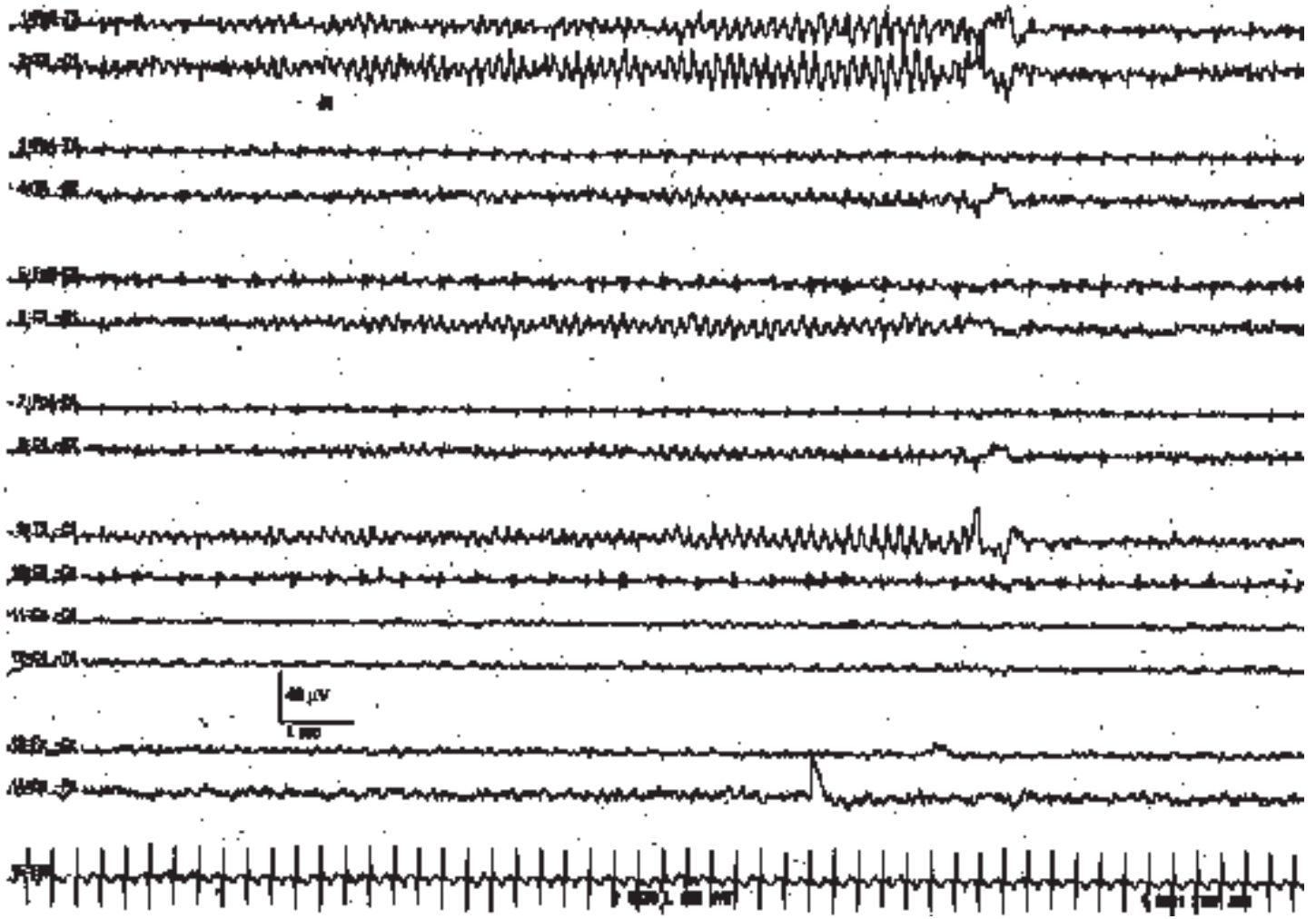


FIG. 6.11. Clonic limb movement artifact in an infant 47 weeks of conceptional age who had recently suffered cardiac arrest. Clonic movement of the left arm mimicked an electrographic seizure (*arrow*). When the technologist restrained the left arm, the artifactual "seizure" ceased.

seizure activity. In most cases, the frequency of the movement is relatively invariant, and the EEG does not show the typical frequency evolution of seizure activity. If the technologist briefly restrains the shaking extremity, the movement artifact "seizure" subsides, allowing for interpretation of background cerebral activity.

Single electrode "pops" (Fig. 6.12) may be confused with pathological positive sharp waves, but the initial deflection is nearly vertical—similar to the discharge of a charged capacitor and too rapid to be of cerebral origin.

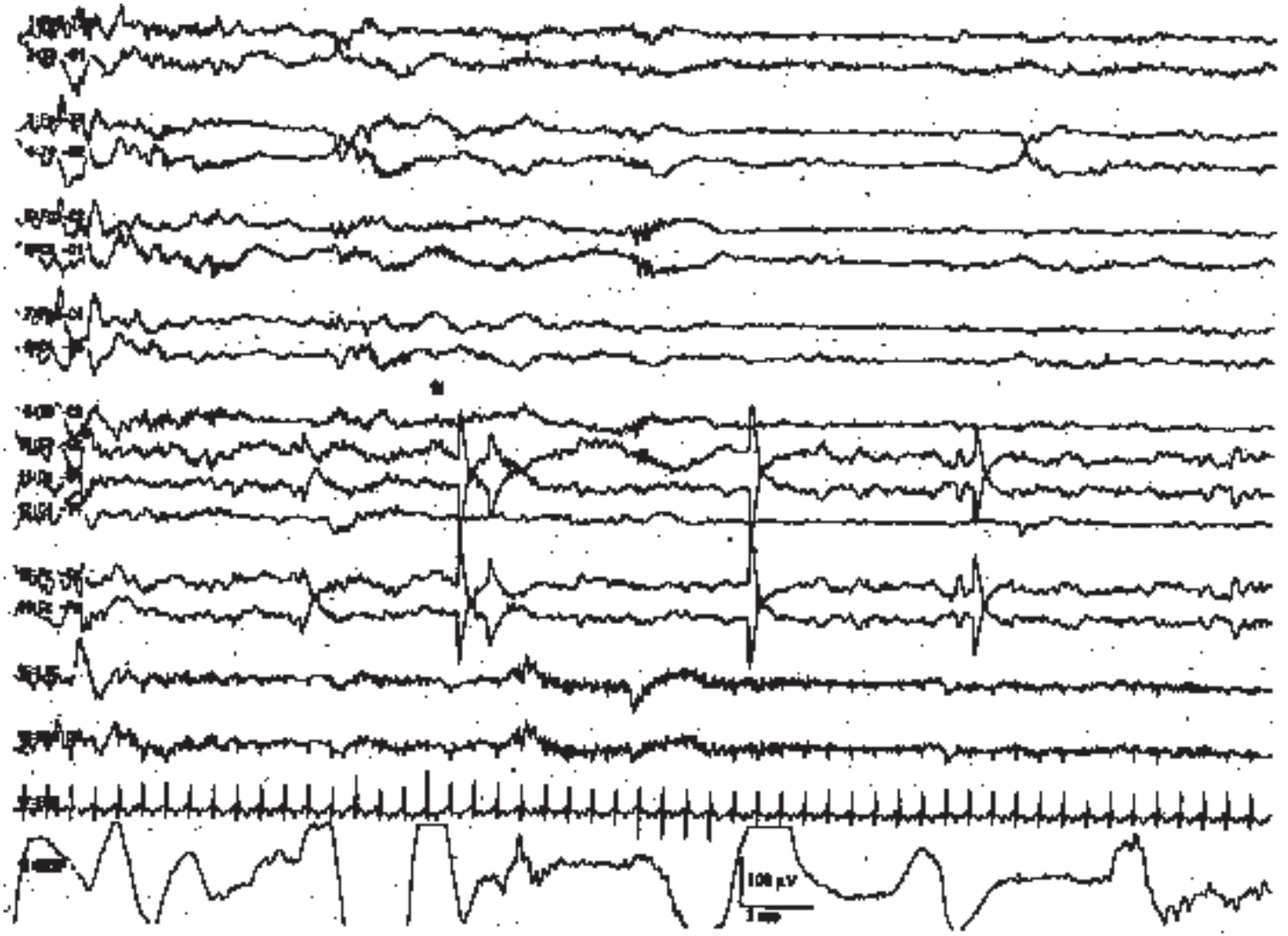


FIG. 6.12. Electrode artifacts-in an infant 34 weeks of conceptional age with complex congenital heart disease. Electrode pops (*arrow*) can be confused with genuine positive sharp waves. Note that the initial deflection is nearly vertical—too rapid to be of cerebral origin.

VISUAL ANALYSIS OF THE NORMAL NEONATAL ELECTROENCEPHALOGRAPHIC BACKGROUND

Conceptional Age, State, and Medical Status

Conceptional Age

It is necessary to know several relevant definitions of *age* in order to properly understand and interpret the neonatal EEG. The estimated gestational age (EGA) is the age of the fetus since conception. This is typically determined by calculation of the length of the gestation from the time of the mother's last menstrual period (LMP) to the day of the infant's birth. If the LMP is unknown or the mother's menses are irregular, gestational age can be estimated by fetal ultrasound examinations early in the pregnancy or by the Ballard examination of physical maturity (6,13), performed shortly after birth. Newborns are considered premature if born before the 37th week of the gestation. Full-term infants are born between the 37th and 42nd weeks of gestation, and post-term infants are born after 42 weeks of gestation.

An infant's legal age is simply the age since birth. For example, if an infant was born 2 weeks ago, the legal age is 2 weeks. Age since conception (conceptional age) is determined by adding the legal age and EGA. Thus, both a 1-week-old (legal age) infant born at 39 weeks of EGA and a 13-week-old (legal age) infant born prematurely at 27 weeks of EGA have a conceptional age of 40 weeks. Conceptional age is the key observation when interpreting the neonatal EEG. EEG maturity is principally determined by the conceptional age, because neurological development is thought to proceed at the same rate during intrauterine and extrauterine life. On occasion, careful assessment of the EEG background can be used to estimate the conceptional age within ±2 weeks if there is no information from other sources about EGA or legal age (43).

State

In the newborn infant, biobehavioral state is simply determined by the operational definitions of *wakefulness* and *sleep.* In sleep, the eyes are closed, and in wakefulness, the eyes are open. This operational definition of state is not applicable to the extremely premature infant born before the eyelids are unfused (which typically occurs at approximately 23 to 24 weeks of EGA). In children and adults, state can be further characterized by a constellation of behavioral and physiological variables that determine the presence of full alertness, drowsiness, active or rapid-eye-movement (REM) sleep, and light to deep quiet (non-REM) sleep. In healthy older infants, there is a predictable and well-defined agreement (*concordance*) in various sleep states between behavioral and physiological observations (e.g., phasic movements of the limbs during REM sleep) accompanied by a specific appearance of the EEG. However, this concordance between the clinical and electrographic expressions of state is not well developed in very premature infants; it evolves in a predictable manner as term approaches.

In a well-developed infant in active sleep, the infant's eyes are closed. There are a variety of small and large body movements, sucking, and even crying behaviors that are punctuated by bursts of predominantly horizontal rapid eye movements—the REM phase of active sleep. Brief apneas are relatively common, especially before term. During active sleep, the EEG background resembles the low-voltage, continuous EEG of quiet wakefulness. Newborn infants often enter into active sleep from wakefulness, thus mimicking the sleep patterns of "narcoleptic" older persons. This pattern of sleep onset continues until about 4 months post-term, at which time quiet sleep precedes active sleep.

In a well-developed infant in quiet sleep, the eyes are closed and there are few head, trunk, or limb movements. Respirations are exquisitely regular, deeper, and slower. Apnea is uncommon. Occasional startles or arousals may briefly interrupt quiet sleep, but usually the infant settles back down quickly unless the arousal was sufficient to provoke a change longer than a minute and a transition to wakefulness or active sleep. Quiet sleep is the state in which the infant's EEG is most vulnerable to adverse medical or neurological conditions. In sick newborns, the amount of time spent in well-defined quiet sleep diminishes at the cost of increasing the percentage of time in indeterminate sleep. In EEG recording, it is essential to try to capture quiet sleep because it may be the only sleep state in which some EEG abnormalities may be detected. In infants with some mild encephalopathies, the awake and active sleep recording may appear normal, but quiet sleep recordings reveal previously unrecognized abnormalities.

Even in healthy newborns, much of sleep is *indeterminate* or *transitional:* That is, even with a good-quality EEG and careful behavioral observation, it is not possible to determine precisely whether the child is in active or quiet sleep. This is clearly the case when the infant transits from one behavioral state to another (transitional sleep), but it also applies when an exact designation of active or quiet sleep cannot be assigned. A large proportion of total sleep time is indeterminate at term and increases in the setting of medical or neurological illness (Fig. 6.13) (98).

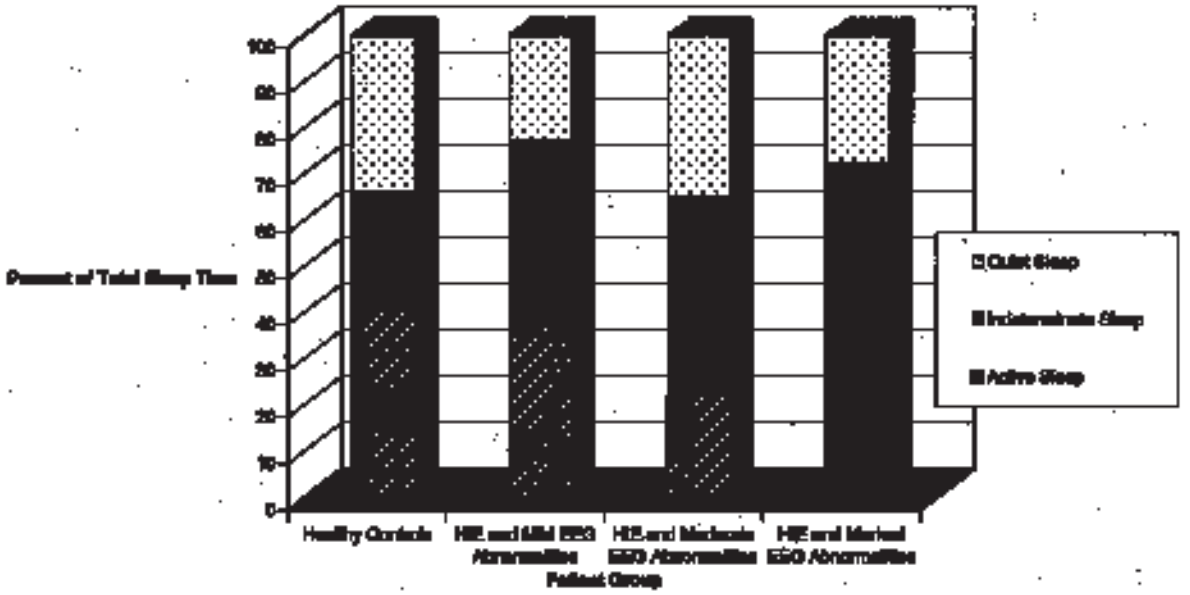


FIG. 6.13. The percentage of total sleep time occupied by indeterminate sleep is significantly increased in sick newborns with abnormal electroencephalographic backgrounds. (Adapted from Watanabe K, Miyazaki S, Hara K, et al. Behavioral state cycles, background EEGs and prognosis of newborns with perinatal hypoxia. *Electroencephalogr Clin Neurophysiol* 1980;49:618–625.)

Medical Status

Knowledge of the overall medical/neurological status of the newborn is also vital for properly interpreting the results of the EEG examination. Medically sick infants are exposed to a wide variety of conditions such as shock, respiratory failure, sepsis, and metabolic disturbances. Just as nonspecific EEG background abnormalities may be recorded in medically ill older persons, mild to moderate degrees of abnormalities may be observed in sick neonates. Often, these are reflections of the presence of medical disease and do not necessarily imply the existence of fixed, permanent brain dysfunction or damage. Likewise, the administration of medications intended to reduce pain (e.g., fentanyl, morphine), agitation (e.g., diazepam, lorazepam), or seizures (e.g., phenobarbital) may introduce unknown, hard-to-quantify effects into the EEG. Some newborns with critical cardiorespiratory conditions are given neuromuscular blocking agents (e.g., pancuronium, vecuronium) to achieve therapeutic paralysis. This obscures the clinical assessment of biobehavioral state and creates an additional challenge to the EEG interpretation. Critically ill neonates may undergo ECMO to prevent cardiocirculatory collapse. These infants are often given both neuromuscular paralyzing drugs and long-term inhalation anesthetics (e.g., isoflurane). "Third-spacing" of fluid accumulates within a few days, and significant scalp edema develops. Because the right carotid artery is preferred for ECMO cannulation, the infant's head position is maintained to face to the left; therefore, the scalp edema is asymmetrical, greater on the dependent left side. It can be a considerable challenge to interpret the EEGs of such patients.

Timing of Electroencephalographic Examinations

The timing of EEG examinations may have a substantial impact on their meaningful interpretation. It is generally inadequate to simply record a single study near the end of the patient's hospital course. Substantial "nonspecific" normalization may occur after the peak of an illness (the time when the EEG is likely to reveal its maximal degree of abnormality, which is important in formulating a prognosis), and the EEG may show substantial improvement in parallel with early clinical signs of neurological recovery

(92,93) (Fig. 6.14). Because EEGs are most commonly obtained in an acute medical or neurological crises, it is critical that one or more studies be obtained when the infant is likely to display the most revealing prognostic information. If, when the infant is sickest, the worst EEG is still relatively well preserved and normal, it is reasonable to conclude that the illness has not severely affected CNS function. On the other hand, if, at the height of the illness, the EEG background demonstrates severe disturbances, it is reasonable to conclude that brain function has been adversely affected, and the prognosis is substantially worse. A note of caution, however, is in order: EEGs obtained in the *immediate* wake of a brief acute event (cardiac arrest, seizure, drug administration) may be misleading. The record may initially appear very abnormal but quickly show substantial improvement in just a few hours. It is desirable to repeat the examination the next day to determine whether the severe abnormalities are lasting or have resolved.

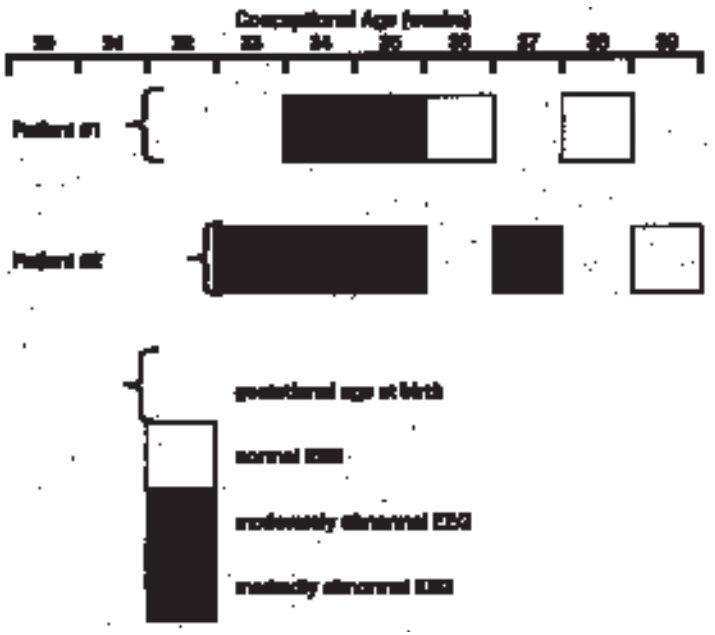


FIG. 6.14. Substantial, nonspecific normalization of the electroencephalographic (EEG) background may occur over time. Neurological prognosis is based on the most abnormal of serial EEG examinations. (Adapted from Tharp B, Scher M, Clancy R. Serial EEGs in normal and abnormal infants with birth weights less than 1200 grams—a prospective study with long term follow-up. *Neuropediatrics* 1989;20:64–72.)

The other consideration about EEG timing pertains to serial EEG examinations in premature infants. The sequential changes in EEG background during brain maturation should progress at the same rate whether the child is inside or outside the uterus. Thus, in the infants of very low birth weight, it would be reassuring to demonstrate that the tracings sequentially mature at the proper tempo from preterm birth until the conceptional age approaches full term. This is especially true in preterm infants with chronic lung disease (bronchopulmonary dysplasia), in whom clinical and electrographic maturity may be delayed (36,37,42,55,57,70,80,90–92).

General Properties of the Electroencephalographic Background

Continuity

The earliest vestiges of EEG activity are believed to arise after the eighth week of gestation. The EEG tracing appears as a completely discontinuous recording in which brief periods of electric activity ("bursts") are interrupted by periods of quiescence ("interburst" intervals). As such, the overall signal is a series of EEG bursts separated by flat or low-voltage interburst intervals (IBIs). With the development of CNS maturity and the increased influence of the deep grey structures that modulate cortical function, the duration of the burst (burst interval [BI]) increases, whereas the length of the IBI decreases.

EEG signals that regularly vary between the high-amplitude "on" periods of the bursts and low-amplitude "off" periods of the IBI are called *discontinuous* EEGs. Those that display a relatively steady amplitude are considered *continuous*.

The duration of the IBIs is a semiquantitative measurement of one aspect of the neonatal EEG. A typical, representative portion of the discontinuous portion of the EEG is selected for review, and the duration of the IBIs is measured and counted over a specific period of time: for example, a 10-minute sample. In that representative portion of time, numerous measurements of the IBI are made and the mean, median, and longest IBI values can be measured. The prime determinant of measures of the IBI is the infant's conceptional age. A typical median IBI at the conceptional age of 24 weeks is 10 seconds; this gradually decreases at older conceptional ages to values around 2 to 4 seconds (Fig. 6.15) (10,22,29,31,33,35,42,44, 57,88,93).

In a study of mortality in premature infants, those whose IBIs decreased with advancing conceptional age had a much higher chance of survival than those whose IBIs remained constant or increased with conceptional

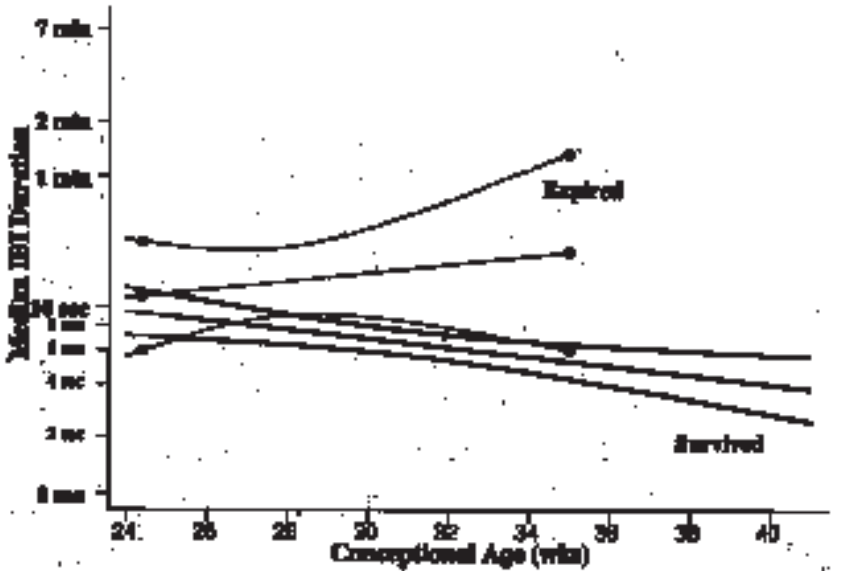


FIG. 6.15. Median interburst interval (IBI) duration decreases with advancing conceptional age in survivors of prematurity. The premature infants who died are characterized by IBIs that are significantly longer in duration than the IBIs of survivors. (Adapted from Clancy R, Rosenberg H, Bernbaum J, et al. Survival outcome prediction in premature infants with IVH by cranial ultrasonography and EEG. *Ann Neurol* 1994;36:489.)

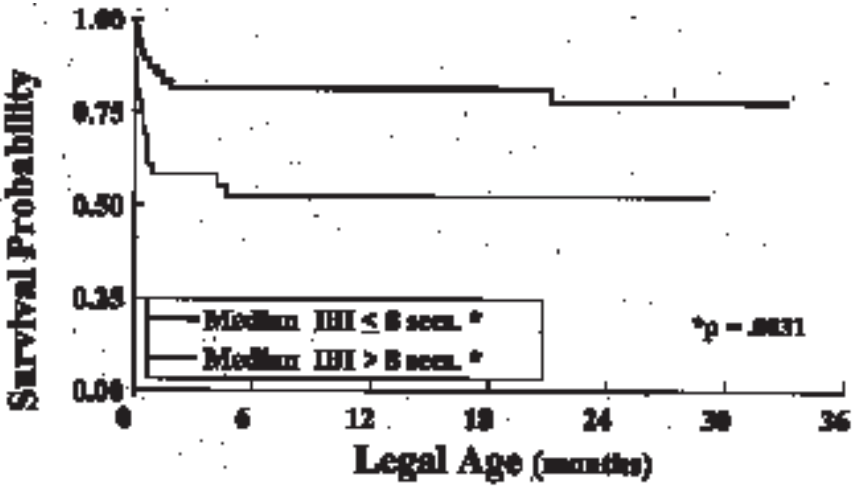


FIG. 6.16. Kaplan-Meier survival curve shows that premature infants with median interburst intervals (IBIs) of 8 seconds or less had a significantly higher incidence of survival than did those with longer duration IBIs. (Adapted from Clancy R, Rosenberg H, Bernbaum J, et al. Survival outcome prediction in premature infants with IVH by cranial ultrasonography and EEG. *Ann Neurol* 1994;36:489.)

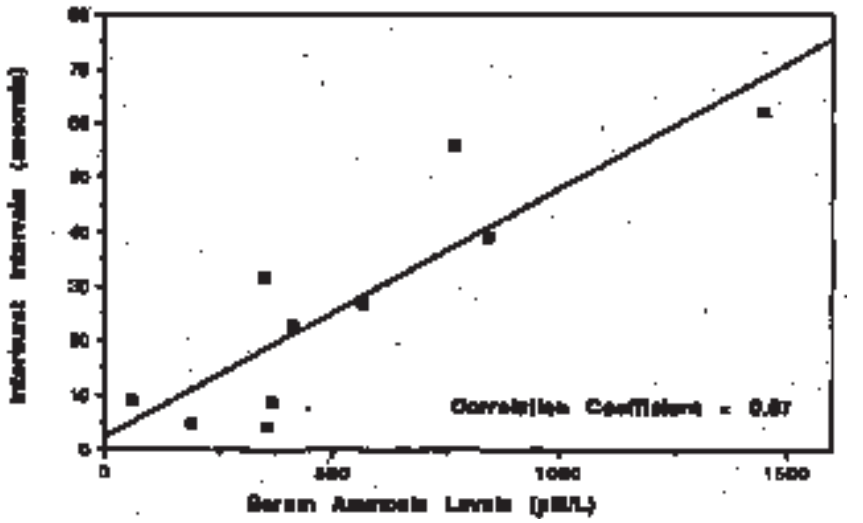


FIG. 6.17. There is a significant linear relationship between the serum ammonia levels and the interburst interval in this group of three neonates with citrullinemia. (Adapted from Clancy R, Chung H. EEG changes during recovery from acute severe neonatal citrullinemia. *Electroencephalogr Clin Neurophysiol* 1991;78:222–227.)

age. In general, infants at a conceptional age of 30 weeks and older with median IBIs of 8 seconds or less had a significantly higher incidence of survival than those with longer median IBIs (22) (Fig. 6.16). In an individual infant, IBI can be affected by transient influences such as noxious stimulation, arousals, hypoxia, drug administration (e.g., lorazepam), and seizure. The duration of the IBIs may correlate with measures of medical illness. Prolonged IBIs have been associated with elevated serum ammonia levels in citrullinemia (18) (Fig. 6.17) and with transient hypoxia in respiratory distress syndrome (30,89) (Fig. 6.18). Measurement of the IBIs in a brief sample of EEG is thus a simple approach for quantifying one aspect of neonatal EEG.

Earlier investigators reported a wide range of possible IBI values for premature infants. However, because IBI are dependent not just on conceptional age but also on medical status (e.g., degree of hypoxia and hypercarbia in respiratory distress syndrome), interpretation of IBI data from older

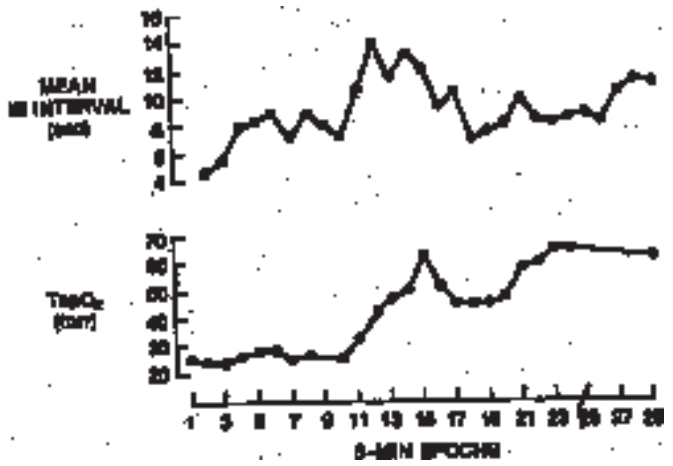


FIG. 6.18. The relationship between oxygenation and the mean interburst interval in a premature infant with hypoxic-ischemic encephalopathy and pulmonary hypertension. (Adapted from Tharp B. Intensive video/EEG monitoring of neonates. In: Gumnit R, ed. *Advances in neurology, vol. 46: Intensive neurodiagnostic monitoring.* New York: Raven Press, 1986:114.)

studies should be tempered by the knowledge that their measurements also reflected the medical conditions of their patients at that time. For example, Lombroso (55) reported that IBIs of up to 2 minutes can be "normal". Perhaps this should now be interpreted to mean that some infants with IBIs of this duration may be fortunate to survive with a good outcome, but an IBI of 2 minutes is no longer considered normal in current practice. Advances in high-risk neonatal care progress rapidly, and normative values will require renormalization as innovations such as artificial surfactant, high-frequency jet ventilation, ECMO, and nitric oxide administration are made more widely available.

Symmetry

Normal EEG activity arising between the two hemispheres or homologous brain regions should be essentially symmetrical. There are two facets of background symmetry to be judged: *amplitude* and *waveform composition* (Figs. 6.19 and 6.20). Amplitude symmetry implies that, in a suitably large sample of cerebral electrical activity, the background voltages between the hemispheres or specific regions are approximately equal. There is no universal agreement as to what amount of amplitude asymmetry constitutes an electrographic abnormality. A useful interpretation guideline is that an abnormality may be suspected if the amplitude difference between two regions exceeds a 2:1 ratio (3,55–57).

Interhemispheric Synchrony

Synchrony and asynchrony also reflect CNS maturation in the developing neonate. Interhemispheric synchrony and asynchrony are *temporal* electrographic features that can be measured during the discontinuous portions of the EEG. *Asynchrony* is defined as bursts of morphological similar of EEG activity in homologous head regions separated by more than 1.5 to 2.0 seconds in time (Fig. 6.21). Somewhat paradoxically, infants at a conceptional age of less than 30 weeks exhibit hypersynchrony, whereby the majority of bursts arising within the two hemispheres appear at the same time (Fig. 6.22). The physiological basis for interhemispheric hypersynchrony is unknown. After the conceptional age of 30 weeks, hypersynchrony gives way to the appearance of asynchronous bursts of cerebral electrical activity between the two hemispheres. About 70% of bursts during quiet sleep are synchronized at the conceptional age of 31 to 32 weeks, increasing to 80% at 33 to 34 weeks, 85% between 35 and 36 weeks, and 100% after 37 weeks (55,57,88,90).

Overview of Electroencephalographic Ontogeny

The development of the fetal brain undergoes explosive changes with regard to its overall anatomic appearance, synaptic connectivity, time-dependent genetic expression of neurotransmitter receptor subunits, and their consequent functional abilities. In parallel with these anatomical and functional changes is an orderly, predictable pattern of neonatal EEG characteristics that emerge simultaneously with advancing maturity of the fetal brain (Fig. 6.23). For practical reasons, the discussion of EEG ontogeny begins with the infant at 24 weeks EGA, near the current boundary of fetal viability (33).

24 to 29 Weeks of Conceptional Age

EEGs obtained from the very premature infant are, for the most part, discontinuous recordings. The normal record consists of brief periods of moderate-amplitude cerebral electrical activity (composed of recognizable,

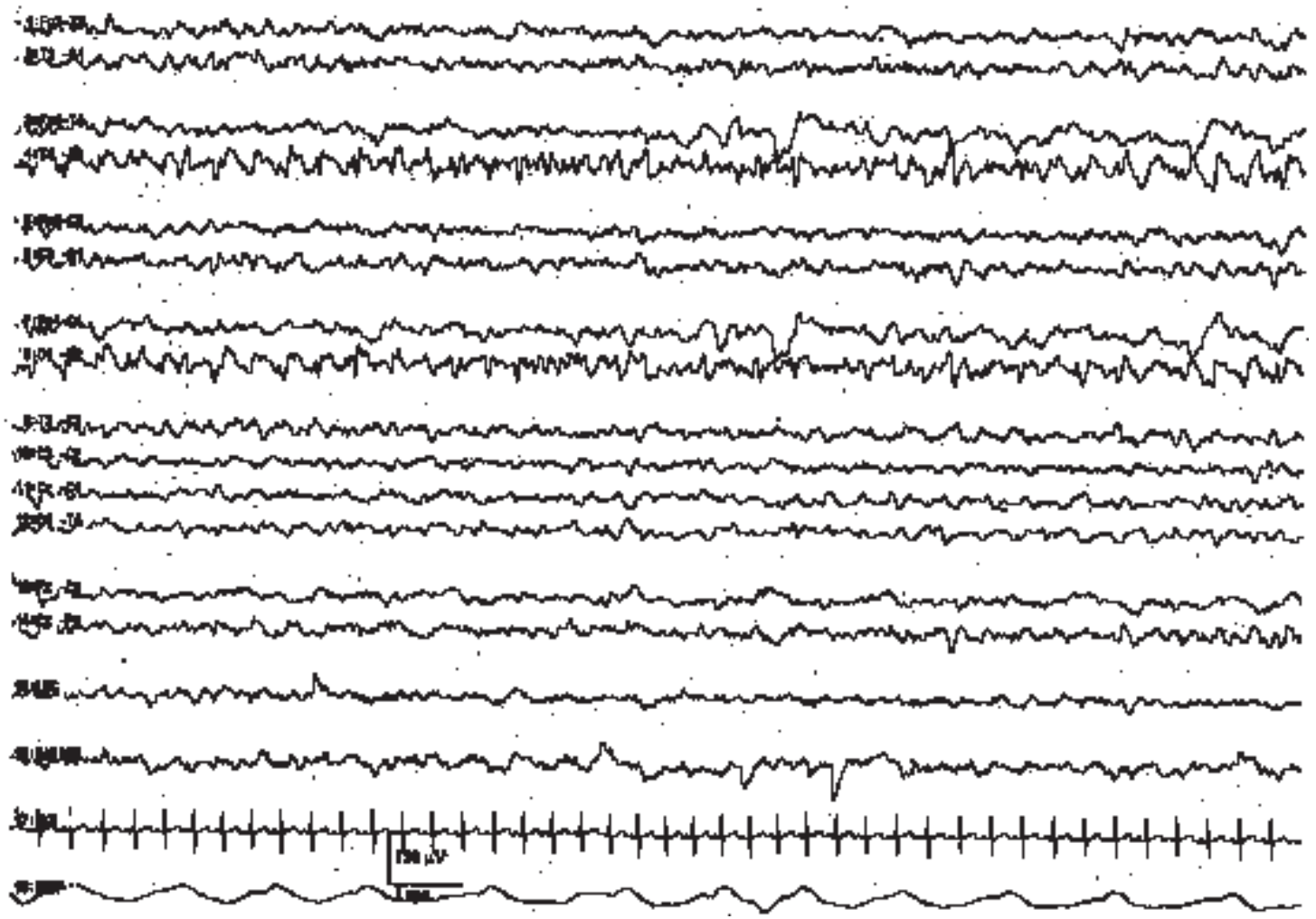


FIG. 6.19. Asymmetry secondary to cerebral pathology in an infant 41 weeks of conceptional age with Sturge-Weber syndrome affecting the right hemisphere. The right occipital region is slow and contains sharp waves, in comparison with the normal-appearing left hemisphere.

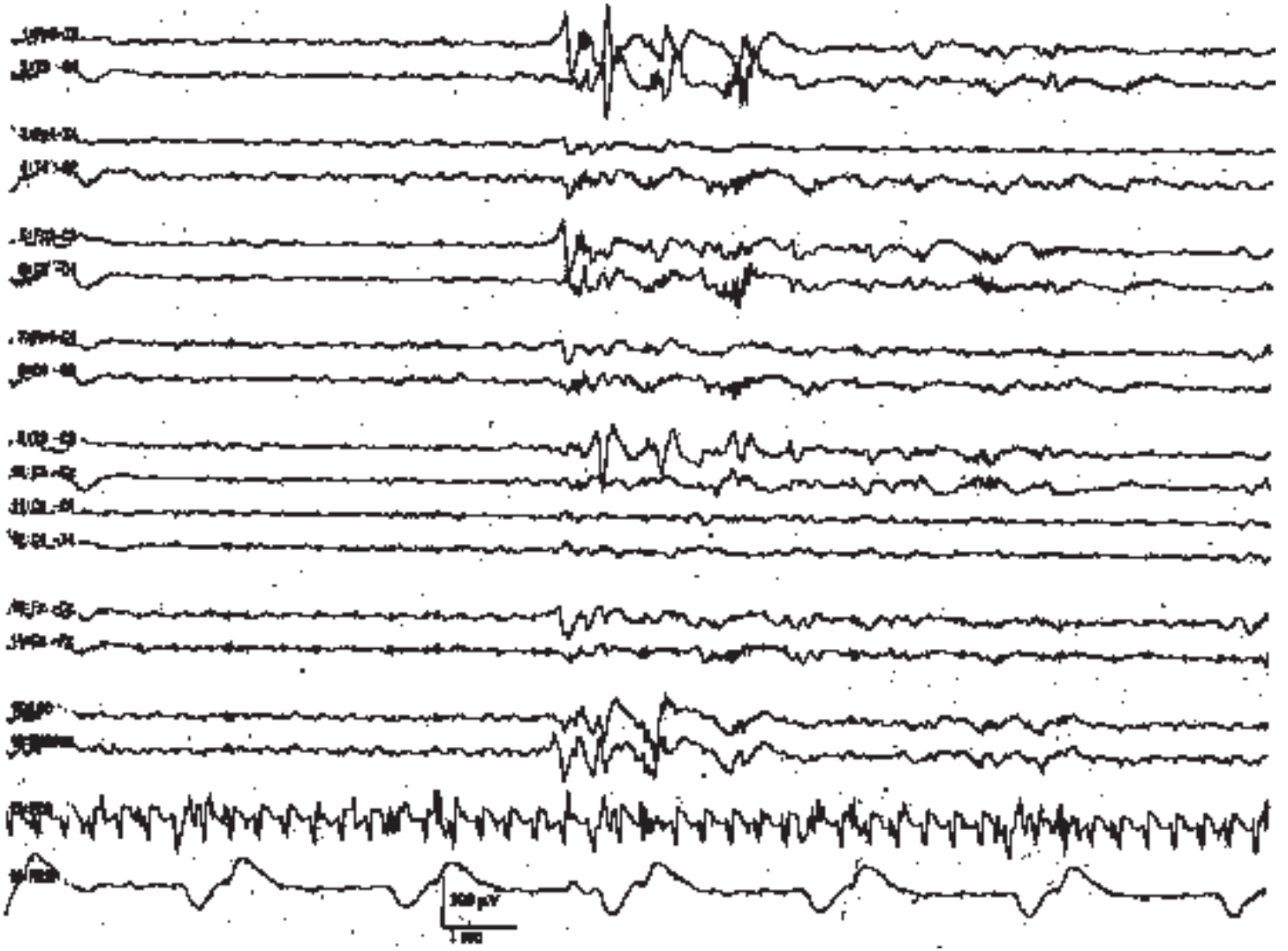


FIG. 6.20. Asymmetry secondary to scalp edema in an infant 41 weeks of conceptional age with tetralogy of Fallot and seizures. The infant's head was turned to the right, and marked right scalp edema was present. The amplitude is decreased on the right side, but the background composition is similar to the that of the left. The asymmetry disappeared after the scalp edema resolved.

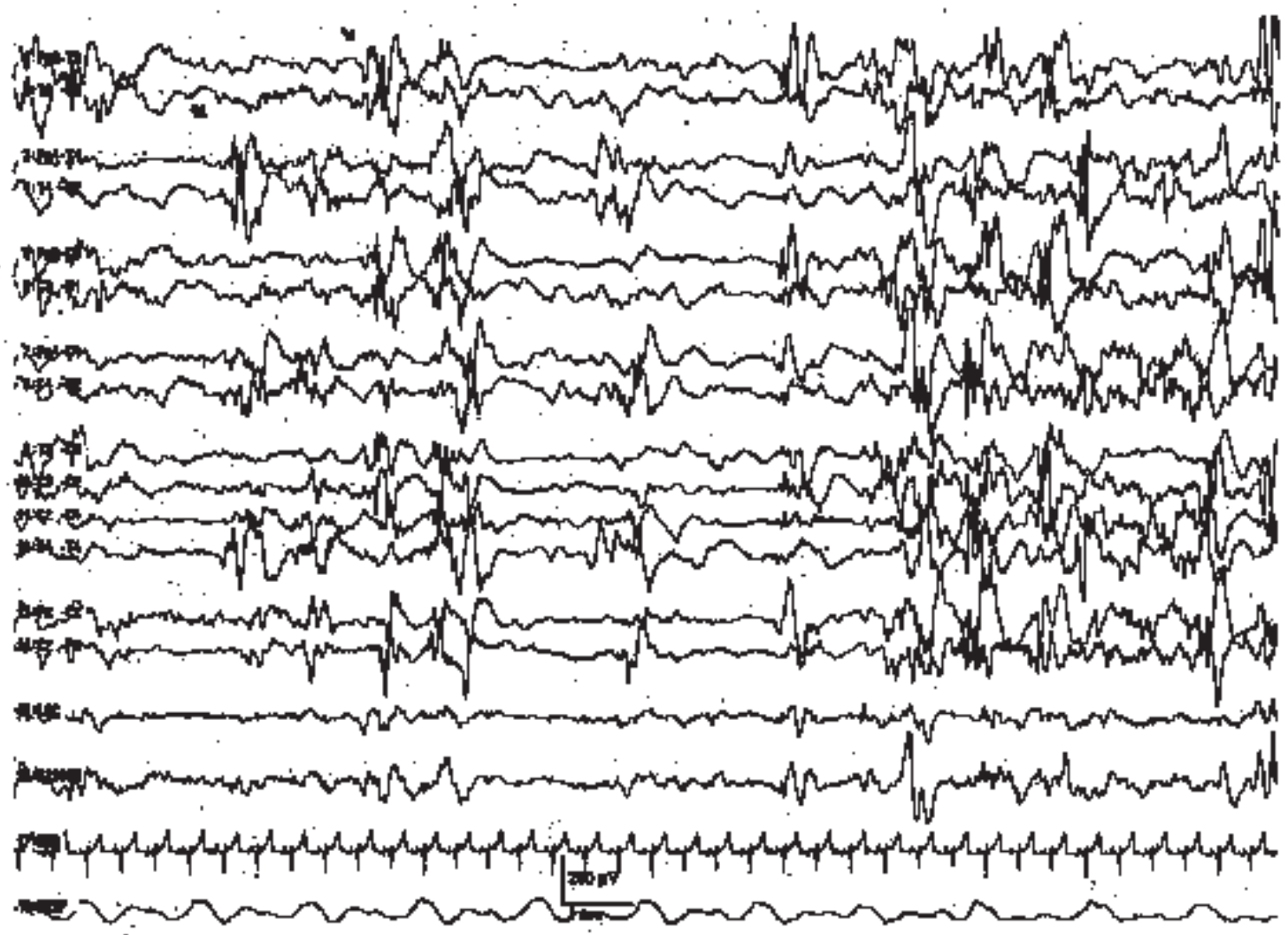


FIG. 6.21. Excessive asynchrony in an infant 46 weeks of conceptional age infant with nonketotic hyperglycinemia. Bursts of right (*large arrow*) and left (*small arrow*) hemispheric activity are not synchronized.

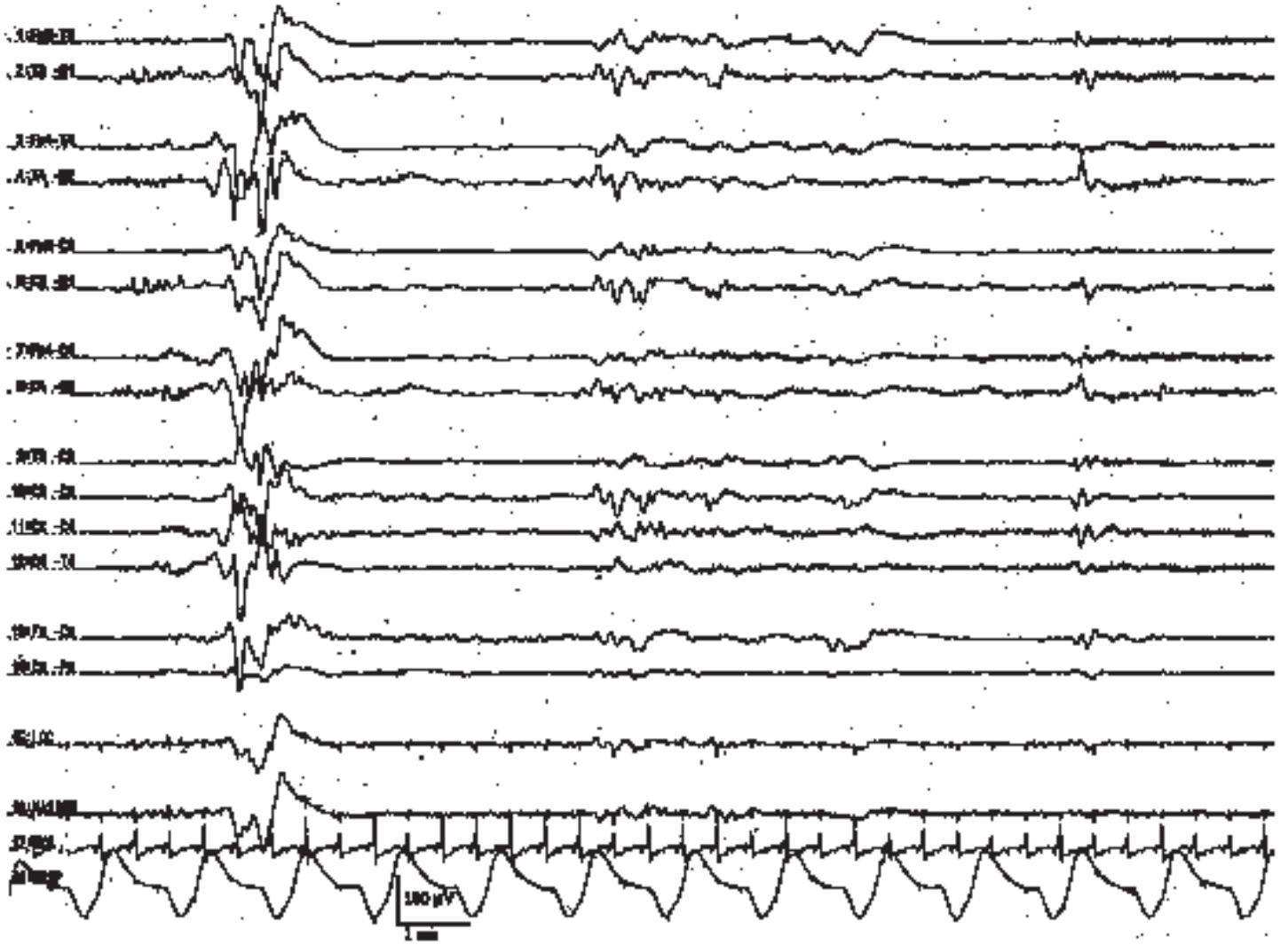


FIG. 6.22. Synchrony in a premature infant 27 weeks of conceptional age with dysmorphic facial features. Cerebral activity is well synchronized between the hemispheres.

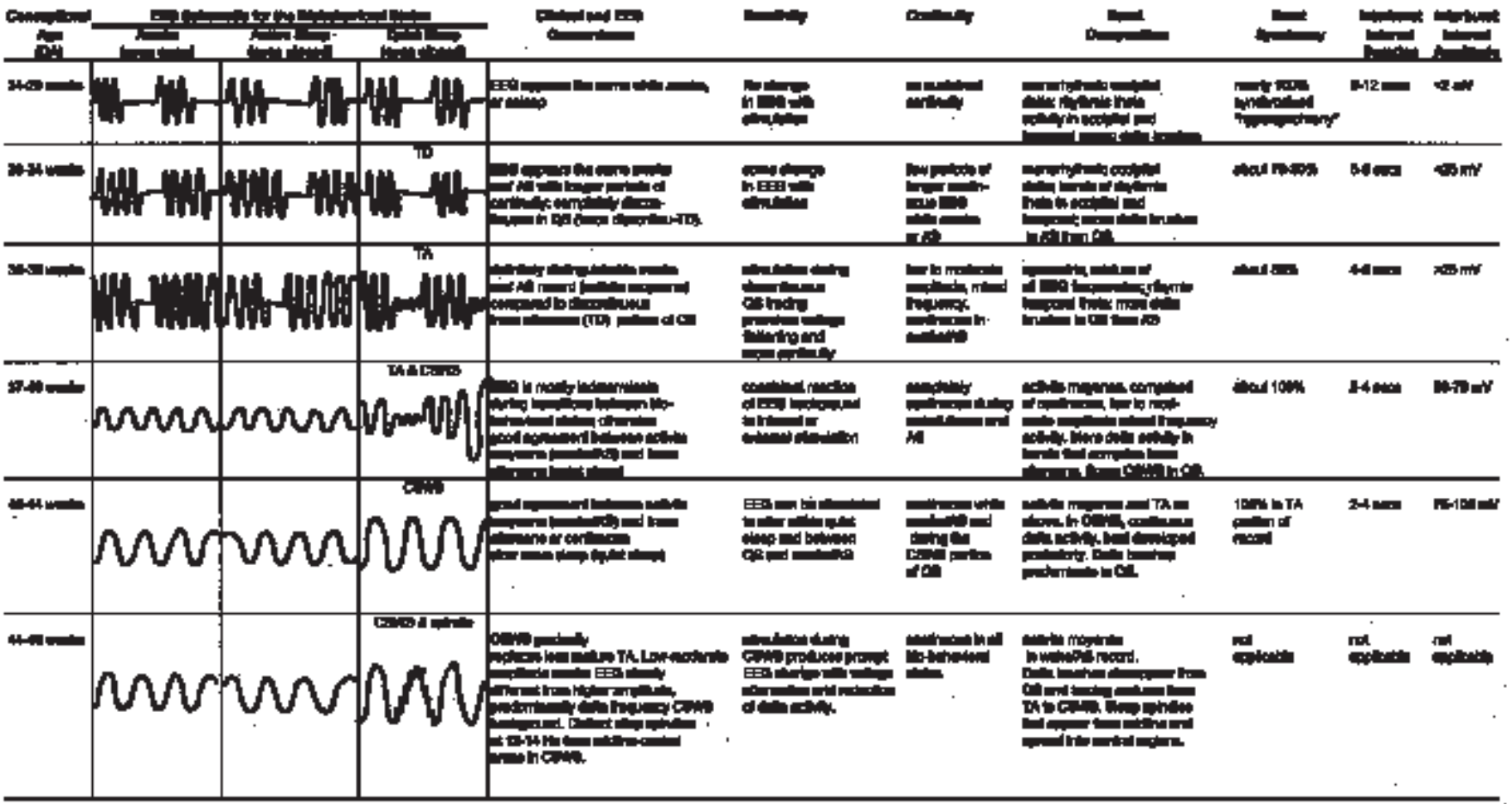


FIG. 6.23. Overview of development of electroencephalographic background between 24 and 46 weeks of conceptional age.

named patterns such as the delta brush, monorhythmic occipital delta activity, and bursts of rhythmic occipital and temporal theta activity) that are regularly punctuated by low-voltage (<25-μV) quiet periods. The duration of the low-voltage IBIs varies with age, being longer in the youngest patient and decreasing in duration as the brain matures. The typical IBI averages about 6 to 12 seconds in physically healthy infants at this age. Most of the EEG bursts are well synchronized, appearing simultaneously (within 1.5 to 2.0 seconds) between the left and right cerebral hemispheres. Although infants clinically cycle through awake/asleep periods with eye opening (i.e., wakefulness) and eye closure (i.e., sleep), there is qualitatively little difference in the appearance of the EEG background. The EEG appears essentially monotonous with no definite state organization regardless of the infant's clinical status. There is little concordance (agreement) between the clinical and electrographic expressions of the biobehavioral state at this conceptional age.

30 to 32 Weeks of Conceptional Age

By this conceptional age, there first appears some differentiation of the EEG pattern that distinguishes wakefulness (or REM/active sleep) from non-REM, or quiet, sleep. There is some concordance between the appearance of the background EEG and behavioral state. During wakefulness or active sleep, the EEG begins to "fill in" some of the low-voltage IBIs that had previously remained monotonously invariant. The awake/active sleep EEG is relatively more continuous, with longer duration BIs. The actual composition of the bursts still largely resembles that at earlier gestational ages, dominated by the synchronized, monorhythmic occipital delta activity, some of which are incorporated into posterior delta brushes. The brief bursts of rhythmic theta activity have migrated more from the occipital to the temporal areas. There are still many portions of the record that are discontinuous, even during wakefulness and active sleep, but the IBIs are a little briefer, about 5 to 8 seconds on average. During well-developed quiet sleep, the record is persistently discontinuous and is distinguishable from the awake/active sleep tracing. The term *trace discontinu* (discontinuous tracing) is first applied to this early form of a healthy quiet sleep recording in which bursts of normal cerebral electric activity are regularly interspersed with low-voltage (<25 μV) periods of quiescence. The record may be marginally reactive to external stimulation: if the patient is provoked during quiet sleep, there is a visible change of the actual EEG background (not just EMG or movement artifact from patient motion) with the appearance of a more continuous background resulting from the arousal.

33 to 34 Weeks of Conceptional Age

By this conceptional age, there is further consolidation of the biobehavioral states: active and quiet sleep are more clearly distinguishable both clinically and electrographically, and the concordance between the appearance of the EEG and behavioral state is easier to recognize. Less of the EEG is indeterminate—that is, lacking in the distinguishing characteristics that allow definitive classification into specific biobehavioral states. In the awake and active sleep record, the background is more continuous with further filling in of the gaps between the EEG bursts. The IBIs are fewer and briefer than before. The monorhythmic occipital delta activity is fading, and most of the bursts of rhythmic theta activity appear in the temporal regions. Up to this conceptional age, there are more delta brushes per minute in the awake and active sleep portions of the recording than during quiet sleep. Trace discontinu continues to be the quiet sleep pattern, and the IBIs range from 5 to 8 seconds, but the synchrony of the bursts is, paradoxically, less than at earlier conceptional ages. Only about 70% to 80% of the bursts in the discontinuous portions of the study are synchronized, occurring within 1.5 to 2.0 seconds between the two hemispheres.

35 to 36 Weeks of Conceptional Age

By this conceptional age, biobehavioral states are easily distinguished, and the EEG shows definite and reproducible reactivity to external stimulation. In wakefulness and active sleep, the EEG is essentially continuous and is composed of low- to moderate-amplitude, mixed-frequency activity. This normal pattern that typifies the awake and active sleep record is commonly called *activité moyenne* ("average activity"). There is little left of the high-amplitude monorhythmic occipital delta and only few remnants of the rhythmic theta bursts. The signal is composed of admixed, coexisting frequencies ranging from delta to beta frequencies and a few delta brushes in the occipital, central, and temporal areas. The quiet sleep record remains discontinuous, but the amplitude of the IBI gradually increases as the duration further declines. At this point, the typical IBI duration is about 4 to 6 seconds, and its amplitude clearly exceeds 25 μV. The name of this normal immature, discontinuous quiet sleep pattern is *trace alternant,* indicating a pattern that alternates between high-amplitude burst intervals and low-amplitude IBIs.

These bursts are typically more synchronized than at the prior conceptional age; about 85% appear simultaneously between the two hemispheres. Delta brushes are more abundant in quiet sleep than in active sleep, and much of the record can be assigned to definite sleep categories.

37 to 40 Weeks of Conceptional Age

In healthy full-term infants, there are clearly and easily recognizable periods of wakefulness/active sleep and quiet sleep. About 25% of total sleep time is occupied by indeterminate sleep (98). Once quiet sleep is established, trace alternant first appears with typical IBIs of 2 to 4 seconds, and essentially all of the bursts arise synchronously. If the infant remains asleep for awhile, trace alternant gives way to a moderate- to high-amplitude, uninterrupted delta activity, the earliest expression of continuous slow-wave sleep (CSWS). This sets the stage for the EEG background that typifies quiet sleep for the rest of the life span. Trace alternant and CSWS comingle at this age. Delta brushes remain more abundant in quiet sleep than in active sleep, and the amplitude of background delta activity is highest posteriorly, an early expression of a frequency-amplitude gradient (86).

41 to 44 Weeks of Conceptional Age

In healthy infants of this conceptional age, *activité moyenne* continues to constitute the background during wakefulness/active sleep, whereas delta brushes gradually disappear by 44 weeks. On occasion, the awake EEG displays broad biphasic lambda waves in the occipital regions bilaterally, coincident with visual fixation. In quiet sleep, CSWS gradually replaces trace alternant, except at the onset of quiet sleep. The bursts of activity in trace alternant are well synchronized, but the IBI durations are quite brief, typically less than 2 to 4 seconds, and their amplitudes exceed 50 μV. By the end of this epoch, all of the discontinuous portions of quiet sleep have been "filled in" and trace alternant is completely replaced by CSWS.

45 to 46 Weeks of Conceptional Age

The distinguishing characteristic of this period is the first appearance of *sleep spindles* in CSWS (31,50). Once they arise, they appear with their usual frequency (about 12 to 14 Hz) and are typically centered over the midline (Fz-Cz region), spreading to the neighboring left or right central regions (C3 or C4). In the course of the entire quiet sleep record, there are about the same numbers of sleep spindles spreading into the left and right central regions (i.e., they are symmetric), but they are not well synchronized. Indeed, they do not achieve full synchronization until about the age of 2 years.

Composition of Electroencephalographic Background Activity (Named Patterns)

EEG background refers to the presence of all the aggregated patterns, waveforms, and frequencies that collectively constitute the ongoing cerebral electric activity. As such, it represents an infrastructure or stage that may be punctuated by fleeting EEG transients (physiological or pathological sharp waves) or electrographic seizures. The appearance and composition of the background varies with state and conceptional age, but the predominant frequencies that constitute the neonatal EEG are represented by theta and delta activity. There are, however, several specific components appearing in premature and full-term infants that warrant individual description and illustration.

Monorhythmic Occipital Delta Activity

This activity represents a conspicuous, stereotyped run of monomorphic, high-amplitude, surface polarity–positive, 0.5- to 1-Hz delta waves, often appearing synchronously in the occipital scalp regions (Fig. 6.24). A run of monorhythmic occipital delta activity can last from 2 to 60 seconds and appears relatively symmetrically and synchronized bilaterally. It is present at the conceptional age of 23 to 24 weeks, peaks in abundance between 31 and 33 weeks, and then significantly fades by 35 weeks. Persistence of well-developed monorhythmic delta activity after 35 weeks conceptional age is often considered evidence of electrographic "immaturity." This pattern represents the dominant rhythmic activity in the posterior brain regions and serves as the delta constituent of occipital delta brushes (see later discussion). This is also a sturdy rhythm in that it may persist in the presence of severe, acute encephalopathies, long after other specific patterns have disappeared.

Rhythmic Occipital Theta Activity

This specific pattern appears as brief (2- to 10-second) bursts of stereotyped, rhythmic, sinusoidal 4-Hz theta activity in the occipital regions (Fig. 6.25), sometimes spreading into the temporal regions. These bursts

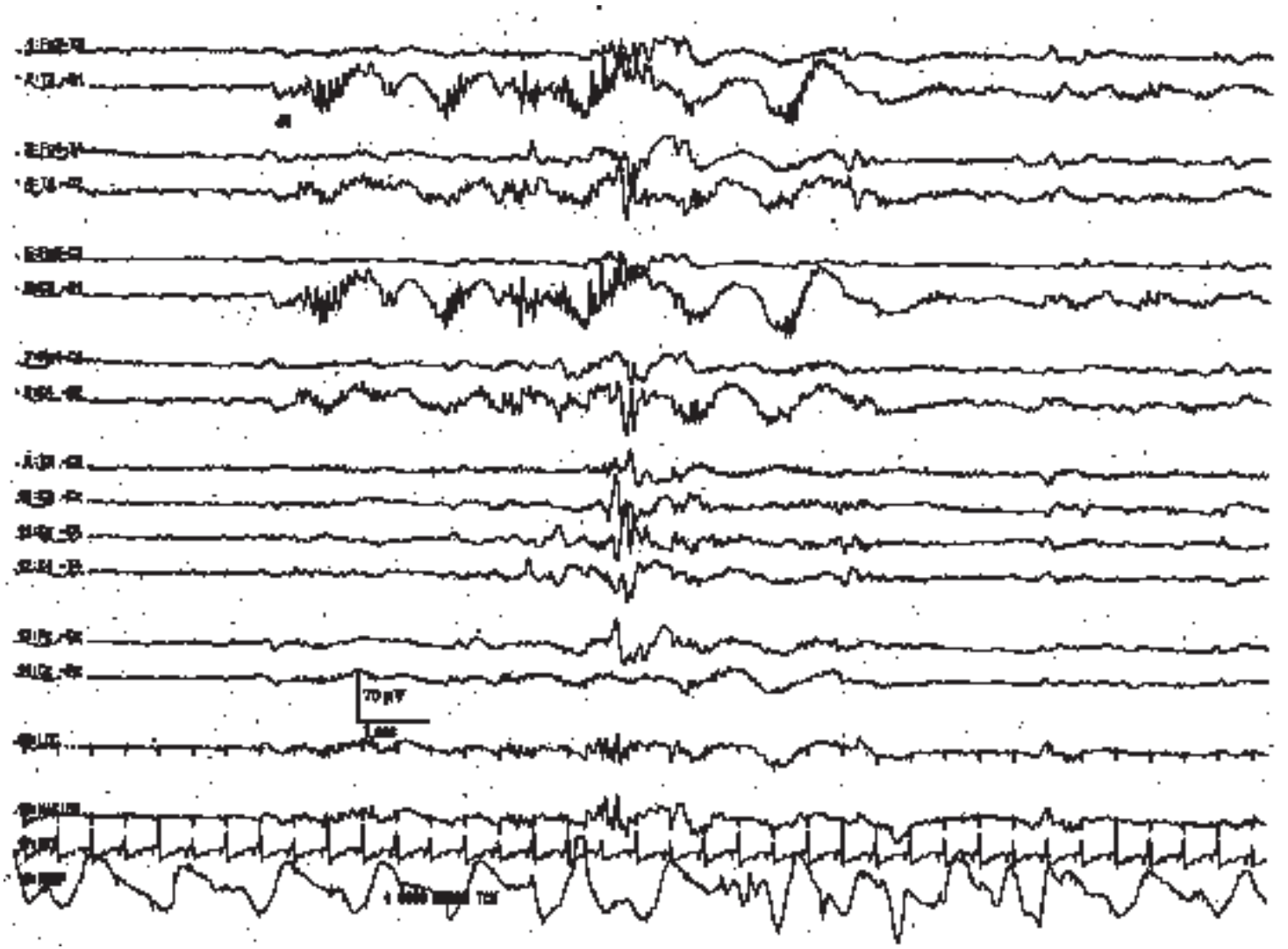


FIG. 6.24. Monorhythmic occipital delta activity in an infant 31 weeks of conceptional age with apnea. Occipital delta activity with delta brushes (*arrow*) is present. Note that the occipital delta transients are synchronized between the two hemispheres.

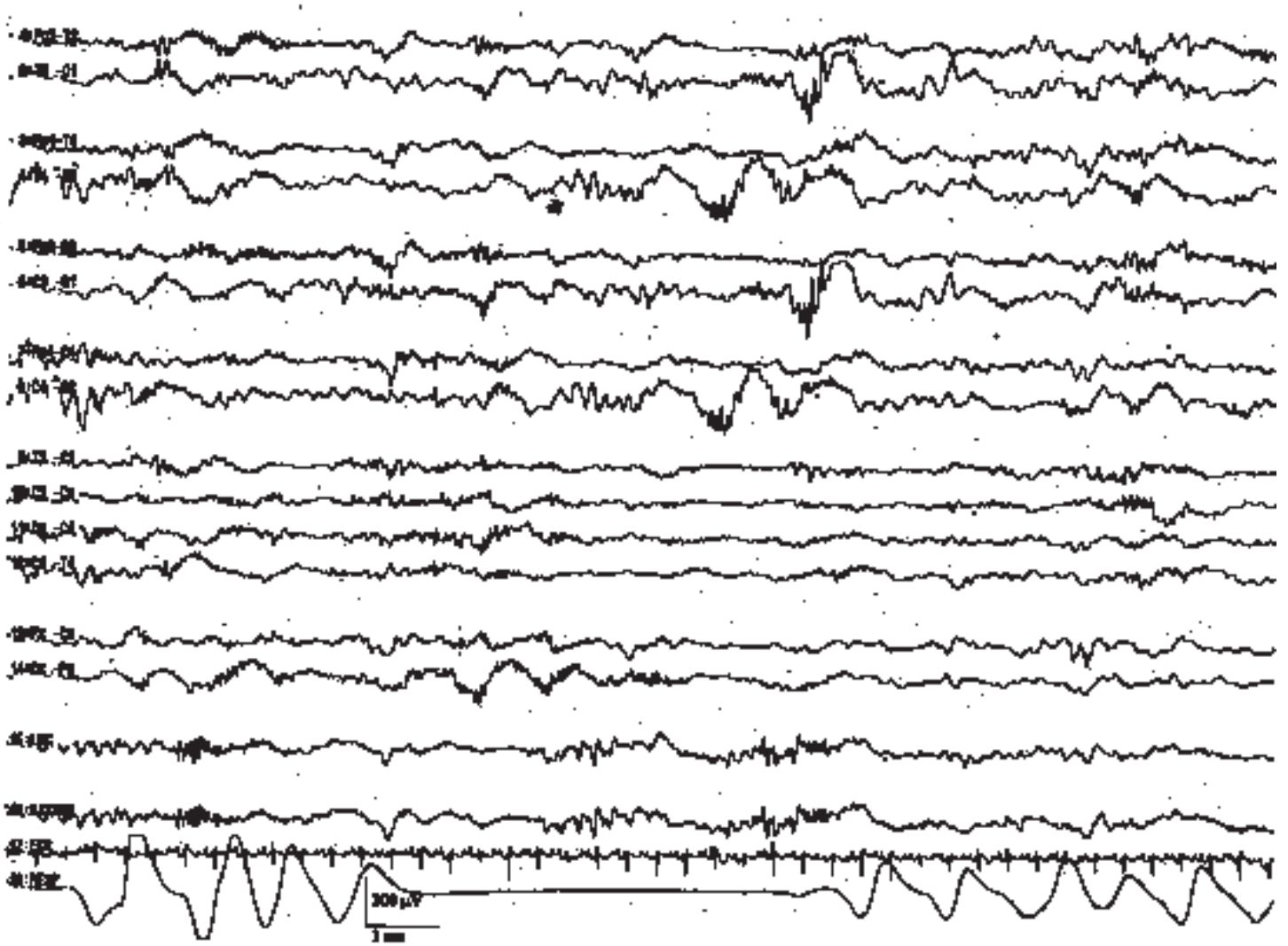


FIG. 6.25. Rhythmic occipital theta activity in an infant 30 weeks of conceptional age who underwent fetal surgery for repair of myelomeningocele. Bilateral rhythmic occipital theta activity (*arrow*) is present, although more on the right side than on the left.

commonly mingle or superimpose on coincident monorhythmic occipital delta activity. They are present in the awake or sleeping infant and are apparent at the conceptional age of 23 to 24 weeks. They peak in abundance by 30 weeks and then fade from the occipital areas by 33 weeks; the rhythmic theta pattern migrates anteriorly to the temporal areas at older ages.

Rhythmic Temporal Theta Activity

This pattern is morphologically similar to that arising in the occipital regions. It peaks between the conceptional ages of 31 and 33 weeks. It appears as brief paroxysms simultaneously or independently in the temporal areas (Fig. 6.26). However, over a long time period, these bursts are equally represented bilaterally. They are occasionally "sharply" contoured, which raises the concern that they are a brief ictal discharge, but they do not evolve in morphology or frequency. On occasion, an abortive or larval burst of this pattern gives rise to a "sharp wave," but close examination shows that it is merely a morphological fragment of an abbreviated run of rhythmic temporal theta activity.

Centrotemporal Delta Activity

This pattern is represented by the intermittent appearance of sustained trains of conspicuous, 0.5- to 2-Hz delta activity, often with a prominent surface-positive polarity in the C3-C4 to T3-T4 areas (Fig. 6.27). They may appear semirhythmically, but they are not usually as regular and well modulated as monorhythmic occipital delta activity. This pattern serves as the delta wave foundation for rolandic and temporal brushes. It peaks by the conceptional age of 30 weeks and fades after 33 weeks.

Delta Brushes

These patterns (also called "brushes," "ripples of prematurity," and "spindle-like fast rhythms") are often considered the premier electrographic signature of the premature infant. The pattern is composed of a combination of a specific delta frequency transient with a superimposed "buzz" of 8- to 20-Hz activity (see Figs. 6.24 and 6.27). Brushes are symmetrically represented between the two hemispheres and homologous brain regions. They are not commonly displayed synchronously except when they arise in concert with runs of monorhythmic occipital delta activity. They appear in awake and sleeping infants, and so they should not be considered a type of precursor of the "spindle" of mature quiet sleep, which first appears around the conceptional age of 46 weeks. Up to the conceptional age of 33 weeks, there are more brushes per minute in active sleep than in quiet sleep. After the conceptional age of 34 weeks, brushes are more numerous in quiet sleep. Brushes may appear in any scalp region but are scarce in the frontal areas. In the youngest premature infants, brushes are mostly expressed in the rolandic regions. At their peak expression (during the conceptional ages of 32 to 34 weeks), they arise mostly in the occipital, central, and temporal areas. By term, brushes may still persist in immature trace alternant but have largely vanished from the awake and active sleep portions of the recording. By 1 month post term, they are no longer in evidence.

Anterior Dysrhythmia

This pattern appears as paroxysmal, brief bursts of frontally dominant, 50- to 100-μV, semirhythmic delta activity (Fig. 6.28). Their morphological features may subtly evolve over a few seconds and acquire a sharp contour, commonly admixing and blending with a related rhythm, *encoche frontale.* Runs of anterior dysrhythmia tend to arise symmetrically and synchronously between the frontal regions and may be present in all behavior states. They are most conspicuous in the transition from active to quiet sleep but scarce in the period of active sleep immediately after quiet sleep. Despite the usual connotation of the "dys-" prefix, anterior dysrhythmia is a normal developmental electroencephalographic pattern. However, in the wake of definite encephalopathies such as hypoxia-ischemia or meningitis, its excessive presence may be considered a nonspecific electrographic abnormality (14,30,42). Marked and persistent asymmetries of their number, morphology or amplitude may also represent an electrographic abnormality. Its counterpart pattern, frontal sharp waves (*encoches frontales*) are described later.

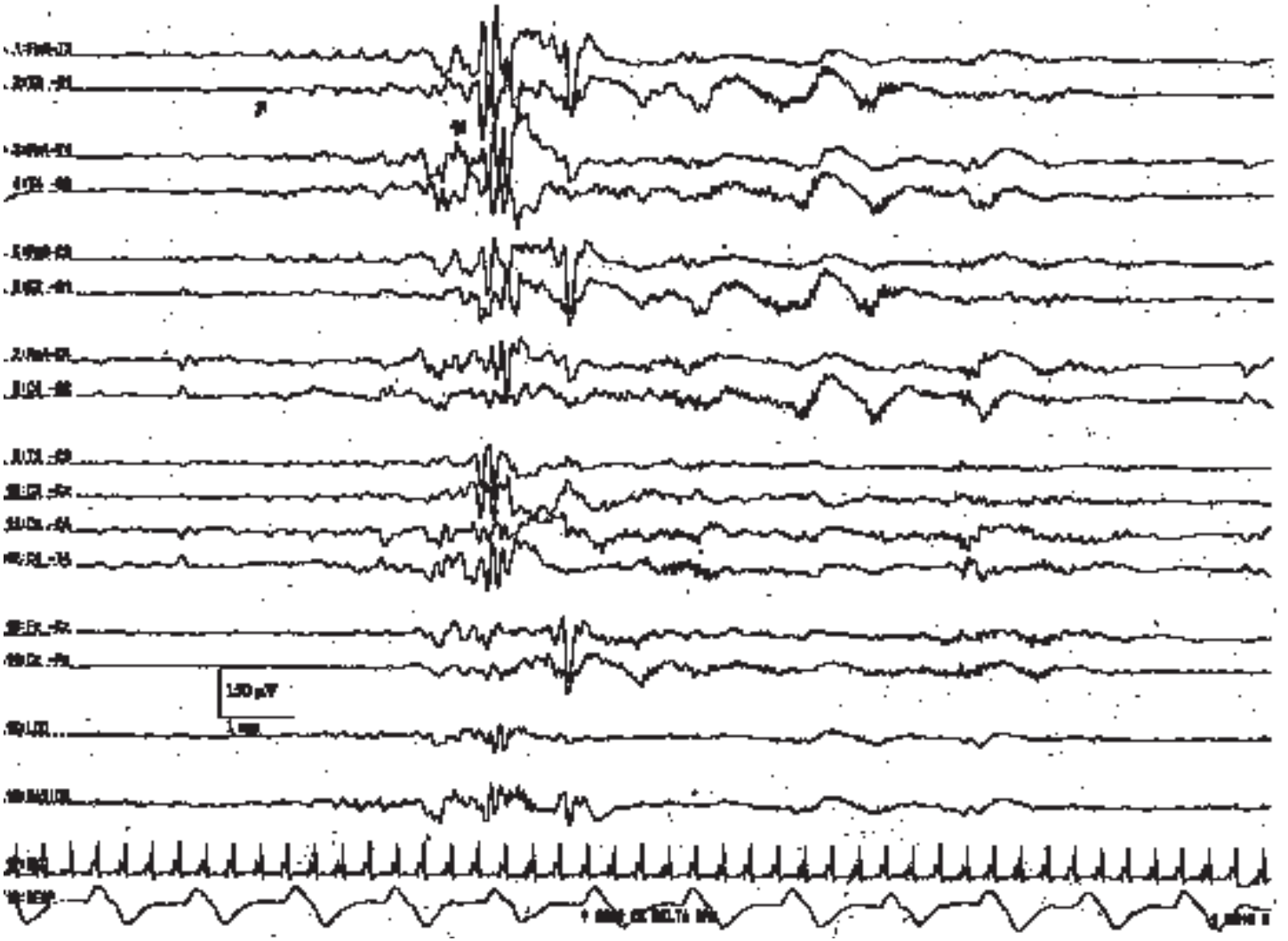


FIG. 6.26. Rhythmic temporal theta activity in an infant 31 weeks of conceptional age with pneumonia. Sharply contoured rhythmic temporal theta activity (*large arrow*) is present. Also, note a run of low-amplitude, positive left temporal sharp waves (*small arrow*), which are considered normal transients for age.

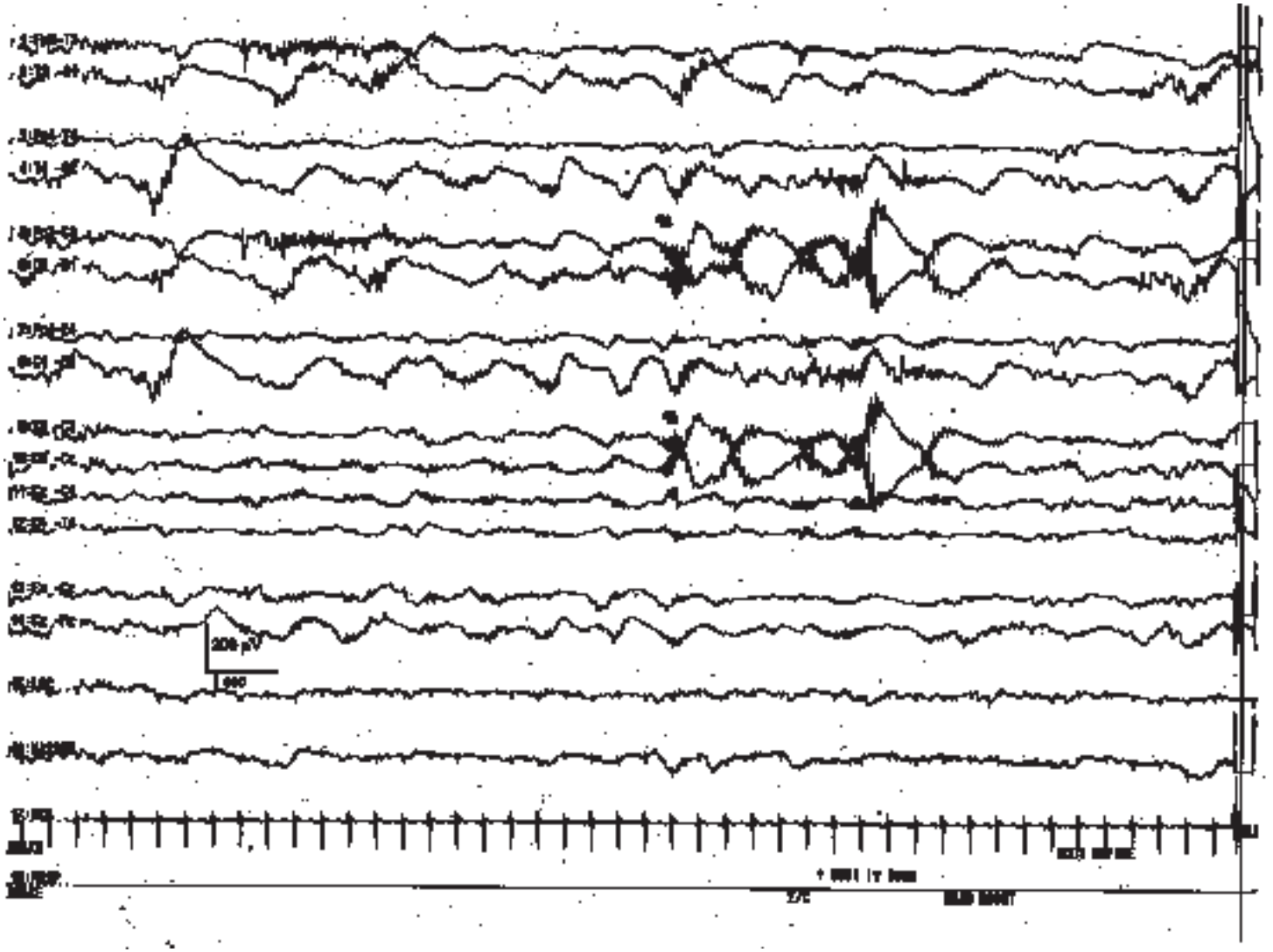


FIG. 6.27. Rhythmic centrotemporal delta activity in an infant 31 weeks of conceptional age with dysmorphic facial features. *Arrows* indicates left centrotemporal delta activity admixed with delta brushes.

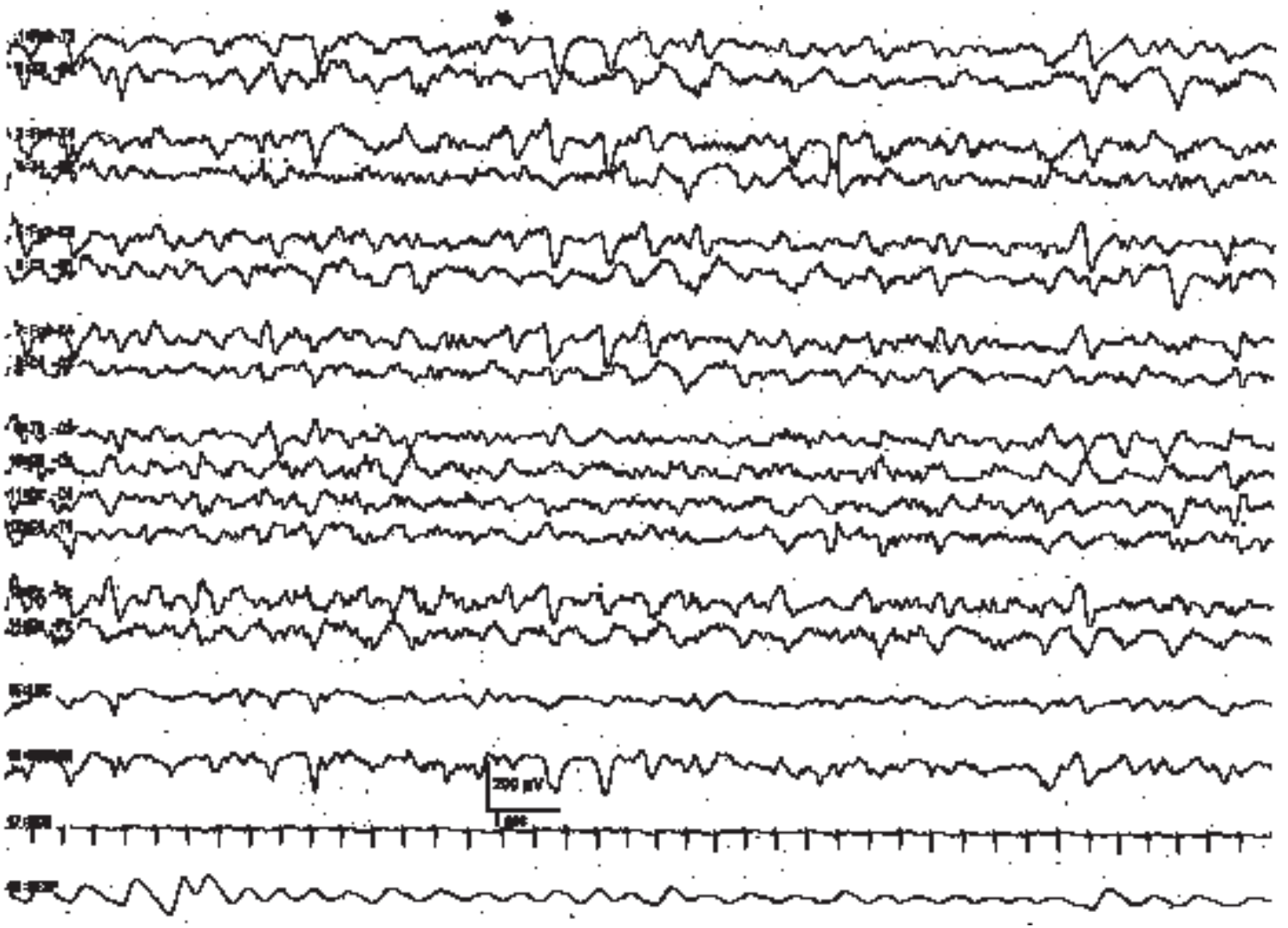


FIG. 6.28. Anterior dysrhythmia in an infant 40 weeks of conceptional age with pneumonia. Bilateral frontal anterior dysrhythmia (*arrow*) is admixed with poorly formed *encoches frontales.*

Specific Neonatal Electroencephalographic Background Patterns and State

Wakefulness and Active Sleep

The waking EEG resembles the background of the onset of active sleep, composed of low-amplitude (<25-μV), predominantly 4- to 7-Hz theta and low-amplitude delta activity (Fig. 6.29). There are two basic active sleep patterns in neonates older than 36 weeks of conceptional age.

Neonates usually enter their sleep cycle in active sleep, and the duration of active sleep cycles vary between 10 and 45 minutes. As the infant enters active sleep the first time, the background is composed of moderate-amplitude (25- to 50- μV) irregular theta and delta activity with relatively few frontal transients (*encoches frontales*) (Fig. 6.30) (29). Subsequent cycles of active sleep have lower amplitude, more theta activity, and less delta activity and resemble the EEG of the awake state (*activité moyenne*).

Trace Discontinu

Trace discontinu is an important EEG maturational milestone, inasmuch as it is the first EEG pattern to emerge that differentiates wakefulness from sleep in the premature infant. With the development of trace discontinu, there is, for the first time, some concordance between the infant's clinical state and the EEG background. During quiet sleep, the trace discontinu pattern develops; it consists of bursts of high-amplitude (≤200-μV) activity separated by periods of relative quiescence with amplitudes of less than 25 μV (Fig. 6.31). The bursts are composed of normal theta and delta activity, and the acceptable range of the IBIs durations is determined by the conceptional age.

By 32 to 34 weeks of conceptional age, the trace discontinu pattern is well developed. Wakefulness and active, quiet, and indeterminate (transitional) sleep EEG stages emerge with improved clinical concordance. Trace discontinu remains the EEG pattern of quite sleep until 36 weeks of conceptional age, when the IBI amplitude exceeds 25 μV, which defines the more mature pattern of quite sleep, trace alternant.

Trace Alternant

Between 34 and 36 weeks of conceptional age, the trace discontinu pattern of normal quiet sleep begins to evolve into the more mature pattern of trace alternant (Fig. 6.32) (29). In both trace discontinu and trace alternant, the tracing is discontinuous. The fundamental distinction between trace discontinu and trace alternant lies in the amplitude of the IBI. In trace discontinu, it is less than 25 μV, whereas in trace alternant, it is greater than 25 μV. The bursts of cerebral activity in trace alternant consist of symmetrical delta activity, admixed with faster frequencies, with amplitudes of 50 to 300 μV. The duration of the bursts varies considerably but typically is more than 2 seconds. The composition of the IBI of trace alternant resembles the EEG during wakefulness and active sleep and consists of mixed frequencies with amplitudes of 25 to 50 μV. The duration of the IBI shortens as term approaches and normally does not exceed 2 to 4 seconds by 38 to 40 weeks of conceptional age (89). Trace alternant itself begins to wane by 38 to 40 weeks of conceptional age, although fragments may persist until 44 to 46 weeks of conceptional age. Trace alternant is gradually replaced by the more mature pattern of CSWS (31,97).

Continuous Slow-Wave Sleep

CSWS is the final major stage developed in the ontogeny of the EEG in quiet sleep. CSWS consists of nonstop delta and theta activity with amplitudes of 50 to 300 μV; it resembles stage 3 and 4 sleep seen in older patients. Discontinuity with BIs and IBIs are no longer present. The first fragments of CSWS emerge around 35 weeks of conceptional age. In one study, CSWS accounted for about 10% of total quiet sleep time at 36 weeks of conceptional age, 40% at 40 weeks, and 100% by 44 to 45 weeks (97). (Fig. 6.33)

Sleep spindles (Fig. 6.34) first appear between 44 and 49 weeks of conceptional age and consist of 12- to 14-Hz activity at the Cz, C3, or C4 electrode. Spindles are only rare at first but are well developed by 3 months post term, occurring at a mean rate of 4.2 spindles per minute (31). Spindles in infancy are typically asynchronous between the two hemispheres and remain so until the age of 2 years.

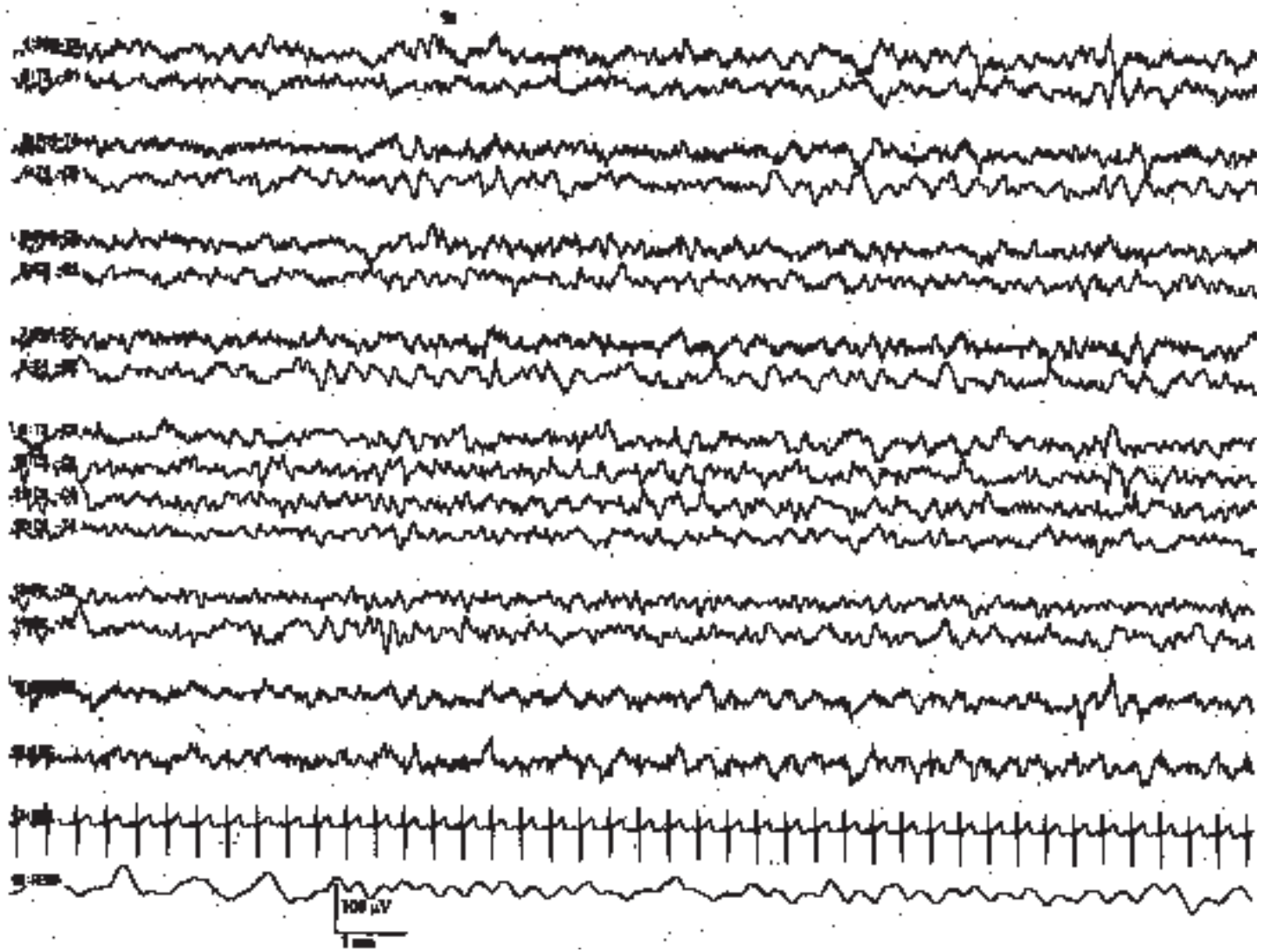


FIG. 6.29. Wakefulness in an infant 41 weeks of conceptional age evaluated for staring episodes. The tracing consists of continuous, mixed-frequency activity of low to medium amplitude (*activité moyenne*). Muscle activity (*arrow*) suggests wakefulness and helps to distinguish this pattern from that of active sleep.

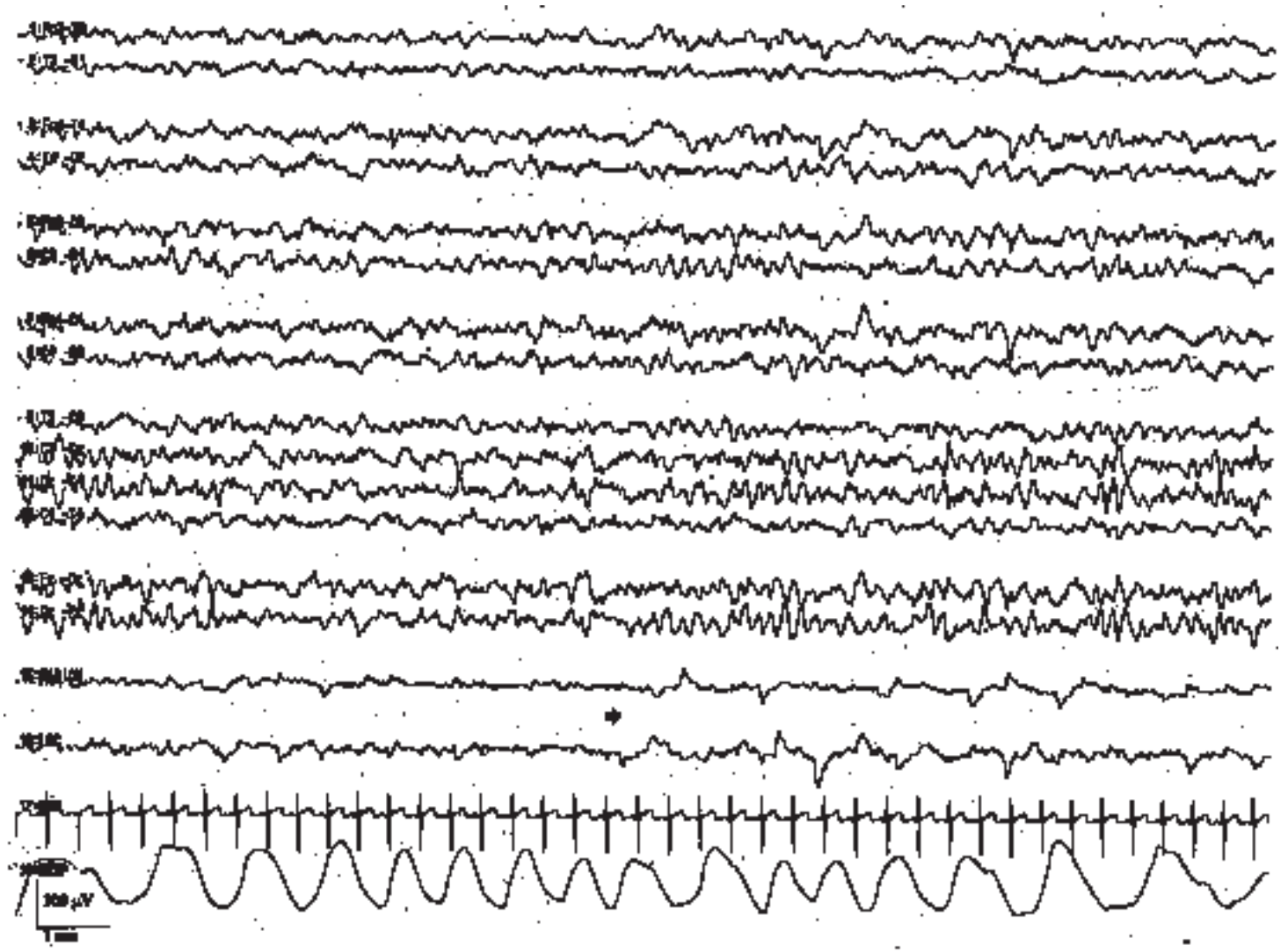


FIG. 6.30. Active sleep-in the same infant as in Fig. 6.29. The tracing also consists of continuous activity of low to moderate amplitude (*activité moyenne*). Rapid eye movements (*arrow*) and the lack of tonic muscle activity indicate active sleep.

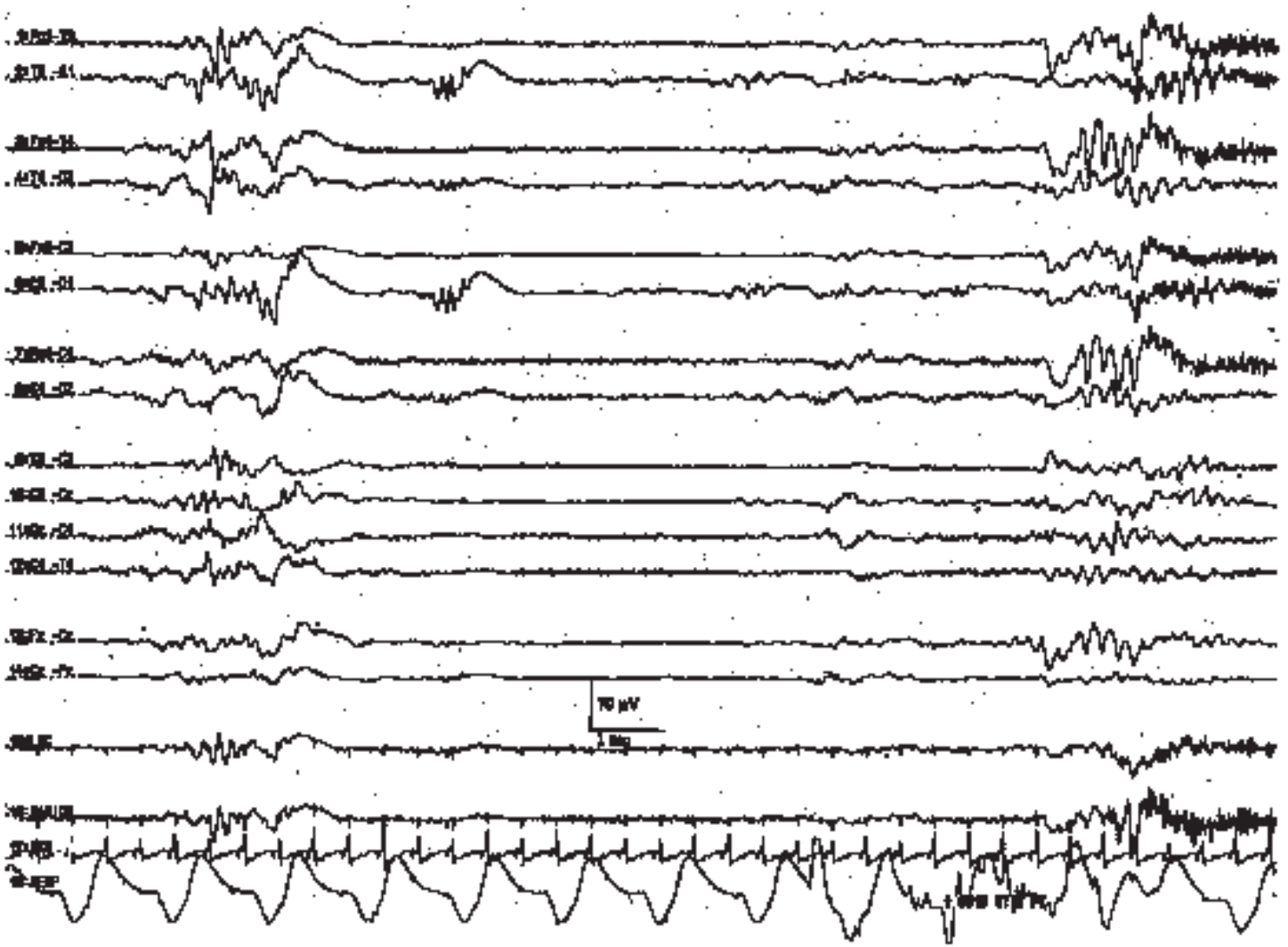


FIG. 6.31. Trace discontinu in an infant 31 weeks of conceptional age with apnea. The tracing is discontinuous. Bursts of activity are composed of normal patterns for age, and the amplitude of the interburst interval is less than 25 μV.

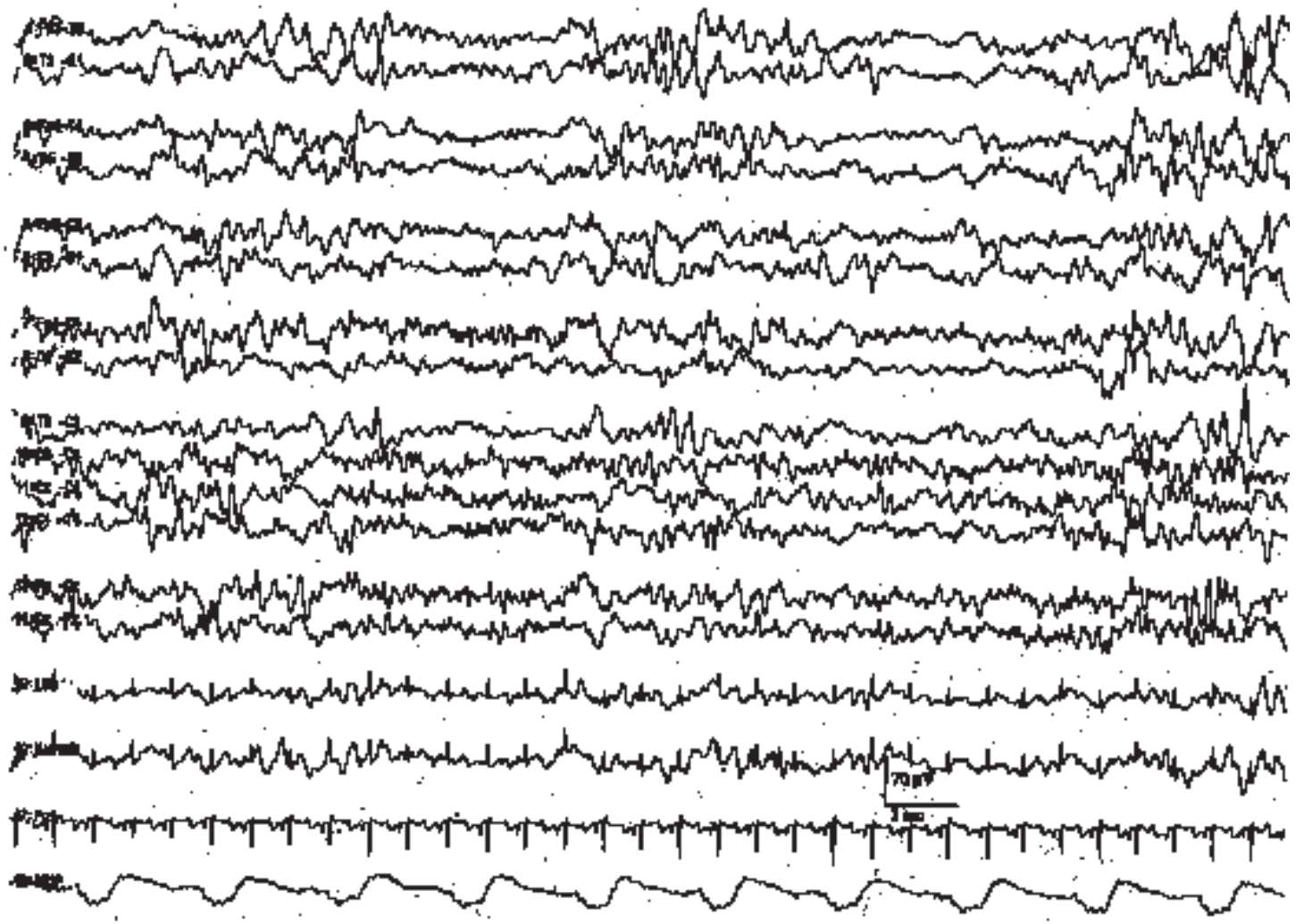


FIG. 6.32. Trace alternant in an infant 37 weeks of conceptional age with hypotonia. The tracing is discontinuous. Bursts of higher amplitude patterns, which are normal for age, *alternate* with lower amplitude activity. The amplitude of the interburst intervals exceeds 25 μV.

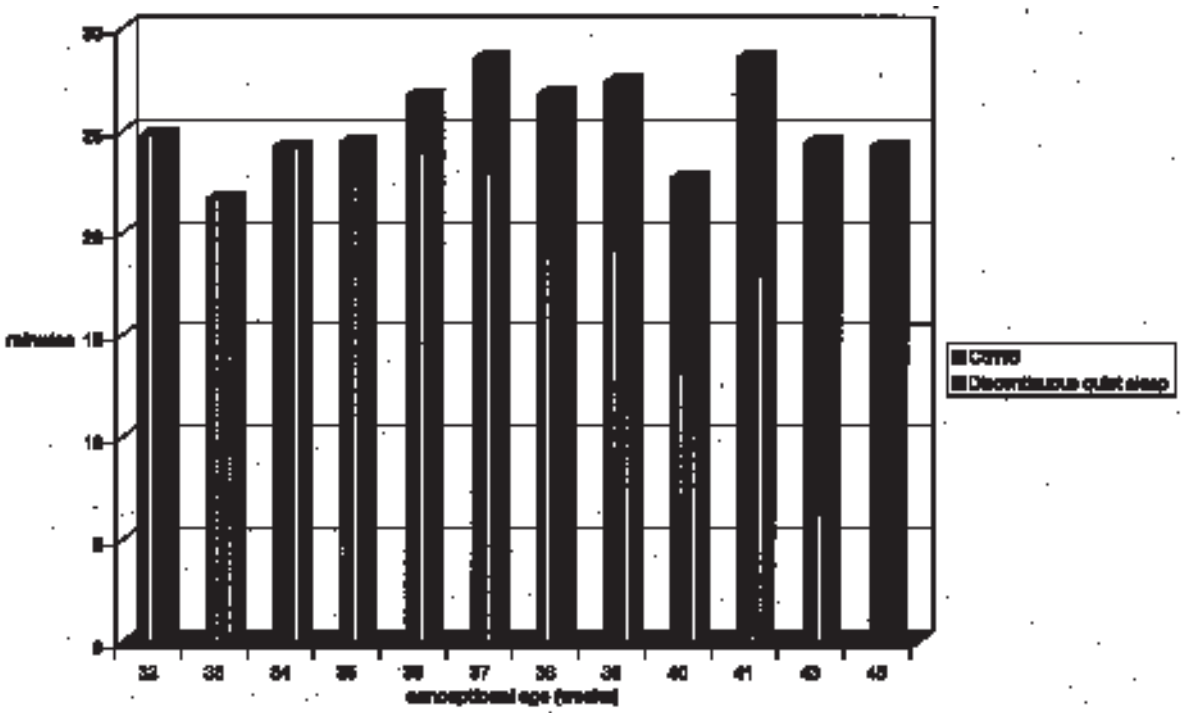


FIG. 6.33. Evolution of quiet sleep from immature trace alternant to continuous slow-wave sleep (CSWS) in normal infants. At 32 weeks of conceptional age, all quiet sleep is discontinuous. By 46 weeks, all quiet sleep in CSWS. (Adapted from Watanabe K, Iwase K, Hara, K. Development of slow-wave sleep in low-birthweight infants. *Dev Med Child Neurol* 1974;16:23–31.).

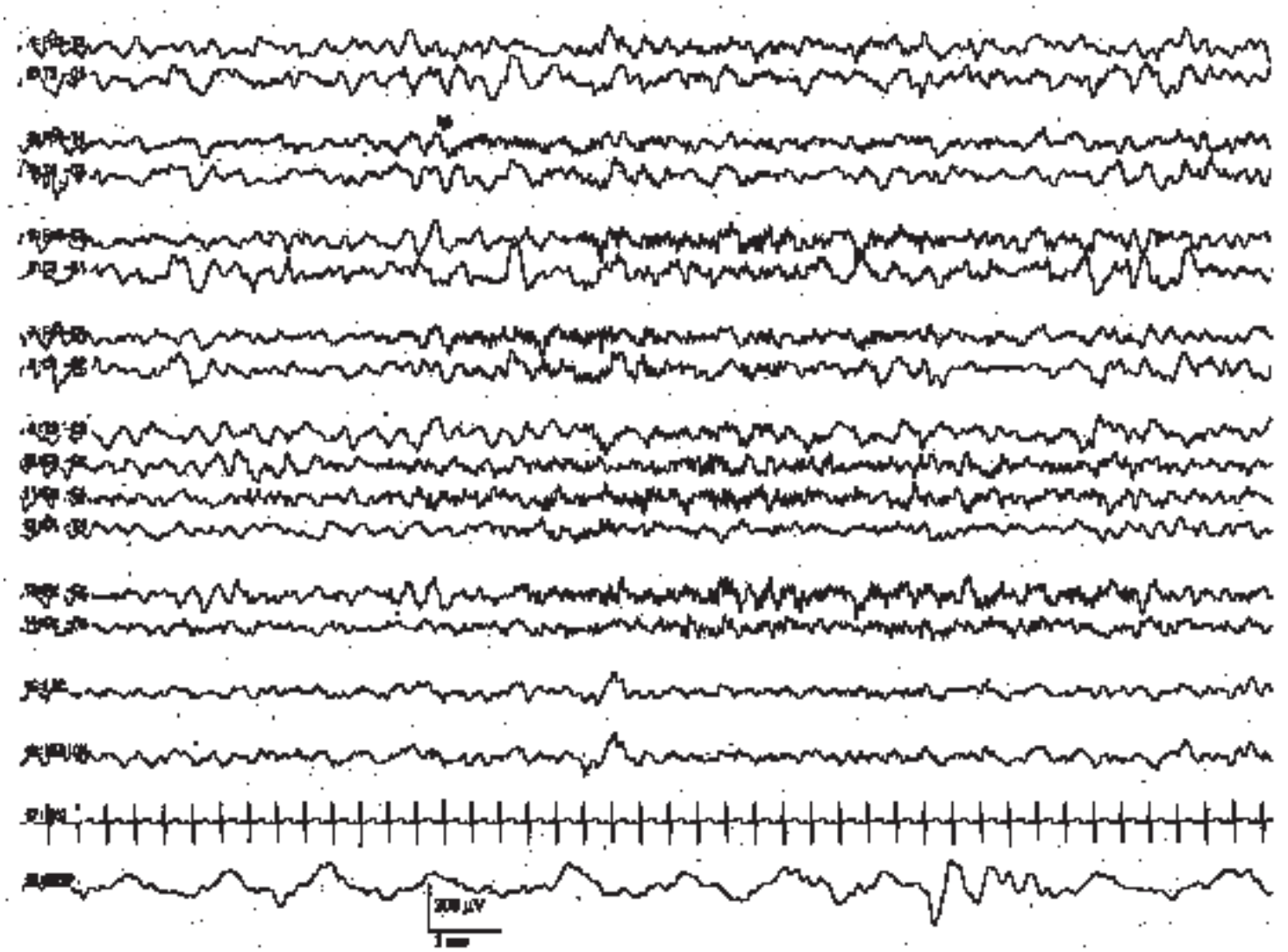


FIG. 6.34. Continuous slow-wave sleep with sleep spindles in an infant 48 weeks of conceptional age with episodes of staring and stiffening. *Arrow* indicates sleep spindles, arising asynchronously between the two hemispheres.

TYPES AND SIGNIFICANCE OF ABNORMAL ELECTROENCEPHALOGRAPHIC BACKGROUNDS

Just as the characteristics of the normal neonatal EEG background may be described in terms of continuity, synchrony, composition, and voltage, abnormal EEGs may also be judged from similar perspectives. Abnormal EEGs commonly display multiple, overlapping pathological features such as low voltage, excessive discontinuity, and poorly developed patterns and rhythms. The major characteristics of each type of abnormality are considered separately.

Excessive Discontinuity

A discontinuous EEG is an appropriate finding in the premature infant. With increasing conceptional age, the discontinuous EEG is confined to behavioral quiet sleep, and by 44 to 46 weeks of conceptional age, even quiet sleep is composed entirely of CSWS as the remnants of trace alternant disappear. EEGs that have inappropriately long IBIs or an overrepresentation of discontinuous activity are *excessively discontinuous* for conceptional age (Fig. 6.35). Because trace discontinu and trace alternant are normal, age-specific EEG patterns in healthy infants, the terms are inappropriate to apply to tracings that are abnormal and excessively discontinuous for conceptional age recorded from encephalopathic or medically ill neonates.

When the EEG appears excessively discontinuous, it is important to scrutinize the composition of the bursts. If the burst activity is well preserved and demonstrates a rich variety of the patterns and rhythms appropriate for the conceptional age, the excessive discontinuity may have relatively little significance. However, if the tracing is excessively discontinuous and if the bursts are poorly developed and lack normal background patterns, greater pathological significance can be presumed.

Burst-Suppression Pattern

The most extreme degree of discontinuity is burst-suppression (Fig. 6.36), characterized by an invariant, excessively discontinuous background with prolonged IBIs of very low voltage (<5 μV) that are interrupted by brief (1- to 10-second) bursts of paroxysmal higher voltage theta, delta, and other frequencies. These synchronous or asynchronous bursts may be admixed with sharp waves. Differentiation among biobehavioral states is lost. Burst suppression should not be confused with the immature quiet sleep patterns of tracé discontinu and tracé alternant. Burst-suppression tracings are *excessively* discontinuous and invariant. The IBI duration may be exceedingly long—30 minutes or more. The discontinuity is completely unreactive to noxious stimulation, and no spontaneous cycling of state is apparent. Furthermore, in burst-suppresion, the burst periods themselves are devoid of the anticipated conceptional age–specific patterns (34).

It is important to be able to confidently recognize burst-suppression because it is commonly seen in severe encephalopathies and has clear unfavorable prognostic implications for both premature and full-term infants. Only exceptional infants enjoy a normal outcome in the wake of burst suppression. However, confirmation of a persistent burst-suppression pattern with serial EEGs is recommended before a definitive unfavorable prognosis is rendered. Tharp's (93) prospective study of 81 at-risk newborns of low birth weight (<1,200 g) included 41 EEGs with burst-suppression patterns. The 5-year follow-up revealed that 85% (35 of 41) had a very poor outcome, including eight deaths. In the full-term infant, burst suppression is also a nonspecific pattern of a severe degree of encephalopathy that may be caused by numerous conditions, including asphyxia, stroke, encephalitis or meningitis, metabolic disorders, inborn errors of metabolism such as non-ketotic hyperglycinemia, and cerebral dysgenesis. The rate of poor outcome for full-term infants with burst suppression is also high, ranging from 85% to 100% in recent studies (64,72,87,91,92).

Excessive Discontinuity for Conceptional Age

Some critically ill, very young premature infants may not display all of the usual criteria for burst suppression. The presence of discontinuity per se may be appropriate, even though the duration of the IBIs is usually quite excessive. The bursts themselves may still preserve a few of the named background premature patterns, especially delta brushes or monorhythmic occipital delta activity. Although such tracings fall short of the criteria for burst suppression, they also carry an ominous prognosis.

Less disturbed EEG backgrounds that also do not fulfill the criteria for burst suppression may nonetheless be judged abnormal by excessive discontinuity for conceptional age, determined by measuring the mean or median duration of IBIs or the duration of the record's longest IBI measurement. After 30 weeks of conceptional age, those with a *median* IBI duration of less than 8 seconds fared better than those with longer IBIs (22). Hahn et al. (35) provided useful data concerning the values of the single *longest* acceptable IBI duration for different conceptional ages (Table 6.1). There

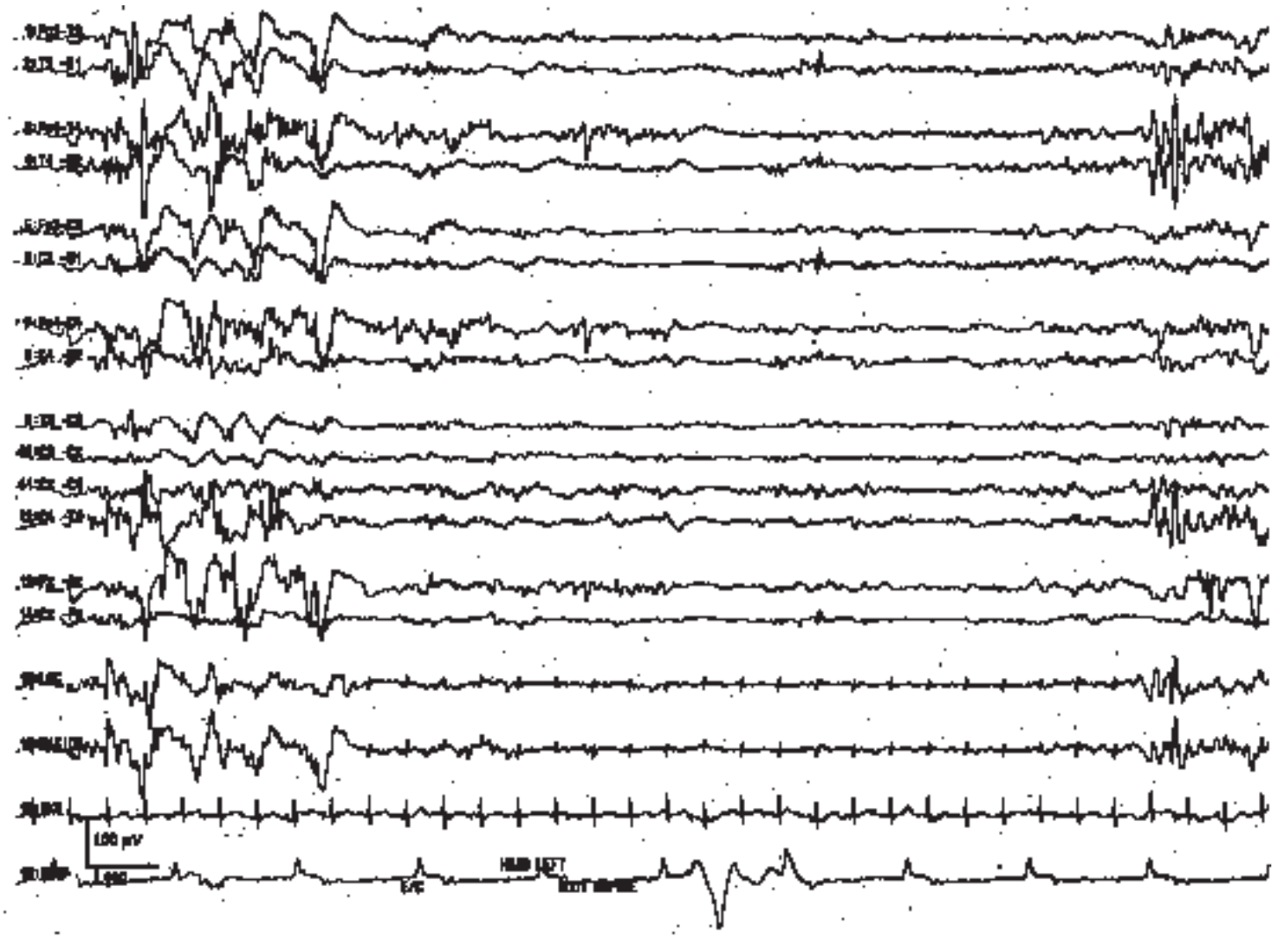


FIG. 6.35. Excessive discontinuity for age in an infant 37 weeks of conceptional age with cervical teratoma. The interburst interval is 11 seconds, which is excessive for an infant of this age.

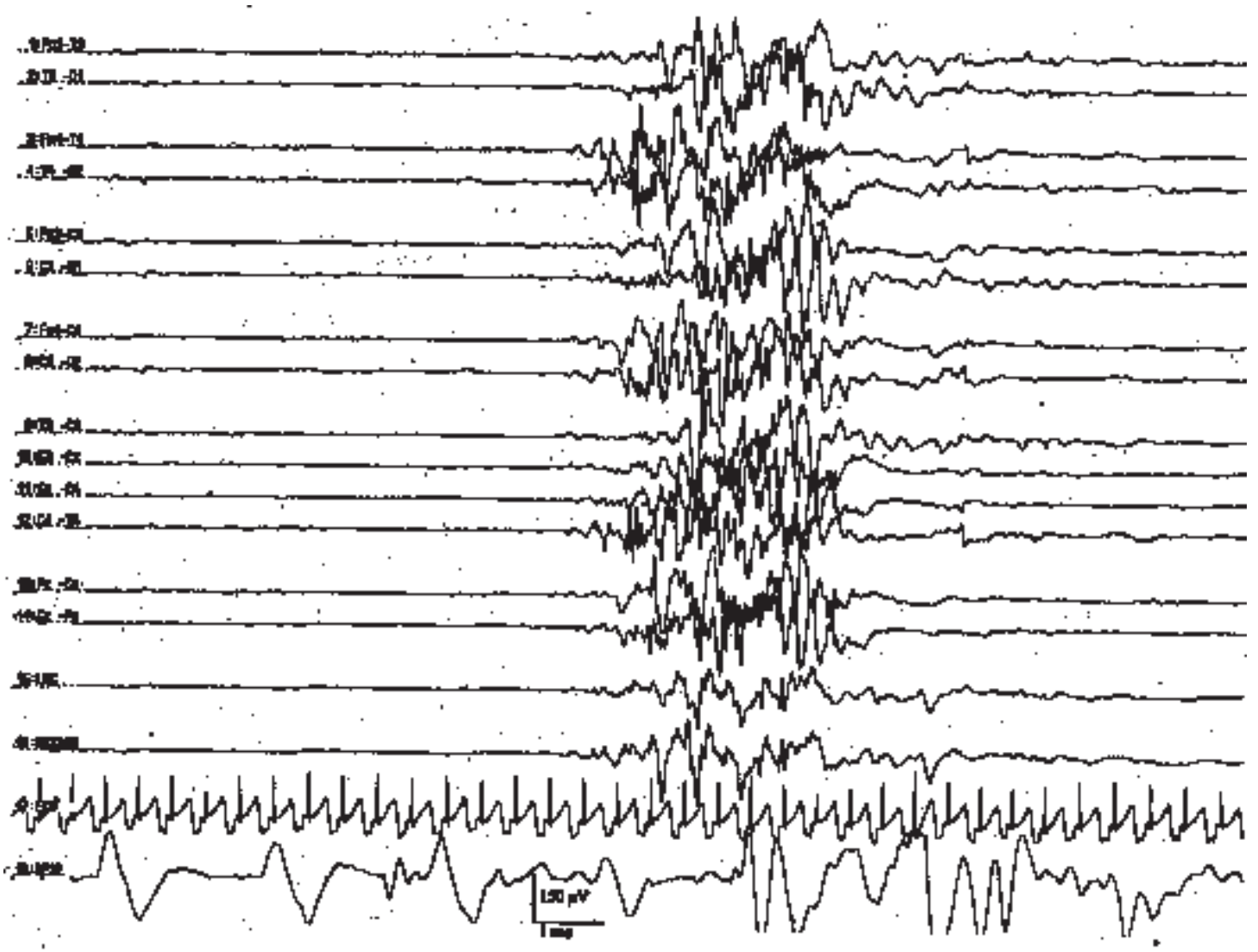


FIG. 6.36. Burst suppression in an infant 38 weeks of conceptional age with multiple contractures and dysmorphic features. The burst of activity is clearly abnormal and contains obvious sharp waves and spikes. The interburst interval is very low amplitude. This pattern persisted for the duration of the recording and did not react to noxious stimulation.

TABLE 6.1. *Longest acceptable single interburst interval (IBI) duration values for conceptional age*

Conceptional age	<30 weeks	31–33 weeks	34–36 weeks	37–40 weeks
Maximal IBI	30–35 s	20 s	10 s	6 s

Adapted from Hahn J, Monyer H, Tharp B. Interburst interval measurements in the EEGs of premature infants with normal neurological function. *Electroencephalogr Clin Neurophysiol* 1989;73:410–4.

are no universally agreed-upon IBI duration criteria that define the exact boundaries of "mildly," "moderately," or "markedly" excessive discontinuity for conceptional age. Previous studies (90–93) suggested that 30-second IBIs were moderately prolonged for a conceptional age of less than 30 weeks or 45 seconds for a conceptional age of 30 weeks or more. Typical IBIs exceeding 60 seconds were markedly abnormal for any conceptional age. However, these earlier criteria have not been revalidated for contemporary practice and are possibly outdated. Certainly, 30-second IBIs would be considered prolonged by today's standards. Like burst suppression, excessive discontinuity is an etiologically nonspecific EEG background abnormality.

Abnormal Voltage

The voltage or amplitude of a normal neonatal EEG regularly and predictably varies with conceptional age and biobehavioral state. For example, the voltages of the EEG bursts during quiet sleep in a premature infant are quite robust, whereas those during active sleep after quiet sleep are much lower in full-term infants. Several descriptions of background abnormalities caused by low voltage have been proposed. Other than the isoelectric recording, no single proposal has been universally accepted.

Persistent Low Voltage

The background in a persistently low-voltage record is attenuated and usually composed of 5- to 15-μV activity during wakefulness and 10- to 25-μV activity during quiet sleep (64). Faster frequencies may be especially "depressed" or of low voltage, but the EEG should otherwise have the normal states, patterns, and frequencies expected for conceptional age. This pattern has been described in some full-term newborns and is prognostically significant only if it persists into the third week after term.

Depressed and Undifferentiated

In this abnormal pattern, the term *depressed and undifferentiated* describes the reduction of rich, complex, faster "polyfrequency" background EEG patterns and does not directly imply a depression of voltage, even though many records of this variety are, in fact, of very low amplitude (<10 μV) (Figs. 6.37 and 6.38). These records may also be excessively discontinuous and do not change with state or stimulation. Low-amplitude, poorly organized electrographic seizures of the "depressed brain type" may be recorded. This is a nonspecific pattern that may be present in many severe conditions, including asphyxia, cerebral hemorrhage, overt dysgenesis, CNS infections, and inborn errors of metabolism. However, postictal states, hypothermia, high drug levels, and very abnormal acid-base status may briefly cause similar EEG patterns and should therefore be ruled out before a prognosis is made.

Isoelectric

When the neonatal EEG is performed in accordance with the established technological criteria to determine electrocerebral silence (ECS) in cases of suspected brain death, the absence of any definite cerebral electrical activity greater than 2 μV constitutes an *isoelectric* tracing (Fig. 6.39). The challenge is to distinguish the ubiquitous recording artifacts in the electronically hostile environment of the neonatal intensive care unit from genuine cerebral electrical activity. Unfortunately, different recording sensitivity criteria have historically been used to define this pattern in neonates. Reported amplitudes in isoelectric recordings have ranged from less than 2 to 10 μV, depending on the investigator. However, the absence of discernible background activity with the sensitivity set at 2 μV in a continuously nonreactive record remains the formal criteria of the American Electroencephalographic Society (2).

Abnormal Asymmetry

A persistent interhemispheric amplitude asymmetry of more than 50% is considered an electrographic abnormality (4,52,55). Persistent amplitude asymmetries may be broadly attributable to excessively high amplitudes in one area or excessively low amplitudes in another. In individual patients, it may be difficult to decide which hemisphere is "abnormal" on the basis of amplitude criteria alone. Neonatal EEG activity is commonly classified in

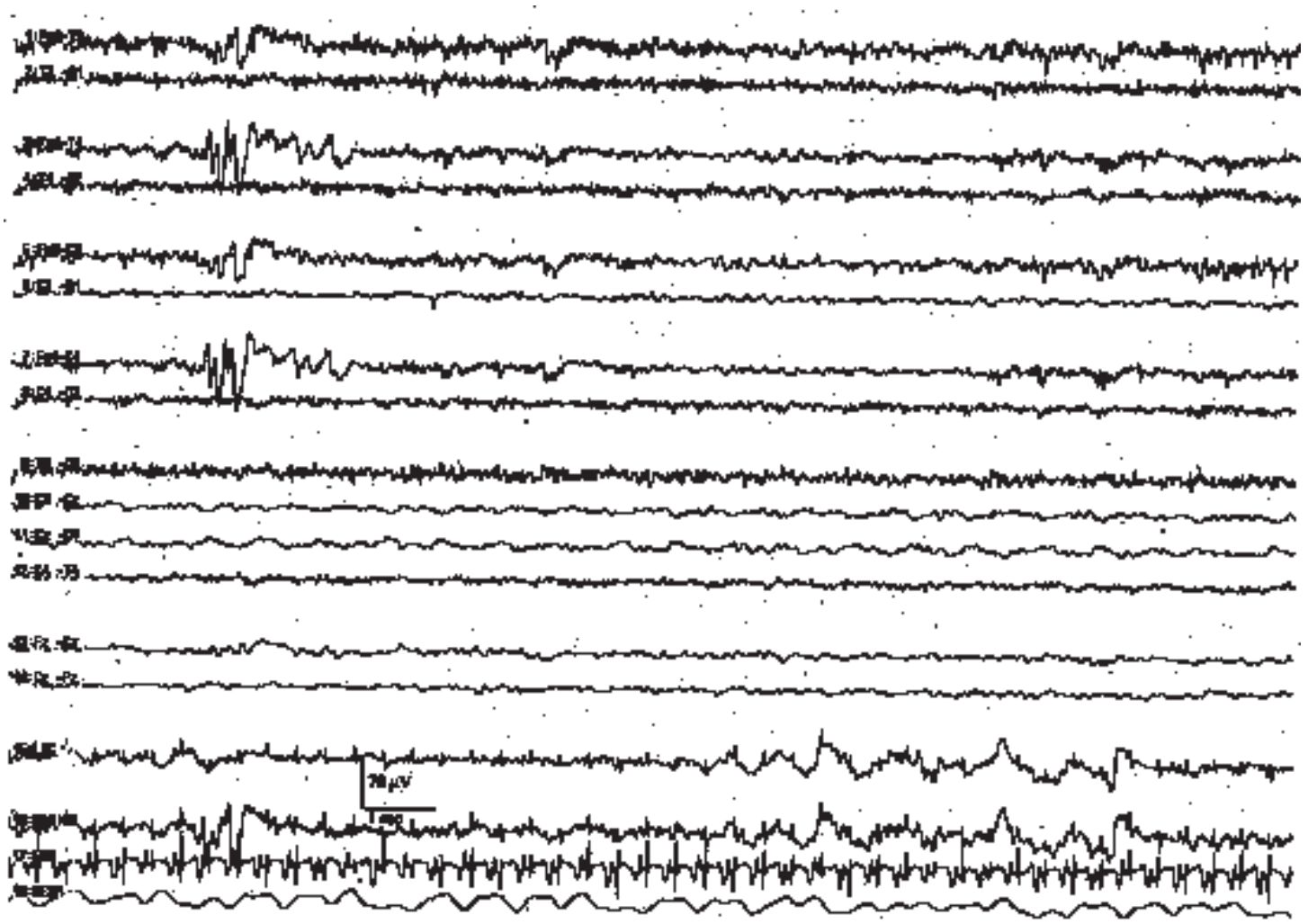


FIG. 6.37. Depressed and undifferentiated background in an infant 41 weeks of conceptional age with birth trauma. The background shows little of the rich, polyfrequency activity expected in a healthy infant of this age.

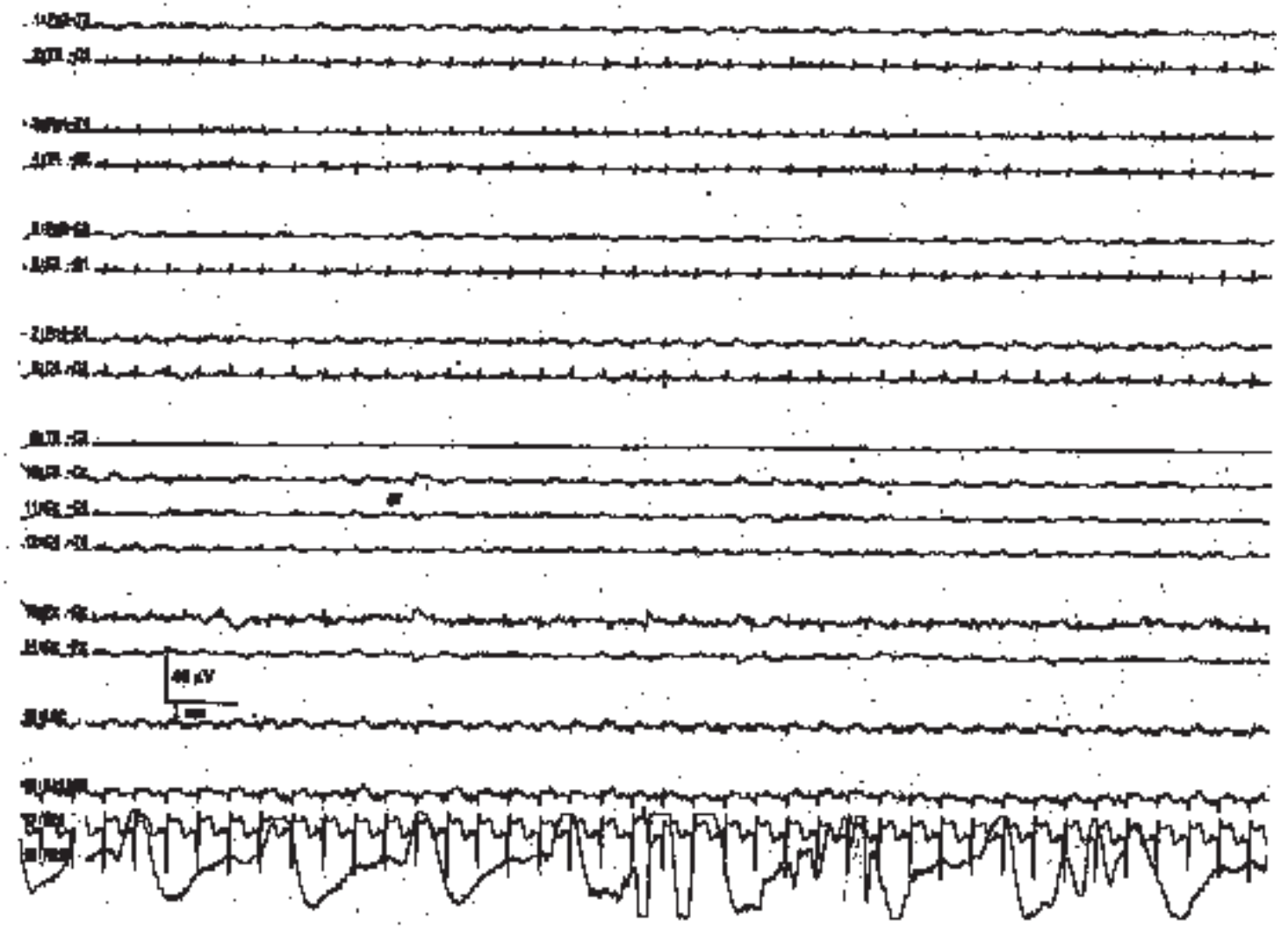


FIG. 6.38. Extreme low voltage background in an infant 39 weeks of conceptional age with severe hypoxic-ischemic encephalopathy. Cerebral activity is nearly absent, except for some minimal slow activity at Cz (*arrow*).

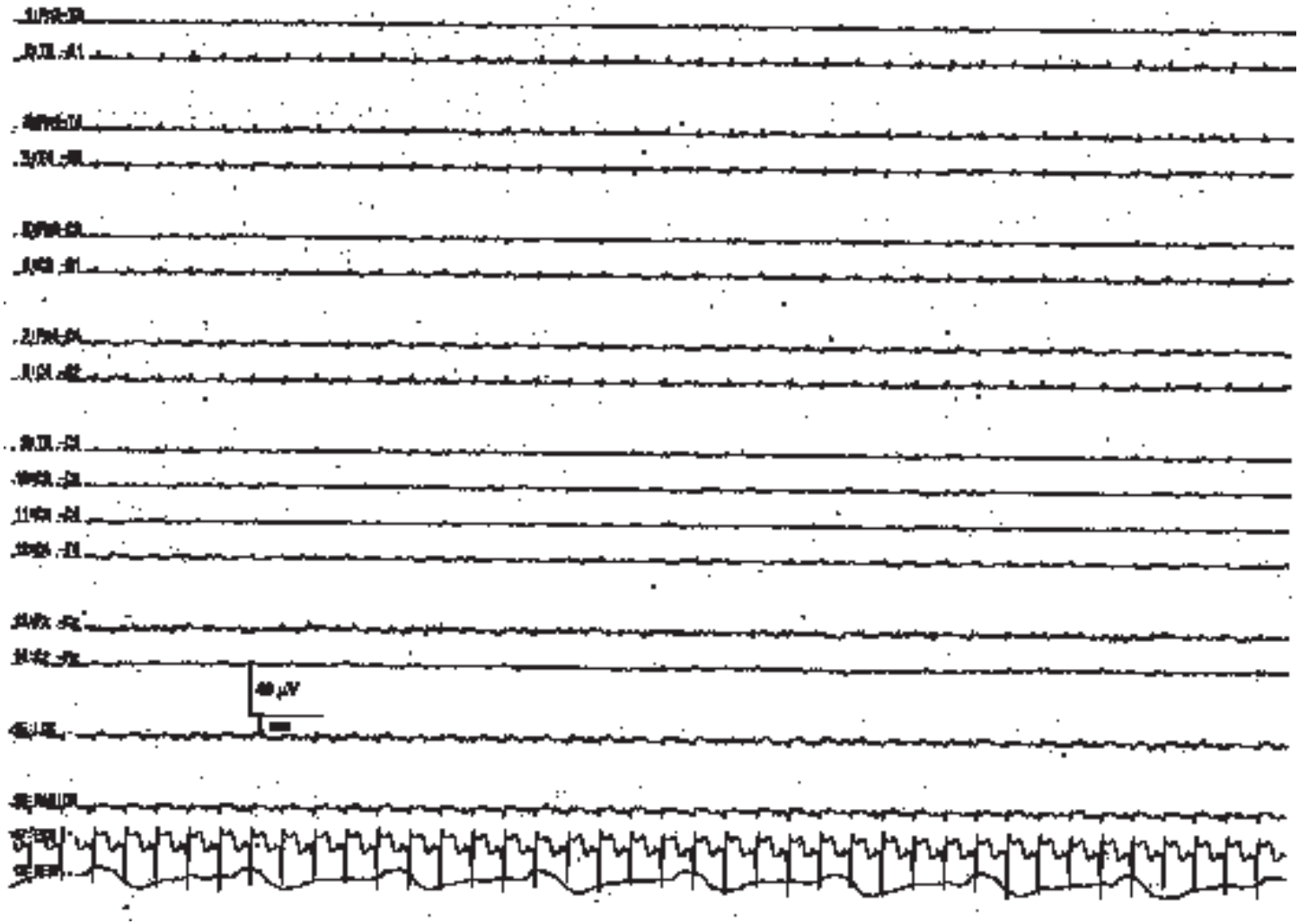


FIG. 6.39. Isoelectric or electrocerebral silence (ECS) in an infant 39 weeks of conceptional age with clinical brain death from severe hypoxic-ischemic encephalopathy. No definite cerebral activity is seen at maximal recording sensitivity. Electrocardiographic artifact is present.

bipolar montages as low (<25 μV), medium (25 to 50 μV), and high (50 to 200 μV) in amplitude. Although extremely high or low amplitudes may themselves technically constitute an abnormality, the interpreter should carefully inspect the EEG background composition before making the definitive determination of abnormal asymmetry.

Most causes of acute encephalopathy in the neonate arise from diffuse pathological conditions such as global hypoxia-ischemia, metabolic abnormalities, or sepsis with meningitis, and EEGs recorded in these circumstances display symmetric abnormalities. Focal brain injury may be caused by localized cerebral infarction (stroke), venous or dural sinus thrombosis, abscess, restricted hemorrhage, contusion, or similar pathological processes. The EEG asymmetries in these circumstances often appear as a voltage reduction (from loss of signal generators), seizures arising from a limited number of brain regions, depression of normal background patterns, focal slowing, or sharp waves (see Fig. 6.19). On the other hand, when the electrographic asymmetry is purely a loss of voltage (see Fig. 6.20), with preservation of the composition of the background, a technical problem (e.g., electrode spacing or asymmetrical scalp edema) or possible subdural fluid collection could be responsible.

The unfavorable prognostic significance of this abnormality has been reported by several authors (3,4,52,55,95). In the setting of meningitis, Chequer et al. (14) reported that persistent EEG asymmetries correlated well with specific localized injuries such as abscess or large vessel infarction. Tharp et al. (91) noted that in nine patients with more than 50% amplitude asymmetry persisting in all states, the prognosis was poor, including death or definite neurological handicaps. In contrast, neonates with less than 50% interhemispheric asymmetry with an otherwise normal EEG for conceptional age enjoyed a favorable prognosis, even if the abnormality persisted throughout the record.

Abnormal Interhemispheric Asynchrony

Synchrony is typically determined by analyzing 5 minutes of the discontinuous portion of the EEG (64,93). Interhemispheric bursts separated by more than 1.5 to 2 seconds of each other are considered asynchronous. The percentage of EEG bursts that are synchronized approach 100% in the healthy full-term infant. Gross asynchrony of the EEG is rarely encountered in isolation; instead, it is usually accompanied by other obvious background abnormalities such as excessive discontinuity or burst suppression. Excessive asynchrony can be seen in a variety of *acute* causes of encephalopathy, such as hypoxic-ischemic encephalopathy (HIE) or meningitis, and in *chronic* conditions, such as cerebral dysgenesis. Neuropathological findings in infants with an abnormally asynchronous EEG include periventricular leukomalacia, intraventricular hemorrhage, and any developmental abnormality of the corpus callosum (4). Aicardi's syndrome is confined to girls and characterized by distinctive retinal colobomas, agenesis of the corpus callosum, occasional interhemispheric cysts, striking degree of interhemispheric EEG asynchrony, and refractory, early-onset seizures that include infantile spasms (88).

Abnormal Maturation

In the setting of acute encephalopathies such as HIE or trauma, the common EEG background abnormalities of excessive discontinuity, depressed background composition, and impaired reactivity are useful yardsticks for measuring the impact of the disease on functional CNS integrity. However, infants exposed to subacute, prolonged illness may never experience a sudden, sentinel clinical event; rather, they are neurologically stressed over extended time frames. Examples of such infants are premature infants who require long-term mechanical ventilation because of bronchopulmonary dysplasia and full-term infants affected with congestive heart failure from a congenital heart defect. In these infants, the CNS may not mature at the appropriate rate. Such chronically ill infants experience an actual delay or arrest of physical brain development that can be reflected as "immaturity" in serial EEG examinations (37,93).

A neonatal EEG record is considered immature or dysmature (Fig. 6.40) if it contains patterns that indicate that its current maturity is 2 or more weeks younger than the stated conceptional age (52). Interpretative criteria used to determine dysmaturity include the degree of discontinuity during quiet sleep, the degree of interhemispheric asynchrony, the frequency and location of delta brushes during active sleep and quiet sleep, the presence of *encoches frontales,* and the number of temporal theta bursts. Rating an EEG as dysmature is relatively subjective, although normative scales have been suggested to aid with the diagnosis (11,35,54,69).The pathological correlate of a persistently immature EEG is actual CNS dysmaturity, visible as inappropriately delayed neuronal migration and maturation. Transient dysmaturity is not correlated with a poor prognosis, although persistent dysmaturity on serial EEGs can be associated with an unfavorable outcome.

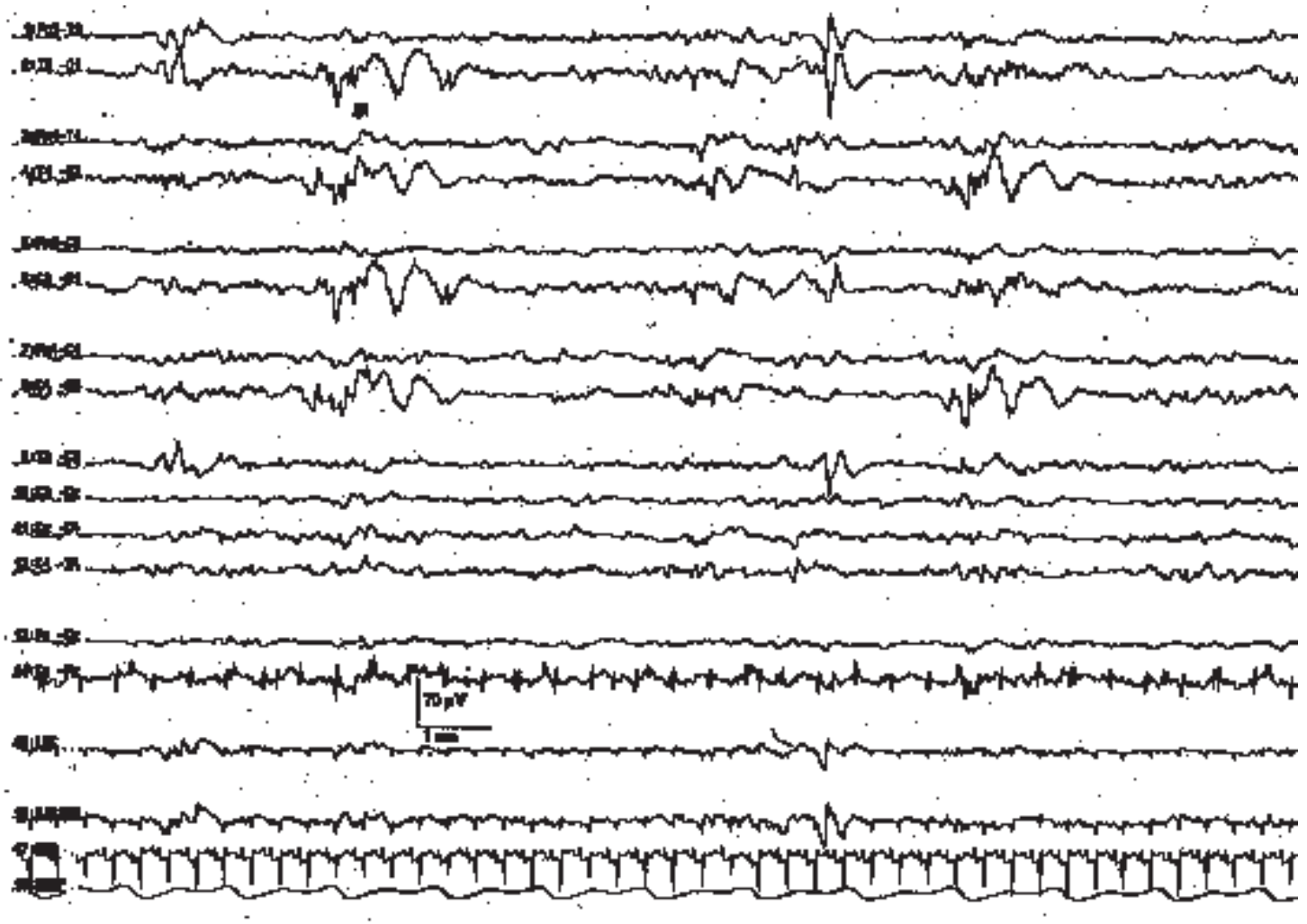


FIG. 6.40. Immature background for age in an infant 42 weeks of conceptional age with complex congenital heart disease. Rhythmic occipital delta activity (*arrow*) is not normally present in infants of this conceptional age.

Classification of the Electroencephalographic Background and Its Implications

The EEG background correlates strongly with a neonate's clinical neurological status, prognosis, and eventual neurological outcome. Several grading systems of the neonatal EEG background have been suggested (24,25,41, 53,64,91,92,98). Although there are minor differences among the grading scales, the main features are similar and broadly classify tracings as normal or mildly, moderately, or markedly abnormal according to criteria describing continuity, voltage, reactivity, and background composition (Table 6.2).

TABLE 6.2. *Classification of electroencephalographic background activity*

1. Normal
2. Transient or persistent immaturity (dysmaturity)
3. Mildly abnormal
   a. Mildly excessive discontinuity during the discontinuous portions of the tracing
   b. Mildly excessive interhemispheric asynchrony for conceptional age
   c. Poor concordance between clinical and electrographic sleep states
   d. Mild poverty of anticipated background rhythms for conceptional age (e.g., mild decrease in monorhythmic occipital delta activity, rhythmic occipital or temporal theta activity, brushes)
   e. Mild focal abnormalities (e.g., excessive sharp waves in temporal or central regions, focal voltage attenuation)
4. Moderately abnormal
   a. Moderately excessive discontinuity during the discontinuous portions of the tracing
   b. Moderately excessive interhemispheric asynchrony for conceptional age
   c. Poverty of anticipated background rhythms for conceptional age
   d. Definite focal abnormalities (e.g., persistent focal delta activity or focal depression of expected background patterns such as brushes)
   e. Persistent low voltage (generalized reduction of voltage <25 μV for all states)
5. Markedly abnormal
   a. Markedly excessive discontinuity for age, despite the preservation of some age-appropriate background patterns
   b. Burst suppression pattern
   c. Gross interhemispheric asynchrony
   d. Extremely low voltage (<5 μV)
   e. Depressed and undifferentiated
   f. Isoelectric

Adapted from Clancy R, Tharp B. Positive rolandic sharp waves in the electroencephalograms of premature neonates with intraventricular hemorrhage. *Electroencephalogr Clin Neurophysiol* 1984;57:395–404.

Most infants with markedly abnormal EEG backgrounds have an abnormal mental status (lethargy or coma) caused by severe, diffuse acute encephalopathy and face a very high risk of an unfavorable outcome such as death or permanent neurological disability (84). Infants with an *unexplained,* grossly abnormal EEG background may harbor an unexpected cerebral dysgenesis such as holoprosencephaly. Infants with normal serial EEGs usually have normal mental status, as assessed by examination, and were exposed to mild or minimal diffuse pathological processes or to definite but restricted injuries. For example, an infant with an acute embolic stroke usually has a normal mental status and a well-preserved overall EEG, although focal abnormalities may be evident (21). Most infants with normal or mildly abnormal tracings have a favorable outcome. However, those with genetic disorders such as Down's syndrome who have not experienced any type of acute encephalopathy also display nearly normal records, despite the realistic expectation for an abnormal neurological outcome. Moderately abnormal EEGs fall between these two extremes with regard to the coincident mental status, the cause or causes of the encephalopathy, and the chances of an adverse outcome.

The prognostic value of serial EEGs in premature infants has been shown in many studies, including the study by Tharp et al. (92) of 81 infants younger than 36 weeks of EGA. Markedly abnormal EEGs were associated with a 96% incidence of death or adverse outcome. Worsening on serial EEGs was seen in 41% of the children with major neurological sequelae but only in 3% of patients with normal outcome and 15% of those with minor sequelae. Tharp et al. (93) investigated infants weighing less than 1,200 g who were admitted to their neonatal intensive care unit and found that EEG was better than the clinical neurological examination at predicting poor outcome (72% versus 39%). Normal outcome was predicted with equal accuracy by the clinical examination and the EEG. In the study by Clancy et al. (22) of 101 premature infants with EEG and head ultrasound (HUS) examinations, survival rates were significantly better among those with normal or mildly abnormal recordings (Fig. 6.41). The prognostic value of serial EEG has also been investigated in full-term infants. Watanabe et al. (98) assessed 173 full-term infants after HIE and found that infants with mild background abnormalities that lessened over the first few days of life had a good outcome. Poorer outcome was noted if markedly abnormal abnormalities persisted more than 4 days or if milder abnormalities lasted many days.

What are the neuropathological correlates of the abnormal EEG? Few investigators have attempted to address this important question by directly

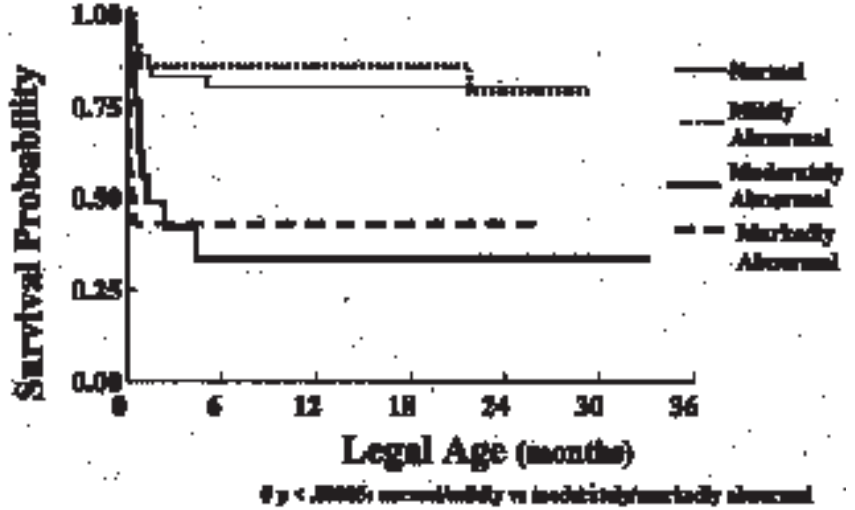


FIG. 6.41. Kaplan-Meier survival curve shows significantly greater survival in premature infants with normal or mildly abnormal electroencephalographic backgrounds than in those with moderately or markedly abnormal tracings. (Adapted from Clancy R, Rosenberg H, Bernbaum J, et al. Survival outcome prediction in premature infants with IVH by cranial ultrasonography and EEG. *Ann Neurol* 1994;36:489.)

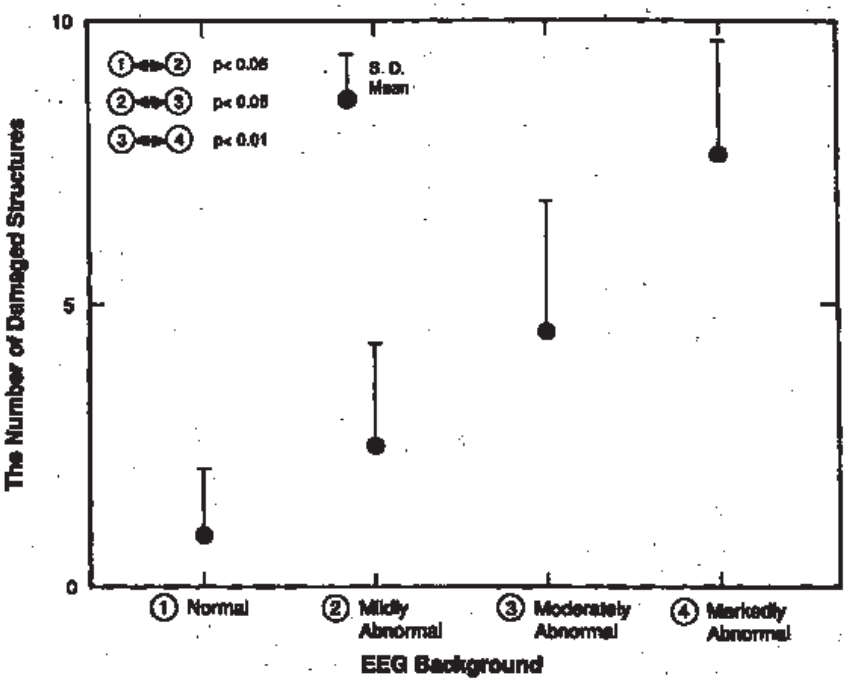


FIG. 6.42. The correlation between the electroencephalographic background and the number of neuropathological lesions. (Adapted from Aso K, Scher M, Barmada M. Neonatal electroencephalography and neuropathology. *J Clin Neurophysiol* 1989;6:103–123.)

associating the varieties and severities of EEG background patterns with the results of postmor tem brain e xaminations (3,4,73,92). Because mark edly abnormal EEGs empirically confer an adv erse neurological outcome, it is reasonable to attempt to understand its neuropatholo gical basis. In the largest study of its type, Aso et al. (3) analyzed 107 EEGs in 47 infants who later died during the neonatal period and on w hom autopsy was performed. Macroscopic and microscopic e xaminations were performed in selected anatomical structures: the cerebral cor tex, subcortical white matter, corpus callosum, thalamus, h ypothalamus, corpus striatum, midbrain, pons, and medulla. Normal EEGs cor related with histolo gically normal brains, whereas progressively abnormal EEGs were associated with more extensive and severe neuropathological processes. The degree of EEG abnor mality significantly correlated with the number of damaged brain re gions counted at autopsy (F ig. 6.42). Some interesting electro graphic-neuropathological associations were also re vealed. Isoelectric EEGs w ere correlated consistently with widespread encephalomalacia and , commonly, with ischemic necrosis of the cortex, thalamus, corpus striatum, midbrain, and pons. Burst suppression patterns were also associated with multifocal lesions, including widespread neuronal necrosis b ut variably present intra ventricular hemorrhage (IVH), peri ventricular leukomalacia, cerebral infarctions, and pontosubicular necrosis. There was no single lesion present in all inf ants with burst suppression. Interhemispheric amplitude asymmetries of more than 50% were correlated with localized cerebral lesions, including inf arctions and IVH. The hemisphere with more EEG attenuation was the worst affected pathologically. Excessive asynchrony was identified in 9 of 18 patients older than 31 w eeks of conceptional age. Their anatomical abnor malities were mild to moderate in se verity but specifically involved the cor pus callosum in only two. Conversely, no child with nor mal synchrony had a callosal

lesion. Positive rolandic sharp waves (PRSs) were always associated with white matter lesions but did not consistently correlate with any other type of neuropathology. PRSs were a highly specific but insensitive marker, inasmuch as the incidence of PRS was only 32% in those with proven white matter lesions.

SHARP ELECTROENCEPHALOGRAPHIC TRANSIENTS

Sharp EEG transients (SETs) are defined as sharply contoured waves of brief duration that are clearly distinguishable from the ongoing background activity. In the neonatal EEG, the definitions of a sharp wave and a spike are slightly different from those used in pediatric and adult EEG. SETs with a duration between 100 and 500 milliseconds are called *sharp waves,* whereas those with a duration of 100 milliseconds or less are *spikes.* The polarity of sharp waves or spikes may be monophasic, biphasic, or polyphasic. SETs may appear in any scalp location. Just as SETs in older persons may be innocent (e.g., lambda waves or small sharp spikes) or pathological, a similar situation exists in the interpretation of neonatal EEGs. Interpretative criteria to assist in the discrimination between physiological and pathological SETs have been proposed.

Frontal Sharp Electroencephalographic Transients

Morphologically, physiological frontal sharp waves (*encoches frontales*) are high-amplitude (>150- μV), broad, biphasic (negative-positive) transients seen maximally in the frontal regions (Fp3 and Fp4). They generally appear symmetrically, bilaterally, and synchronously; however, when they first appear at around 34 weeks of conceptional age, they may arise somewhat asynchronously. *Encoches frontales* may appear alone or may intermingle with runs of slow 2- to 4-Hz waves (anterior dysrhythmia) (Fig. 6.43). Frontal sharp waves are most abundant during the transition from active sleep to early quiet sleep and are scarce in the period of active sleep that immediately follows arousal from quiet sleep. They persist until about 4 weeks after birth, at which point they begin to disappear (29). *Encoches frontales* are normal, physiological, age-dependent SETs that do not suggest a "lowered seizure threshold."

Several characteristics of pathological frontal sharp waves distinguish them from the innocent *encoches frontales.* A clearly excessive amount of frontal slowing and *encoches frontales* in active sleep/wakefulness may be seen in the context of resolving or mild HIE, meningitis, or metabolic encephalopathies. Frontal SETs that are atypical in morphology (e.g., true spikes) or are markedly asymmetrical may also be considered electrographic abnormalities (Fig. 6.44).

Temporal and Central Negative Sharp Electroencephalographic Transients

The initial and predominant deflection of negative SETs is surface polarity negative in standard bipolar derivations. They may be found in any scalp region but are most frequent in the temporal and central regions. Negative centrotemporal SETs are best evaluated during the low-voltage, continuous portions of the tracing, which correspond to wakefulness and active sleep. It is difficult to quantitatively evaluate sharp waves that may occur during the bursts of activity in immature quiet sleep, because many infants generate "spikey" or sharp-quality quiet sleep bursts. Few data describing SETs before the conceptional age of 33 to 34 weeks are available.

The significance of abnormal negative sharp waves is controversial. Some authors consider them a nonspecific electrographic finding that may occur in a variety of pathological conditions without a clear relationship to clinical or electrographic seizures (55,56). This situation has a counterpart in adult EEGs in that sharp waves may be seen in uremia, hypoxia with ischemia, and drug withdrawal without the presence of clinical or electrographic seizures and may be interpreted as nonspecific electrographic abnormalities (23). However, there is also evidence in neonates that some characteristics of negative, centrotemporal SETs are epileptiform and are encountered more commonly in infants with seizures. Clancy (16) examined the EEG backgrounds and characteristics of SETs in 78 EEGs from 30 neonates with confirmed electrographic seizures and compared them with the EEG characteristics of SETs recorded from 69 healthy neonates without seizures. Both the EEG background and specific features of negative SETs were contrasted in the seizure and comparison groups. In the seizure group, 41 (52.6%) of 78 tracings had EEG backgrounds classified as moderately or severely abnormal, in comparison with 0 of 69 abnormal backgrounds in the comparison group. Centrotemporal SETs were characterized in terms of *abundance* (number of SETs counted during a 10-minute continuous EEG epoch), *morphology* (spike versus sharp wave), *repetitive behavior,* and *spatial distribution* (among locations C3, C4, T3, and T4).

In infants without seizures, centrotemporal SETs (Fig. 6.45*A* and *B*) occurred at a rate of less than one per minute (Fig. 6.46) and were evenly distributed between both hemispheres (T3 and C3 versus T4 and C4), both

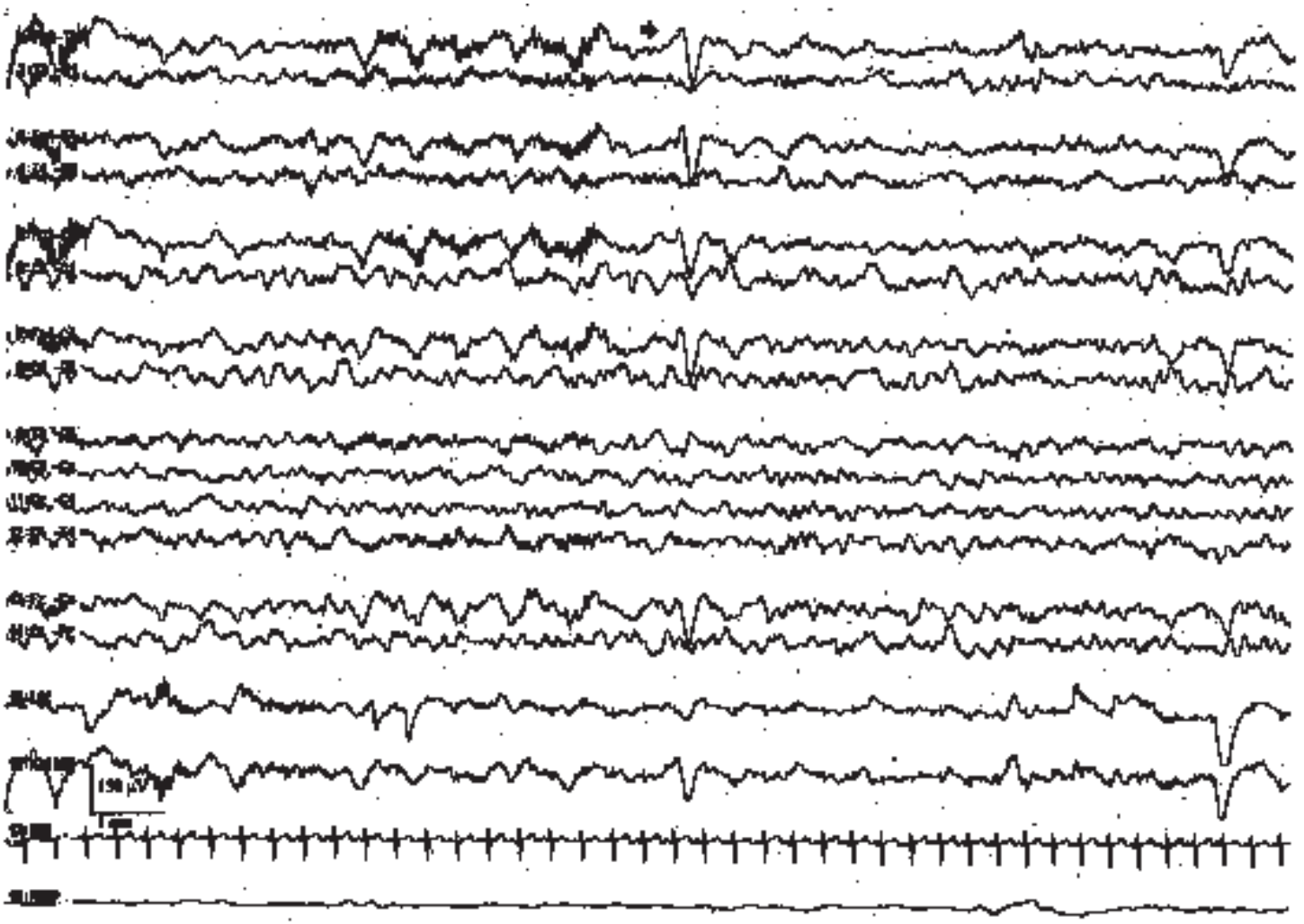


FIG. 6.43. *Encoches frontales* in an infant 40 weeks of conceptional age with clinically suspected seizures. Normal frontal sharp waves—*encoches frontales*—(*arrow*) are admixed with anterior dysrhythmia.

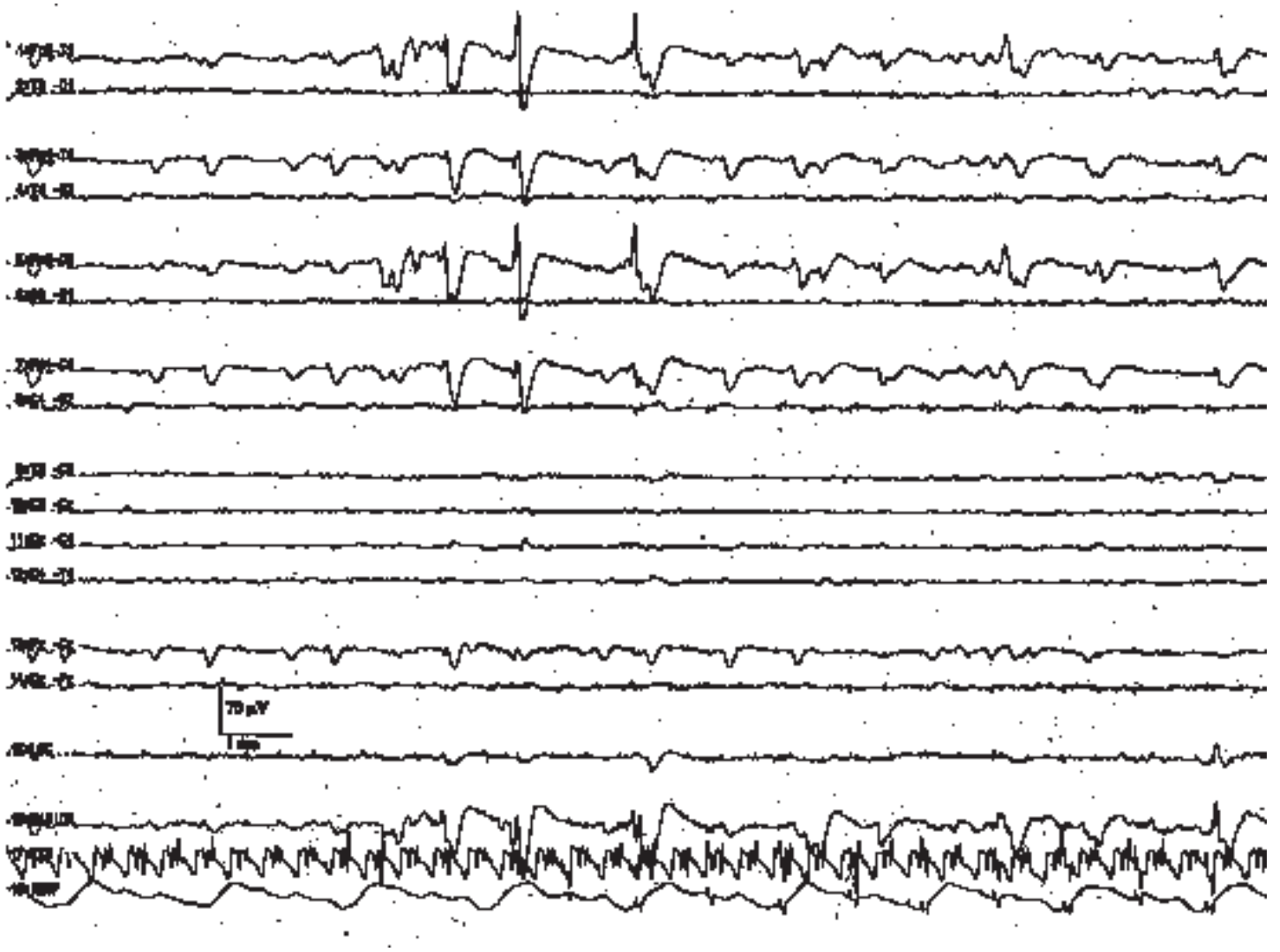
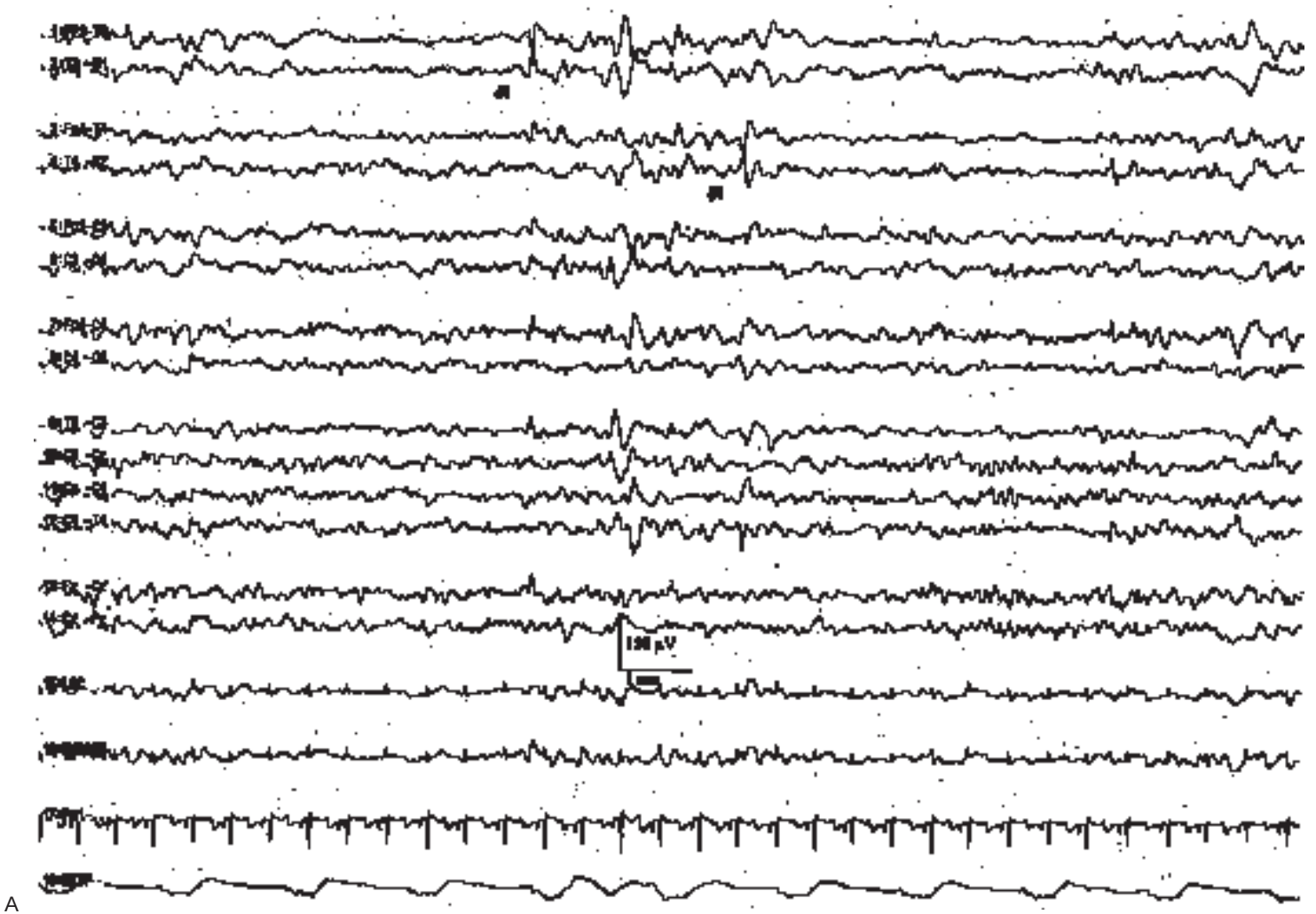
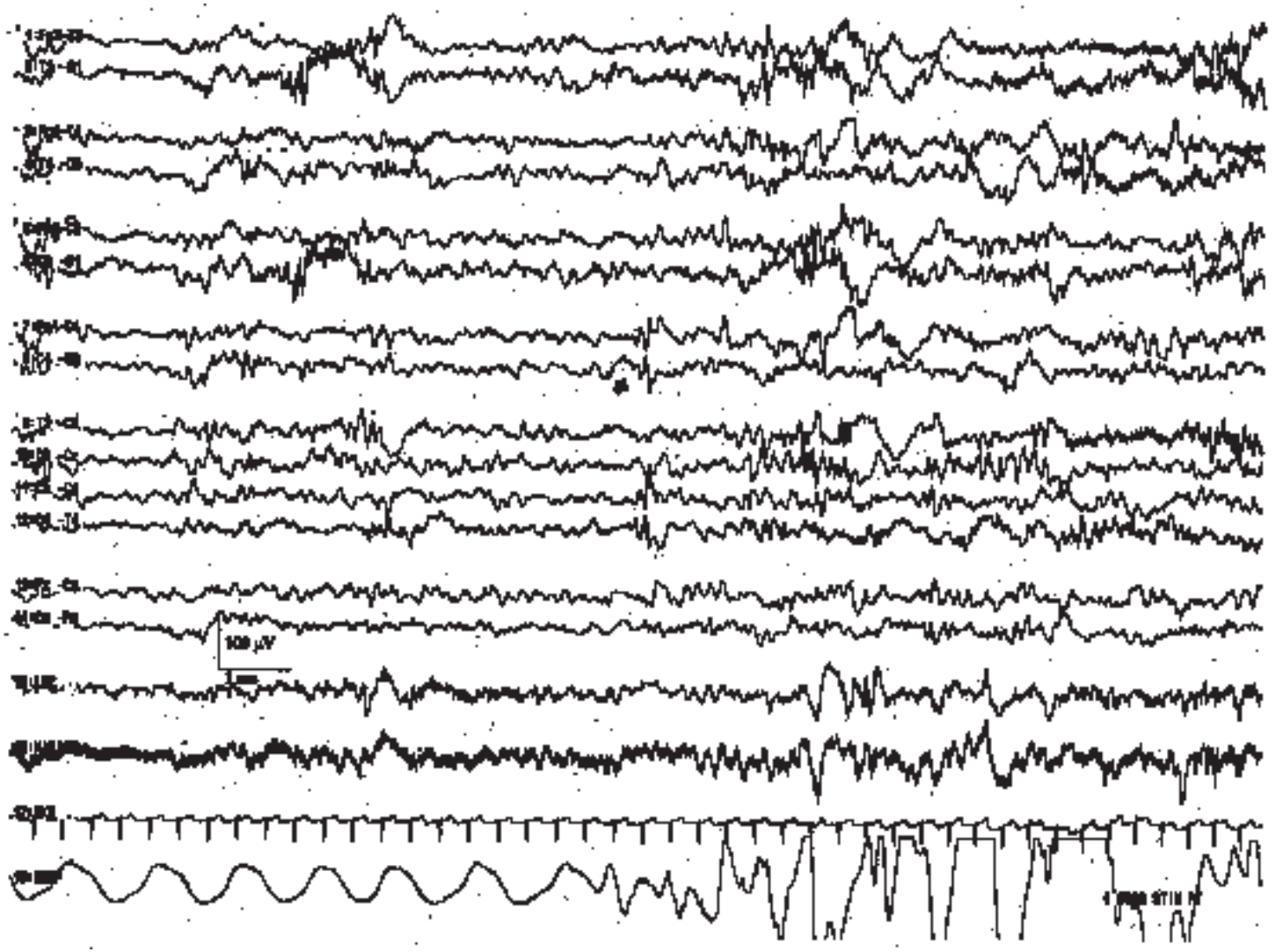


FIG. 6.44. Abnormal frontal sharp waves in an infant 41 weeks of conceptional age with head trauma. Frontal sharp waves are excessively sharp and superimposed on a featureless background.



A

FIG. 6.45. A: Normal temporal sharp electrographic transients (SETs) in an infant 43 weeks of conceptional age with pneumonia. Right and left temporal SETs (*arrows*) are present. In this tracing, SETs were infrequent and were equally distributed between both temporal regions. (*Figure continues*.)



B

FIG. 6.45. *Continued.* **B:** Normal central SETs in an infant 39 weeks of conceptional age with Pierre Robin syndrome. *Arrow* indicates a normal-appearing right central negative sharp wave. Rare right and left temporal and central negative sharp waves were present in this record.

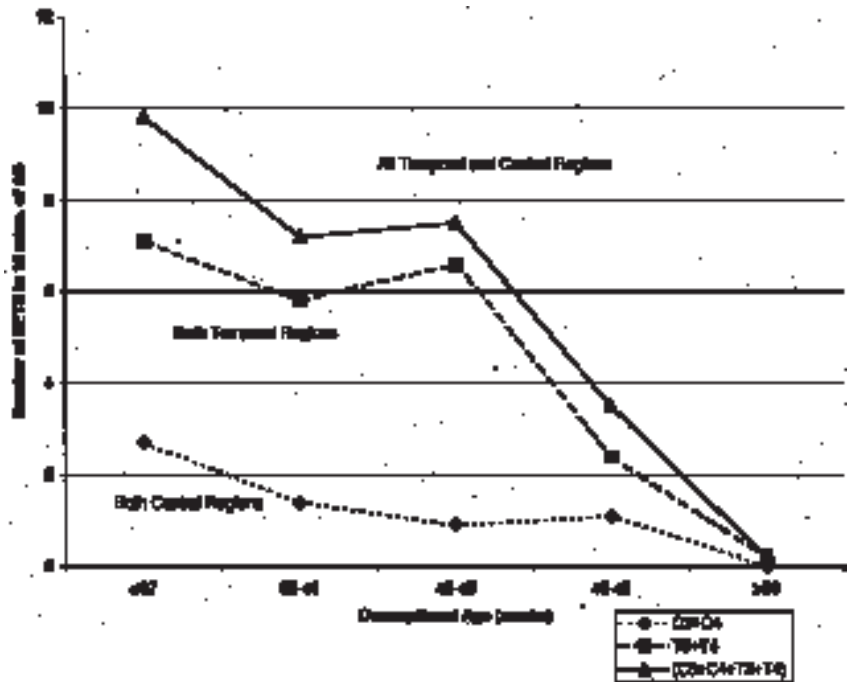


FIG. 6.46. Normal abundance of sharp electroencephalographic transients by location and conceptual age. (Adapted from Clancy R. Interictal sharp EEG transients in neonatal seizures. *J Child Neurol* 1989;4:30–38.)

temporal regions (T3 versus T4), and both central regions (C3 versus C4). SETs were more abundant in the temporal areas than in the central areas (Fig. 6.46). In this group, SETs consisted of sharp waves and only rare spikes; runs or bursts of SETs were not seen. In the seizure group, centrotemporal SETs usually occurred more frequently than two per minute, were often spikes (rather than sharp waves), and often recurred in repetitive runs. In the seizure group, SETs were more often nonrandomly distributed: significantly distributed to favor one location or hemisphere more than others (Fig. 6.47). These distinctions between the groups, however, were not absolute. Of 78 EEGs from the seizure group, 16 (21%) had relatively normal backgrounds and SETs that behaved similar to those of the comparison group. Most neonates with EEG-confirmed seizures had interictal tracings characterized by abnormal backgrounds and excessive spikes or sharp waves that sometimes recurred in brief runs and were distributed nonrandomly in the temporal and central regions.

This study has implications for interpreting EEG abnormalities in infants with seizures that are suspected but not specifically confirmed by recording electrographic seizures. Neonates with abnormal backgrounds and abnormal negative SETs are considered to display patterns of abnormalities similar to those in infants with electrographically confirmed seizures. They may be considered to have EEG characteristics of a "lowered seizure threshold" at that time. However, this constellation of interictal EEG findings is not diagnostic of neonatal seizures. In contrast, neonates with abnormal backgrounds and normal negative SETs have nonspecific cerebral dysfunction. But this does not exclude the possibility of neonatal seizures.

Neonates with normal backgrounds and abnormal SETs are relatively uncommon. However, in the context of the "well neonate" with seizures who has a normal EEG background with abnormal SETs, the diagnostic possibilities should include conditions such as simple hypocalcemia, in which excessive sharp waves tend to arise in the central or central vertex regions (96), and mild subarachnoid hemorrhage, which may "irritate" the cortex.

Negative Sharp EEG Transients in Other Locations

Just as electrographic neonatal *seizures* can arise from any scalp regions, abnormal negative spikes or sharp waves may arise from any or many areas. Multifocal SETs may be recorded from some infants with diffuse encephalopathies, including those involving the midline (Fz, Cz, or Pz) and occipital regions (Figs. 6.48 and 6.49). However, the significance of finding excessive SETs that are limited to the occipital and midline areas is unclear, inasmuch as few studies have systematically examined them (32,61,82).

Positive Sharp Waves (Rolandic, Vertex, and Temporal)

Positive sharp waves may appear in the sick neonate as sharp EEG transients (duration, less than 400 to 500 milliseconds) (7,8,12,15,19, 24,25,27,28,45,59,60,67,68) with an initial and predominant surface-positive polarity. They may arise from the rolandic regions (PRSs) (Fig. 6.50), the central vertex (positive vertex sharp wave [PVS]) (Fig. 6.51), and the

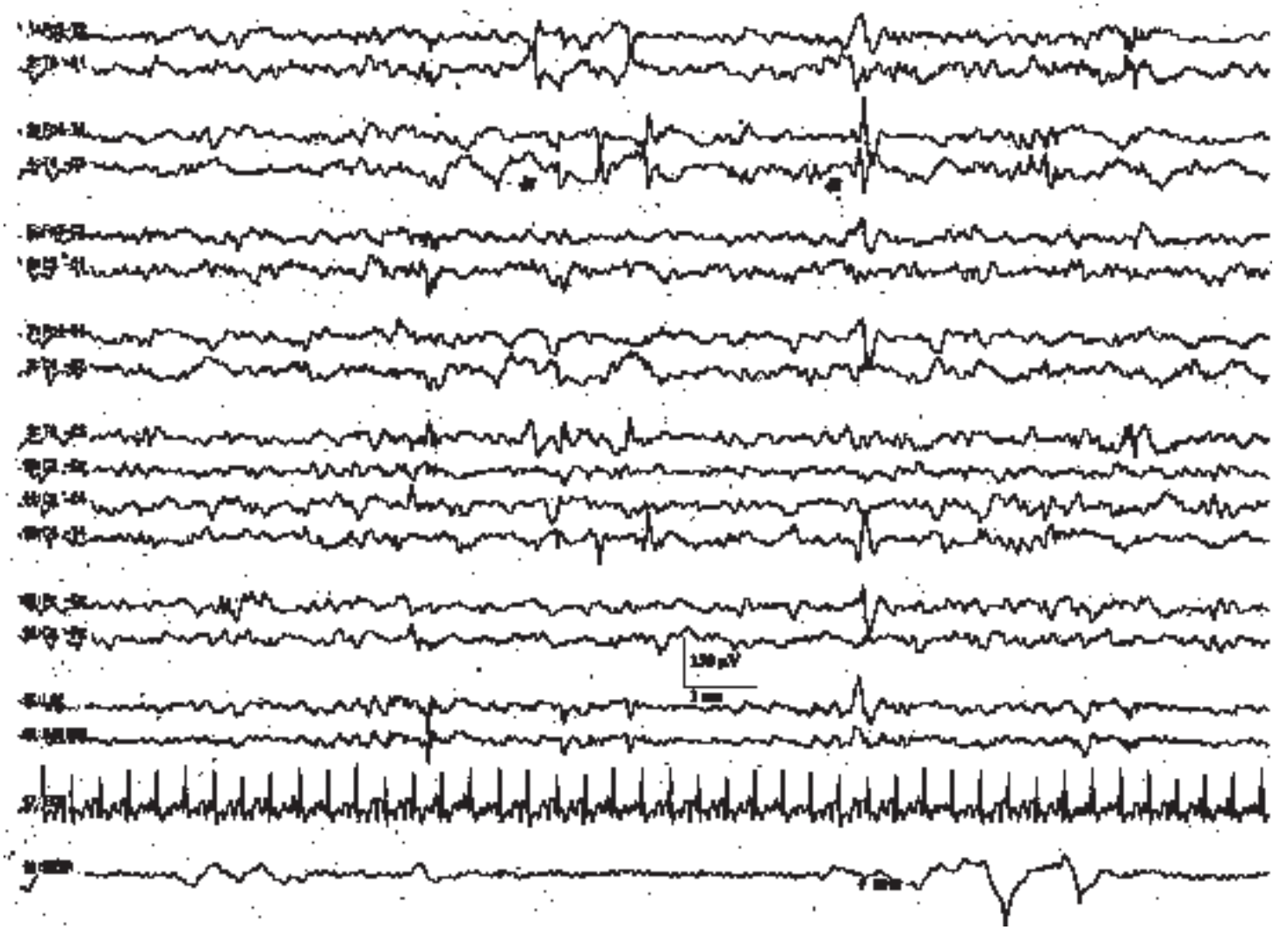


FIG. 6.47. Abnormal temporal sharp electrographic transients (SETs) in an infant 38 weeks of conceptional age with persistent pulmonary hypertension and seizures. Multiple right temporal sharp waves are present (*arrow*). In this record, left temporal sharp waves are rare.

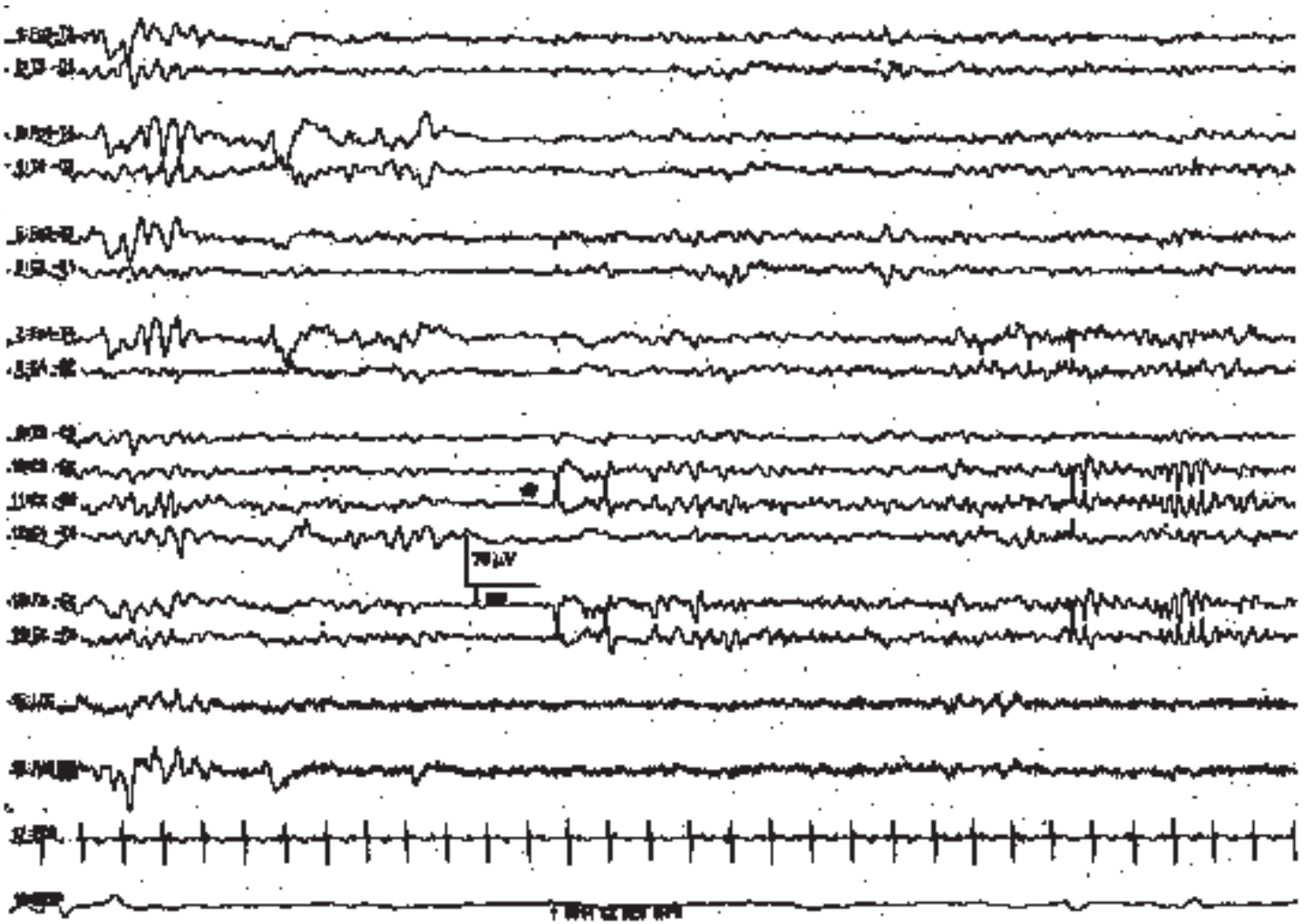


FIG. 6.48. Abnormal vertex sharp electrographic transients (SETs) in an infant 43 weeks of conceptional age with seizures. Sharp waves isolated to the central vertex are seen (*arrow*). If electrode Cz had been omitted from the montage, these SETs would have been missed.

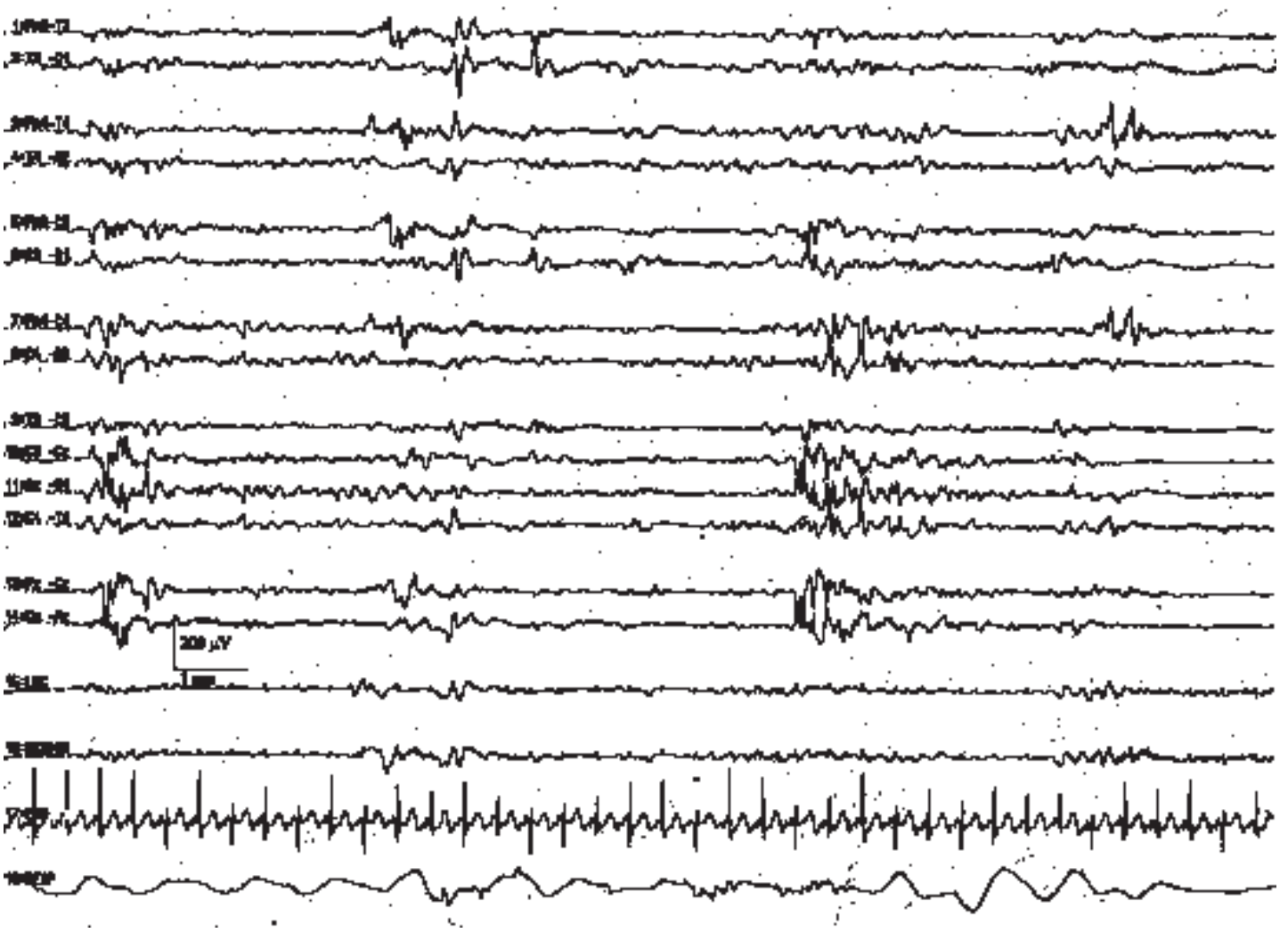


FIG. 6.49. Multifocal negative sharp waves in an infant 37 weeks of conceptional age with hypoxic-ischemic encephalopathy and seizures. Abnormal sharp EEG transients are present at T3, C3, C4, and Cz.

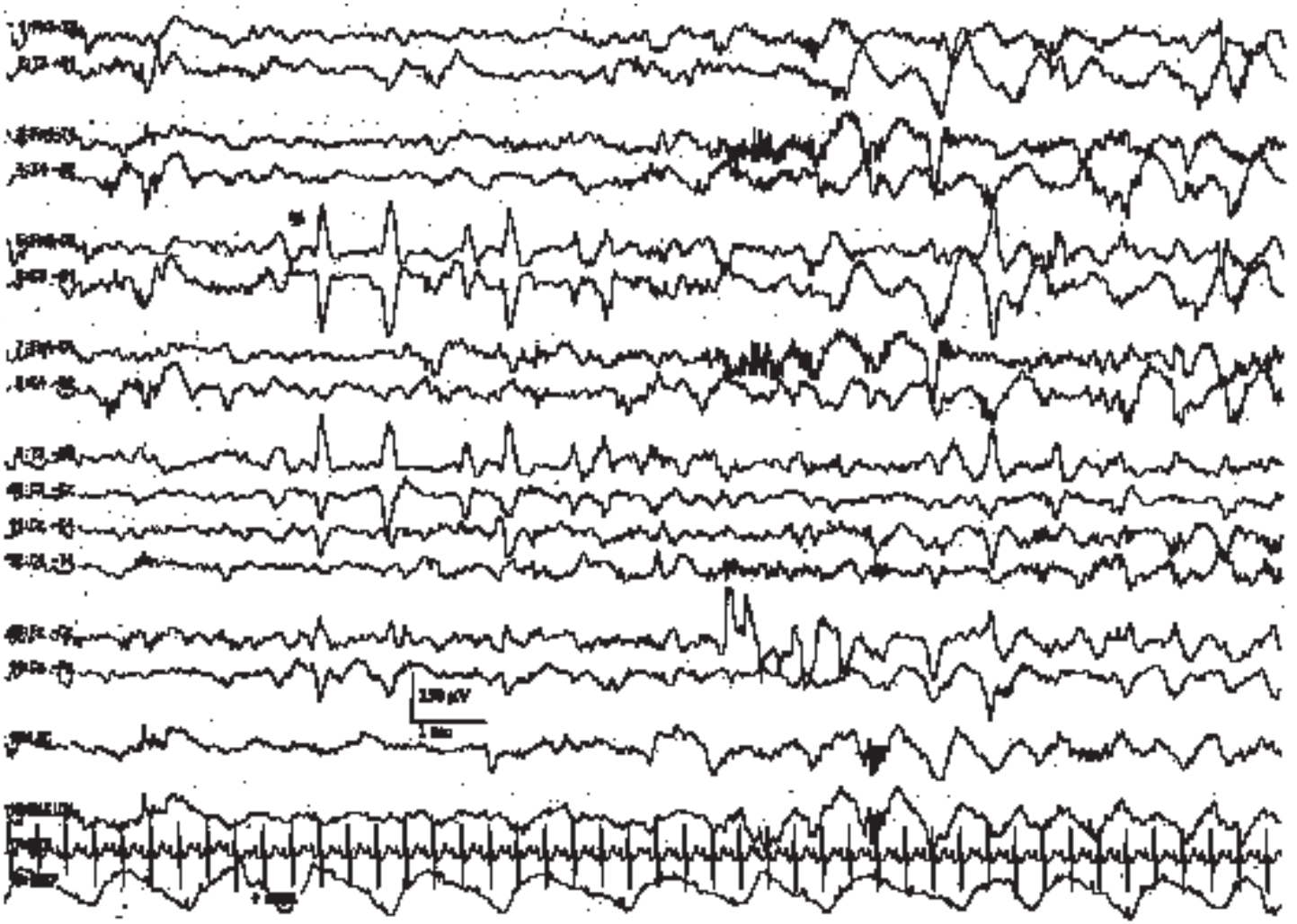


FIG. 6.50. Positive rolandic sharp waves in an infant 34 weeks of conceptional age with left-sided grade IV intraventricular hemorrhage. Repetitive positive rolandic sharp waves are seen at C3 (*arrow*).

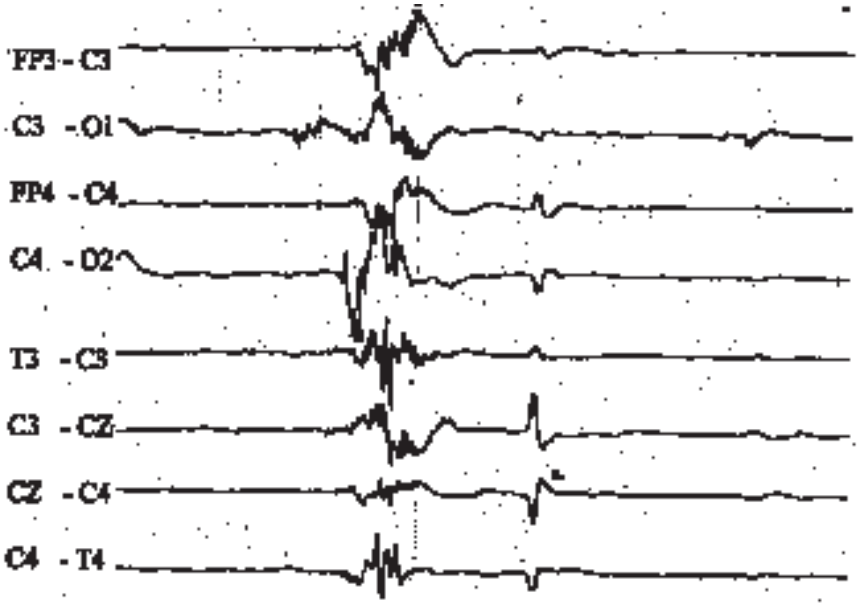


FIG. 6.51. Positive vertex sharp waves in an infant 29 weeks of conceptional age with right-sided grade III intraventricular hemorrhage. Positive vertex sharp waves are seen at Cz (*arrows*). In this case, a recording montage that included Cz was necessary to record these abnormal transients.

temporal regions (positive temporal sharp waves [PTS]) (Fig. 6.52). These pathological waveforms are not indicative of a "lowered seizure threshold" but rather are electrographic markers of parenchymal brain injuries, especially in the deep cerebral white matter, and can be seen in a variety of conditions, including periventricular leukomalacia, IVH, hydrocephalus, meningitis, inborn errors of metabolism, and HIE. The usual locations of pathological positive sharp waves in the premature infant are the midline vertex (Cz) and rolandic (C3 and C4) regions. PVSs and PRSs occur singly or in brief runs with moderate to high voltages (50 to 250 μV) and sometimes are comingled with beta activity.

The clinical significance of identifying PRSs and PVSs in premature infants has been investigated by several authors. Clancy et al. (24) investigated 44 infants with IVH verified by computed tomography or autopsy. PRSs were present in 13 infants with IVH and in 22 of the 30 EEGs. However, PRSs were present in only one premature infant without IVH. Clancy et al. concluded that PRSs have low sensitivity but high specificity for destructive IVH. Among infants with larger hemorrhages (grades 3 and 4), there was a higher incidence (69.2%) of PRSs than among infants with lower grade hemorrhages (31.8%). PRSs and PVSs were most commonly observed between the fifth and eighth postnatal day of life and gradually disappeared by 3 or 4 weeks of age. It is difficult to ascertain the prognostic significance of these patterns per se, because they are often observed in the context of substantially abnormal EEG backgrounds, which themselves forecast adverse outcomes. However, they may be best considered electrographic signs of underlying structural brain abnormalities.

PTSs (see Fig. 6.52) in full-term infants are maximally expressed in the midtemporal regions (T3 and T4) (15,28). They have received less attention than PRSs and PVSs but share similar morphological features and also appear to be linked to structural brain lesions, including periventricular leukomalacia, intracerebral hemorrhages, and infarctions. In the study of Chung and Clancy (15), more than 1,000 neonatal EEGs were reviewed for the presence of PTSs. Forty-six EEGs from 31 full-term infants were found to have "excessive" PTSs, "excessive" being defined as greater than one PTS per minute during the low-voltage, continuous portions of the tracing. EEG backgrounds were normal in nine records and abnormal in the others. In 25 of the 31 infants, a neuroimaging study or an autopsy was performed; 16 (64%) of the 25 patients were found to have focal or diffuse structural lesions, the most common of which were infarction and hemorrhage. In patients with focal lesions, the side of the lesion correlated with the laterality of the PTS. PTSs appeared within 2 to 3 days of the acute illness and disappeared within 4 to 5 weeks. Other studies (7,45,68) have also found PTSs to be correlated with hypoxia-ischemia or structural brain pathological processes. Some authors, however, have questioned the significance of isolated PTS in the absence of other EEG background abnormalities (56). There is agreement, however, that PTS are not specifically epileptiform and are not directly associated with neonatal seizures.

Little is known about the significance of PTSs in the premature infant. PTSs of low to moderate amplitude have been noted in the EEGs of healthy premature infants, with a frequency of 15% at 33 to 34 weeks of conceptional age, decreasing to 0.75% by 39 to 40 weeks of conceptional age (80). The morphological features and amplitudes of these benign PTSs differed from those of the pathological PTSs noted in full-term infants (see Fig. 6.52).

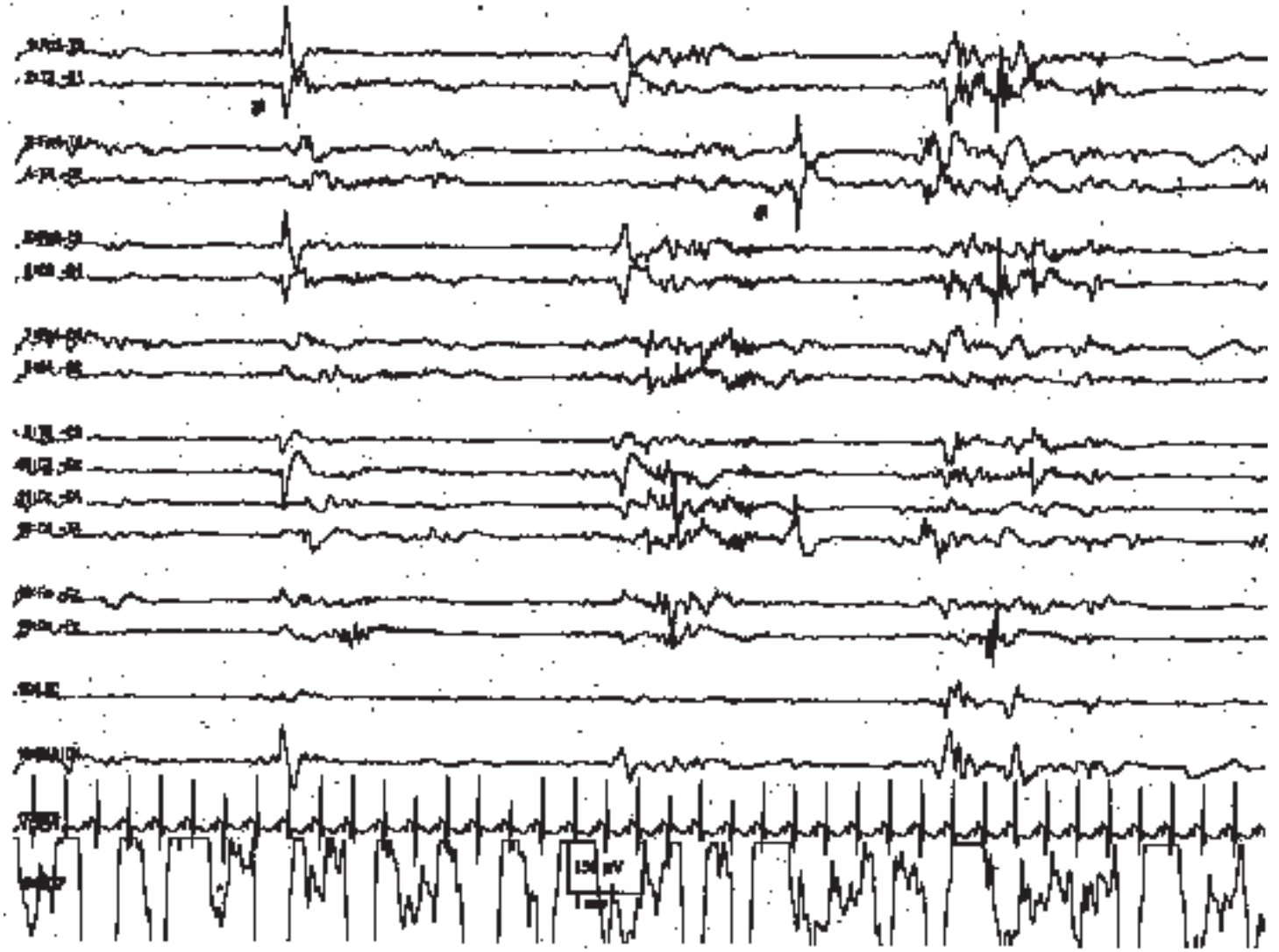


FIG. 6.52. Positive temporal sharp waves in an infant 40 weeks of conceptional age with hypoxic-ischemic encephalopathy and seizures. Left- and right-sided positive temporal sharp waves (*arrows*) are present.

ELECTROGRAPHIC NEONATAL SEIZURES AND CLINICAL CORRELATIONS

It is a challenge for all involved in the care of neonates to distinguish epilepsy-based neonatal seizures from the wide array of nonepileptic paroxysmal behaviors that may occur in healthy or sick infants. The essential role of video-EEG monitoring for accurate diagnosis of suspected neonatal seizures was established by Mizrahi and Kellaway (62), who analyzed video-EEGs from 349 neonates between the conceptional ages of 28 and 44 weeks in whom there was a clinical suspicion of seizures. A total of 415 paroxysmal clinical events were found in 71 patients, but only 119 (29%) of these events in 23 patients had a close temporal association with an ictal EEG discharge; another 11 patients had occult seizures, which are electrographic seizures without conspicuous clinical signs. Other studies have found significantly higher numbers of neonates with occult seizures (71,99). For example, Scher et al. (81) found that 92 (2.3%) of 4,020 neonates admitted to an intensive care nursery over a 4-year period had an electrographic neonatal seizure (ENS), but clinical signs accompanied these seizures in only 28 (45%) of 62 preterm infants and 16 (53%) of 30 full-term infants.

The hallmark of an ENS is the sudden appearance of a repetitive discharge event consisting of a definite beginning, middle, and end. ENS evolve in frequency, morphological appearance, and amplitude (Fig. 6.53) (19,20,48,99,100). An interpretative pitfall for the electroencephalographer is to distinguish ENS from rhythmic extracerebral artifacts, which are typically monomorphic and do not evolve in frequency, morphological appearance, or amplitude. The characteristics of ENS can be described in terms similar to those used for pediatric and adult electrographic seizures: location, duration, morphological appearance, and amplitude.

Location. The overwhelming majority of ENSs are focal in onset. Generalized, bilateral, synchronous spike and slow-wave discharges have only rarely been described. An ENS may be recorded from any scalp region, but the central and temporal regions are the most common sites of origin. Repetitive ENSs originating from a single scalp region are termed unifocal, whereas recurrent ENSs arising from multiple scalp regions are termed multifocal. Recurrent ENSs arising from a single scalp region should raise the suspicion of a focal or lateralized structural lesion such as an infarction from an embolism (21), but not all unifocal ENSs are accompanied by localized abnormalities on neuroimaging studies. Both unifocal and multifocal ENSs may propagate to adjacent or distant scalp locations (see Fig. 6.53). Simultaneous and independent ENSs may arise from multiple scalp regions (Fig. 6.54).

Duration. A minimum ictal duration of 10 seconds is conventionally (and perhaps arbitrarily) required for the designation of ENS in most studies. The average duration of an ENS is brief. In one study of 487 ENSs (20), 230 (47%) lasted less than 1 minute, and 90 (18%) lasted between 1 and 2 minutes; the finding of a mean duration of 2.25 minutes in this study was influenced by rare prolonged seizures that lasted up to 46 minutes. Discharges lasting less than 10 seconds and showing typical evolution in frequency, morphological appearance, or amplitude have been termed brief ictal rhythmic discharges (BIRDs) (85) and are of unclear significance. BIRDs (Fig. 6.55) clearly suggest a lower seizure threshold and may have the same significance as the longer duration ENS. It is uncommon to encounter a single electrographic seizure in most routine ictal recordings. Instead, multiple ENSs are usually encountered (Fig. 6.56). The precise difference between multiple ENSs and status epilepticus in the neonate is unknown. It is difficult to apply the traditional definitions of status epilepticus (continuous seizure activity for 30 minutes or recurrent seizures without full recovery of consciousness) to neonates. An alternative definition of neonatal status epilepticus used in some studies is (a) total seizure duration exceeding 30 minutes or (b) the sum of the duration of individual seizures exceeding 50% of the tracing (72). According to these criteria, status epilepticus was present in 22 (27%) of 81 neonates with EEG-proven seizures (72).

Morphological Appearance. ENSs are characterized by a rich variety of ictal morphological appearances, both between patients and in a given individual. All frequencies (delta, theta, alpha, and beta) are represented (Figs. 6.57 and 6.58). Ictal waveforms range from simple sinusoidal patterns to complex, bizarre ictal patterns. Evolution of morphological appearance within an ENS is helpful in distinguishing ENS from artifact.

Amplitude. Just as ENSs display evolution of waveform morphological appearance, they also typically evolve in amplitude. ENSs commonly first appear at relatively low amplitudes, which gradually increase as the seizure evolves (Fig. 6.59).

It is challenging to design a clinically useful approach for the use of EEG in the high-risk neonate. One strategy is to limit the use of serial tracings to tracings with clinically suspected seizures. This approach risks the underdiagnosis of ENS, in view of the high frequency of occult seizures in this age group. Another strategy, outlined by Laroia et al. (47), is to use the initial EEG background to decide which high-risk infants would benefit from subsequent prolonged monitoring. In the study validating that approach, 51 infants with risk factors for seizures (such as HIE or meningitis) underwent a 30- to 60-minute screening EEG, followed by continu-

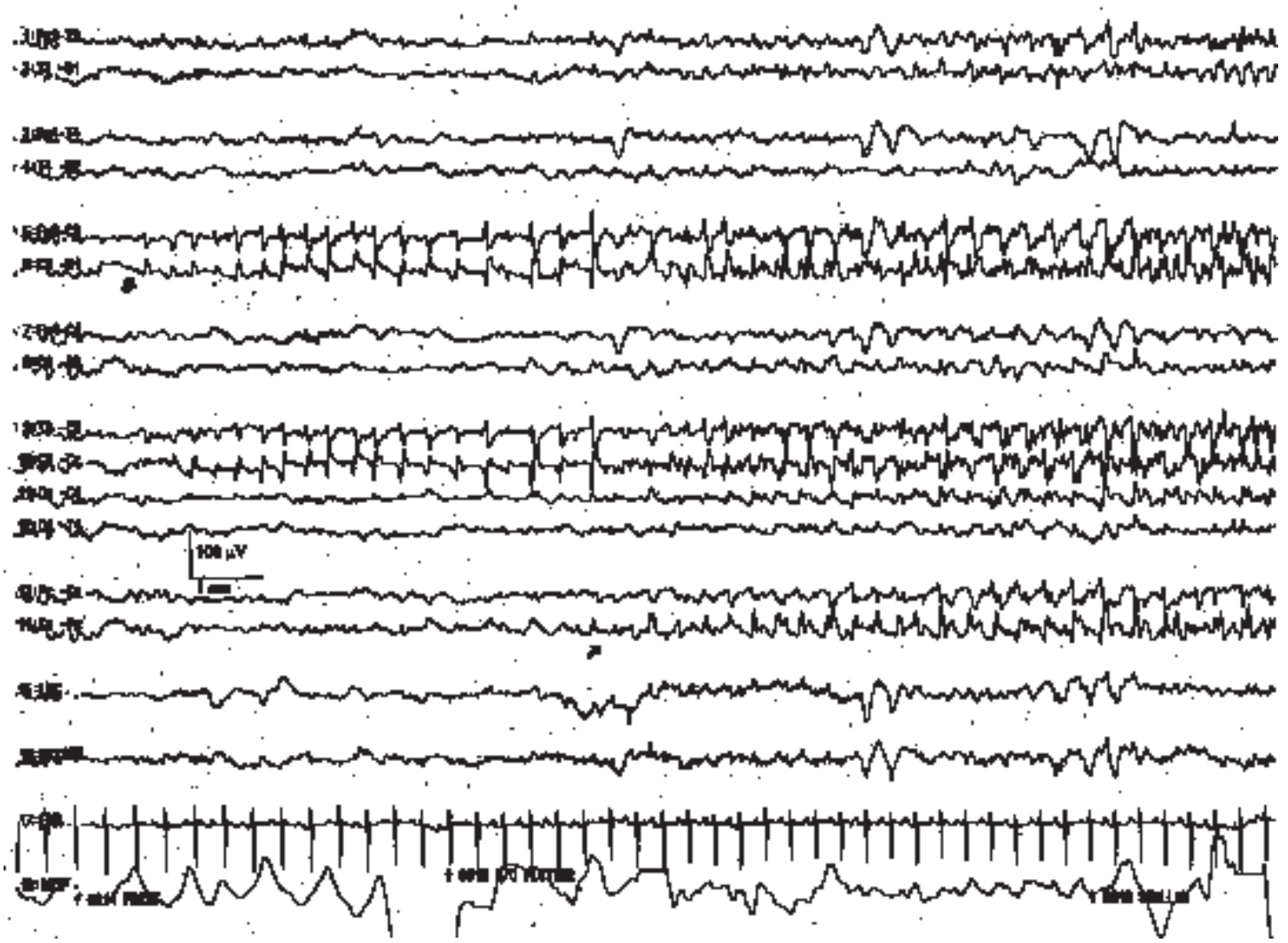


FIG. 6.53. Ictal onset and propagation in an infant 40 weeks of conceptional age with hypoxic-ischemic encephalopathy and seizures. Ictal onset is seen over the left central region (*large arrow*), with subsequent propagation to the central vertex region (*small arrow*). Eventually, ictal activity is also seen in the left temporal region.

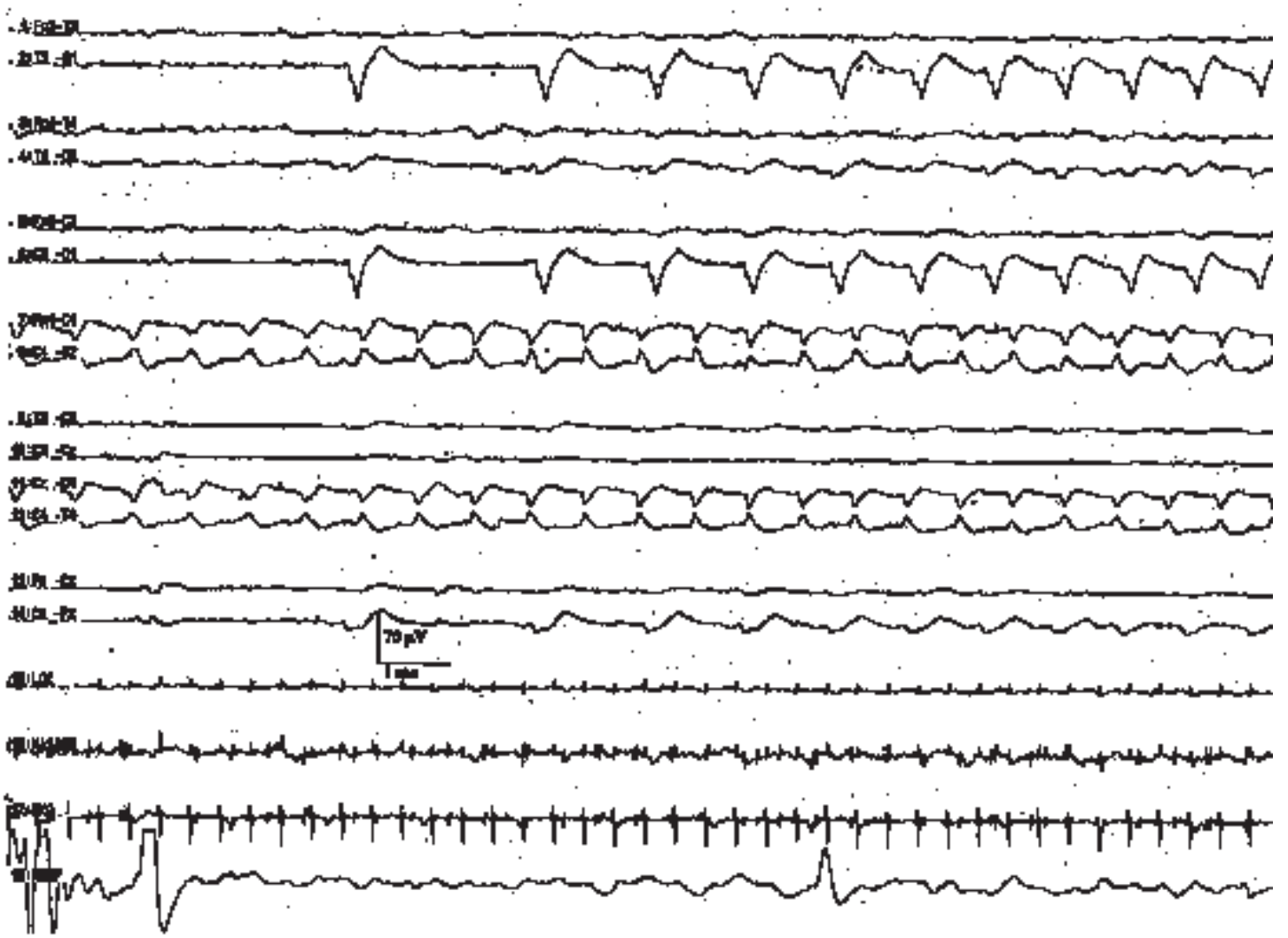


FIG. 6.54. Simultaneous, independent seizures in an infant 37 weeks of conceptional age with hypoxic-ischemic encephalopathy and seizures. Independent seizures are present simultaneously at C4 and O1.

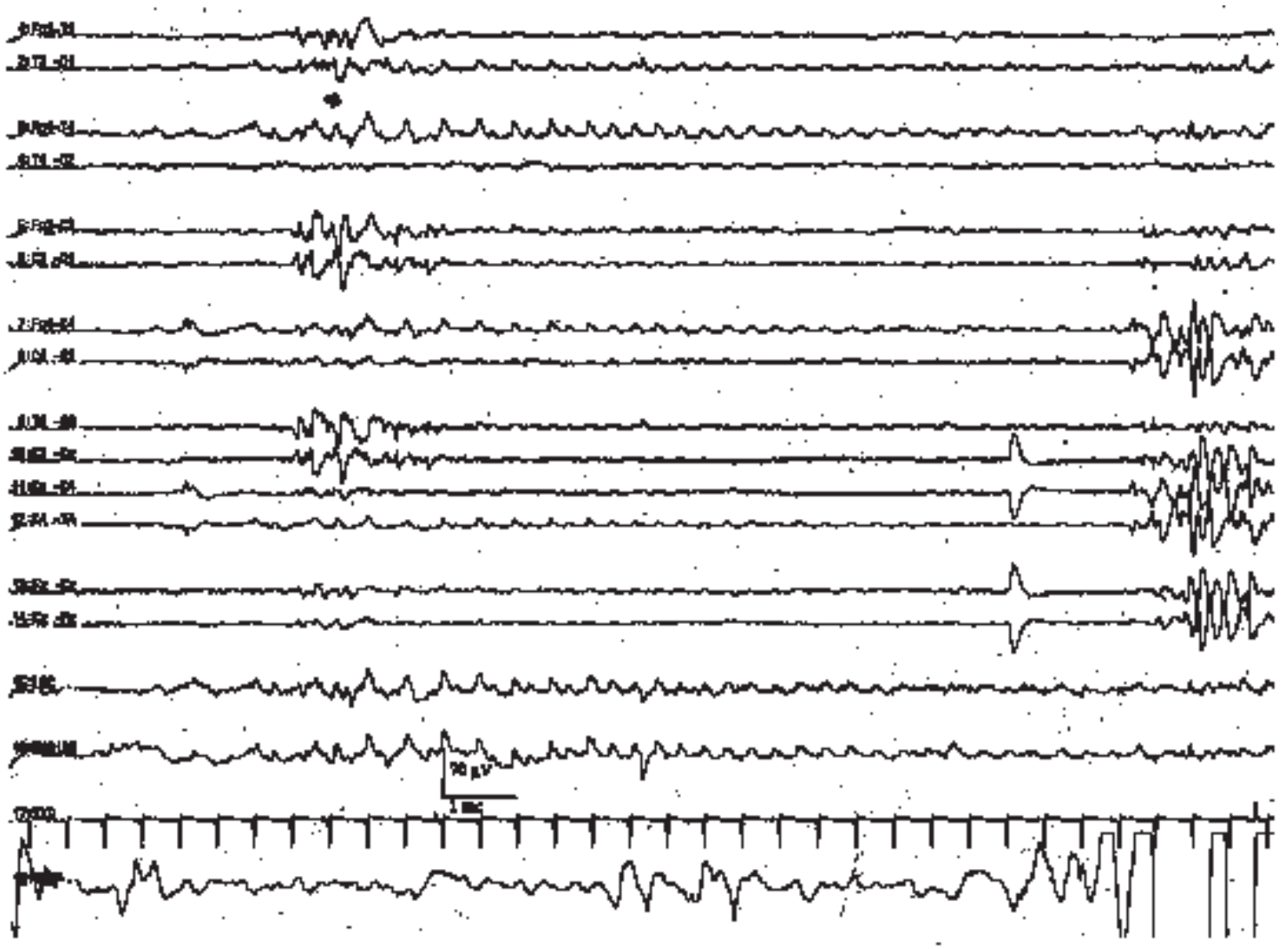


FIG. 6.55. Brief ictal rhythmic discharge (BIRD) in an infant 42 weeks of conceptional age with double-outlet right ventricle and a history of cardiac arrest. A BIRD is present at Fp4 (*arrow*) and T4. The evolution in morphological appearance and amplitude and the presence of a physiological field distinguishes this BIRD from artifact.

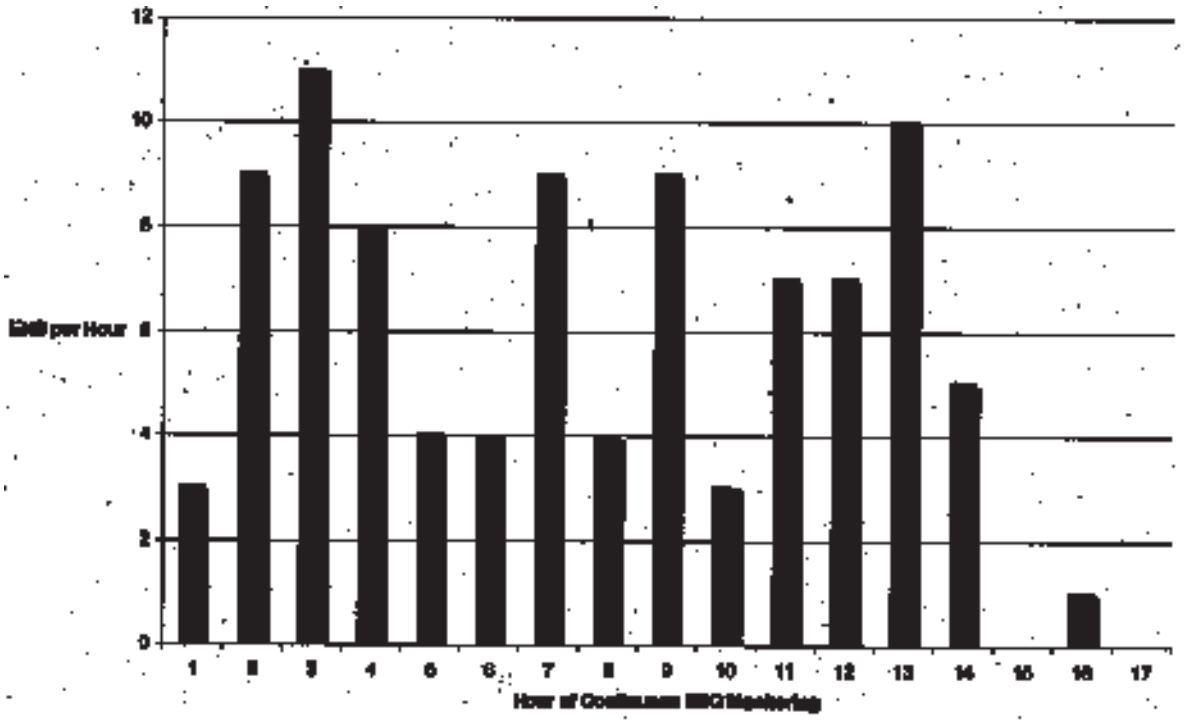


FIG. 6.56. Continuous video-electroencephalographic monitoring of an infant 40 weeks of conceptional age with birth trauma revealed numerous electrographic seizures each hour until the infant was treated vigorously with thiopental. Many acutely ill neonates experience multiple seizures.

ous EEG monitoring for 18 to 24 hours. The EEG background of the initial tracing was classified as normal, immature for age, mildly abnormal, moderately abnormal, or severely abnormal. Only 1 (4.2%) of 24 infants with normal or immature EEG backgrounds had subsequent ENSs. However, 22 (81%) of 27 infants with abnormal EEG backgrounds had ENSs. Thus, a normal or immature initial EEG background predicted the absence of seizures in the subsequent 18 to 24 hours with a sensitivity of 96% and a specificity of 81% (Table 6.3).

A developing strategy is the use of automated, computer-based ENS detection algorithms. Such systems are highly sensitive when used to detect seizures in older children and adults (46) but are more challenging to design for use in neonates because of the different ictal waveform frequencies and characteristics. Brief, low-amplitude ENS are especially difficult to detect. Nonetheless, computer-aided detection systems with sensitivities of 71% to 84% have been reported (51,76).

The impact of ENS per se on subsequent neurological outcome is difficult to determine. Outcome is heavily dependent on the underlying cause of the seizures and the degree of background abnormality. Those with benign neonatal seizures fare well (58,78), whereas infants whose seizures are provoked by acute illness face a much higher risk of permanent neurological handicap. In general, neonates with seizures superimposed on a normal EEG background have lower risks of adverse outcomes, whereas those with ENS and a moderately or severely abnormal background have worse outcomes (83). In their classic study of 137 full-term neonates with *clinically diagnosed seizures,* Rose and Lombroso (75) found that 67 (78%) of 85 infants with normal backgrounds or a unifocal abnormality on initial EEG had normal outcomes, whereas only 4 (8%) of 52 patients with multifocal abnormalities and low-amplitude or periodic backgrounds had normal outcomes. In a later study, Rowe et al. (77) examined outcome after clinically diagnosed seizures in 74 preterm and full-term infants. Normal or mildly

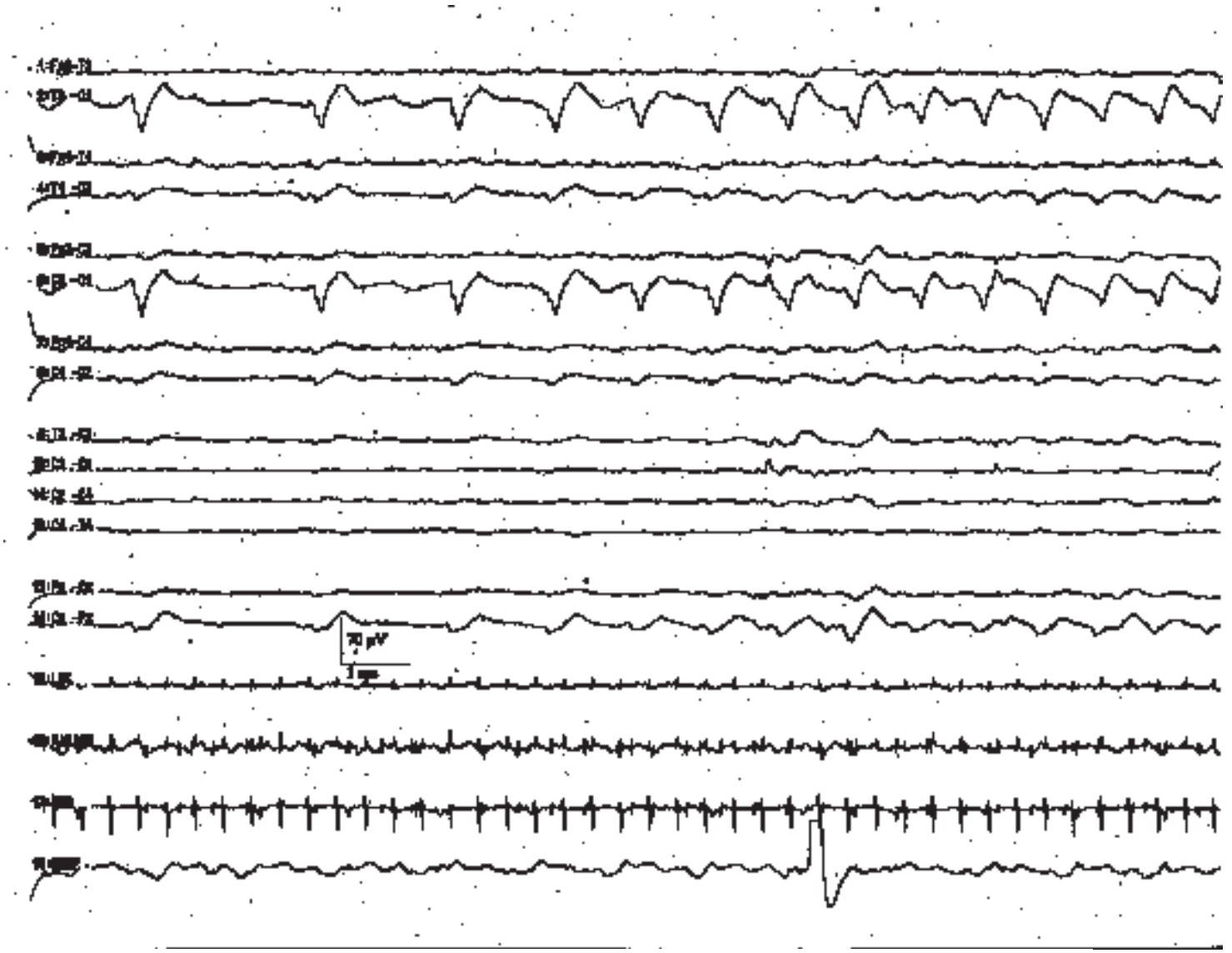


FIG. 6.57. Delta frequency seizure in an infant 37 weeks of conceptional age with hypoxic-ischemic encephalopathy and seizures. A delta frequency seizure is seen to evolve from O1.

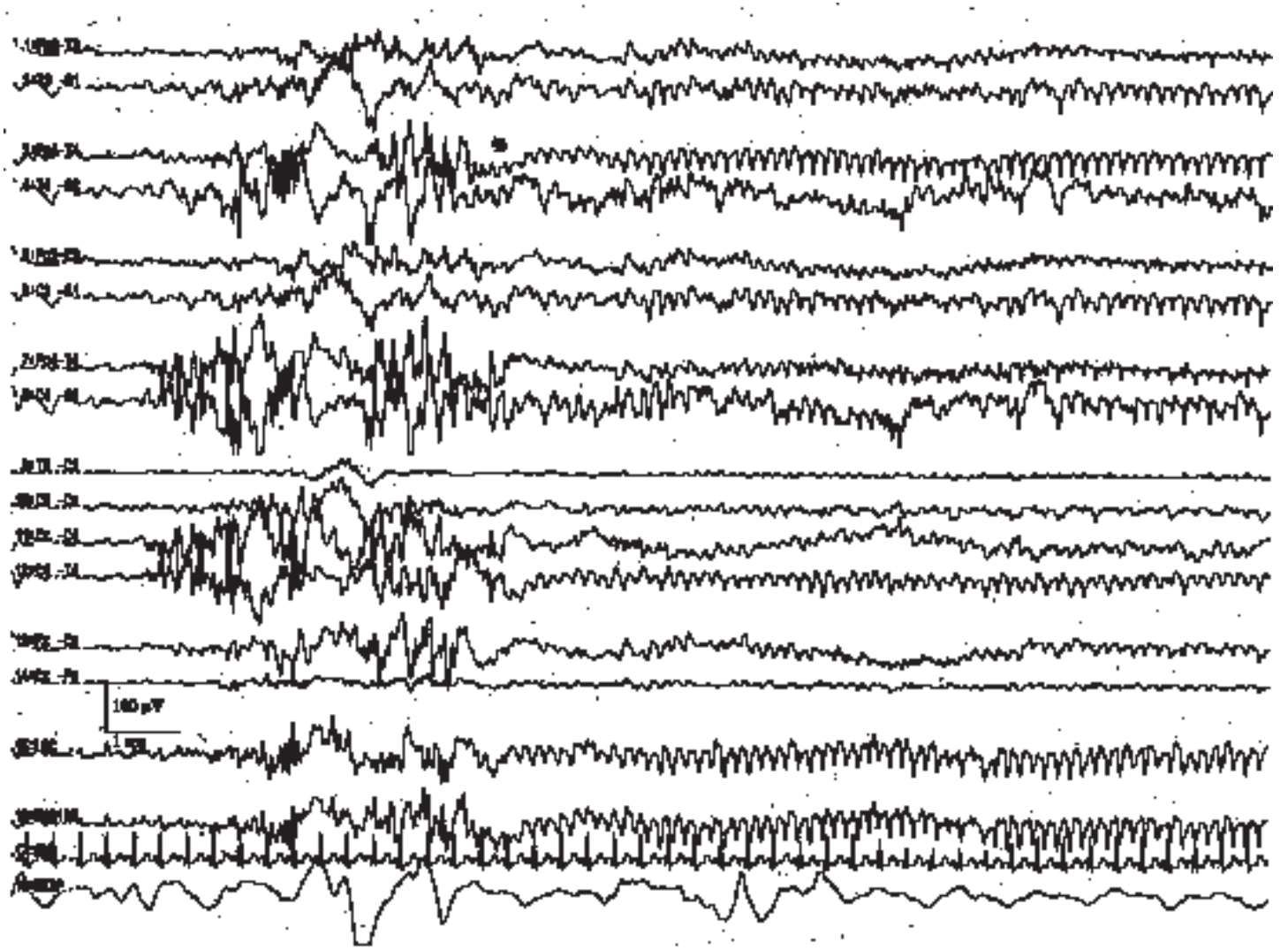


FIG. 6.58. Theta frequency seizure in an infant 36 weeks of conceptional age who had recently suffered cardiac arrest. After a burst of cerebral activity, an ictal discharge with a frequency of 5 Hz begins over the right frontal region (*arrow*).

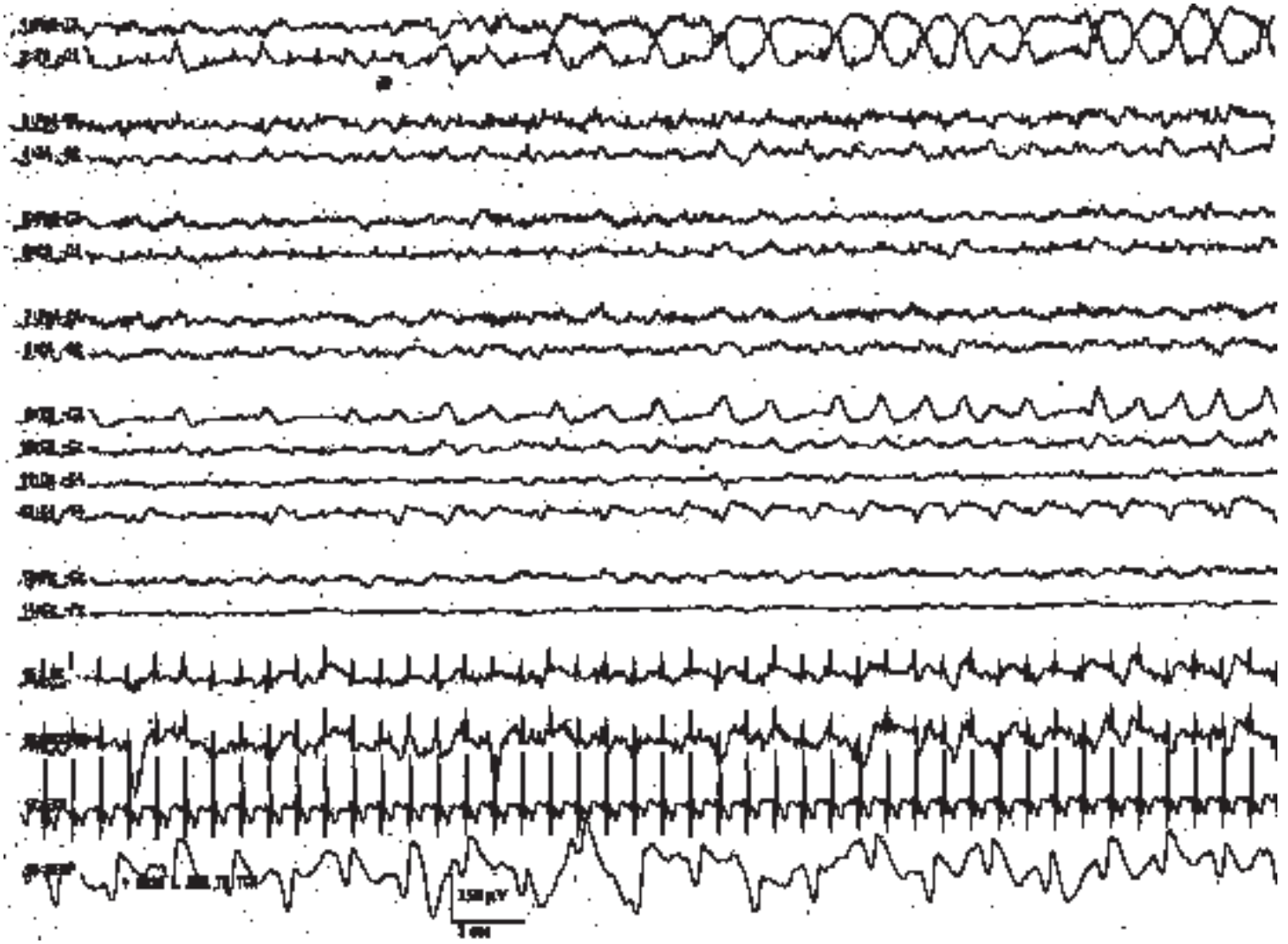


FIG. 6.59. Amplitude evolution of an electrographic seizure in an infant 40 weeks of conceptional age with respiratory syncytial virus pneumonia. A seizure is evolving in amplitude at T3 (*arrow*).

TABLE 6.3. *Association of electroencephalographic (EEG) background and electrographic neonatal seizures*

	Normal or immature EEG background	Abnormal EEG background
No electrographic seizures	23	5
Electrographic seizures	1	22

Adapted from Laroia N, Guillet R, Burchfiel J, et al. EEG background as predictor of electrographic seizures in high-risk neonates. *Epilepsia* 1998;39: 545–551.

abnormal outcomes were found in 22 (85%) of 26 infants with normal EEG backgrounds, in 5 (45%) of 11 infants with moderately abnormal backgrounds, and in 1 (2.7%) of 37 infants with severely abnormal backgrounds. In two other studies, researchers examined outcome after *EEG-confirmed* neonatal seizures. Scher et al. (81) reported that 56 (61%) of 92 neonates with EEG-confirmed seizures survived. Normal outcome was documented in 9 (25%) of 36 preterm infants and in 12 (60%) of 20 full-term infants. Legido et al. (49) monitored outcomes in 40 neonates with EEG-confirmed seizures. Twenty-seven (68%) survived, but outcome was unfavorable in 70% of those survivors. Factors associated with unfavorable outcome included etiology (such as asphyxia, meningitis, or cerebral dysgenesis), moderately or severely abnormal EEG background, and higher seizure frequency.

AN ORGANIZED APPROACH TO VISUAL ANALYSIS OF THE NEONATAL ELECTROENCEPHALOGRAM AND COMMON INTERPRETATION PITFALLS

This final section intends to serve as a template to review a typical neonatal EEG examination, emphasizing the common high points for interpretation and identifying areas that commonly introduce interpretative difficulties. Before beginning the inspection of the neonatal EEG, several pieces of historical data are needed to prepare a mental picture of the expected range of anticipated findings by which to judge the actual EEG while it is produced. The two main facts are the *conceptional age* at the time the EEG was recorded and the patient's *biobehavioral state* (awake, transitional, indeterminate sleep, active sleep, and quiet sleep). The accurate clinical assessment of *state* requires ample notes from the recording technologists describing whether the eyes are open or closed, the presence of REMs and large or small body movements. It is also necessary to distinguish artifacts introduced by the handling of the patient by health care providers. Information about medical and neurological status can also help create the proper context in which to interpret the patient's EEG. Infants who are known to have systemic illnesses can be reasonably expected to show at least mild disturbances of the EEG background, which do not necessarily imply fixed and lasting CNS insults. Commonly, the EEG improves or normalizes after the correction of the underlying medical illness. Specifically, conditions such as mild hypoxia or hypercarbia from respiratory disease, congenital heart defects, sepsis, simple metabolic disorders such as hyponatremia, and the administration of CNS-active drugs (for pain, agitation, or sedation) can all introduce mild, transient background abnormalities that have no special prognostic significance. Finally, the condition of the infant's scalp should be known. Increased thickness of the scalp usually attenuates the apparent amplitude, and the EEG may appear underdeveloped or "washed out" in a generalized or localized region. Scalp thickness may be increased from local or generalized swelling caused by a caput succedaneum, cephalohematoma, or the tremendous third spacing of fluid during sepsis, ECMO, or hydrops fetalis. Collectively, these considerations broadly provide the context in which to anticipate the expected background composition and continuity or discontinuity of the record.

In a typical patient, the beginning of the EEG may show a brief period of wakefulness, because the patient has just been stimulated by the technologist with measuring, marking, and rubbing the scalp surface. The patient may then be calmly awake for a brief period before the eyes close and the infant transitions from the awake to a sleeping state. At the onset of sleep in neonates, active sleep usually emerges first, and there is little qualitative change in the background between the awake and the active sleep states. *Continuity* is determined first. In very young premature infants, the background is discontinuous, even when the infant is awake, and it is necessary to count several representative IBIs in seconds to decide whether the discontinuity is excessive. There is a range of counted values with some unusually brief or long IBIs, but the typical IBIs should not exceed the values found in Table 6.1. The tracing is considered excessively discontinuous if the patient's typical IBIs clearly exceed the norms for age. After the continuity of the record is judged, the composition of the tracing is evaluated. What are the patterns, rhythms, and frequencies that constitute the background? Are there specific, named, identifiable normal patterns present, such as monorhythmic occipital delta activity, bursts of rhythmic theta activity in the

occipital or temporal regions, delta brushes in the occipital or centrotemporal regions, and runs of anterior dysrhythmia and *encoches frontales? Symmetry* is judged as an overall impression of the amount, amplitude, and composition of background activity contrasted between homologous areas and both hemispheres. Even major interhemispheric asymmetries that arise just transiently have little significance. A *persistent* difference of at least 50% is usually necessary to declare a background abnormality on the basis of asymmetry alone. More often, significant asymmetries are detected in the company of other background abnormalities such as excessive discontinuity or an abnormal profile of sharp EEG transients.

After a brief portion of active sleep, perhaps 15 to 20 minutes, the undisturbed infant may make another transition to quiet sleep. It is important to continue the study long enough to capture some quiet sleep because in some infants, electrographic abnormalities may be observed only during this specific state. During transitional sleep, the EEG background is indeterminate and does not conform entirely to the characteristics of wakefulness, active sleep, or quiet sleep. Once definite quiet sleep has emerged, it is possible to compare the appearance of the earlier awake/active sleep EEG to that of quiet sleep. In older neonates, there should be easily distinguishable differences between the awake/active sleep and quiet sleep segments of the study. The degree of discontinuity is again judged by counting or estimating the duration of typical IBIs and comparing these with norms. At the end of the study, it is important to vigorously stimulate the patient in quiet sleep to demonstrate that the observed discontinuity is reactive.

Sharp EEG transients are very common in the neonatal EEG. Virtually all healthy infants display the ubiquitous *encoches frontales* admixed with anterior dysrhythmia. In the central and temporal regions, SETs are relatively common, up to 1 per minute in wakefulness or active sleep, appearing as solitary transients that are about equally distributed between the left and right temporal areas and are much rarer in the central areas. In discontinuous quiet sleep, many infants have a sharp or "spikey" quality to the bursts, but this has no known significance. Electrographic seizures should be recognized as a sustained event that evolves in amplitude, frequency, and morphological appearance.

The report of the EEG examination should comment on the appearance of the overall background, whether it is appropriately mature for the stated conceptional age, and the degree of background abnormality and possible prognostic significance, if any. If clinically warranted, a follow-up examination may be suggested to monitor the progress of the infant's encephalopathy and electrocerebral maturation. If the study is technically limited, the examination should be repeated. Abnormalities of the EEG background provide limited insight into the cause of the encephalopathy. This fact can be recognized in the report by statements such as "Such EEG abnormalities are not specific from the viewpoint of etiology." If electrographic seizures are present, it is helpful to the clinician to note whether any or all of the ENSs are accompanied by distinctive clinical signs so that the bedside observer might have an indication of how accurate visual quantification may be for a specific patient. In some infants, virtually none of the ENSs are accompanied by clinical seizures, and the clinician should be alerted to that information. In patients with abnormal backgrounds who display a clear excess of SETs, it can be stated that such patterns raise the concern for a lowered seizure threshold, even if no actual clinical or electrographic seizure has been detected. Positive sharp transients in the temporal, central, or midline vertex regions are not associated with seizures but rather with underlying structural abnormalities such as periventricular leukomalacia, stroke, or hemorrhage. Naturally, the presence of structural CNS abnormalities is best determined by specific neuroimaging techniques such as ultrasonography, computed tomography, or magnetic resonance imaging.

There are several common pitfalls of the neonatal EEG examination: (a). Neonatal EEG examinations are not commonly performed and interpreted in some laboratories. Consequently, each time a patient is examined, the process seems uncertain and unfamiliar. One solution is to maintain a small "reference library" of normal EEGs at several conceptional ages that can be reviewed as needed to compare with those of the patient undergoing an examination. These serve as quick reminders of the normal EEG appearance at a variety of developmental ages. (b) Inadequate use of the polygraphic aspects of neonatal EEG makes interpretation very difficult. The neonatal EEG is a specialized kind of sleep study that can be understood only when the patient's state and behaviors are clearly known. It is critical that the patient be stimulated adequately during the examination to produce a state change and electrographic reactivity (not just EMG artifact from nonspecific muscle activity). (c) Serial EEG examinations, including those conducted during the peak of the infant's medical or neurological illness, are necessary to capture the electrographic findings of greatest prognostic significance. (d) It is very tempting to "overcall" physiological sharp EEG transients as *pathological* unless the interpreter is comfortable with the relatively broad range of normal sharp EEG transients that can be encountered in the healthy neonate. On the other hand, electrode "pops" can remarkably resemble some pathological positive waves. Genuine PTSs, PRSs, and PVSs may be exquisitely confined to the T3 and T4, C3 and C4, or Cz electrodes

without field spread to adjacent electrodes. (e) Rhythmic EEG artifacts from limb tremors, hiccups, ECMO pump artifact, and pulse can, in the occasional patient, create a very convincing recording pattern that at least superficially resembles an electrographic seizure. The diagnosis of neonatal seizures mandates an immediate and thorough diagnostic evaluation by the clinician, often including lumbar puncture, transportation outside the safer confines of the nursery to a brain scanner, and the administration of medications. These steps may be unnecessary if the seizure was actually an innocent electrographic artifact!

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Chapter 7

Benign Electroencephalographic Variants and Patterns of Uncertain Clinical Significance[1]

Barbara F. Westmoreland

Rhythmic Patterns
- Rhythmic Temporal Theta Bursts of Drowsiness (Psychomotor Variant Pattern)
- Alpha Variant
- Subclinical Rhythmic Electrographic (Theta) Discharge in Adults
- Midline Theta Rhythm
- Frontal Arousal Rhythm

Benign Patterns with an Epileptiform Morphology
- Fourteen- and Six-Hertz Positive Bursts
- Small Sharp Spikes (SSS)
- Six-Hertz Spike-and-Wave Bursts ("Phantom Spike and Wave")
- Wicket Spikes
- Breach Rhythm

Conclusion

References

There are several benign variants of electroencephalographic (EEG) activity, including variations of normal rhythms, rhythmic patterns, and patterns with an "epileptiform" morphology, which the electroencephalographer should recognize to avoid overinterpreting them with regard to their significance.

Some patterns represent a superimposition of background frequencies producing activity that may simulate "epileptiform-like" discharges, and one must consider the context of the background activity from which the waveform is arising (20). Other EEG patterns have an epileptiform appearance but are non-epileptogenic in that they have no established association with clinical seizures. Although there is controversy and difference of opinion regarding some of these patterns, most of the nonepileptogenic epileptiform patterns described in this chapter are now considered to be normal variants or patterns of uncertain clinical significance (20,25,32,33). These can be subdivided into rhythmic patterns and patterns with an epileptiform morphology.

RHYTHMIC PATTERNS

Rhythmic patterns consist of rhythmic activity that may be in the theta, alpha, or beta frequency ranges. They may also consist of a mixture of two or more frequencies or be a reflection of harmonic frequencies. The rhythmic patterns consist of rhythmic temporal theta bursts of drowsiness (RTTD), the alpha variant patterns, the midline theta rhythm, the frontal arousal rhythm (FAR), and subclinical rhythmic electrographic discharge of adults (SREDA).

Rhythmic Temporal Theta Bursts of Drowsiness (Psychomotor Variant Pattern)

The term *psychomotor variant pattern* was originally used (9,10) because of the occurrence of this pattern over the temporal regions and because of its rhythmic nature, which seemed to resemble a "psychomotor" or temporal lobe seizure discharge. It has also been called "rhythmic midtemporal discharges" (RMTDs) (17). The preferred term is now *rhythmic temporal theta bursts of drowsiness* (1). The temporal theta pattern of drowsiness (4,6,9,10,17,22,32,39) is characterized by bursts or serial trains of rhythmic theta waves ranging from 5 to 7 Hz with a flat-topped, sharp-contoured, or notched appearance. The notching occurs as a result of either (a) a superimposition of faster frequencies or (b) harmonics of the resting background frequency (Fig. 7.1). The bursts occur predominantly over the temporal regions and are usually maximal in the midtemporal electrodes. There can be some spread to the parasagittal regions. The temporal theta bursts occur bilaterally or independently over the two hemispheres, or they show a shifting emphasis from side to side. The trains usually begin and end with a gradual increase and decrease in amplitude. The pattern differs from a true seizure discharge in that it is usually a monomorphic or monorhythmic pattern that does not evolve into other frequencies or waveforms. It occurs predominantly during relaxed wakefulness and drowsiness and is seen mainly in adolescents and adults. Gibbs et al. (10) reported an incidence of approximately 0.5%, whereas Maulsby (25) found the pattern in 2% of selected normal adults. Although some authors have related this pattern to various symptoms, it is now considered a non-specific finding in the EEG that has no significance with regard to seizures or other neurological symptoms (20).

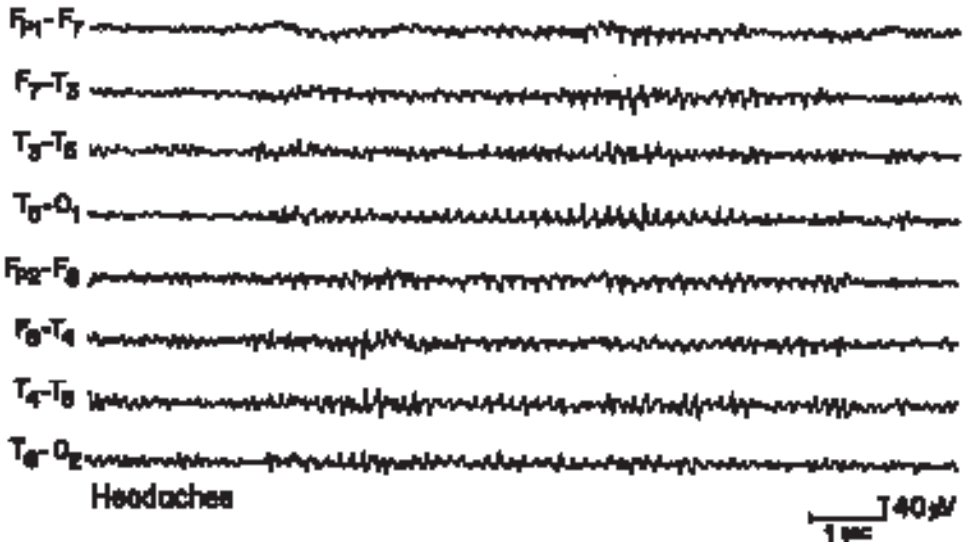

FIG. 7.1. Rhythmic temporal theta bursts of drowsiness in a 40-year-old woman. (From Westmoreland BF. EEG in the evaluation of headaches. In: Klass DW, Daly DD, eds. *Current practice of clinical electroencephalography*. New York: Raven Press, 1979:381–394, with permission of Lippincott Williams & Wilkins.)

Alpha Variant

Alpha variant patterns consist of activity over the posterior head regions that have a harmonic relationship to the alpha rhythm and show similar reactivity and distribution (11).

Slow Alpha Variant Pattern

The slow alpha variant pattern is a subharmonic of the alpha rhythm that has a frequency about half that of the alpha rhythm, usually in the range of 4 to 5 Hz. The waveforms usually have a sinusoidal or notched appearance and can alternate or be admixed with the regular alpha activity (1,11) (Fig. 7.2). The alpha variant pattern is seen mainly in adults during relaxed wakefulness and is considered a physiological variant of the alpha rhythm. The slow alpha variant sometimes has a notched appearance and may resemble the RTTD, except that it occurs over the posterior head regions.

Fast Alpha Variant

The fast alpha variant pattern has a frequency that is usually twice that of the resting alpha rhythm and ranges from 16 to 20 Hz, with a voltage of 20–40 μV; it alternates or is admixed with the alpha rhythm (1). It arises from the posterior head regions, and its reactivity resembles that of the alpha rhythm.

Subclinical Rhythmic Electrographic (Theta) Discharge in Adults

This uncommon pattern is seen mainly in people older than 50 years (26,28,29,46,48). SREDA may occur at rest or during drowsiness, and occasionally occurs mainly during hyperventilation. The pattern is a distinctive one and consists of mixed-frequency components in the delta and theta frequency ranges that evolve into a rhythmic pattern consisting of sharp-contoured components 5–7 Hz (Figs. 7.3 and 7.4) (30,46,48). SREDA usually occurs in a widespread distribution with maximal amplitude over the parietal–posterior temporal head regions. Usually it is bilateral, but it may occur in a more focal or asymmetric fashion. The duration of the SREDA pattern may range from 20 seconds to a few minutes; however, the average duration is 40–80 seconds. In half the patients, SREDA may have an abrupt onset in which the background activity is suddenly replaced by repetitive monophasic sharp waveforms (Fig. 7.3). In other patients, the discharge begins with a single, high-voltage, monophasic

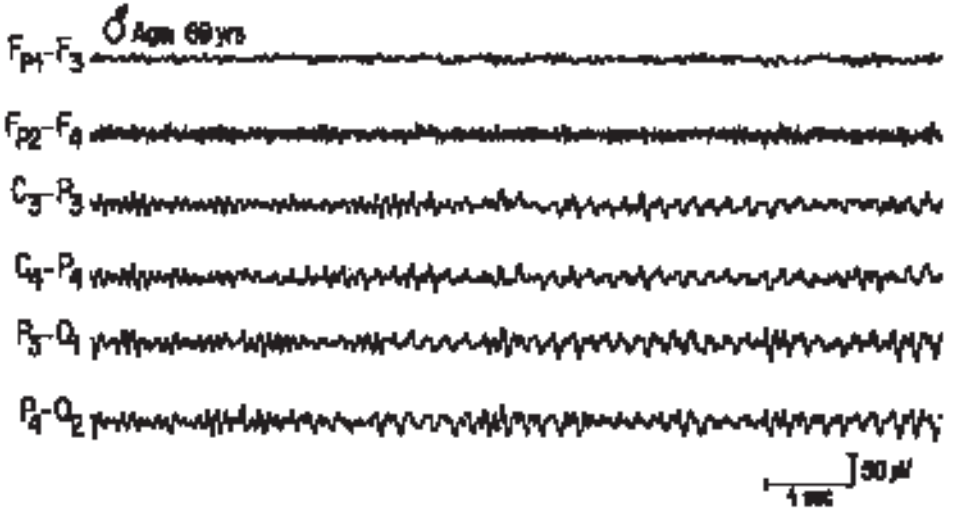

FIG. 7.2. Example of slow alpha variant pattern in a 69-year-old man.

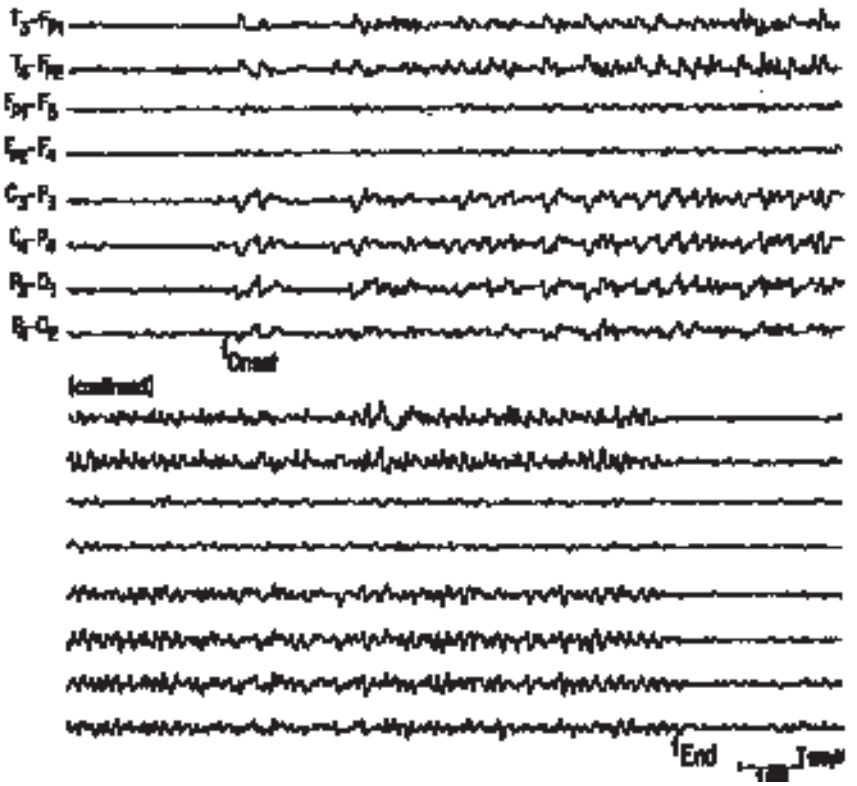

FIG. 7.3. Subclinical rhythmic electrographic discharge (SREDA) in a 52-year-old woman. (From Westmoreland BF. Benign EEG variants and patterns of uncertain clinical significance. In: Daly DD, Pedley TA, eds. *Current practice of clinical electroencephalography*, 2nd ed. New York: Raven Press, 1990:243–252, with permission of Lippincott Williams & Wilkins.)

sharp- or slow-wave component that is followed 1 second or several seconds later by other sharp waves, progressively recurring at shorter intervals and then increasing in frequency to merge into a sustained, rhythmic, sinusoidal pattern of 5–7 Hz (26,46,48) (Figs. 7.4 and 7.5). Although the pattern may resemble a subclinical EEG seizure discharge, it does not have any correlation with clinical seizures. A single-photon emission computed tomographic (SPECT) study was performed on a patient with a focal SREDA pattern involving the right occipitotemporal region and showed no change in bloodflow. The authors concluded that this provided evidence that SREDA was not an "epileptic pattern" (43). SREDA has been seen in patients with diverse clinical complaints. No clinical alteration is associated with the pattern, and the patient does not complain of any subjective symptoms while the pattern is present. Although its mechanism of origin remains uncertain, SREDA seems to represent a benign EEG phenomenon that has little or no diagnostic significance (26,30,46,48).

Midline Theta Rhythm

The midline theta rhythm occurs as a focal rhythm over the midline region and usually is most prominent in the central vertex (Cz) lead (47) (Fig. 7.5). Occasionally, there is some spread to adjacent electrodes. It consists of a rhythmic train of 5–7 Hz activity and usually has a smooth, sinusoidal, arciform, spiky, or mu-like appearance. The midline rhythm is of variable duration and tends to wax and wane. It is present during wakefulness and drowsiness and shows variable reactivity to eye opening, alerting, and limb movement.

The pattern was originally described by Cigánek (2) as "theta discharges in the middle line." Cigánek initially saw this in patients with temporal lobe epilepsy and believed that it occurred predominantly in such patients. Later, Mokrán et al. (27) reviewed a less selected group of patients and found that this rhythm was also present in patients without epilepsy. A more recent review has shown that a midline theta rhythm can occur in a heterogeneous group of patients, and, although its mechanism is uncertain, the midline rhythm appears to represent a nonspecific variant of theta activity (47).

Frontal Arousal Rhythm

FAR, a rhythm that was initially described by White and Tharp (51), occurs in children following arousal from sleep. The pattern consists of trains of 7- to 20-Hz waveforms that occur predominantly over the frontal regions in runs lasting up to 20 seconds (Fig. 7.6). There may be varying harmonics, which give the pattern a notched appearance and a superficial resemblance to a rhythmic discharge pattern. FAR, however, usually disappears once the child is fully awake. Although FAR was initially described in children with minimal cerebral dysfunction (51), it is considered to be more a nonspecific pattern of no clinical significance.

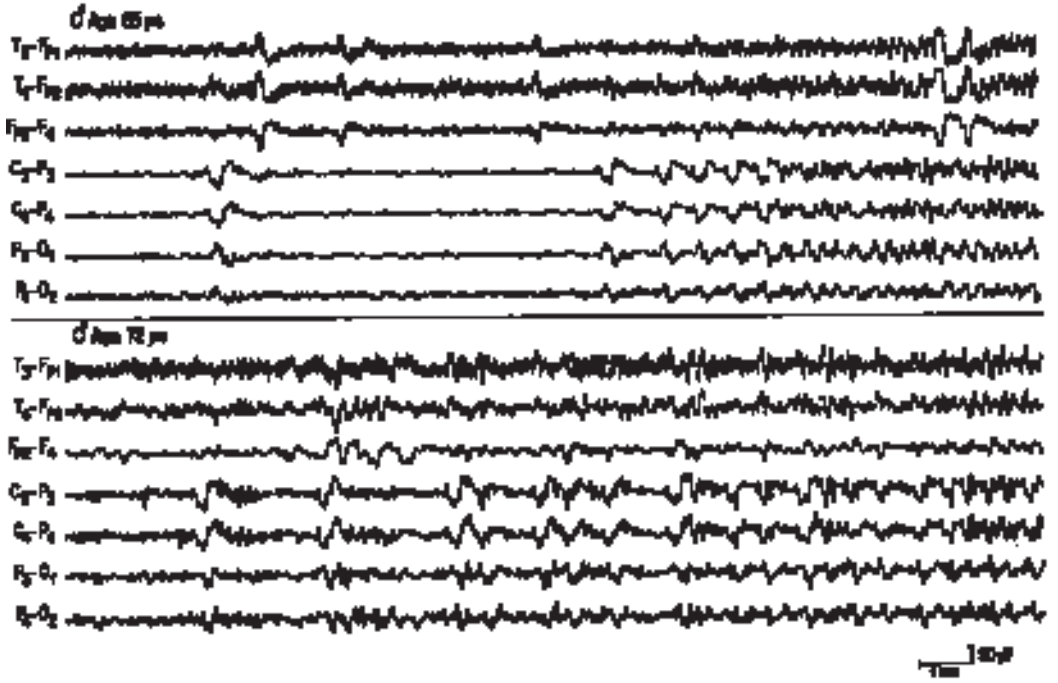

FIG. 7.4. Onset of SREDA in two patients. **Top:** An initial sharp wave complex, followed several seconds later by repetitive sharp waves that merge into a sustained theta rhythm. **Bottom:** Repetitive sharp waves gradually increasing in frequency to a repetitive theta rhythm. (From Westmoreland BF. Benign EEG variants and patterns of uncertain clinical significance. In: Daly DD, Pedley TA, eds. *Current practice of clinical electroencephalography*, 2nd ed. New York: Raven Press, 1990:243–252, with permission of Lippincott Williams & Wilkins.)

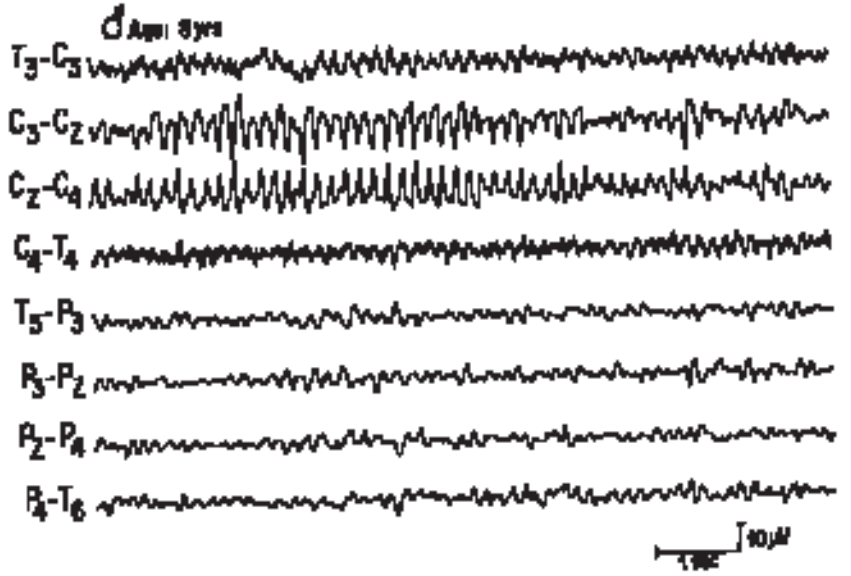

FIG. 7.5. Midline theta rhythm (seen predominantly in the CZ electrode) in an 8-year-old boy. (From Westmoreland BF. Benign EEG variants and patterns of uncertain clinical significance. In: Daly DD, Pedley TA, eds. *Current practice of clinical electroencephalography*, 2nd ed. New York: Raven Press, 1990:243–252, with permission of Lippincott Williams & Wilkins.)

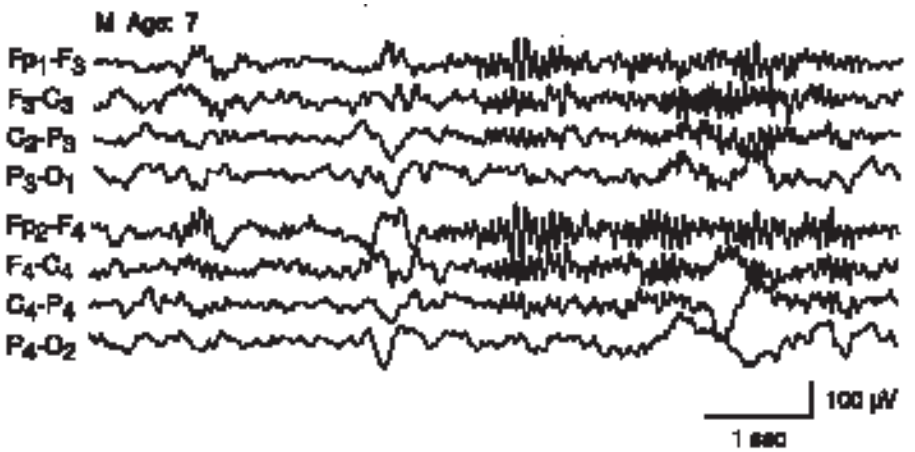

FIG. 7.6. Frontal arousal rhythm in a 7-year-old boy.

BENIGN PATTERNS WITH AN EPILEPTIFORM MORPHOLOGY

These patterns have an epileptiform appearance but are not epileptogenic; that is, they are not associated with seizures. They include 14- and 6-Hz positive bursts, small sharp spikes (SSS), 6-Hz spike-and-wave bursts, wicket waves, and the breach rhythm.

Fourteen- and Six-Hertz Positive Bursts

These bursts were originally called "14- and 6-Hz positive spikes"; the term *ctenoids* (23) had also been used for this phenomenon (1,4,5,7–9, 12,14,18,20,23,25,32–34,37–39,52). The preferred term now is *14- and 6-Hz positive bursts* .

These bursts occur predominantly during drowsiness and light sleep and consist of short trains of arch-shaped waveforms with alternating positive spiky components and a negative, smooth, rounded waveform that resembles a sleep spindle with a sharp positive phase (Fig. 7.7). The bursts occur at a rate of 14 Hz or 6–7 Hz and last from 0.5 to 1 second. Usually, the faster frequency is the more prevalent, but the slower rate can occur either independently or in association with a train of 14-Hz positive bursts. The waveform is best displayed on a long-distance or referential montage to the ear. It usually has maximal amplitude over the posterior temporal region. The bursts can occur asynchronously or independently over the two

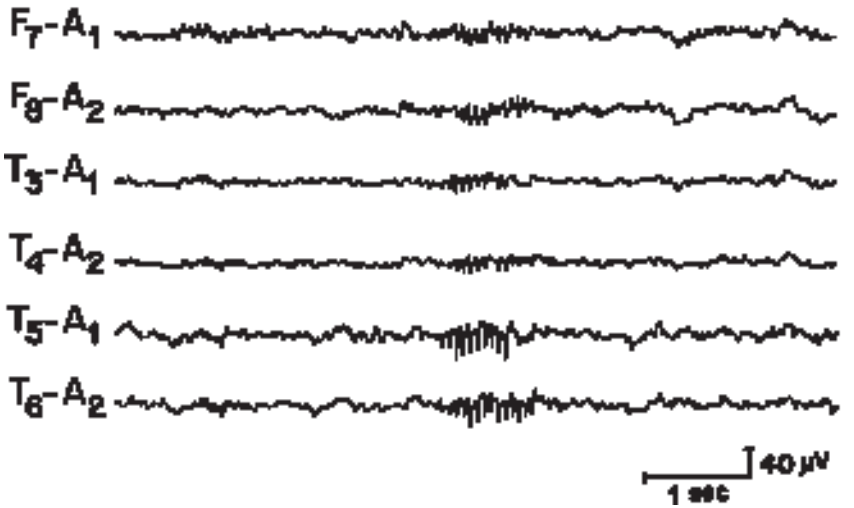

FIG. 7.7. A 14- and 6-Hz positive burst, on a referential montage, in a 29-year-old woman. (From Westmoreland BF. EEG in the evaluation of headaches. In: Klass DW, Daly DD, eds. *Current practice of clinical electroencephalography*. New York: Raven Press, 1979:381–394, with permission of Lippincott Williams & Wilkins.)

sides but may preferentially involve one side; they may also shift from side to side in predominance.

In a normal population, 14- and 6-Hz positive bursts begin to appear in children between 3 and 4 years old, are maximally expressed in the adolescent age group (with a peak at age 13–14 years), and then progressively decrease in incidence with increasing age (20).

In the past, this pattern has been associated with various clinical symptoms, including headaches, dizziness, vertigo, abdominal complaints, emotional instability, rage, violence, and "thalamic" or "hypothalamic" epilepsy. However, 14- and 6-Hz positive bursts occur in normal control populations and in asymptomatic persons. Moreover, depending on the study, these bursts were present in 10%–58% of subjects. Differences in the incidence may be due to the age group studied, the amount of EEG recorded during drowsiness and light sleep, and the montage used (20,32). Most authorities now regard this as a benign variant of no clinical significance.

Small Sharp Spikes (SSS)

"Small sharp spikes" (7,9,16,19–21,25,32–34,36,38,40,45,49,50) is the original name used by Gibbs and Gibbs (7,9). The pattern has also been referred to as "benign epileptiform transients of sleep" (BETS) (50) and "benign sporadic sleep spikes" (BSSS) (20). SSS are seen mainly in adults during drowsiness and light sleep. They are generally of low voltage, usually less than 50 μV; however, they occasionally may have a higher amplitude (Fig. 7.8). SSS are of short duration, usually less than 50 milliseconds. The waveform usually consist of single monophasic or diphasic spike with an abrupt ascending limb and a steep descending limb (Fig. 7.8). SSS have a single aftercoming slow-wave component or may be associated with an aftercoming dip in the background; however, they do not have the prominent aftercoming slow wave that temporal spikes have, and they do not occur in repetitive trains. The morphology varies from patient to patient and with different types of montages, so not all SSS have a stereotyped appearance (20,49). Because SSS have a broad, sloping potential field, they are seen best in derivations with long interelectrode distances and are displayed most clearly in the temporal and ear leads (20).

SSS occur predominantly as a unilateral waveform. However, provided that the EEG recording is of sufficient length, SSS are almost always are bilaterally represented, either occurring independently or having some reflection to the opposite hemisphere (Fig. 7.8). In addition, the field sometimes corresponds to an oblique transverse dipole across the two hemispheres, with opposite polarity on the two sides of the head, a topography that is unusual for spikes of cerebral origin (19–21,36). The two phases of the same discharge also may vary in distribution in an anteroposterior direction (20). Unlike the more significant epileptogenic discharges that can arise from the temporal areas, SSS usually do not distort the background, are not associated with rhythmic slow-wave activity, do not occur in trains, and tend to diminish or disappear with deeper levels of slow-wave sleep.

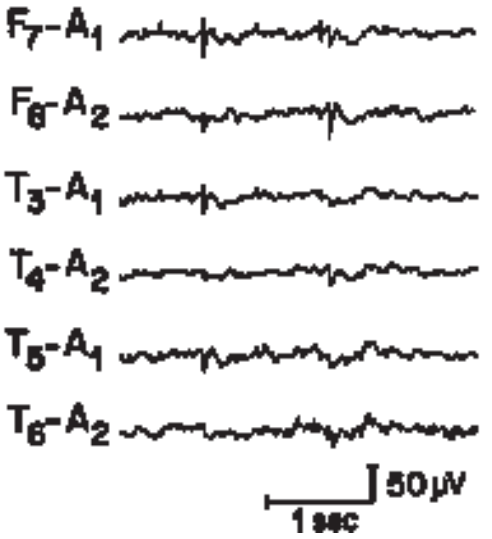

FIG. 7.8. Examples of small sharp spikes (benign sporadic sleep spikes) occurring over the left and right temporal regions, as seen on a referential montage. (From Westmoreland BF. Benign EEG variants and patterns of uncertain clinical significance. In: Daly DD, Pedley TA, eds. *Current practice of clinical electroencephalography*, 2nd ed. New York: Raven Press, 1990:243–252, with permission of Lippincott Williams & Wilkins.)

The incidence of SSS in a normal control population or in asymptomatic subjects is approximately 20%–25% (20,50). In a study on the significance of this phenomenon, White and associates (50) found BETS (or SSS) in 24% of normal subjects and in 20% of unselected patients. The current consensus is that SSS have no significance in the diagnosis of epileptic seizures (20,32–34,36). In addition, the bilateral occurrence of the BSSS should not be misinterpreted as representing bilateral epileptogenic foci (20).

Six-Hertz Spike-and-Wave Bursts ("Phantom Spike and Wave")

The 6-Hz spike-and-wave discharges (1,7,9,13,15,24,31,39,41,42) have a repetition rate of 6 Hz, with a range of 5–7 Hz (Fig. 7.9). The bursts are usually brief, lasting 1 or 2 seconds, although rarely they persist for 3 or 4 seconds. The pattern has also been called the "phantom spike and wave" (1,44) because of the evanescent nature of the spike, which is usually very brief and small in amplitude, in contrast to the more prominent slow-wave component, which has a higher amplitude and a more widespread distribution. At times, the spike may be difficult to see.

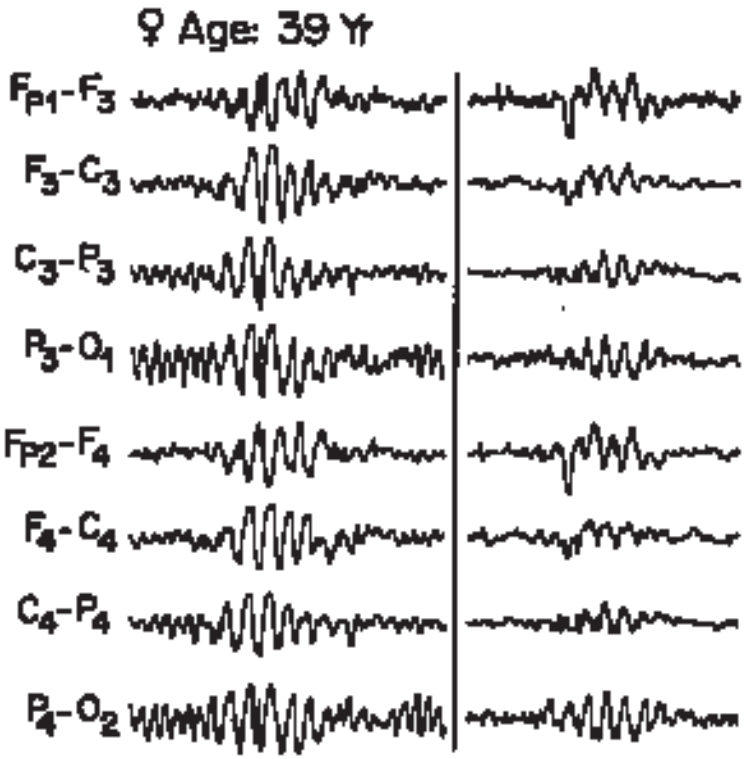

FIG. 7.9. Six-Hertz spike-and-wave bursts in a 39-year-old woman. (From Westmoreland BF. EEG in the evaluation of headaches. In: Klass DW, Daly DD, eds. *Current practice of clinical electroencephalography*. New York: Raven Press, 1979:381–394, with permission of Lippincott Williams & Wilkins.)

The 6-Hz spike-and-wave pattern is seen in both adolescents and adults, with an overall incidence of 2.5%. It occurs mainly during relaxed wakefulness and drowsiness and disappears during deeper levels of sleep.

The 6-Hz spike-and-wave bursts usually occur in a bilaterally synchronous and diffuse manner, although the bursts can occur in an asymmetrical fashion or predominate over the anterior and posterior head regions. There may be some resemblance to the 6-Hz positive bursts described above, and there may be a transition between the two types of waveforms, which can occur in the same person (37).

Although there is still some difference of opinion about the exact significance of the 6-Hz spike-and-wave burst, it has not proved to be a reliable indicator of seizures (20,42). One of the problems may be the difficulty in distinguishing the atypical forms of 6-Hz spike-and-wave discharge from fragments of more significant spike-and-wave complexes. Two types of 6-Hz spike-and-wave discharges have been described by Hughes (13), who used the acronyms of FOLD and WHAM to describe the two variants. FOLD (female occipital-predominant low amplitude and drowsiness) describes the characteristics seen with the more benign variant of the 6-Hz spike-and-wave pattern, and WHAM (wake high-amplitude anterior predominance in male) refers to the variant that is more likely to be associated with seizures. Seizures are more likely if the spike discharges are high in amplitude and the rate is less than 5 or 6 Hz. Another helpful way of making the distinction is that the benign 6-Hz spike-and-wave burst tends to disappear during sleep, whereas more significant types of spike-and-wave discharges tend to persist or even become more prominent with deeper levels of sleep (20).

Wicket Spikes

These waveforms, described in detail by Reiher and Lebel (35), consist of intermittent trains or clusters of monophasic arciform waveforms or single spike-like waveforms that look like a Greek mu or wicket (Fig. 7.10). When they occur as a single waveform, wicket spikes can be mistaken for a temporal spike discharge; however, if the single waveform is analyzed and compared with a train of wicket spikes, the wicket spikes have a morphology similar to that of a train of wicket-like activity. Another feature that distinguishes a wicket spike from the more pathological spike is that it is not associated with either (a) an aftercoming slow-wave component or (b) a distortion or slowing of the background that occurs with a true temporal spike.

Wicket spikes are seen mainly during drowsiness and light sleep. They may be present during the awake recording but are often masked by other

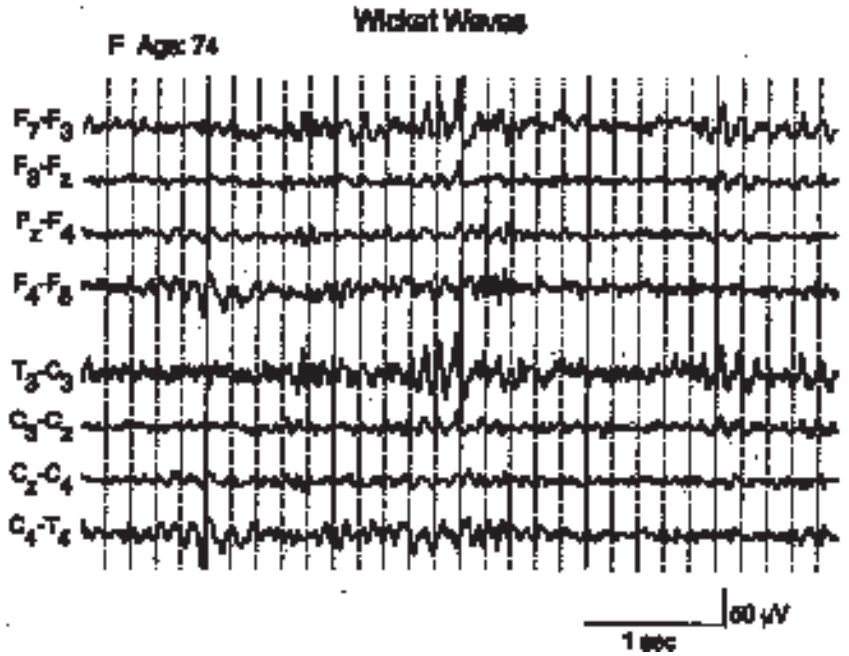

FIG. 7.10. Wicket spikes in a 74-year-old woman.

background rhythms and usually emerge or become apparent during drowsiness, when the alpha and other awake patterns disappear. Wicket spikes are seen predominantly over the temporal regions and occur bilaterally or independently over the two temporal regions. They may have a shifting predominance or may be more consistently evident on one side. Wicket spikes usually occur with a frequency of 6–11 Hz and have an amplitude ranging from 60 to 200 µV. They are seen predominantly in adults older than 30 years and have an incidence of 0.9% (35). They likely represent fragments of so-called "temporal alpha activity."

Breach Rhythm

The breach rhythm was described by Cobb and associates (3) in 1979 and refers to high-voltage activity that occurs in the region of a skull defect. The breach rhythm frequently has a spiky appearance and consists of sharply contoured arciform waveforms that usually have a frequency of 6–11 Hz but may sometimes be associated with faster or slower wave activity. The breach rhythm is most prominent when recorded over the central and temporal regions, and, at times, it may have a threefold increase in amplitude compared with activity in other regions (Fig. 7.11). The activity over the central regions often reflects mu activity and, like mu activity, responds to touch or movement. The other prominent location for the breach rhythm is over the temporal areas, where wicket spikes and other spike-like activity can be quite prominent. The breach rhythm usually is easily recognizable when it occurs in serial trains. A problem may arise when one sees single spike-like or sharp-contoured waveforms that may be mistaken for potentially epileptogenic activity. It is helpful to compare this with the waveforms of the rhythmic activity constituting the breach rhythm to determine whether these are distinct waveforms or whether they are similar to the activity that constitutes the breach rhythm. Other factors that help make the distinction between a breach rhythm and more significant epileptogenic abnormalities are the absence of aftercoming slow-wave components and lack of spread to other areas. The presence of the breach rhythm should not be considered an indicator of epilepsy or recurrence of a tumor or underlying lesion.

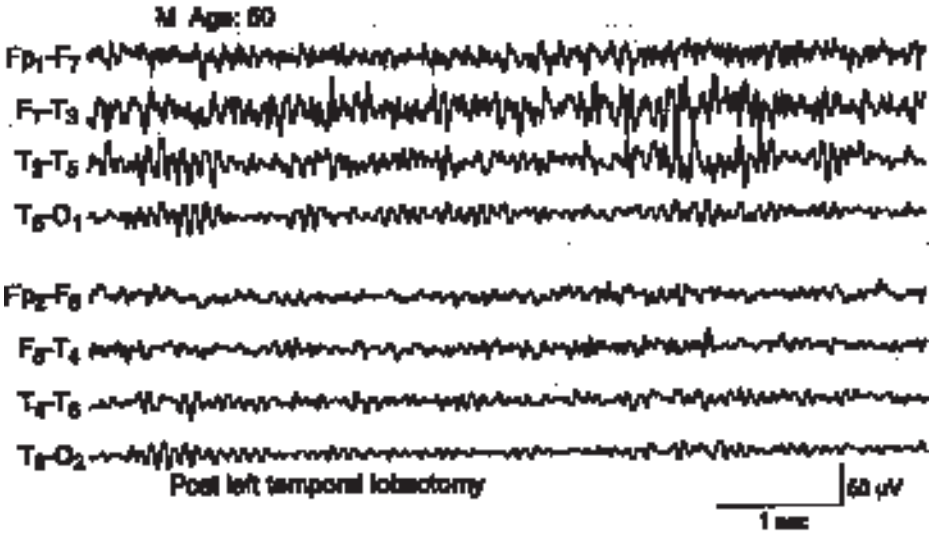

FIG. 7.11. Breach rhythm over the left midtemporal region following a left temporal lobectomy in a 50-year-old man.

Although bone reabsorption or absence of bone in the area of the skull defect has a major role in the prominence of the breach rhythm, other factors may also be involved (see Chapter 11 for additional discussion).

CONCLUSION

This chapter has discussed some of the EEG patterns that represent benign variants of EEG activity or activity of uncertain significance. None should be considered abnormal. These patterns can occur in normal or asymptomatic persons, or in patients with various complaints, and they should be differentiated from true epileptogenic or abnormal activity. In making the distinction, the electroencephalographer needs to consider various parameters of EEG activity, including the morphology, topography, distribution, phase relations, amplitude, duration, frequency, coexisting background from which the activity is arising, reactivity, and state of the patient (20,32,33). Critical evaluation of the various types of EEG activity is important in making the distinction between patterns that are benign and those that are associated with epilepsy.

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Chapter 8

Activation Methods

Bruce J. Fisch and Elson L. So

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References

Electroencephalographic (EEG) activation as defined by the International Federation of Clinical Neurophysiology Societies (75) includes any procedure designed to enhance or elicit normal or abnormal EEG activity, especially epileptiform abnormalities. Activation stimuli include various sensory modalities, electrical and pharmacological stimulation, and changes in behavioral state and consciousness. Activation procedures used routinely in the EEG laboratory are hyperventilation, photic stimulation, and sleep. Hyperventilation and photic stimulation are most useful for activating epileptiform abnormalities, whereas drowsiness and sleep are useful for activating all forms of EEG abnormalities as well as normal epileptiform patterns (so-called pseudoepileptiform patterns). In addition to these routine activating procedures, other procedures are used in patients with

abnormal paroxysmal behaviors that can be triggered by a specific stimulus. Examples of the latter include reading (reading-induced myoclonus or seizures), music (musicogenic epilepsy), mental calculation (calculation-induced seizures), and even immersion in water (so-called hot tub seizures). Direct electrical activation of the brain is performed using either needle, subdural, or depth electrodes to evoke afterdischarges or electrographic seizures. Pharmacological activating procedures include the withdrawal of antiepileptic drugs (AEDs) and the administration of convulsant medications such as pentylenetetrazol. Behavioral activation procedures, in contrast to EEG activation procedures, are performed during EEG recording to activate behavioral events that do not typically elicit epileptiform abnormalities. Examples include postural changes in patients with movement disorders or generalized or localized orthostatic ischemia (e.g., limb-shaking transient ischemic attacks [TIAs]), emotional changes in infants with possible breath-holding spells, or a variety of suggestion techniques in individuals with suspected psychogenic pseudoseizures. Procedures used for the activation of epileptiform abnormalities are summarized in Table 8.1.

TABLE 8.1. *Activation methods known to induce epileptiform activity*

Visual Stimulation
Visual exploration
Stroboscopic flash stimulation
Pattern stimulation
Television
Eye closure
Somatosensory Stimulation
Tactile
Electrical
Water immersion
Auditory Stimulation
Nonspecific sounds
Music
Sleep
Pharmacologically induced
Spontaneous
Sleep deprivation
Hyperventilation
Pharmacological Agents
Anticonvulsant medication withdrawal
Pentylenetetrazol
Pentylenetetrazol and photic stimulation
Bemegride
Methohexital
Metabolic Toxicity
Hypoglycemia
Hypoxia
Special Stimuli
Startle
Reading
Writing
Mental calculation
Mental imagery
Eating

EEG reactivity procedures are distinguished from activating procedures as being intended to verify the presence or absence of normal EEG responses to exogenous sensory or endogenous cognitive stimulation. Examples of routine reactivity procedures include eye opening and closure in alert patients to demonstrate the alpha rhythm, or vigorous stimulation in patients in coma to demonstrate evidence of cortical responsiveness. Pharmacological reactivity procedures include the quantitative EEG analysis of drug-induced beta activity (e.g., diazepam) or EEG monitoring during intracarotid amobarbital (Wada) testing. This chapter focuses on activation methods used to provoke EEG abnormalities.

HYPERVENTILATION

Hyperventilation is the oldest EEG activating procedure. In 1934, Hans Berger was the first to describe the effect of hyperventilation on the human EEG (13). Using a polygraphic four-channel recorder with EEG, respiration, and electrocardiogram (ECG) (Fig. 8.1), he demonstrated that "The alpha waves increase in amplitude and merge into separate groups of 0.3–0.5 second duration."(58) Berger's findings on the effects of hyperventilation were published in the same year that Adrian and Matthews confirmed his claim that the human EEG could be recorded from the scalp (5). The initial use of hyperventilation as an EEG activating procedure arose from the discovery in 1924 that epileptic seizures could be triggered by hyperventilation (49,129). The year after Berger's report on hyperventilation, Frederick Gibbs, Hallowell Davis, and their colleagues (56,57) provided a more detailed description of the effects of hyperventilation. The effectiveness of hyperventilation in inducing generalized epileptiform activity was quickly established (108), and remains clinically important in this context.

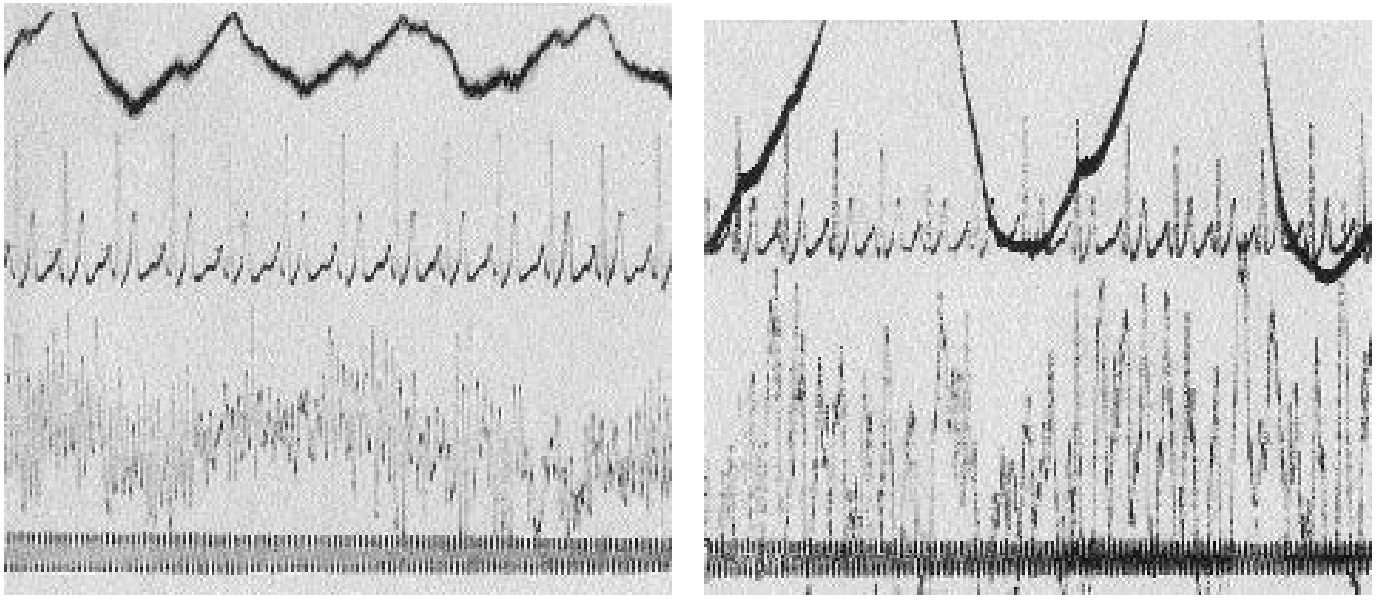

FIG. 8.1. First EEG recorded in a human during hyperventilation. **A:** Normal respiration in a 33-year-old woman with idiopathic epilepsy. Top channel is respiration, followed by ECG, EEG, and time marker with 1- to 10-second cycles. Recorded from the forehead and occiput with chlorided needle electrodes. **B:** Hyperventilation in the same subject several minutes after onset. Note higher amplitude and slower respiratory effort and slowing and increased amplitude of the EEG activity. (From Gloor P. Hans Berger on the electroencephalogram of man: fourteen original reports on the human electroencephalogram. *Electroencephalogr Clin Neurophysiol Suppl* 1969;28, with permission.)

Normal Response to Hyperventilation

The typical hyperventilation response consists of a buildup of medium- to high-amplitude, bisynchronous delta and theta waves and an increase in amplitude of theta and alpha waveforms. The distribution of delta and theta activity is typically anterior dominant in adolescents and adults but can be either anterior or posterior dominant in children. The hyperventilation response often includes frontal intermittent rhythmic delta activity (FIRDA; Fig. 8.2) or, particularly in children, occipital intermittent rhythmic delta activity (OIRDA; Fig. 8.3). Although spontaneously occurring FIRDA or OIRDA indicates the presence of a diffuse cerebral dysfunction, their isolated appearance in hyperventilation is considered normal. Similarly, occasional sharply contoured components may be intermixed with FIRDA or OIRDA patterns (particularly if the EEG contains prominent alpha and beta waveforms) that can be misinterpreted as generalized epileptiform activity. As noted above, alpha frequency activity often increases in amplitude (33). Moreover, the alpha rhythm may first appear clearly in the recording only after hyperventilation, perhaps because of its relaxing effects. Technologists should therefore be instructed to perform hyperventilation early in the recording if a well-defined alpha rhythm is not apparent. In normal individuals, the record usually returns to baseline less than 1 minute after hyperventilation ends. The magnitude of the hyperventilation response depends on several factors, including effort, age, posture, and blood sugar. Younger individuals tend to produce the

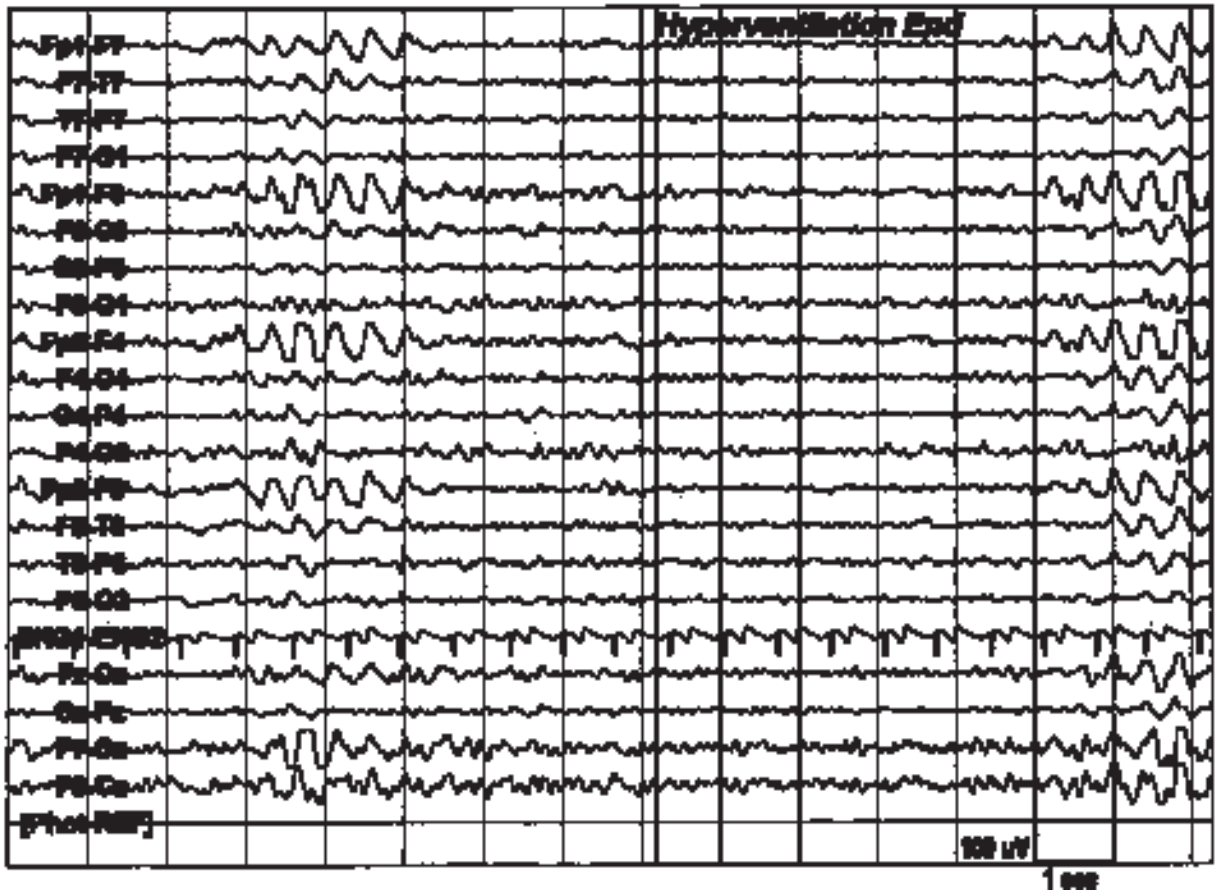

FIG. 8.2. Frontal intermittent delta activity produced by hyperventilation in an adolescent referred for the evaluation of possible migraine headache. Note the persistence of FIRDA immediately following the instruction to end hyperventilation.

largest responses, whereas elderly individuals often fail to show any EEG change (170).

The first quantitative EEG study of hyperventilation was performed by Gibbs and colleagues (55). Their observations mirrored those of routine visual inspection. They found that, as CO_2 measured from the internal jugular vein fell with increasing hyperventilation, the overall amount of EEG measured as total spectral power (i.e., the total area between the EEG waveforms and the zero baseline) increased and the mean frequency of the EEG decreased. A comparison of more recent quantitative studies suggests that the older the subject is, the more likely hyperventilation will produce an overall increase in EEG amplitude without decreasing the mean frequency (1,84). This may be partly due to the overall greater magnitude of response that occurs in children compared to adults. By routine visual EEG inspection, over 70% of children show a clear response to hyperventilation, whereas, in adults, a response may

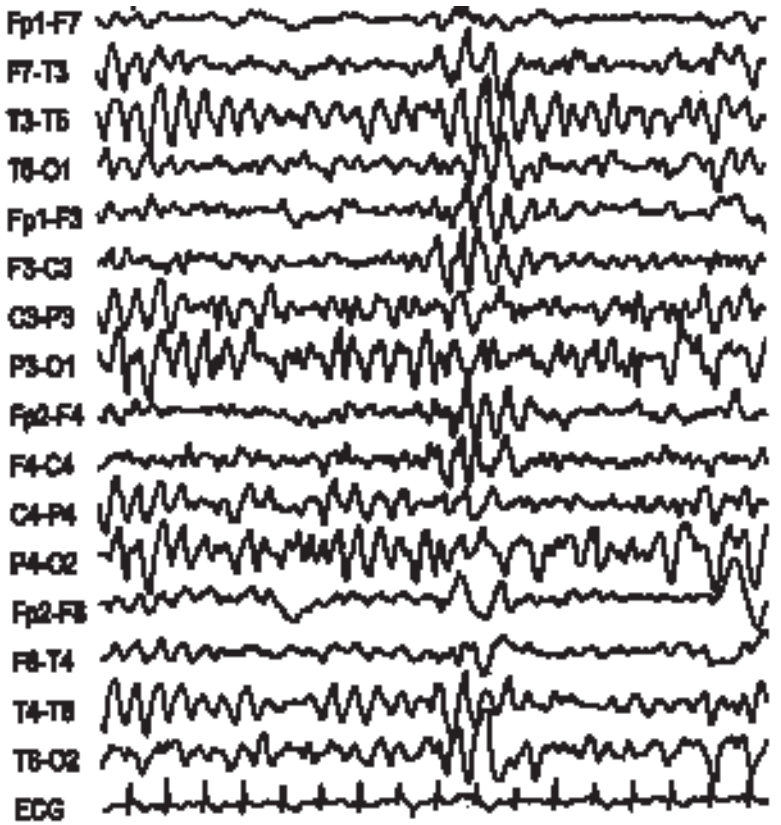

FIG. 8.3. Posterior delta activity produced by hyperventilation in a 6-year-old boy. Older adolescents and adults typically show anterior-dominant slowing in response to hyperventilation.

be seen in less than 10% of individuals during routine EEG laboratory testing (54). The maximum frequency of response occurs between the ages of 8 and 12 years, when up to 85% of subjects have some type of hyperventilation response; interestingly, this is about the same age range in which most individuals with idiopathic epilepsy and photosensitivity develop photosensitivity (see below) (23,115). In a study of 37 normal children ages 6–17 years in which ventilation, partial pressure of oxygen (PO_2), and partial pressure of carbon dioxide (PCO_2) were measured, Konishi (84) found a nearly inverse relationship between EEG slowing and age using a standardized hyperventilation protocol. The effect of hyperventilation on the EEG begins earlier in children than adults and is apparent in 50% of cases within the first minute and 90% within the first 2 minutes (34).

Hyperventilation Procedure

Hyperventilation is routinely performed by asking the patient to overbreathe for at least 3 minutes. The recording technologist should encourage deep breathing over rapid shallow breathing to enhance air exchange and decrease in PCO_2. It is often helpful if the EEG technologist intermittently places a hand in front of the patient's mouth to monitor the level of effort and provide encouragement. Young children can be encouraged to hyperventilate by asking them to blow on a colorful pinwheel. In general, more vigorous and prolonged hyperventilation is desirable for activating seizures. A minimum 1-minute baseline recording is made before starting hyperventilation.

Blood gas monitoring is not routinely performed during hyperventilation, but the standardization of hyperventilation using blood gas monitoring appears to significantly enhance the likelihood of detecting EEG changes. Zwiener and colleagues (171) found that, when volunteers underwent standardized hyperventilation (in which PCO_2 was maintained at 15 mm Hg), a nearly sixfold increase in delta frequency band power was produced compared to nonstandardized hyperventilation. Remarkably, there have been no recent attempts to correlate blood gas changes with the activation of epileptiform patterns or with the effects of anticonvulsant medications on activated patterns. Unless blood gas monitoring is used, it is impossible to know if hyperventilation has been adequately performed, particularly in patients with absent or minimal responses.

The importance of continuing the EEG recording for at least 6 minutes following hyperventilation has been emphasized by Achenbach-Ng and colleagues (1). In a study of nine normal adult subjects, they found that PCO_2 fell continuously during hyperventilation and then immediately began to increase. In contrast, PO_2 increased during hyperventilation but then decreased to an average of 25 mm Hg below baseline at 5.2 minutes following the cessation of hyperventilation. The posthyperventilation decline in PO_2 that is presumably related to hypocapnia-induced hypopnea also occurs in children (170). Although Zwiener and colleagues (171) failed to find a significant decline in posthyperventilation PO_2, the time course of declining PO_2 found in these other studies more closely parallels EEG slowing in patients with moyamoya disease. Indeed, in individuals with border-

line cerebral perfusion disorders, hyperventilation can be deleterious because of hypocapnia-induced ischemic vasoconstriction and shunting effects, posthyperventilation hypoxia, or both. As recommended by the American Clinical Neurophysiology Society (formerly the American Electroencephalographic Society), hyperventilation should not be performed in certain clinical settings, including acute stroke, recent intracranial hemorrhage, large-vessel severe stenosis and associated TIA (e.g., limb-shaking attacks), documented moyamoya disease, severe cardiopulmonary disease, and sickle cell disease or trait.

Response testing is used to document lapses in consciousness at the time of hyperventilation-induced epileptiform activity. The simplest form of response testing consists of asking the patient to repeat or recall words presented during the abnormal activity. A more precise method consists of having the patient press a button to mark the EEG record in response to the presentation of an auditory signal given by the technologist. The electroencephalographer must take care not to misinterpret the clinical significance of response testing during hyperventilation, particularly in children. The significance of impaired responsiveness is most likely to occur during generalized high-amplitude 2- to 3-Hz activity—a phenomenon referred to as *pseudo-absence seizures*. Epstein and colleagues (42) found that 12 of 12 normal children tested demonstrated an impairment of verbal memory, and 8 of those 12 failed to respond to repeated auditory clicks during periods of hyperventilation-induced slowing that was greater than 100-μV voltage and consisted of 3- to 5-Hz waveforms lasting 3 seconds or longer, using an average reference montage. None of the children manifested automatisms or abnormal motor activity. It is also well known that episodic changes of consciousness or awareness, numbness, dizziness, tingling, transient blurring of vision, and ringing in the ears are common manifestations of hyperventilation attacks that can occur in the absence of EEG slowing—possibly as a result of increased autonomic activation (51,106). Therefore, response testing alone should not be used to classify an EEG change as an epileptiform abnormality during hyperventilation. Impaired responsiveness during hyperventilation can be confidently interpreted as a manifestation of a seizure only if: (a) an abnormal EEG pattern is combined with motor phenomena (e.g., automatisms or convulsive movements) or (b) the EEG contains well-defined electrographic seizure activity.

Physiological Basis of the EEG Response to Hyperventilation

Alteration of PCO_2, rather than pH or PO_2, is the most important factor in producing the EEG response to hyperventilation, whereas the most obvious and dramatic physiological effect of hyperventilation is decreased cerebral blood flow. EEG hyperventilation changes are more likely to occur with blood sugar levels below 80 mg per 100 mL and less likely to occur with levels over 120 mg per 100 mL. All of these observations led Davis and Wallace (36) to propose that the EEG changes that accompany hyperventilation are caused by ischemic cerebral hypoxia. Their view is supported by the observation that the hyperventilation response is reduced by hyperbaric oxygen (117,125). An alternative explanation was proposed by Gibbs and colleagues (54), who believed that cerebral hypoxia sufficient to cause EEG slowing cannot occur because the vasodilatory effects of anoxia should override the constrictive effects of hypocapnia. Instead, they concluded that cerebral hypocapnia is directly responsible for the typical EEG changes. As noted by Patel and Maulsby (114), several observations support the idea that EEG slowing results from the direct effects of hypocapnia on the brainstem: (a) hyperventilation does not modify the EEG in animals in the *cerveau isole* preparation (22), (b) the effects of hyperventilation on chemically induced spike foci, electrical afterdischarges, and cortical responsiveness are interrupted or dampened by surgically isolating the cortex (137), and (c) the hyperventilation effect can be blocked by lesions of the anterior thalamus (138). In the brainstem model of hyperventilation, it remains to be determined if hypoxia of the brainstem or of other subcortical structures is most critical.

Abnormal EEG Responses to Hyperventilation

Hyperventilation produces three main kinds of EEG abnormalities: (i) lateralized or localized slowing, (ii) delayed symmetrical or lateralized slowing, and (iii) epileptiform patterns.

Hyperventilation may increase or provoke localized slowing in the presence of an underlying lesion or localized area of cortical dysfunction, but it does not produce abnormal slowing or significant-amplitude background asymmetries in normal individuals. Abnormal slowing usually begins within the first 2 minutes of hyperventilation and may either persist or sometimes become more obvious after hyperventilation ceases. A buildup of slowing several minutes after hyperventilation ends is highly suggestive of moyamoya disease (Fig. 8.4) (83). As noted above, the time course of the onset of slowing roughly parallels the decline of PO_2 caused by posthyperventilation reduced ventilatory drive (1,78,148). The delayed buildup of slowing in moyamoya disease is often maximal approximately 5 minutes after hyperventilation ends. It may be unilateral or bilateral. Because of the remote risk of stroke, hyperventilation is avoided in patients with known moyamoya disease.

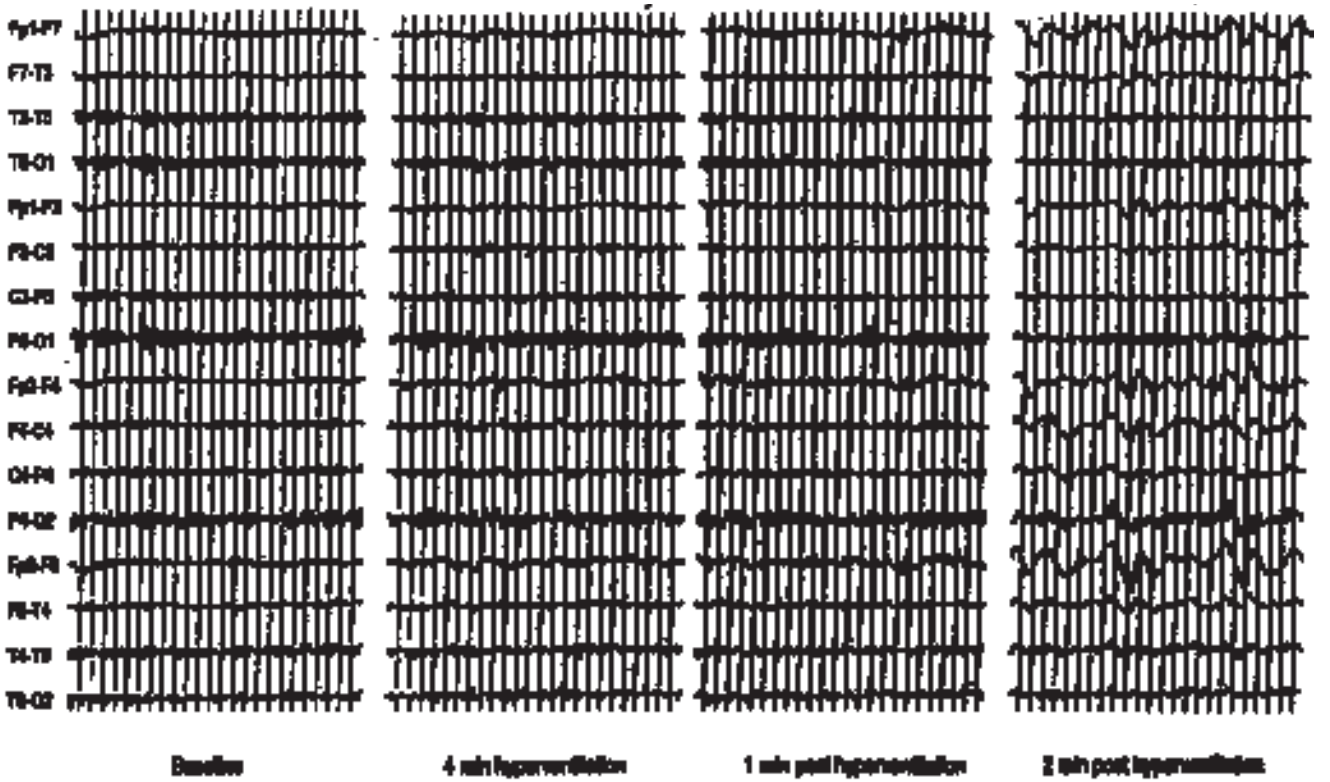

FIG. 8.4. Typical pattern of delayed hemispheric slowing after hyperventilation in a 15-year-old with moya-moya disease.

Hyperventilation is the most effective method for activating ictal and interictal epileptiform activity associated with typical absence seizures. According to Dalby (32), hyperventilation will activate seizures in over 80% of untreated children with absence seizures. As demonstrated by Adams and Lueders (4), hyperventilation is more effective than a 6-hour passive recording in detecting the typical 3-Hz spike-and-wave pattern in children with absence seizures. Indeed, in an untreated child, if hyperventilation evokes prominent slowing, or PCO_2 monitoring shows a substantial decline to a level of less than 20 mm Hg, and epileptiform activity does not appear, then the diagnosis of absence seizures becomes doubtful. Approximately 35% of children with absence seizures demonstrate prolonged, spontaneous runs of localized rhythmic 2.5- to 3.5-Hz occipital-dominant delta activity. During hyperventilation, this activity may evolve directly into the typical anterior-dominant 3-Hz spike-and-wave epileptiform pattern. Although this occipital pattern in the absence of 3-Hz spike and wave may be quite striking, only 30%–40% of children who have it actually have epilepsy. Yet virtually all children who have the occipital pattern and also have absence seizures will demonstrate typical 3-Hz spike-and-wave discharges with prolonged hyperventilation. Cobb and colleagues (29) found that children with epilepsy with this pattern usually stopped having seizures between the ages of 10 and 12 years.

Hyperventilation is most likely to produce epileptiform activity in patients with typical absence seizures, but it may activate almost any type of

seizure or interictal epileptiform activity (46). The overall effectiveness of hyperventilation in epilepsy is currently difficult to assess because, as previously noted, uniform methods employing a similar duration of effort with monitoring to control for variations in blood gases have not been used. With routine hyperventilation (i.e., without blood gas monitoring) approximately 50% of those patients with generalized slow spike-and-wave patterns who are able to perform hyperventilation demonstrate activation of epileptiform patterns (21,97). Miley and Foerster reported that hyperventilation activated focal interictal epileptiform activity in greater than 6% of 255 patients with complex partial seizures and clinical seizures in over 4% (101). Even higher rates of activation in patients with partial seizures have been reported more recently (71,135). In our experience, hyperventilation rarely if ever activates partial seizures, but various investigators have emphasized the need for long duration and intensive hyperventilation, particularly in patients with partial seizures (135). Until CO_2 monitoring is used to verify the efficacy of effort, the potential usefulness of hyperventilation in epilepsy will remain unclear.

Hyperventilation rarely provokes paroxysmal attacks in patients with multiple sclerosis (109,156). The EEG is usually unchanged or shows a mild, normal activation pattern. The attacks typically last 1–2 minutes and may include tonic spasms. When the manifestations include ataxia, diplopia, or dysarthria, then a seizure disorder is highly unlikely. Individuals with paroxysmal attacks of any kind that are triggered by emotional upset are often suspected of having psychogenic pseudoseizures. However, it should be remembered that, during episodes of crying or panic attacks, hyperventilation occurs and may trigger an epileptic seizure in susceptible individuals. Thus a strong association between emotional attacks and seizures alone should not lead to the conclusion that the attacks represent psychogenic pseudoseizures.

Pathophysiological Basis of Ictal and Interictal Epileptiform Activation

The mechanism underlying the activation of ictal and interictal epileptiform activity during hyperventilation is probably central nervous system excitation combined with altered thalamocortical function. The scalp-recorded negative direct current (DC) shift that commonly accompanies excitatory phenomena, such as an electrographic seizure, is also produced during hyperventilation in humans, and its amplitude may be reduced by pretreatment with anticonvulsant medications (127). Evidence for corticospinal excitation has been reported by Kukumberg and colleagues (86) and Seyal and colleagues (136). Both groups found that hyperventilation increased the amplitude of transcranial magnetic motor evoked potentials, whereas Seyal and colleagues (136) found that hyperventilation to an end-tidal PCO_2 of 15 mm Hg also shortened the latency of transcranial magnetic motor evoked potentials and increased the amplitude of F waves. In some individuals, the role played by hypocapnia has been questioned because activation can occur so quickly after the onset of hyperventilation. Interestingly, this observation is consistent with the rapid onset of a substantial (10%) decrease in the cortical (but not white matter) functional magnetic resonance imaging (MRI) signal in the first 20 seconds of hyperventilation reported by Posse and colleagues (118). However, in their study, MRI signal changes were delayed in comparison to PCO_2 changes. Positron emission tomography scan activation of corticospinal motor pathways also occurs with hyperventilation, with a significant increase in activity of the frontal premotor and primary motor cortices compared to that of the temporal, occipital, or parietal lobes (73).As noted previously, hyperventilation can induce changes in consciousness (42,51,106), and it can also reduce the amplitude of long-latency auditory and somatosensory evoked potentials (72). It is reasonable, therefore, to consider that, as in the corticoreticular model of primary generalized epilepsy, cortical excitation and altered thalamocortical function combine to facilitate epileptiform activity and seizures during hyperventilation.

PHOTIC STIMULATION

Richard Caton (1842–1926) is credited with the discovery of spontaneous electrical brain activity in mammals (26). In his original experiments, he also tested the electrical reactivity of the brain to various stimuli. Among the various sensory stimuli he tested, the strongest EEG reaction was consistently produced by retinal light stimulation (26). Adrian and Matthews (5) performed the first investigation of the effects of light stimulation on the human EEG. Following the discovery that light stimulation could trigger seizures, the modern technique of stroboscopic photic stimulation was developed by Walter and colleagues (161). Since that time, stroboscopic stimulation has become part of routine screening for photosensitive epilepsy in laboratories throughout the world. Seizures activated by photic stimulation are the most common form of reflex epilepsy, accounting for nearly one-third of such cases. Photic stimulation is most effective for provoking generalized epileptiform activity or generalized seizures; rarely, focal epileptiform activity or partial seizures with occipital onset can be activated (77).

Photic Stimulation Procedure

Photic stimulation is routinely performed with a stroboscopic diffuse light flash at frequencies ranging between 1 and 30 Hz. A generally accepted protocol is described in Table 8.2 (14,80). If an abnormal epileptiform response occurs during stimulation, then the stimulus train is repeated to verify that the abnormal activity is temporally related to the flash stimulus. Repetition using the same frequency of stimulus train should not be repeated immediately because there is evidence that habituation with blocking of the response will occur (155). Therefore, either more than 30 seconds of nonstimulation should separate trials of the same frequency of stimulation or the interposition of a different frequency stimulus train is recommended before repeating the activating flash frequency.

The effectiveness of diffuse light stimulation is determined by flash frequency, stimulus intensity (luminance), level of consciousness, and direction of gaze. Photic stimulation is less effective when performed during sleep. The intensity of ambient lighting may also play a role in the effectiveness of the stimulus in some individuals. Unilateral monocular stimulation or stimulation during conjugate ocular deviation away from the stimulus is less effective than binocular gaze–directed stimulation.

The stimulator should be placed directly in front of the patient's eyes at a distance of no more than 30 cm. The patient is usually instructed to begin with the eyes open, but stimulation may also be performed with the eyes closed, particularly if the light source is too irritating. In addition to stimulating at fixed frequencies, some investigators believe that using flash stimuli that gradually increase or decrease in frequency during the stimulus train is activating in some patients. Technologists performing this procedure must be skilled in identifying epileptiform patterns so that stimulation can be immediately terminated at the onset of an epileptiform pattern. Otherwise a generalized tonic–clonic seizure (GTCS) may be provoked. Surprisingly, many commercially available photostimulators lack the features essential to effective photostimulation, including a high-intensity flash, a large circular surface area, and a fairly consistent luminance at different flash frequencies from 1 to 60 Hz (see Table 8.2).

Following the seminal studies of Grey Walter and colleagues (161), it was found that diffuse light stimulation produces three main categories of electrographic response: (i) photic driving, (ii) the photomyogenic (formerly referred to as photomyoclonic) response, and (iii) the photoepileptiform response (PER) (also referred to as the photoparoxysmal response [PPR]).

TABLE 8.2. *Standardization of screening methods for photosensitivity*

Photostimulator Characteristics (equivalent to setting 4 on a Grass model PS22)
A maximal intensity > 100 Nit-s per flash
Circular field diameter of 13 cm
Granular diffuser producing light diffusion similar to that of the Grass stimulator
Central fixation point on diffuser
Attachment of patterns available
Single flashes or trains that can be delivered with constant intensity from 1 to 60 Hz
Procedure
IPS should not be performed during or within 3 min of hyperventilation
Nasion-to-lamp distance of 30 cm
Longitudinal bipolar or common reference montage
Flash trains of 10 s with at least 7-s intervals
Eyes open for first 5 s of IPS and then closed
Eyes fixated on center of stimulator
IPS frequencies: 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 60, 50, 40, 30, 25
IPS is stopped abruptly if a PPR appears

IPS, intermittent photic stimulation; PPR, photoparoxysmal response.

Adapted from Kasteleijn-Nolst Trenite DG, Binnie CD, Harding GF, et al. Photic stimulation: standardization of screening methods. *Epilepsia* 1999;40[Suppl 4]: 75–79.

Photic Driving Response

The photic driving response consists of rhythmic, occipital-dominant waveforms that either show a one-to-one relationship with each flash or appear as a harmonic (an integer multiple) or subharmonic (an integer dividend) of the flash frequency. The term *photic driving* describes an induced rhythm, not the isolated visual flash evoked potentials that occur with very slow rates (< 5 Hz) of stimulation. Driving is typically seen at stimulation rates between 5 and 30 Hz. Large positive occipital sharp transients of sleep (POSTS) and lambda waves in response to scanning a complex pattern are predictive of a prominent driving response. The onset of the occipital response usually occurs with a 70- to 150-millisecond delay from the onset of the flash stimulus. Higher amplitude driving responses usually appear at frequencies that are close to the frequency of the ongoing posterior background rhythm. This apparent entrainment of the background activity may briefly outlast the flash stimulus. At slower flash rates (< 5 Hz), the photic response consists of a diffuse light evoked potential (Fig. 8.5).

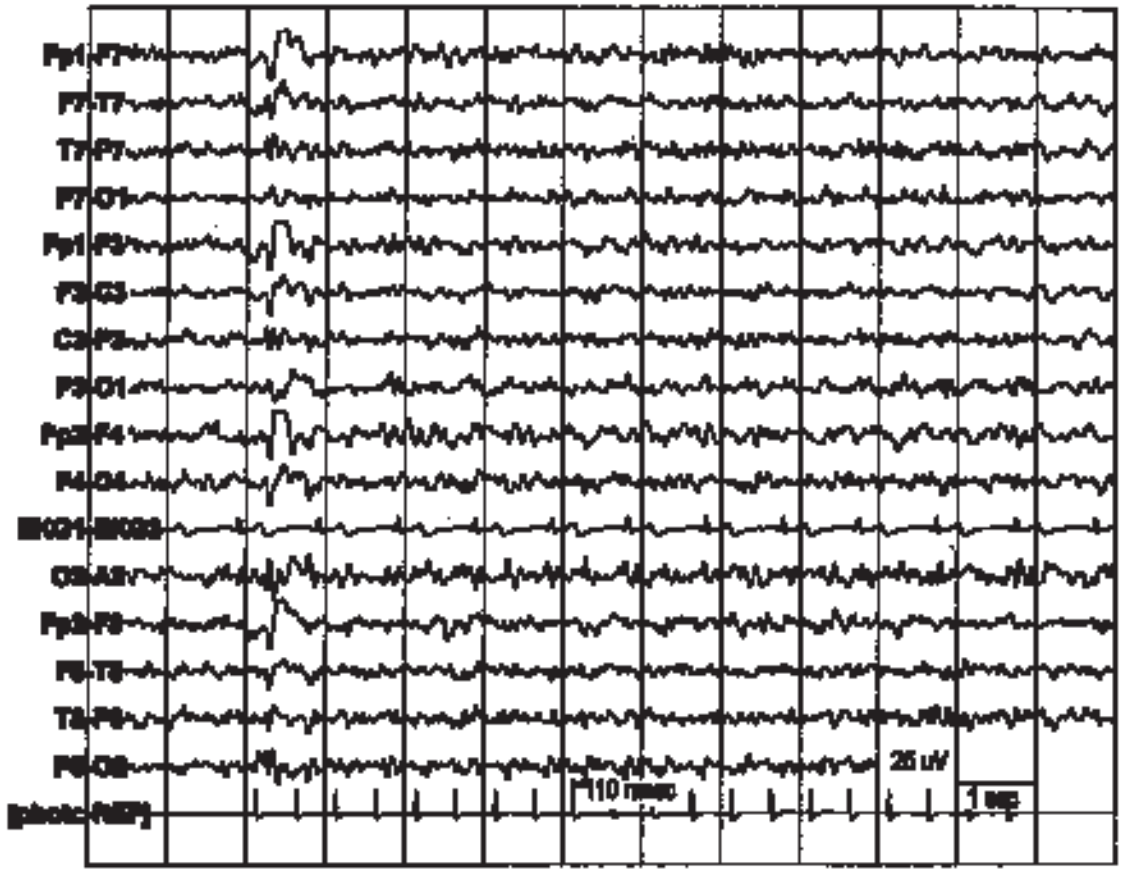

FIG. 8.5. "On effect" at the beginning of 4-Hz photic stimulation. At slow rates of stimulation, the photic response, when present, consists of flash evoked potentials. As indicated in the figure, the initial positivity occurs with a delay of approximately 110 milliseconds.

Abnormal Responses in Specific Cerebral Disorders

Just as POSTS or lambda waves may be strikingly asymmetrical in normal individuals, an asymmetrical driving response is considered normal unless accompanied by other EEG abnormalities (30). In normal individuals, asymmetrical POSTS or lambda waves are usually associated with a similar asymmetry of the driving response (46). Cortical epileptogenic lesions or skull defects can enhance the amplitude of the photic driving response ipsilaterally, whereas destructive lesions can attenuate it ipsilaterally (14). In some abnormal individuals with unilateral photic driving, the only other EEG abnormality may be a failure of the contralateral alpha rhythm to attenuate with eye opening (i.e., Bancaud's phenomenon)(46).

Adults who have abnormal background slowing and who demonstrate high-amplitude photic driving at very slow flash rates usually suffer from progressive degenerative cerebral disorders. Similarly, individuals at any age who demonstrate high-amplitude epileptiform spikes time locked to very slow photic flash rates often suffer from either progressive degenerative or acute structural brain disorders (Fig. 8.6). High-voltage occipital spikes that occur in a time-locked fashion in response to slow rates of stimulation in individuals in late infancy or childhood with intellectual decline, myoclonus, and optic

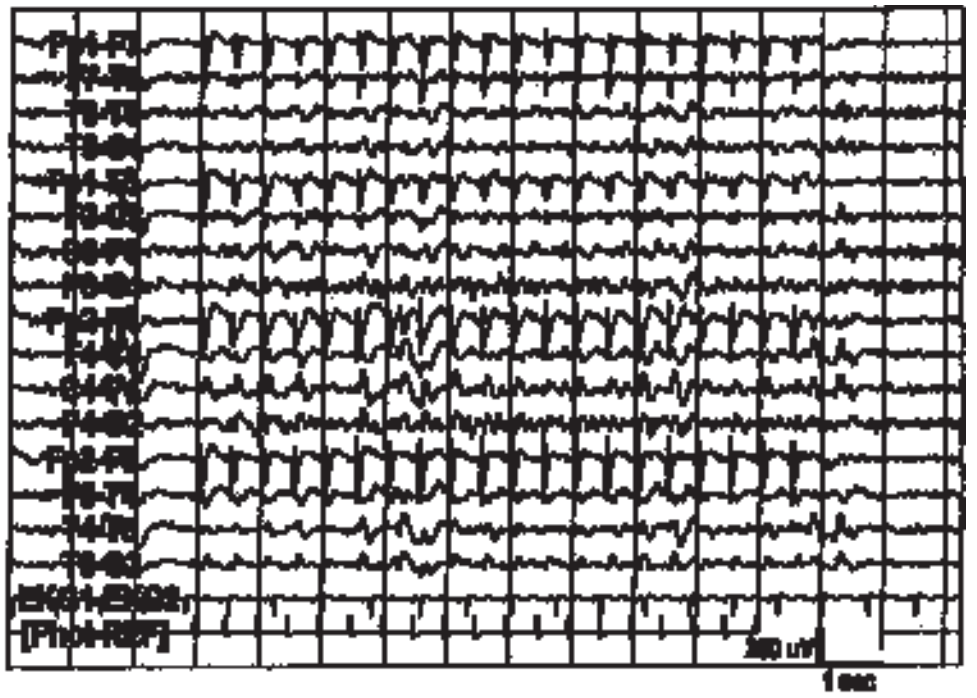

FIG. 8.6. Prominent right parieto-occipital sharp waves evoked by 2-Hz photic stimulation in an adult woman during an exacerbation of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes).

atrophy are virtually pathognomonic for the late infantile form of ceroid lipofuscinosis (Bielschowsky-Jansky form of Batten's disease) (110,116).

Victor and Brausch (160) originally described the photoparoxysmal response (see below) occurring in the majority of patients in alcohol withdrawal. Fisch and colleagues (47) subsequently studied photic responses to diffuse light and patterned stroboscopic stimulation in patients undergoing untreated alcohol withdrawal. None of their patients had a PPR, or any form of PER. Therefore, it is now generally accepted that patients in alcohol withdrawal without delirium tremens have little or no increased risk of developing a PPR. Whether or not there is an increased incidence of PPR in delirium tremens remains unknown.

Photomyogenic Response

The photomyogenic (photomyoclonic) response (Fig. 8.7) consists of electromyographic potentials time locked to the flash frequency. It was first described by Gastaut and Remond (53). Bickford and colleagues (16) provided a more detailed description and coined the term *photomyoclonic response* to describe its frequent association with photically induced myoclonus. Typically, muscle artifact time locked to the flash stimulus builds in intensity as the stimulation continues and ceases immediately with the termination of stimulation. Indeed, it is the immediate cessation of the response at the end of stimulation and prominent electromyographic activity that help to distinguish the photomyogenic response from an abnormal photoepileptiform response. It usually appears prominently over the anterior head regions as a result of involvement of the frontalis and orbicularis oculi muscles. Observable movements include stimulus time-locked contraction of the periocular muscles, myoclonic movements of the face, and less often myoclonic movements of the upper body. Rarely, a photomyogenic response may progress to a GTCS. It may be enhanced or provoked by heightened emotional tone or tension or metabolic/toxic states associated with reflex hyperactivity. A prominent, clinically observable response probably occurs

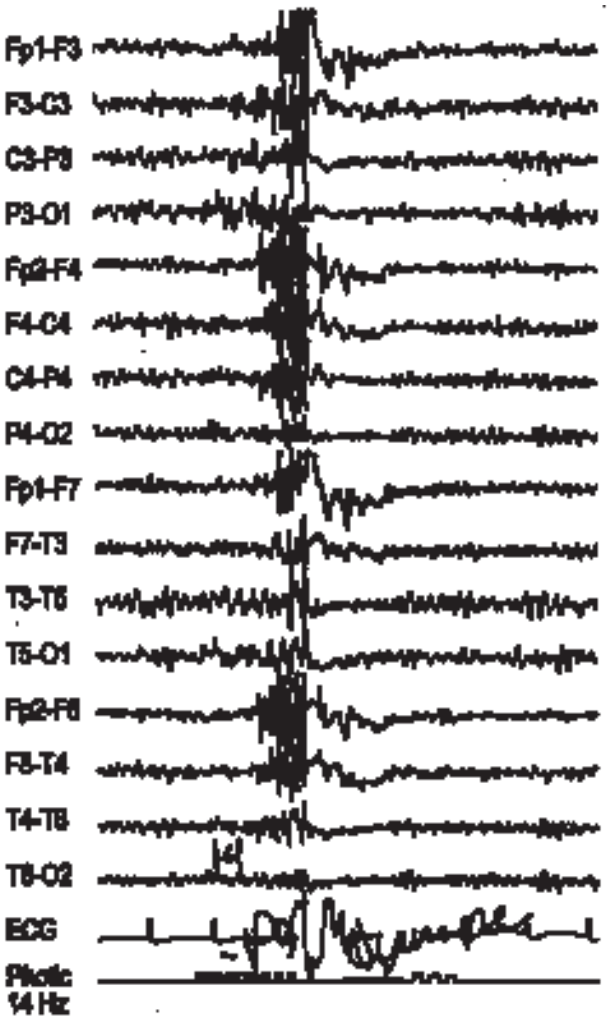

FIG. 8.7. Photomyogenic (photomyoclonic) response to 14-Hz photic stimulation. Prominent frontalis and temporalis myogenic potentials time locked to the flash stimulus end with a whole-body jerk.

in less than 0.1% of normal individuals and less than 1% of individuals with epilepsy (85,100,124,141). Although its appearance is sometimes dramatic and always statistically unusual, the photomyogenic response has no known clinical significance and is therefore considered a normal variant (105).

Photoepileptiform and Photoparoxysmal Responses

Photoepileptiform responses (PERs) are epileptiform patterns that are activated consistently by photic stimulation. Their association with epilepsy varies according to their topography, which can be divided into three main distributions:

1. Anterior dominant or generalized; bisynchronous and approximately symmetrical
2. Occipital dominant; bisynchronous and approximately symmetrical
3. Occipital dominant and localized; unilateral or strongly lateralized

Very rarely, unilateral anterior-dominant spikes are activated. Approximately 40% of bilateral PERs (categories 1 and 2) demonstrate asymmetries, particularly at the onset (17). One form of PER, the photoparoxysmal response (PPR) (formerly referred to as the photoconvulsive response) (Fig. 8.8), is defined as a generalized or anterior-dominant epileptiform pattern (category 1) (27). Although some authors refer to any bilaterally symmetrical and bisynchronous PER (i.e., categories 1 and 2) as highly epileptiform, posterior-dominant responses are far less likely to be associated with epilepsy than generalized or anterior-dominant responses (93,105). This topographical distinction is also found with pattern viewing and television or video game stimulation (64,125). In the closest animal model of human photosensitivity—the photosensitive baboon—photically induced epileptiform activity appears first in the frontorolandic cortex, not the occipital cortex (48). Thus, although the occipital cortex is believed to be involved in the generation of the PPR (18), generalized or anterior-dominant patterns are most closely associated with epilepsy.

The weak correlation between posterior PER and seizures often leads to difficulties in distinguishing between a posterior-dominant PER and an atypical photic driving response. There are no uniformly agreed on criteria for making this distinction, but three features that help to identify a normal variant are (i) a posterior-dominant response that is time locked or appears as a subharmonic or harmonic of the flash frequency, regardless of the amplitude or apiculate appearance; (ii) a prominent posterior response that occurs while photic stimulation is being terminated but ceases abruptly

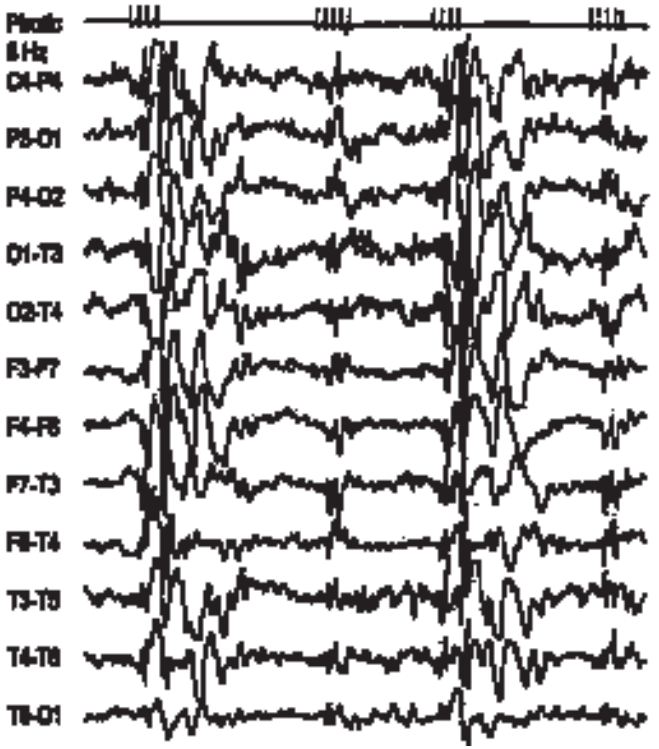

FIG. 8.8. Photoparoxysmal response to 8-Hz photic stimulation in a 6-year-old girl. Note the irregular spike-and-wave complexes and greater amplitudes in more anterior derivations.

within 150 milliseconds of the last flash stimulus; and (iii) a widespread sharp- or spike-and–slow wave complex restricted to the onset or cessation of the stimulus train (the "on response" and "off response," respectively; see Fig. 5) (77). The most suggestive features of a posterior-dominant PER are (i) a response that contains medium- to high-amplitude spikes or sharp waves and persists well beyond (> 200 milliseconds) the termination of the flash stimulus, and (ii) posterior response–associated clinical convulsive or nonconvulsive seizure activity.

Photoparoxysmal patterns are associated with three types of generalized seizure activity: (i) tonic–clonic, (ii) myoclonic, and (iii) absence. Most photoparoxysmal patterns consist of repetitive generalized irregular spike and multiple spike-and–slow wave complexes (see Fig. 8.8). During a self-limited discharge, there may be a slight impairment of consciousness that can be easily documented by a well-trained technologist. As the discharge persists, it becomes more organized and rhythmic at nearly 3 Hz in patients who have photosensitive absence seizures (Fig. 8.9), whereas those who have convulsive attacks often show persistent irregular spike-and–slow wave complexes. If the epileptiform pattern continues, the patient may develop an absence attack or symmetrical myoclonus, or progress directly into the tonic phase of a GTCS. PPRs are most often elicited at flash frequencies of 10–20 Hz (77), with the majority of investigators finding stimulation frequencies between 15 and 20 Hz to be the most effective (77,82,155). In some individuals, the PPR may be enhanced by stimulation with eyes open or with eyes closed or with eye opening and closure during stimulation (111). As previously noted, photosensitivity is reduced by sleep.

Although it is widely held that PPRs that outlast the stimulus are more likely to be associated with epilepsy compared to self-limited PPRs (124), other investigators have not found this to be a discriminating feature (76,142). As noted by Binnie (18), it is highly likely that any well-defined PPR obtained in an EEG laboratory in a patient with suspected epilepsy will be associated with seizures. Electrographic features that may increase the clinical significance of the PPR include an anterior-dominant or generalized response that is easily and consistently elicited, that lasts more than several seconds, and that clearly persists more than 200 milliseconds beyond the termination of the flash stimulation.

Approximately 4% of all individuals with epilepsy have a PPR (167), and between 70% and 77% of individuals with PPRs have epilepsy (76,162). The likelihood of encountering a typical PPR in the normal population is remote. In a study of 13,658 men in the Air Force, Gregory et al. (61) found a PPR that persisted beyond the termination of the flash stimulus in only 5 individuals, and only 1 developed epilepsy. Binnie (18) has estimated the likelihood of a PPR in a normal individual to be approximately 1 in 4,000. Most PPRs occur in adolescents and teenagers, coincident with the peak onset of idiopathic epilepsy syndromes associated with photosensitivity. In Great Britain, approximately 2% of all cases of epilepsy were found to manifest a PPR on the initial EEG (121). However, among those patients between the ages of 7 and 19, the incidence reaches 10%. Similarly, in a prospective study, Jeavons and Harding (77) found that photosensitive epilepsy most often begins at puberty. PPRs have a maximal incidence between 6 and 15 years of age and occur frequently in siblings of identified probands—whether or not the proband has epilepsy. Thus, in most cases, the PPR occurs as phenotypic expression of a genetic process that is variably associ-

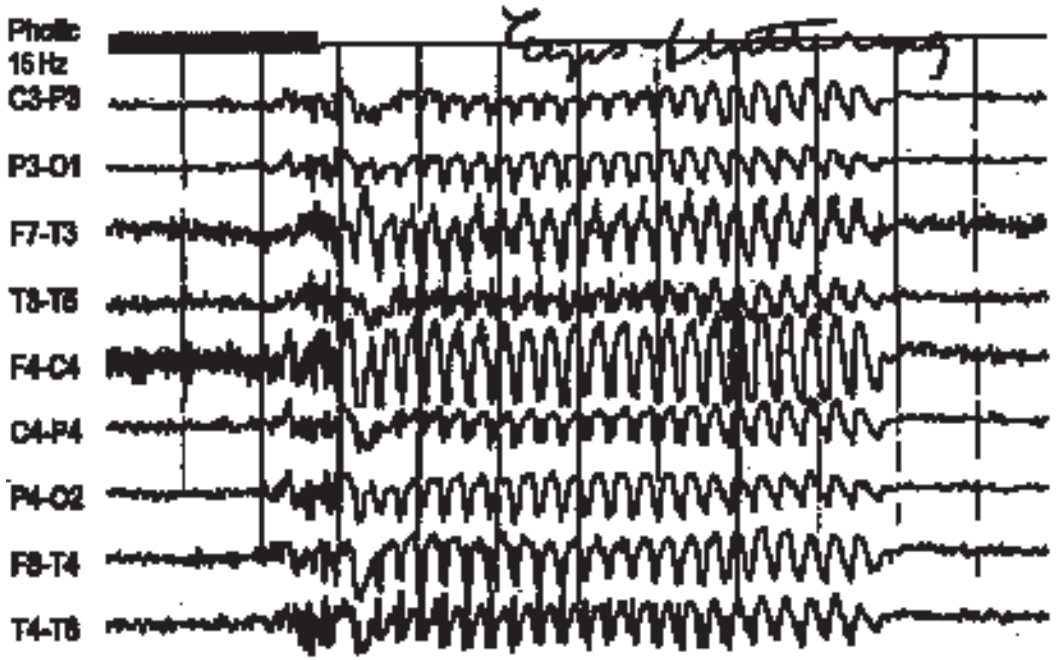

FIG. 8.9. Photoparoxysmal response to 15-Hz photic stimulation with initial fast activity evolving into a typical generalized 3-Hz spike-and-wave pattern. Eye fluttering typical of a myoclonic absence seizure was observed.

ated with the genetic determinant of seizures. In patients with known or suspected seizures, a generalized PPR strongly suggests that the patient has a genetically determined form of primary generalized epilepsy.

At least 30% of individuals with PPRs lose their photosensitivity by age 24, although there is no way of predicting which individuals will do so (63). As the PPR disappears, it is sometimes replaced by a more simplified pattern, lower in amplitude and without prominent spike components. Harding and Jeavons (66) have also shown that AED treatment, particularly with sodium valproate, can produce a similar effect: photosensitivity is diminished to the point where stimulation activates brief bursts of generalized slow-wave activity with absent or rare epileptiform components. It is therefore likely that this pattern of degraded photic activation represents latent photosensitivity. Unfortunately, a degraded PPR can only be identified with confidence in individuals who have previously demonstrated typical PPRs. Its value for predicting the risk of continuing seizures in patients undergoing AED treatment warrants further study.

Pure photosensitive epilepsy occurs in individuals who only have seizures in response to a visual stimulus. It accounts for nearly 40% of all photosensitive individuals with seizures. Seizure types include tonic–clonic (> 80%), absence (6%), partial (2.5%), and myoclonic (1.5%) seizures (18). Juvenile myoclonic epilepsy (JME) is also closely associated with photosensitivity. In a study of 181 patients with JME, PPRs occurred in 38%. Ninety-four percent of all the patients with JME had grand mal seizures, and 24% of all patients had absence seizures (75). In contrast, the syndrome of childhood absence epilepsy (pyknolepsy) with typical absence seizures and infrequent GTCSs is not associated with photosensitivity. Similarly, the syndrome of childhood epilepsy with occipital spikes is not associated with PPR to stroboscopic photic stimulation. Instead, darkness or eye closure activates the PER, whereas visual fixation or photic stimulation may inhibit it (92,112).

Pattern-Activated Photoparoxysmal Responses

In some patients the PPR is more likely to be evoked by stroboscopic pattern stimulation than by diffuse stroboscopic stimulation (64,87). In

such patients abnormalities occurring in response to patterned stimulation may signify the persistence of photosensitive epilepsy, whereas abnormalities occurring in response to diffuse stimulation indicate that the patient is at immediate risk for seizures. Once photosensitivity is identified, it can be diminished by avoiding rapidly varying light sources or by reducing light stimulation by various means (e.g., wearing sunglasses).

The likelihood of patients with a diffuse-light PPR having responses to stationary pattern viewing is probably between 5% and 22% (15,150). Pattern-evoked PERs should not be confused with the normal response to pattern viewing that occurs in some patients with prominent lambda waves (Fig. 8.10). The most effective activating patterns for either stroboscopic pattern stimulation or stationary pattern viewing consist of vertical parallel lines with high contrast (Fig. 8.11) (82). Moving patterns that oscillate between 15 and 20 Hz appear to be more effective than stationary ones and may elicit PPRs in the majority of photosensitive individuals with epilepsy. According to Harding and Fylan (64), responsiveness to stationary stimuli is found in individuals with PPRs, but not in those who have occipital spikes. As noted by Binnie (18), stationary pattern–induced photosensitivity has never been described in a normal individual. Moreover, it is extremely unusual for an individual to have pattern sensitivity without having stroboscopic pattern or diffuse light sensitivity, particularly with repeated testing. Because of the greater overall sensitivity of stroboscopic pattern stimulation, some investigators have recommended its routine use in laboratory testing. Clearly, all large institutional- and university-based laboratories should be equipped to perform pattern stimulation.

Typical absence is the most commonly activated seizure type among individuals with self-induced photosensitive epilepsy or pattern-sensitive epilepsy (113). The goal of identifying pattern sensitivity is the removal of certain patterns (in clothing, flooring, wallpaper, etc.) from the patient's environment. This can be particularly effective in preventing seizures in children.

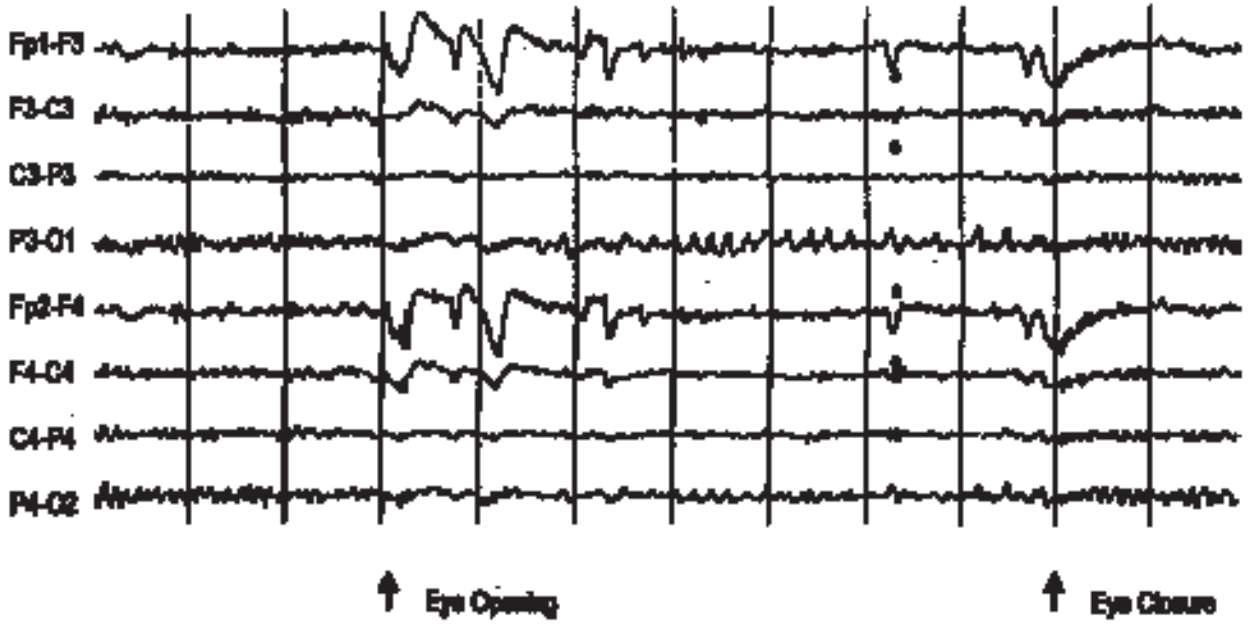

FIG. 8.10. Prominent lambda waves evoked by visual scanning of a complex object. Positive sharp waves arising from the occipital electrodes have the same morphology and topography as positive occipital sharp transients of sleep.

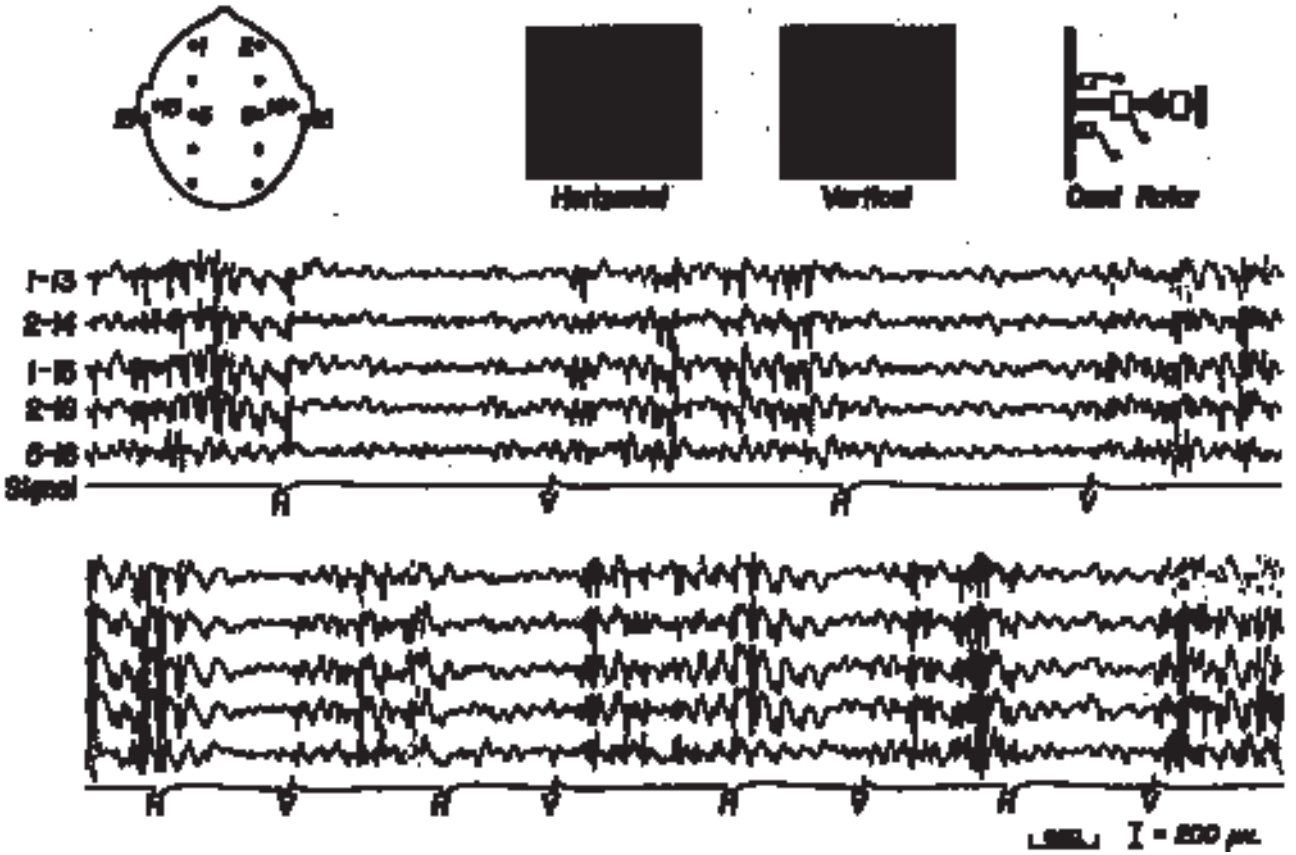

FIG. 8.11. Photoparoxysmal response to stationary pattern viewing of parallel lines. Specificity of vertical line sensitivity over horizontal line sensitivity is demonstrated. (From Bickford RG, Klass DW. Sensory precipitation and reflex mechanisms. In Jasper HH, Ward AA Jr, Pope A, eds. *Basic mechanisms of the epilepsies*. Boston: Little, Brown and Company, 1969:543–564, with permission.)

Photoepileptiform Responses and Partial Seizures

Photic stimulation rarely activates focal or unilateral occipital spikes. In such instances, there is almost always a lesion involving the occipital, parietal, or posterior temporal lobe (see Fig. 8.6). Focal occipital spikes are occasionally activated by other visual stimuli, including simple eye closure (Fig. 8.12). It has been suggested that a PPR that is equally elicited by left or right hemifield stimulation is most likely due to a genetic disorder, whereas unequal responses are more typical of acquired lesions (149). The activation of a focal seizure by photic stimulation is also an unusual occurrence. The first occipital seizure induced by photic stimulation was not reported until 1951 (103). Ludwig and Marsan (90) found that only 3 of 54 patients with occipital lobe

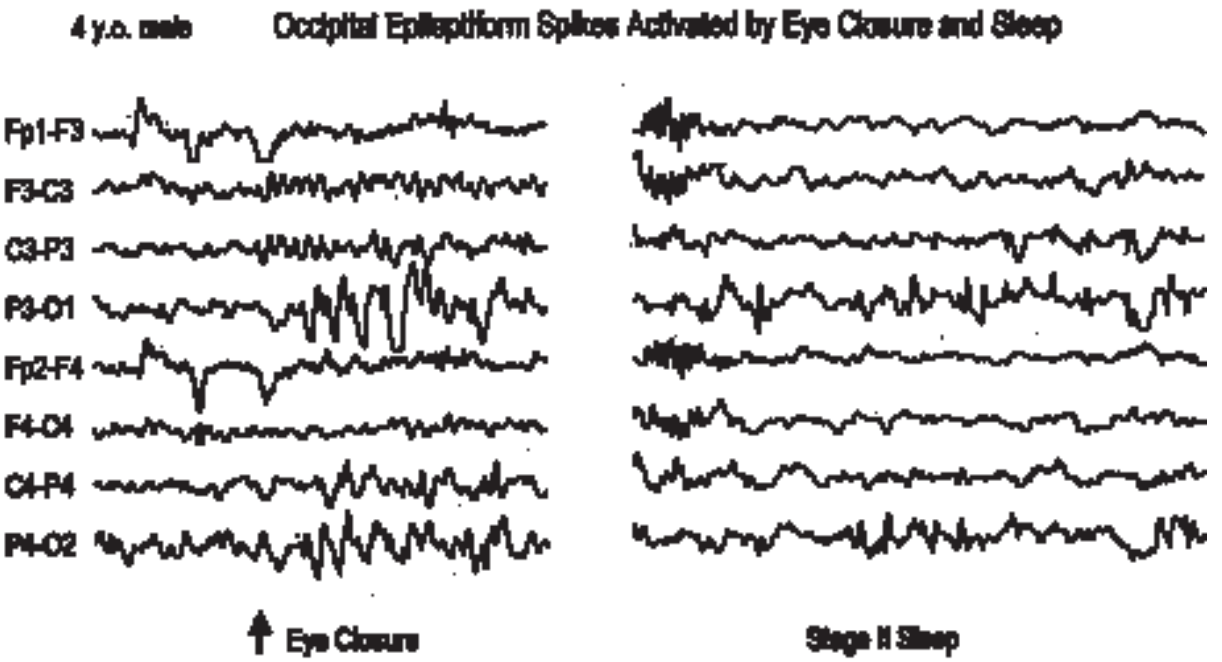

FIG. 8.12. Left occipital epileptiform spikes activated by sleep and eye closure in a 4-year-old boy with partial seizures.

epilepsy developed seizures during photic stimulation. Wolf and Goosses (169) were unable to activate seizures in any of 12 patients with a history of photosensitivity and partial seizures. Photically activated occipital lobe seizures have been demonstrated in patients with absence seizures who have no evidence of occipital lobe lesions, in patients without spontaneous seizures who have migraine, and in patients with benign partial epilepsy with extreme somatosensory evoked potentials (126). Patients with occipital seizures may also have a history of seizures provoked by a variety of light stimuli, including eye opening or closure, sunlight, sudden exposure to or withdrawal from a bright room, car lights, and television (9,11,68,139,152). In a tertiary referral center for epilepsy, Binnie and colleagues (19) found photosensitivity in only 2.8% of individuals with partial epilepsy compared to 21% of those with idiopathic generalized epilepsy. Less than 10% of patients with epilepsy with a PPR have partial seizure disorders. Therefore, a photoparoxysmal pattern in a patient with generalized seizures argues strongly for primary generalized epilepsy.

During epilepsy monitoring, particularly presurgical evaluations, it is important to note that partial seizures activated by photic stimulation may be a manifestation of geneticall y determined epilepsy (77). Several authors have described a syndrome of idiopathic, localized, age-related, photosensitive occipital lobe epilepsy with occipital unilateral or bilateral electrographic ictal onset (62). Triggering stimuli include photic stimulation, television, and computer monitors. The interictal epileptiform activity is limited to the occipital lobes.

SLEEP ACTIVATION

Activation during Sleep

Sleep is a highly effective method for eliciting both generalized and focal interictal epileptiform discharges (IEDs) (7,107,133). In as many as one-third of patients with complex partial epilepsy, IEDs may not be present dur-

ing wakefulness but appear only during sleep (107). Epileptiform discharges are also often more easily detected during sleep. Recordings during wakefulness are often obscured by muscle and movement artifacts, especially in children and adults who are unable to cooperate or relax during the recording. Nearly all patients with IEDs during daytime nap recording have their first discharge within 15–30 minutes of sleep onset (123,143). Thus outpatient EEGs in patients with suspected seizures should always include sleep, but the actual sleep recording generally does not have to exceed 30 minutes in duration. Epilepsy syndromes that commonly show activation with sleep are listed in Table 8.3.

When a sleep EEG recording is clinically indicated and the patient is unable to fall asleep, a short-acting sedative can be used to help induce sleep. Short-acting barbiturates and chloral hydrate are two agents that have been used for this purpose. Chloral hydrate is generally preferred because, unlike barbiturates, it does not induce beta-frequency activity in the background EEG. Every patient considered for sedation should be medically assessed for the risk of sedation. Patients should also be counseled about restricting their activities until the effect of sedation has worn off (see discussion under "Activation by Sleep Deprivation").

The detection and localization of IEDs are both important in routine diagnosis, as well as in presurgical epilepsy evaluations, particularly in the most common type of epilepsy surgery, anterior temporal lobectomy for intractable epilepsy (122). Temporal lobe IEDs during non–rapid-eye-movement (REM) sleep have been observed to become multifocal or more diffuse in distribution than IEDs recorded when the patient is awake. In contrast, IEDs during REM sleep apparently resemble awake IEDs more closely in location and distribution (132,163). Compared with IEDs during non-REM sleep, the location of IEDs recorded during either wakefulness or REM sleep generally corresponds better with the location of the surgical epileptogenic zone. However, because outpatient sleep EEG recordings are usually no longer than 30 minutes, they consist of mostly non-REM sleep and rarely of REM sleep. Nonetheless, a recent study showed that a non-REM sleep EEG of about 25 minutes' duration correctly disclosed lateralizing IEDs in 75% of temporal lobectomy candidates whose EEG during wakefulness had either bilateral or no IEDs (2). However, in patients undergoing presurgical monitoring, special attention should be paid to epileptiform activity during REM sleep.

In many patients, seizures, IEDs, or both occur either exclusively or predominantly during sleep. Table 8.3 lists the epilepsy syndromes in which seizures or IEDs are more likely to occur during sleep. Routine EEG with recording of sleep activity is valuable when any of these syndromes is clinically suspected. Nighttime sleep recording may be indicated when the daytime nap recording is inconclusive.

TABLE 8.3. *Epileptic syndromes with seizures or interictal epileptiform activity activated by sleep*

Continuous spike-and-wave pattern during slow-wave sleep (electrographic status epilepticus in sleep) (151)
Benign occipital epilepsy in infancy (10)
Generalized tonic seizures in chronic childhood epileptic encephalopathies (e.g., Lennox-Gastaut syndrome) (52)
Nocturnal epileptic myoclonus (99)
Benign epilepsy with centrotemporal spikes (benign rolandic epilepsy) (20)
Benign juvenile myoclonic epilepsy (i.e., on awakening) (8)
Epilepsy with generalized tonic–clonic seizures on awakening (74)
Frontal lobe epilepsy (168)
Autosomal dominant nocturnal frontal lobe epilepsy (134)

Activation by Sleep Deprivation

Sleep deprivation is an effective method for activating interictal discharges in many individuals with epilepsy (39). When the initial baseline EEG does not contain IEDs, a repeat EEG recording with sleep deprivation has between a 30% and a 70% probability of showing IEDs. Following sleep deprivation, IEDs may appear even when the patient is awake (50,119, 143,159). Thus the appearance of IEDs on the EEG following sleep deprivation is somewhat independent of the occurrence of sleep during the recording. In addition to sleep deprivation, the placement of additional electrodes may further enhance IED detection (143). In patients whose epilepsy diagnosis is clinically established or whose prior EEG has already revealed IEDs, sleep deprivation is unlikely to alter clinical management (39,159).

Although the effectiveness of sleep deprivation in activating seizures has not been objectively demonstrated by EEG recordings, a study of the effect of stressful life events on seizure frequency clearly showed sleep deprivation to be a significant factor (104). When seizures have not occurred in the first day or two of prolonged video-EEG monitoring, we sleep deprive our patients at least every other night, permitting only about 4 hours of sleep until seizures begin to appear.

Opinions regarding the need to routinely record sleep activity have not been uniform among clinicians. Some prefer to initially attempt recording spontaneous sleep activity (40). If this fails in a patient whose treatment may be altered by the detection of epileptiform abnormalities, sleep deprivation

or pharmacological sedation is then employed for a separate EEG procedure. However, when a second EEG procedure is not practical (e.g., patients who reside far from the laboratory), partial sleep deprivation and pharmacological sedation can both be used for the initial outpatient recording. Patients who have been sleep deprived or pharmacologically sedated for their EEG should be asked to restrict activities such as driving until they have recovered from the effects of sleep deprivation or sedation. Neither sleep deprivation nor pharmacological sedation should ever be used in those patients who cannot observe this precaution.

PHARMACOLOGICAL ACTIVATION

Discontinuing AEDs

There are three main clinical situations in which AEDs are withdrawn: (i) entering a medication-free state after a 1- to 2-year seizure remission (12); (ii) switching from one AED to another AED (38); and (iii) discontinuing the AED for the purpose of increasing the probability of interictal and ictal abnormalities occurring during long-term video-EEG recording. The rate of AED withdrawal varies in these situations. When a medication-free state of seizure remission is being attempted, gradual withdrawal over 2–3 months is recommended. In contrast, AED use is usually terminated abruptly or over a few days in inpatients undergoing video-EEG monitoring. When switching from one AED to another, the rate of AED withdrawal is determined by the urgency of the clinical situation and the pharmacokinetic properties of the AED involved. Our discussion is confined to the rapid withdrawal of an AED for the purpose of recording interictal and ictal events during long-term monitoring.

Activation of Interictal Epileptiform Discharges

Although 1%–2% of individuals without epilepsy have IEDs on their EEG (131), the detection of IEDs is still important in supporting a clinical suspicion of epileptic seizure disorder. As many as 40% of newly diagnosed epilepsy patients do not have IEDs on their initial EEG recordings (6). IEDs can also be absent in a considerable proportion of chronic epilepsy patients. According to Chung et al., approximately 10% of candidates for epilepsy surgery do not have IEDs despite long-term monitoring (28), although this percentage is far lower in our experience. The location of IEDs in epilepsy surgery patients is valuable in predicting the focus of ictal EEG onset (70) and the degree of postsurgical seizure control (122). Indeed, the value of IEDs in predicting the outcome of anterior temporal lobectomy is independent of the MRI findings (122).

The use of AEDs has long been suspected to suppress IEDs. Ludwig and Marsan (91) reported that 10 of 13 patients who had no EEG discharges while on AEDs developed spikes after abrupt drug withdrawal. Fifty-seven percent of all their patients reportedly developed a discrete epileptiform focus after drug withdrawal. Rodin and colleagues (128) also observed that IEDs become less frequent when phenytoin is taken. Intravenous phenytoin can suppress generalized IEDs, but the effect is only transient, lasting 10–20 minutes (102). Paroxysmal EEG activities have been observed in association with barbiturate withdrawal in addicted nonepileptic persons (165), but many of the reported EEG findings are nonepileptiform.

Most studies, including those referred to above, have not considered the role of nonpharmacological factors and have failed to evaluate study variables quantitatively using statistical analysis (158). In addition, serum AED concentrations were unavailable or were not used. More recently, using serum AED concentrations, Gotman and Marciani (60) found no correlation between AED withdrawal and the spiking rate of IEDs. Their findings are consistent with an earlier study of carbamazepine withdrawal in primates with partial epilepsy that failed to show an intensification of spike discharges (35). As yet, the most convincing effect of AEDs on IEDs is that of valproate on generalized spike-and-wave discharges (65). Both animal and clinical studies have demonstrated that valproate suppresses generalized IEDs, and that these discharges reappear after the drug is withdrawn. It is likely that the same findings pertain to other AEDs in patients with absence epilepsy that is successfully controlled.

The occurrence of seizures is a major factor in determining the likelihood and rate of IEDs in patients undergoing long-term video-EEG monitoring during AED withdrawal. Gotman and Marciani (60) found that spiking activity was enhanced after seizure occurrence, and that the effect could last several days. They used a continuous and automated method of spike detection and quantitation during long-term EEG recording. Using the same method of EEG analysis, their observations were duplicated in a kindling model of focal epileptic activity. Their findings raise concerns about the validity of previous studies of AED withdrawal that failed to consider the activating effects of seizures.

Activation of Epileptic Seizures

The abrupt discontinuation of AEDs is well known to exacerbate seizures in persons with active epilepsy. Seizure exacerbation in these patients has been attributed to a transient "rebound" phenomenon, or to a loss of thera-

peutic effect of the AED that was withdrawn. A rebound phenomenon similar to that seen in abstinence syndromes of drug addiction (44,69) was suspected by Marciani and colleagues (96), who observed that seizure frequency increased early as the AED dose or the concentration declined, but not when the dose became minimal. The exacerbation of seizure frequency was also self-limited—it did not always persist toward the end of the AED tapering process. Theodore and colleagues (154) also observed that seizure attack rates were highest when serum concentrations passed below 15 μg per milliliter, but not when concentrations were much lower.

There is also evidence to support a loss of therapeutic effect, rather than a rebound phenomenon, as the basis for increased seizures during AED withdrawal. Studies (24,98) have shown that that seizure frequency increases when serum drug concentrations become subtherapeutic, but not as levels are falling from their baseline values. A comparative assessment of studies in the literature is difficult because the AEDs tapered were not the same between studies, and the order and rate of AED withdrawal were not uniform. The definition of the withdrawal and the baseline periods were mostly dissimilar or unstated. Furthermore, the schedule of serum AED measurement also differed between studies. Thus it is currently not possible to determine with certainty whether a rebound phenomenon or the loss of therapeutic effect is responsible for increased seizure frequency after abrupt AED withdrawal.

Despite difficulty in attributing withdrawal seizure exacerbation to a rebound phenomenon, abrupt discontinuation of barbiturates (44) or benzodiazepines (69) is unequivocally known to produce an abstinence syndrome with withdrawal seizures in individuals without epilepsy. The seizures are almost always generalized convulsive episodes without focal onset, and they mainly occur during the period of the abstinence syndrome. Animal studies suggest that these seizures are subcortical in origin (43). This raises the theoretical possibility of nonlocalizing rebound seizures confounding the identification of the onset of seizures recorded during long-term monitoring in patients undergoing barbiturate or benzodiazepine withdrawal. However, rebound seizures occur in patients abruptly withdrawing from prolonged exposure to very high doses of barbiturates and benzodiazepines. Most cases also involve short-acting barbiturates (e.g., secobarbital and pentobarbital) that are not used for chronic treatment of epilepsy. In epilepsy patients taking clinically appropriate doses, the long half-life of phenobarbital probably prevents acute abstinence syndrome and rebound seizures from developing. In fact, seizures may not increase until several weeks after phenobarbital is discontinued (154), whereas rebound seizures in persons addicted to barbiturates occur within days or hours following medication withdrawal (44).

Localizing Value of EEG Abnormalities Activated by AED Withdrawal

Epileptiform discharges that occur as a result of postictal enhancement have been observed to be more widespread or contralateral to the focus of seizure onset (59). Caution should be exercised when using these IEDs to help localize the focus for epilepsy surgery. Localization of the surgical focus should not be based solely on the location of IEDs, particularly those seen in the hours immediately following seizures.

Drug withdrawal may occasionally unmask a seizure focus that is different from the location where habitual seizures originate (95,147). Spencer and colleagues (147) evaluated the video and depth electrode recordings of 71 baseline and 89 withdrawal seizures in 18 patients. During AED withdrawal, four patients had seizures with EEG or clinical features that were not typical of habitual seizures. One of the four had a poor surgical outcome despite habitual seizures having originated from a single area. It is doubtful that drug withdrawal could activate a de novo seizure focus that was not preexistent. Notably different seizures can also occur when an AED is not yet withdrawn (98). Also, bilaterally independent foci of EEG discharges are often present even before the AED is withdrawn (95). GTCSs occur in nearly half of all partial epilepsy patients undergoing AED withdrawal during long-term monitoring, including many who previously have never had generalized seizures (96). As a rule, these seizures also begin clinically and electrographically as partial seizures that are no different from the patients' habitual seizures (95). The duration of either partial or secondarily generalized seizures is usually unaffected by AED dose reduction (144,153). There is no evidence that AED withdrawal alters the pattern of ictal discharges at the onset of these seizures.

Regardless of the status of AED medication and the number of foci detected, seizures recorded in an epilepsy monitoring unit should always be reviewed and verified with the patient and family, friends, or caretakers to ensure that they are the same as habitual seizures. Multiple seizures should be recorded when localizing the seizure focus for epilepsy surgery, especially in patients whose clinical history or MRI is not consistent with the electrophysiological data. Video-EEG monitoring should be extended to ensure that another epileptogenic focus is not overlooked. One study (67) shows that, in patients with bilateral foci, seizures that occur close to each other in time are more likely to arise from the same hemisphere than seizures that occur farther apart from each other (more than 8 hours in between). The discovery of multiple ictal foci does not preclude surgery, if it can be established that habitual seizures originate from one surgically resectable area (41,145).

Potential Complications of AED Withdrawal and Their Prevention

The most important risk of AED withdrawal is the development of status epilepticus (45,140). More commonly, injuries such as fractures, joint dislocations, and external or internal soft tissue injuries result from isolated seizure episodes. The elderly are especially susceptible to vertebral compression fractures (94).

Most complications of AED withdrawal can be prevented if patients are under the care of experienced staff. Table 8.4 lists measures that can be employed to reduce the risk of AED withdrawal in the video-EEG monitoring environment. Theodore and colleagues (153) observed that GTCSs that stop spontaneously usually do so within 2 minutes. Unless medically contraindicated, intravenous lorazepam should be given for GTCSs that persist more than 2 minutes. If necessary, this can be followed by nonloading doses of fosphenytoin. Rectal diazepam is also appropriate for treating seizure clusters (89), and sublingual lorazepam has also been reported to be effective in controlling seizure clusters in adults (94). In instances when the threat of status epilepticus is not high and there is no immediate need to prevent seizure recurrence, resumption of the oral AED that was withdrawn may be sufficient. Van der Meyden and colleagues (157) have demonstrated that, in 80% of the patients who were not taking phenytoin or carbamazepine, "therapeutic" serum concentrations could be achieved in 4 hours after oral loading with phenytoin and in 8 hours after carbamazepine loading.

TABLE 8.4. *Recommended measures of reducing risk of AED withdrawal in the setting of video-EEG monitoring*

General Measures

1. Incorporate safety features when designing patient areas, such as padding furniture and bathroom fixtures and providing ample space for ambulation.
2. Ensure availability of qualified staff, equipment, and medication for cardiopulmonary resuscitation.
3. Accompany patients when they are ambulating. Use head-protection gear for those at high risk of falling.
4. Evaluate the patient when a seizure occurs, to ensure that ictal and postictal events do not compromise the patient's safety or vital functions.
5. Note the time of occurrence and the severity of each seizure.

Pharmacological Measures

1. Establish and maintain intravenous access throughout the drug withdrawal period.
2. When two or more generalized epileptic convulsions occur within 12 h, consider resuming oral AED or using rectal diazepam.
3. When two or more generalized epileptic convulsions occur within 2 h, consider giving intramuscular or intravenous fosphenytoin. If fosphenytoin is contraindicated, consider phenobarbital, lorazepam, or valproic acid.
4. When epileptic convulsion lasts 2 min or longer, administer intravenous lorazepam if seizure is persisting at the time of administration.
5. In patients with epilepsy, resume oral therapy with the AED withdrawn or with a new AED before discharge from the hospital.
6. When appropriate, check the serum concentration of the AED that the patient will be taking, to ensure that the concentration is in the "therapeutic" range before discharge from the hospital.

Benzodiazepines and short-acting barbiturates should be cautiously withdrawn. Seizures and other withdrawal symptoms may be particularly severe in persons who have been taking either medication at a high dose (44,146). A state of agitation and dysphoria can follow carbamazepine withdrawal (37). Temporary resumption of carbamazepine or the use of an oral benzodiazepine can alleviate the symptoms.

A postictal psychiatric disturbance has been reported to occur in nearly 8% of patients in the video-EEG monitoring unit. Half of these patients never had previous psychiatric disorders (79). Complications of prolonged inactivity can occur during video-EEG monitoring. The complications include venous thromboembolic disorders and postural hypotension. They can be minimized by having the patient exercise on a treadmill or a stationary bike under close supervision. The patient can also exercise in a recumbent position by using a pedaling device attached to the bed frame. In most centers, the risk of major complications can be kept below 1% (94,96).

AED Withdrawal Procedure for Long-Term Monitoring

The schedule of drug withdrawal should be individualized to optimize the probability of recording seizures without undue risk of injury. Because of the concern of injury from unattended seizures, drug tapering is often deferred until after admission or at least one concurrent AED is maintained until admission. After admission, all AEDs can be simultaneously reduced by a third of the maintenance dose every day. Simultaneous withdrawal of AED is advisable because peak activation of seizures can be delayed for weeks if some AEDs are maintained (24).

Abrupt discontinuation of valproate may be appropriate in the setting of video-EEG monitoring because studies have shown that the pharmacological effect of valproate persists beyond its complete elimination from the serum (65,130). Because of the possibility of platelet dysfunction associated with valproate usage (88), we prefer that valproate be withdrawn before epilepsy surgery is performed.

A slower taper of AEDs is warranted when the patient's history suggests that activation of status epilepticus is highly probable, or when the risk of convulsion-related complications is unacceptable. AEDs do not need to be withdrawn if the patient is experiencing daily seizures at the time of admission.

Activation with Parenteral Drugs

Before long-term video-EEG monitoring became technically feasible and clinically practical, there was a much greater need for parenteral drugs to induce interictal and ictal discharges. Intravenous drugs previously used to induce EEG discharges include pentylenetetrazole (31), methohexital (166), and bemegride (Megimide) (164). A study of 133 patients with depth EEG recordings revealed that only 60% of the pharmacologically induced seizures were localized to the same foci as those localized by spontaneous seizures. Moreover, the risk of failure in seizure control with resection of a focus that was localized by drug-induced seizures is two times higher than that with resection of a spontaneous seizure focus (164). The failure rate of resection of drug-induced seizure foci was 39%, compared with 18% with resection of spontaneous seizure foci. For these reasons, drugs are no longer used to induce seizures for localization in epilepsy surgery.

Intravenous alfentanil hydrochloride has been demonstrated to be effective in inducing temporal lobe spikes for intraoperative electrocorticographic and depth electrode recording (25). Alfentanil hydrochloride is a short-duration opioid analgesic used to augment intraoperative anesthesia. It is not used with extraoperative EEG recording because of the need for respiratory support when it is administered.

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Chapter 9

Artifacts

George H. Klem

Physiological Artifacts
- Eye Movements
- Electrocardiographic Artifacts
- Electromyographic Artifacts
- Glossokinetic Artifact
- Galvanic Skin Response
- Physiological Movements

Nonphysiological Artifacts
- Instrumental Artifacts
- Electrode Artifacts
- Environmental
- Digital

References

The recording of any physiological activity is always plagued with having to differentiate between genuine activity and that which is introduced through a variety of extraneous influences. These artifacts may affect the outcome of the recording procedure. Artifacts originate from a variety of sources, and their recognition, identification, and possible elimination are a primary responsibility of the electroencephalographic (EEG) technologist. Even the most expert technologist cannot always eliminate all artifacts. However, it is always a major goal to identify the artifactual activity and to offer proof to the electroencephalographer that it is not of cerebral origin and should not be misinterpreted as such. This can be accomplished in many ways. First one must understand that most recorded physiological activity will have a logical topographic field of distribution with an expected falloff of voltage potentials. Therefore, one must have a firm understanding of the principals of localization and use this knowledge in a logical way, not relying just on pattern recognition (11,13). Whenever something unusual or unexpected occurs during any EEG recording, the source of the activity must be determined. The unusual or unexpected may be something localized to a single electrode, multiple electrodes or channels, and will usually have an illogical distribution that defies the principles of localization mentioned earlier. The source of this activity is usually noncerebral (Table 9.1). Frequently these artifacts will appear genuine and, if unrecognized, can lead to misinterpretation of the recordings.

Artifacts are generally divided into two groups: physiological and nonphysiological (3,16). Physiological artifacts usually arise from generator sources within the body but not necessarily the brain (see Table 9.1). Bioelectrical generators present in the body may produce artifacts when an EEG recording is made directly from the surface of the brain (electrocorticogra-

TABLE 9.1. *Artifact sources*

Physiological	Nonphysiological
Eye Movements	**Instrumental Artifacts**
Horizontal eye movements	Amplifier & electronic components
Vertical eye movements	Sixty cycle (line frequency) (fifty cycle)
Oblique eye movements	Capacitive
"Glass eye" asymmetries	Inductance
Eyelid flutter	Magnetic
Nystagmus	Electrostatic
Electroretinogram	
Electrocardiographic Artifacts	**Electrode Artifacts**
Normal high-voltage QRS complex	"Electrode pop"
Extra systoles	Intermittent contact
Pulse artifacts	Impedance-related artifacts
Ballistocardiographic artifacts	Electrolytes
Pacemaker	Electrode movement
Arrhythmia	Electrode placement
Defibrillators	
Electromyographic Artifacts	**Environmental Artifacts**
Lateral rectus	Radiofrequency artifacts
Single motor units	Line isolation scanners
Frontalis EMG	Bipolar coagulators
Temporalis EMG	Impedance mismatches
Occipital EMG	Multiple ground artifacts
Swallowing, chewing	IV drip, IV pumps
Glossokinetic Artifact	Sequential pressurized stockings
Tongue movements	Static
Galvanic Skin Response	**Digital Artifacts**
Perspiration	DC offset
Salt bridge	Aliasing
Physiological Movements	**Multiplexing Artifacts**
Tremors	
Hypnic jerks	
Nocturnal leg movements	

phy). Nonphysiological artifacts come from a variety of sources, and some of these are also listed in Table 9.1. A good rule to remember is that if the activity in question is limited to a single channel or electrode, it must be assumed to be artifactual in origin until proved otherwise. As technology expands and additional equipment is developed and put into clinical use, novel artifacts will appear. It will remain essential that technologists and electroencephalographers develop the skills necessary to recognize them and thereby avoid misinterpretation (2).

PHYSIOLOGICAL ARTIFACTS

Eye Movements

The eye movements recorded by standard 10-20 electrode placements are generated by the corneoretinal potential. This generator produces a direct current (DC) potential of approximately 50–100 mV. The electrodes involved are the ones closest to the eyeball: Fp1, Fp2, F7, and F8. This potential is best regarded as a dipole with the positive pole localized to the cornea and the negative pole to the retina (18). The electrical potential detected by the electrodes surrounding the eyeball is a positive potential, and the voltage is usually greater than the cerebral potential generated by the brain. The artifact created by this generator is detected whenever there is movement of the eyes. When the eyes are closed, the movement of eyeballs is in a natural upward position (Bell's phenomenon), and this upward movement is detected by a positive potential recorded at the supraorbital electrodes placed at Fp1 and Fp2. As with most physiological potentials, the activity will have a falloff recorded at the next electrode (15). The activity recorded at F3 and F4 will be smaller in amplitude (Fig. 9.1). When the eyeball moves in a downward direction, the inverse occurs.

When the eye moves to the left, the activity recorded at Fp1 and Fp2 remains steady, with no change in potential, because the positive pole of the eyeball position remains constant relative to these electrodes. However, the positive potential is detected by the electrode F7, and it becomes more positive than other electrodes connected to it in the montage. Because the eyes usually move conjugately, the cornea is moving away from the F8 electrode and it becomes less positive, or more negative, because the retina is now closer to this electrode. This horizontal movement to the left produces a positive phase reversal with maximal positive potential at F7, and a negative phase reversal with maximal negative potential recorded at F8. This is shown in the bipolar montage seen in Figure 9.1.

Monitoring vertical and horizontal eye movement is best accomplished by placing electrodes near both the left and right outer canthi and above and below the eyes. The electrodes should be placed close to the eye and will record potentials greater in amplitude than the standard electrodes placed according to the "10-20" international placement system.

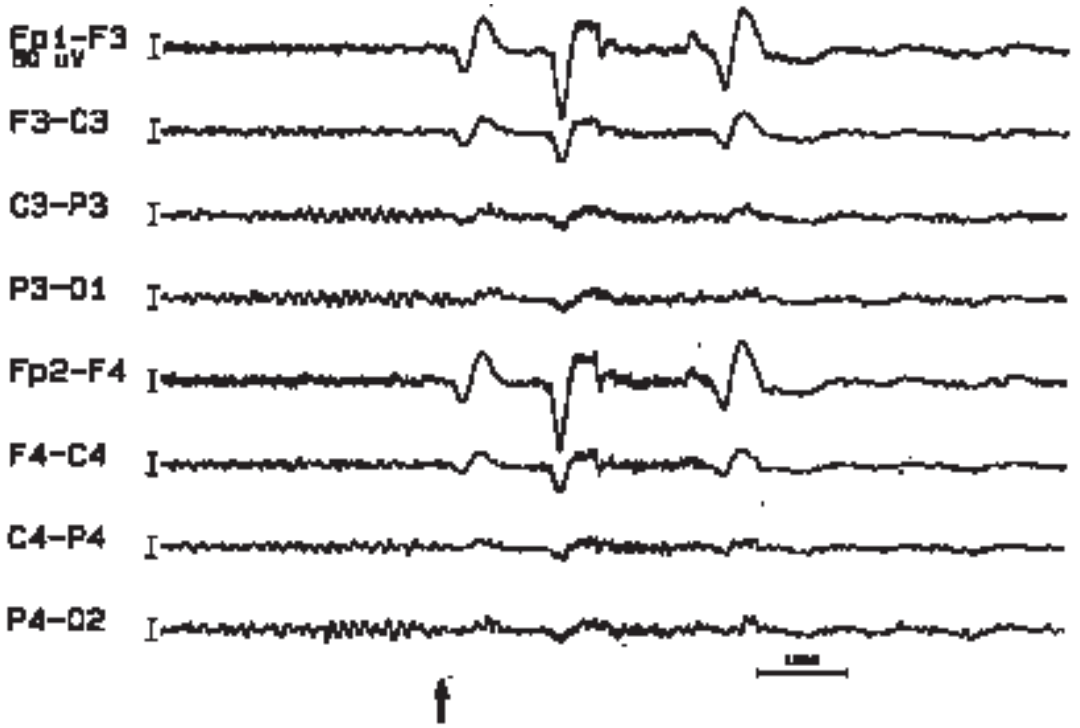

FIG. 9.1. The most common physiological artifact seen in EEG recordings is eye movement. This sample demonstrates the natural falloff of voltages seen with opening of the eyes, and also demonstrates the blocking of the alpha rhythm when this occurs.

Oblique eye movements may be more difficult to detect and are not infrequently misinterpreted as focal abnormalities. An eye movement upward and to the left would generate an equal positive potential recorded in a bipolar montage recording from electrodes Fp1-F7, and a large upward deflection on the channel recording Fp2-F8. This occurs because the positive potential (cornea) involves both Fp1 and F7 relatively equally, and the potential difference recorded with a differential amplifier approximates zero.

The potential difference recorded from the derivation of Fp2-F8 is negative at Fp2 and positive at F8, creating an upward deflection on that channel. This is due to the rules of localization (if input 1 is more negative than input 2, an upward deflection will be recorded). This example is only correct if there is a true 45-degree oblique eye movement. Of course this rarely occurs, and one must be cautious in interpreting this without the use of eye-monitoring electrodes as described above.

Asymmetric eye movements can occur for several reasons (18). The first problem to be looked for is asymmetrical placement of the electrodes. A small deviation from the standard placement can lead to slight asymmetries in the recording. The next most obvious cause for this type of artifact is unilateral enucleation and a prosthetic eye replacement. Patients with a third cranial nerve palsy or external ophthalmoplegia will be unable to produce conjugate upward gaze and will have an asymmetrical eye blink with decreased amplitude, (a smaller deflection) on the side of the paralysis. Asymmetry of eye movement may also be due to a skull defect, usually a craniotomy. Here the eye blink (vertical) artifact will have greater amplitude on the side contralateral to the cranial defect when recorded in a bipolar anterior–posterior derivation. This is, in effect, a "breach" artifact (see Chapter 7). The frontal pole (Fp1) electrode will record the greatest voltage potential because it is closest to the generator source. The

frontal electrode (F3) will record a very similar response as a result of the defect in the skull, and, when the frontal pole and frontal electrodes are connected, they will show a cancellation effect because the two electrodes are recording similar-amplitude eye movements. The homologous electrodes contralateral to the defect record the difference in voltages, with a higher amplitude recorded from the frontal pole electrode and the usual voltage gradient recorded from the frontal electrode.

Eyelid flutter is less easy to evaluate. The patient will frequently produce rhythmic activity, typically at a frequency of 5–8 Hz, that will be intermittent but occurs for many seconds at a time. This activity may mimic intermittent rhythmic slow (IRS) activity in the theta or even delta range. However, it usually consists of low-voltage slowing and is often detected at only the Fp1 and Fp2 electrodes. There may not be a falloff of the voltage detected at F3 or F4 or even at FZ because of the low-voltage of the flutter. This activity can be felt by lightly placing one's fingers over the eyelids and then noting on the recording the presence or absence of the eye movements. The typical monitoring for this type of activity is to record it from electrodes placed on the left or right side above (L/RAE) and under (L/RUE) one eyeball using a bipolar montage.

Horizontal nystagmus normally occurs bilaterally, but it is often only detected unilaterally. The electrode recording this movement is either F7 or F8, and the movement may be recorded only by the electrode on the side of the fast direction of the nystagmus because of the larger positive voltage produced by the proximity of the cornea to that electrode. This artifact will often mimic a calibration square wave with a low-frequency cutoff of 0.12 seconds' duration (Fig. 9.2). Vertical nystagmus is rarely detected from the Fp1 and Fp2 electrodes because of the low voltage generated by this movement and the distance of these electrodes from the eyeball. When seen, it typically follows an eye closure and will produce a positive signal when recorded from Fp1-F3 and Fp2-F4. It is usually semirhythmic and

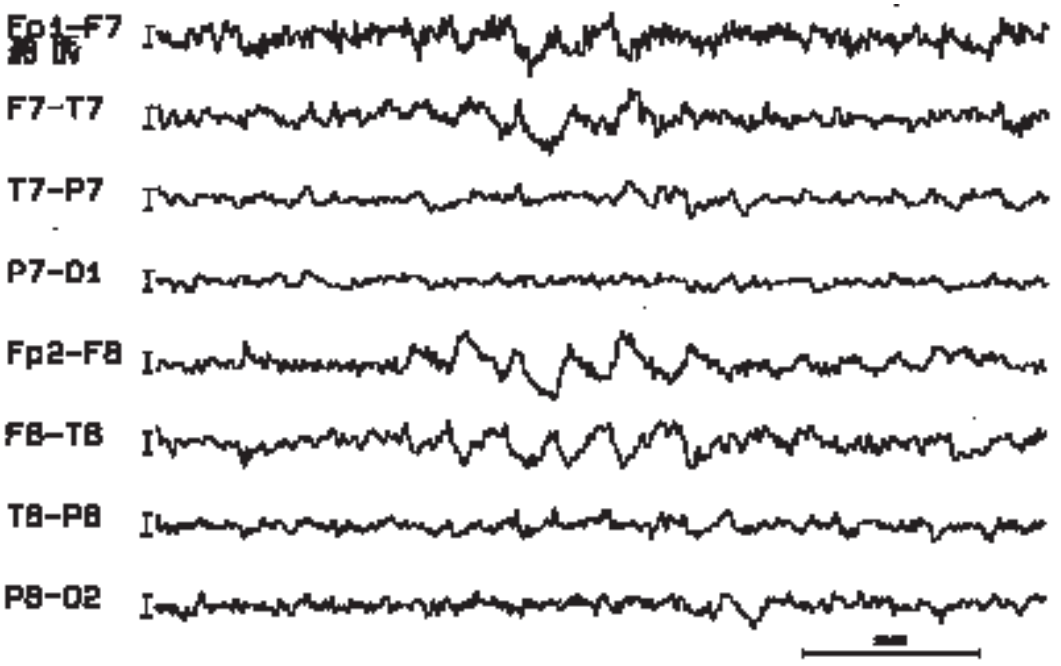

FIG. 9.2. Horizontal nystagmus to the right. There is a positive phase reversal at the F8 electrode as the cornea comes closer to that electrode. There is a lesser negative phase reversal at the same time as the F7 electrode becomes less positive as a result of the cornea moving away from the left temporal area.

may appear to be IRS activity, highly localized to the frontal poles. Rotary nystagmus is rarely detected in the outpatient EEG laboratory. It is more often seen in hospitalized patients requiring bedside recordings. In all cases, monitoring of the nystagmus with extraocular eye electrodes is essential to identify the movements accurately.

The electroretinogram (ERG) is a low-voltage response to light stimulus of the retina. In normal subjects, the voltage typically recorded during an evoked potential ERG is usually less than 50 μV using a contact lens electrode placed directly on the eyeball. The activity consists of two peaks, an A peak and a B peak, that occur approximately 12 and 35 milliseconds following a bright light stimulus (i.e., photic stimulation) (Fig. 9.3). This response is usually obscured by normal EEG activity recorded from the frontal poles, especially when recorded as an analog signal at paper speeds

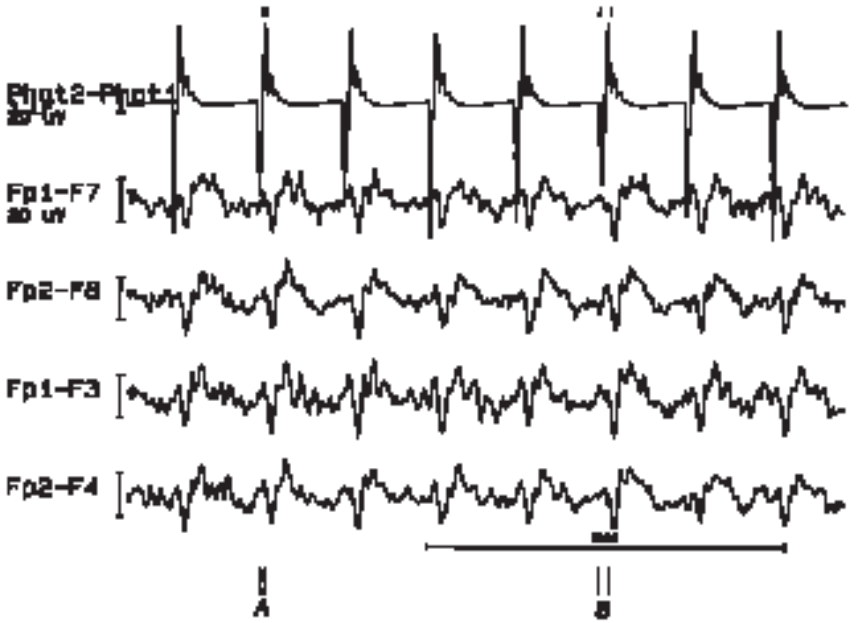

FIG. 9.3. ERG recorded in a bipolar montage. Note that the time scale is increased to measure the latency of the response from the stimulus artifact seen in the first channel. Time at "A" shows a 13-millisecond latency, while the latency at "B" is 33 milliseconds. These correspond to the "a and b" wave of the ERG.

of 30 mm per second. During recordings to determine electrocerebral inactivity (ECI), the background activity is by definition of extremely low voltage, and the retinal response can be seen during photic stimulation. This normal physiological response can be confused with an electrode artifact generated by a silver electrode reacting to the light source (19). To determine which source is causing the artifact, the technologist can simply drive the photic stimulator to produce a signal of approximately 30 flashes per second. If the response recorded maintains a constant amplitude, the source is a faulty electrode. If the amplitude of the response diminishes, it is due to the retinal response being physiologically unable to respond to the faster flash rates. If the response is constant, with no delay to the stimuli, and no decrease in amplitude, then the artifact is most likely due to the silver metal of the electrode being exposed. This can be caused by a chip in the plating of the electrode. This artifact can be identified by shielding the frontal electrodes with an opaque covering that prohibits the light source from being recorded by a faulty electrode.

Electrocardiographic Artifacts

The normal cardiac QRS complex is an easily monitored artifact. It is best recorded by applying electrodes to the chest. Usually two electrodes are attached, one to the left chest and another to the right chest.These electrodes are then connected in a bipolar fashion. The resultant signal is a high-voltage response generated by the electrical field of the heart. This signal is then recorded as an additional channel to the usual montage. In evoked potential terms, ECG recorded at the scalp represents a "far-field" potential. The artifact is most often detected by referential montages, especially those using the ear electrodes as a reference.The field of the heart is oriented to produce a negative polarity signal from one side of the head, detected by the electrode A1 or A2, and a positive polarity artifact from the remaining reference electrode, A2 or A1. ECG is particularly prevalent in obese patients, patients with short necks, and babies, in whom the head is close to the thorax. It can sometimes be detected at the occipital electrodes when a "neck roll" issued to extend the head off the bed. The artifact is especially prominent in ECI recordings (4). It may be possible to reduce the amount of this artifact by changing the head position relative to the position of the thorax.

Extra systoles and cardiac arrhythmias are frequently detected in the temporal chain of bipolar montages but not in the parasagittal derivations, because the temporal electrodes are closer to the electrical field of the

heart. These cardiac beats often mimic cerebral sharp waves, spikes, or even temporal theta activity and may be misinterpreted because the field of electrical activity can have a logical distribution, or electrical field (Fig. 9.4).

Pulse artifact is usually confined to a single electrode and appears as a slow-wave potential (2,10). It occurs when an electrode is placed over surface arteries and is most prominent when the electrode is loosely applied. It is easily monitored by using an electrocardiogram (ECG) lead and recorded close to the artifact. The ECG signal will be time locked to the slow wave and always occurs at the same location in respect to the slow wave (Fig. 9.5).

Another artifact typically seen in ECI recordings is the ballistocardiographic potential. This artifact is more prevalent during repeat studies for ECI than on the first study. It is troublesome to the technologist because, even with good electrode technique, it is difficult to correct, and the artifact frequently obscures the entire recording. Cardiac monitoring demonstrates the relationship of the cardiac signal to these pulsations, although they are not always time locked to any particular phase of the signal. These vibratory pulsations often mimic low-voltage theta, alpha, and beta frequencies, and mixtures of these low-voltage frequencies often resemble cerebral activity.

Pacemaker-generated artifact introduces high-voltage, short-duration spike activity that precedes the usual cardiac signal and is easily monitored with electrodes placed on the chest. This artifact may be continuous or intermittent, depending on the type of pacemaker (continuous or demand).

Cardiac arrhythmias are frequently recorded from the same electrode derivations described above and can be misinterpreted as ictal events,

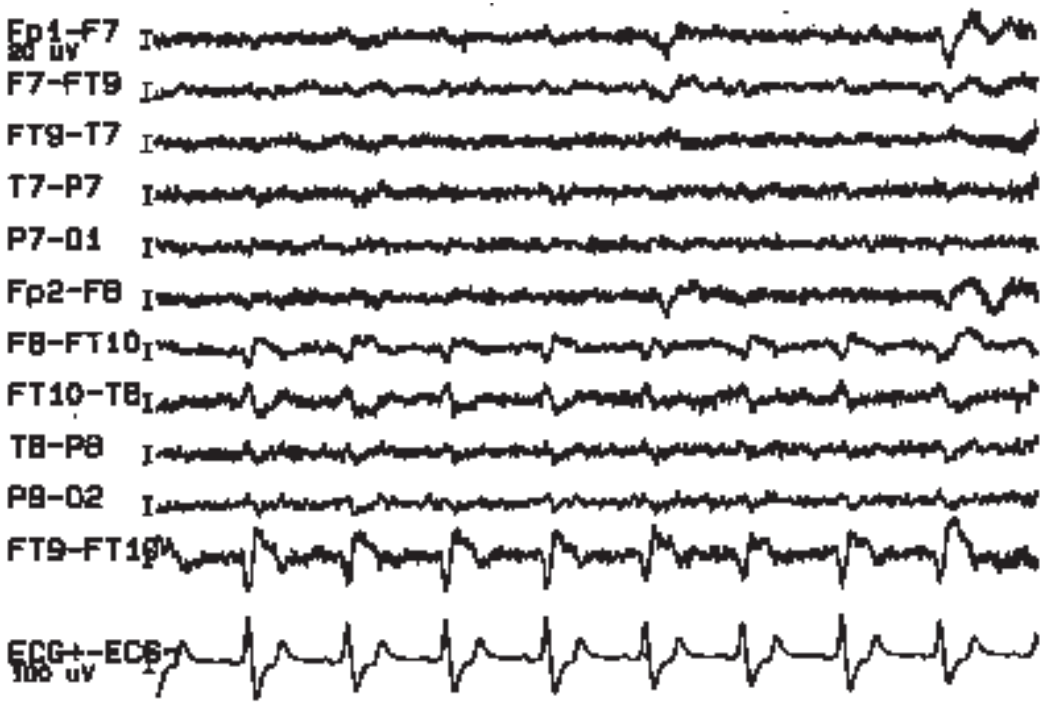

FIG. 9.4. ECG artifact that is recorded from electrodes on the right temporal bipolar montage and mimics a periodic pattern. Without an ECG monitoring channel, one might find it difficult to call this an artifact.

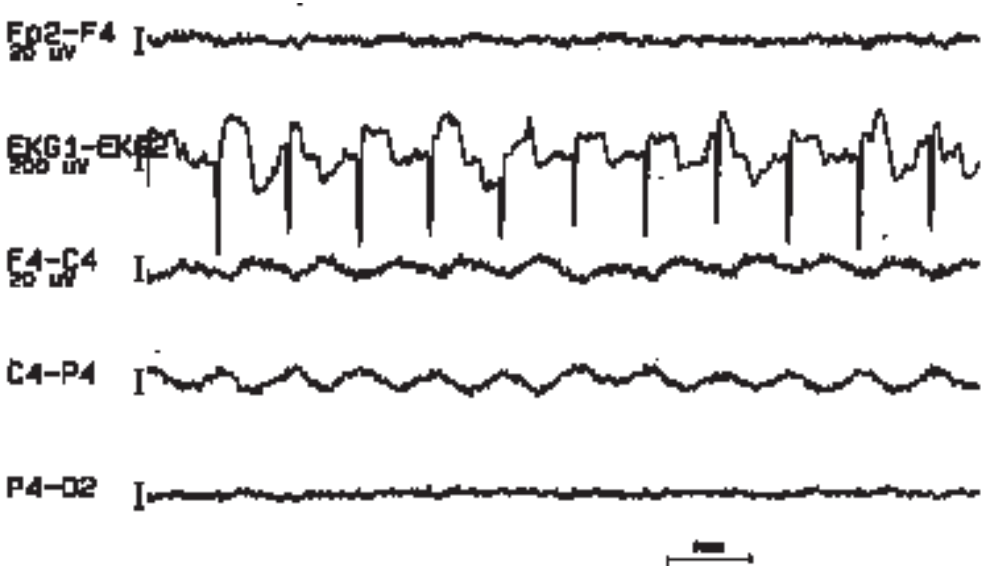

FIG. 9.5. Pulse artifact recorded from the C4 electrode. With digital EEG, it is easy to reformat any montage; in this case the ECG monitoring channel was changed to record the ECG close to the artifact.

because they may present as an evolving pattern. These patterns are easily monitored by recording from electrodes attached to the chest (19).

Electromyographic Artifacts

Lateral rectus artifacts are generated by low-voltage motor unit potentials localized to the lateral rectus muscles (3,19). They are typically recorded from the F7 and F8 surface electrodes, and the positive component is most commonly seen. When recorded in a bipolar montage, the activity is best seen at the electrode closest to the lateral rectus muscle being contracted. The lateral rectus potential appears with a sharp positive deflection of very short duration with a slow falloff as the muscle relaxes. It mimics the appearance of a calibration signal. The activity is usually not seen from the corresponding contralateral electrode.

Single motor units may be recorded from any electrode placed over one of the scalp muscles (19). They appear as repetitive negative or positive deflections that have a comb-like appearance and are typically recorded from a single electrode. Although usually repetitive, they may occur in isolated single deflections that seem random. This artifact is generally not reproduced at adjoining electrodes, and even recording from an electrode placed next to the electrode in question may not produce the same activity.

The frontalis electromyogram (EMG) is recorded from the frontal electrodes and is typically seen in patients who are contracting these muscles, as when tightly closing their eyes. The frontalis muscles are often activated by photic stimulation, and a photomyoclonic response is recorded. This activity occurs approximately 50 milliseconds following each flash. The amplitude of the response can be very large and may thus be recorded from several electrodes because of the natural electrical gradient. At times it may obscure EEG activity and even be confused with a photoconvulsive response (13).

The temporalis EMG is recorded from the electrodes placed over the temporal lobe: F7/8, T7/8, and P7/8. The artifact is seen when patients tightly close their jaws or make chewing movements (Fig. 9.6) and are frequent in patients with oral automatisms prior to or during an ictal event or who have orofacial dyskinesias (Fig. 9.7). EMG actiivity recorded over the frontal and occipital areas are common in tense individuals.

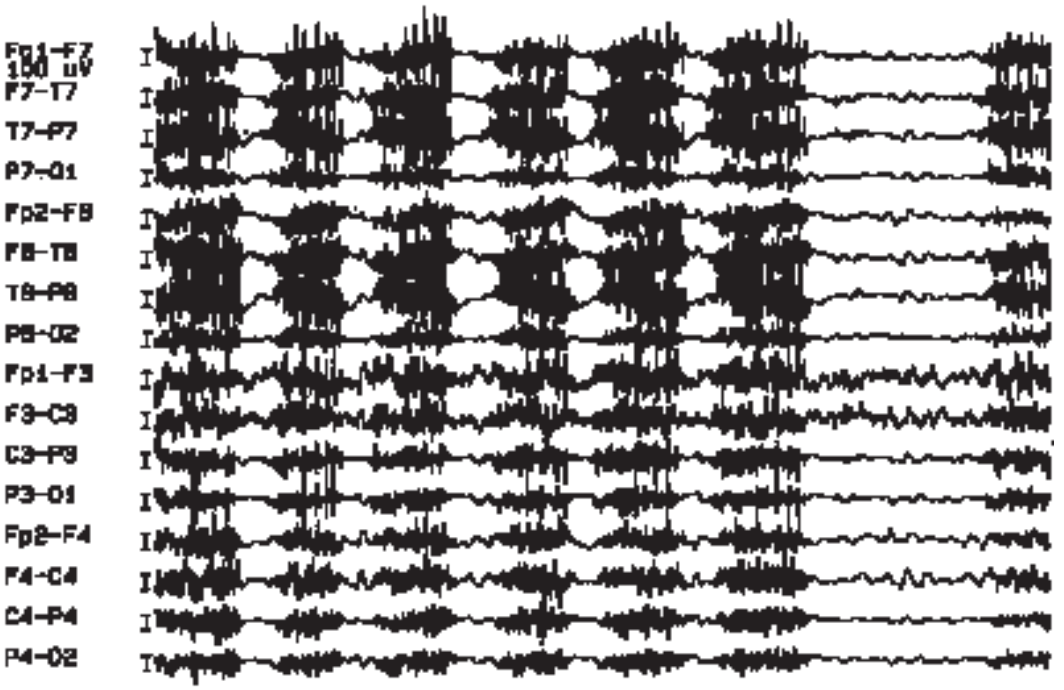

FIG. 9.6. EMG artifact recorded while the patient is eating lunch in a monitoring unit. This artifact is reminiscent of the EMG artifact seen during a temporal lobe seizure with oral automatisms (see Fig. 9.7).

Most EMG artifacts can be reduced or eliminated with the use of relaxation techniques, such as reassuring the patient, comforting the patient, or simply massaging the muscle groups (9). The use of high-frequency filters to eliminate the artifact should be avoided, because these filters rarely eliminate the high frequency; rather, they alter its appearance from a sharp or spike wave to a more sinusoidal frequency that may look more like cerebral beta activity.

Glossokinetic Artifact

Movement of the tongue produces a DC potential similar to the one associated with movement of the eye. The tip of the tongue is negative in polarity with respect to its base, and the potentials generated are frequently recorded as slow movements from the temporal electrodes (19,20). The electrical field generated by these tongue movements is extensive and can be recorded broadly over the entire face or from frontal and temporal scalp areas. The activity may be unilateral or bilateral depending on the direction of the tongue movements. Monitoring the activity is done by placing an electrode on the cheek and another on the submental muscle of the lower jaw (Fig. 9.8). The activity recorded from these electrodes will have greater amplitude than the activity recorded from the standard scalp electrodes, and the frequency will be time locked. The artifact may be reproduced by having the patient repeat words or phrases that produce active tongue movements, such as la-la-la or ta-ta-ta.

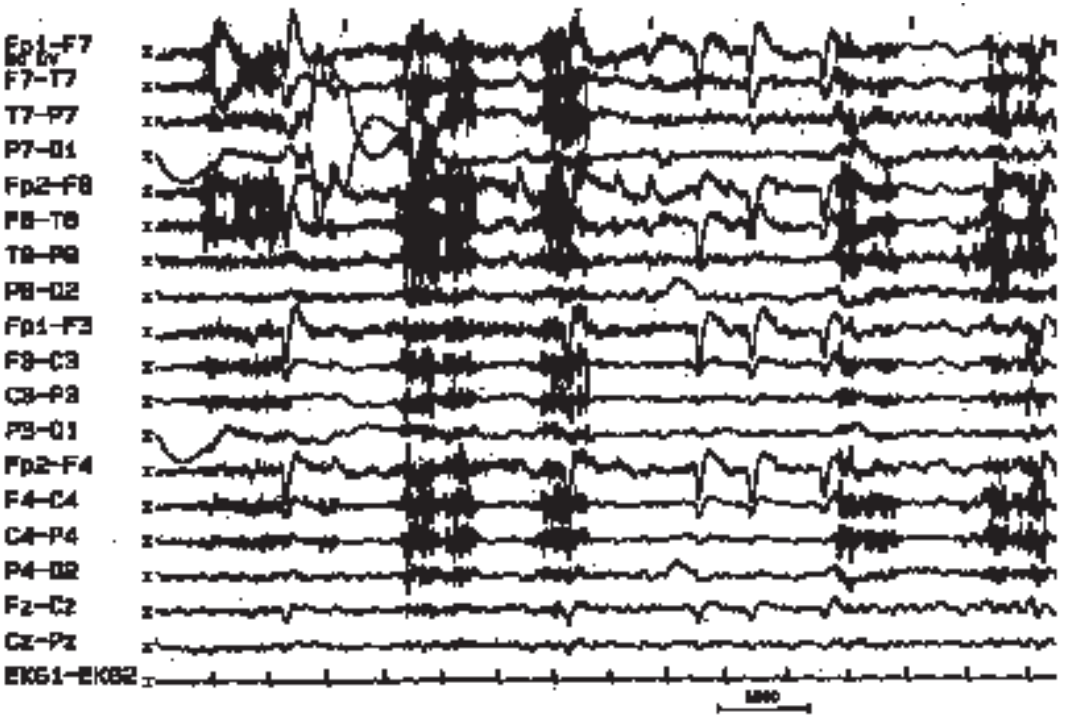

FIG. 9.7. Oral automatisms seen during a clinical seizure, prior to any EEG detectable seizure pattern.

Galvanic Skin Response

Perspiration artifacts are recorded as high-amplitude, very slow potentials. The use of standard low-frequency filters generally reduces the amount of this artifact. They can be recorded from infants as they change states from waking to drowsy or sleep; from babies and children who have been crying during the electrode application; from any febrile patient; and when the room temperature is too high. The amount of this activity may be reduced by cooling the patient or reducing the room temperature, or by use of a cooling fan or air conditioning. Patients resting on perspiration-soaked pillows may display a voltage asymmetry created by a salt bridge that shorts two electrodes contacting the perspiration. This can be eliminated by cooling the patient and taking his or her head off the pillow by using a neck roll (Fig. 9.9).

Physiological Movements

A variety of physiological movements may produce potentials recorded by standard scalp electrodes. The localization of these artifacts is usually related to the movement of the body part involved, the strength of the movement, and the relative location of the electrode wires. Familial essential tremor and the tremor of Parkinson's disease can involve the head, the arms and hands, or both (19). Tremor movement is most often between 4 and 6

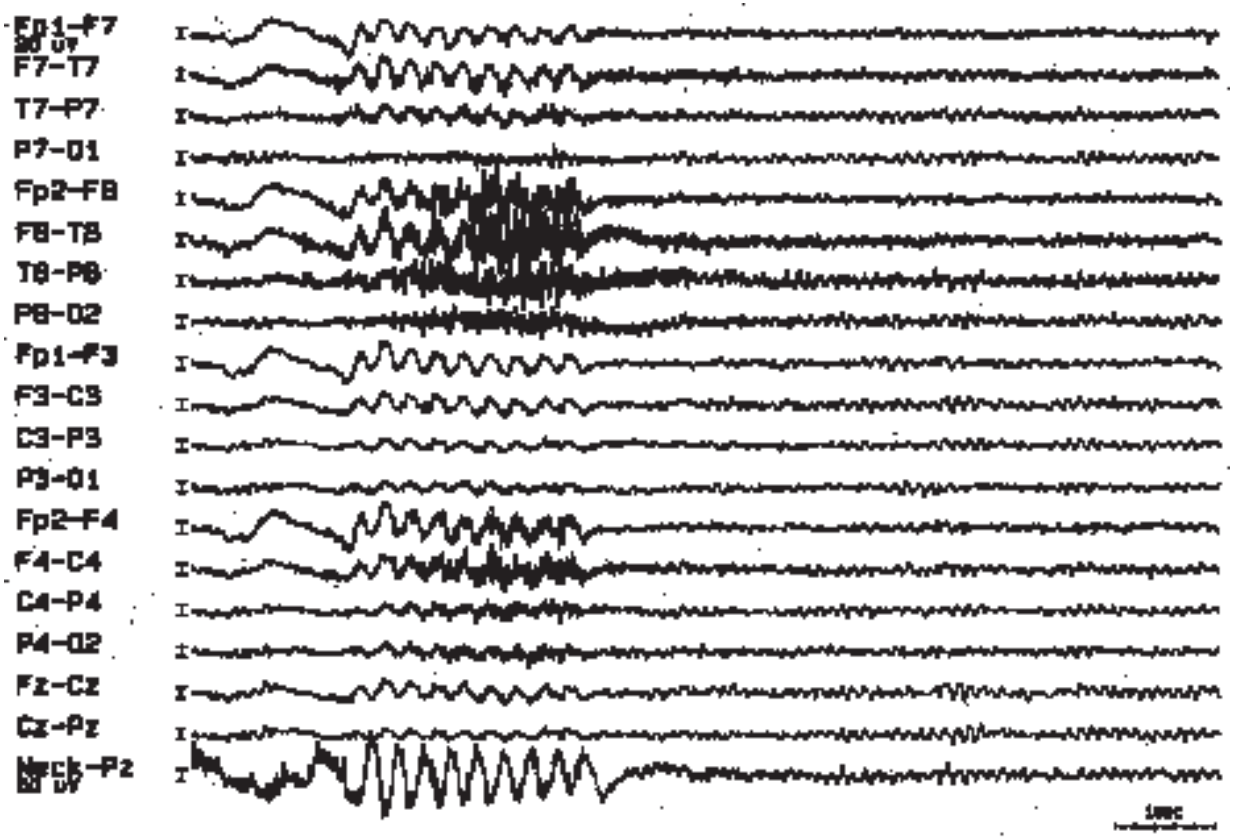

FIG. 9.8. Glossokinetic artifact generated by tongue movement as the patient is instructed to say "la, la, la, la." This is monitored by an electrode placed on the submental muscle and in this case referred to a PZ reference.

Hz. The artifact is caused by movement of the head electrodes in contact with the bed or pillow. If the tremor occurs in the upper limbs, it may be intense enough to cause movement of the head and body especially if there is nuchal rigidity. Tremor artifact may be monitored by placing two electrodes in close proximity on the moving limb or the neck muscles and recording the movements using a bipolar derivation.

Myoclonic limb movements, nocturnal leg movements, hypnic jerks, and even the Mayo reflex of infants can produce enough body movement to move the electrodes or the head, producing a potential in the recording. These movements can be monitored by placing a pair of electrodes on the muscle producing the movement and recording the activity.

NON-PHYSIOLOGICAL ARTIFACTS

Non-physiological artifacts are generated externally or in the environment and come from a vast variety of sources. Many of these originate within the

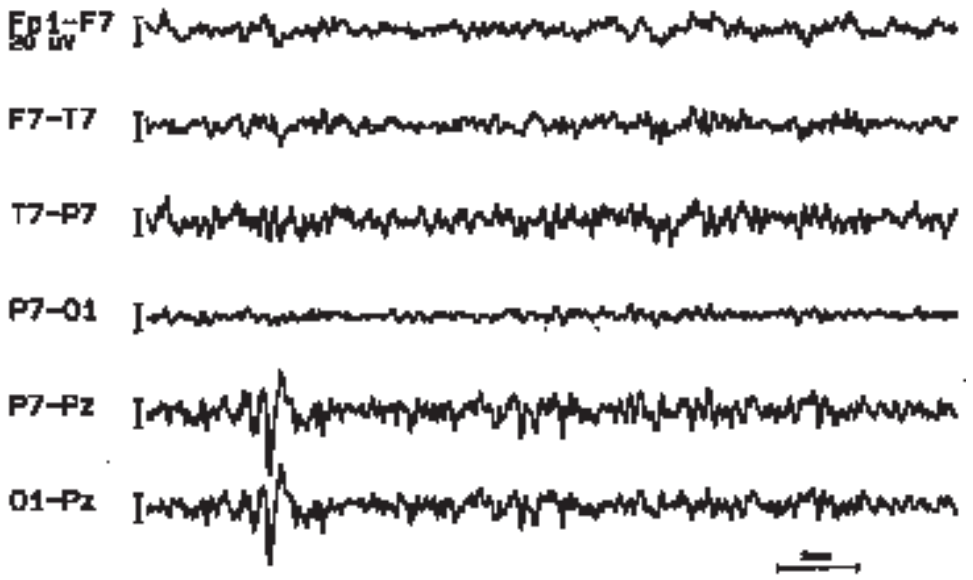

FIG. 9.9. Salt bridge artifact seen in the fourth channel; this is confirmed by recording the electrodes independently to a common reference. Minor differences in amplitude and frequencies seen in channels 5 and 6 are reflected in the fourth channel of the bipolar recording.

equipment used to record the EEG. Others are generated by the actual recording electrodes and environmental sources.

Instrumental Artifacts

Electronic noise generated by moving electrons within the recording amplifiers can be evident at high-gain settings. This high-frequency noise is inherent in all electronic components but generally is a problem only when recording for ECI or in evoked potential records requiring high-frequency responses in the range of several thousand hertz (5).

Sixty-cycle interference recorded in an EEG generally results from poor electrode application. The artifact is often due to high-impedance electrodes that, when connected to the recording device, affect the input circuitry of the amplifier, and also common mode rejection when impedances are not equal. Ensuring impedance measurements of less than 5 kilohms will usually eliminate such line-frequency artifact (1,6,17). Modern EEG amplifiers have greatly reduced the amount of 60-cycle interference seen as a result of the much higher input impedances of the amplifiers compared to earlier models. However, one should be aware that the presence of 60-cycle artifact in all channels of a recording may represent a problem with electrical safety and should be investigated, with particular attention being given to the safety of the patient. In all EEG recordings, care must be taken to avoid ground loops, or double grounding, of any patient (5). This is especially true in recordings made outside of the usual laboratory setting.

Capacitive, inductive, magnetic, and electrostatic artifacts are similar in origin and are usually related to movement of the electrode wires, the electrode input cable, or the alternating current power cable. Of course, all of these affect the recording through the electrodes, but the electrode–disk interface will not be a problem in this case. The most common cause of capacitive artifacts is someone stepping on the input cable. This cable acts as a capacitor because of the multiple insulated wires enclosed in the insulated cable. Moving or stepping on this cable causes the capacitor to discharge, resulting in a relatively high-voltage, transient recorded on the EEG. It should always be obvious that this transient is artifactual, because it will never have a logical distribution of its electrical field.

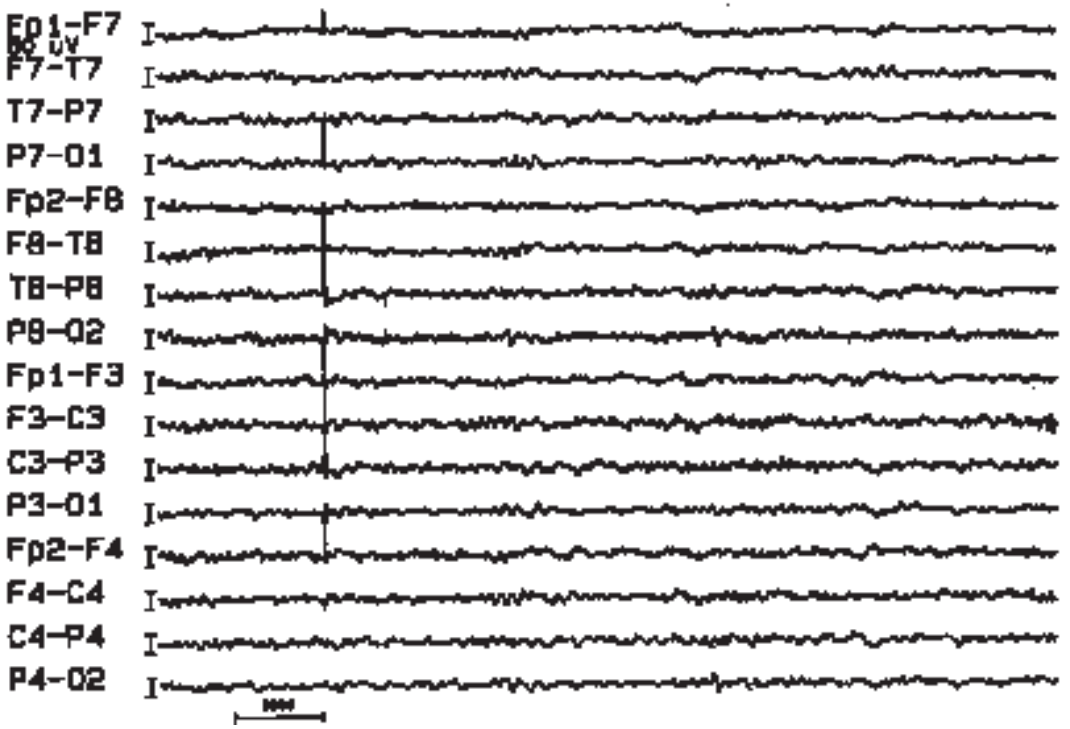

FIG. 9.10. Electrostatic artifact created by IV fluid drip falling near the electrode wires. Notice that there is no logical distribution to this artifact.

Few artifacts are related to inductance. However, the dripartifact frequently seen when recording from patients with intravenous (IV) infusions is produced by an individual drop of IV fluid falling near the electrode wires, producing a change in potentials associated with the arrangement of the electrode wires on the patient's bed (12) (Figs. 9.10 and 9.11). This artifact is relatively rare because IVs are now mostly regulated as micro-drips rather than macro-drips.

Electrostatically induced artifacts, caused by static electricity stored on a variety of clothing and bedding manufactured of synthetic fibers, remain a problem. This voltage may be discharged by touching a metal bed rail, or even passed from person to person. The artifact is again a high-voltage spike transient that will again have an illogical distribution of its electrical field because it is likely to affect the recording electrodes closest to the source. There will be no need to monitor the artifact: Often the technologist is the recipient of the discharge and will automatically know its origin.

Electrode Artifacts

A variety of electrode artifacts can be seen in any EEG recording, and are easily identified by an experienced EEG technologist. Any unusual event that is confined to a single or common electrode must be considered artifactual and monitored to verify its source, with replacement or adjustment made to correct the problem. The proper application of electrodes is one of the most important tasks for any technologist, and particular care and time must be devoted to ensure proper and accurate recordings. Most electrode artifacts will be related to one of several causes: poorly attached electrodes,

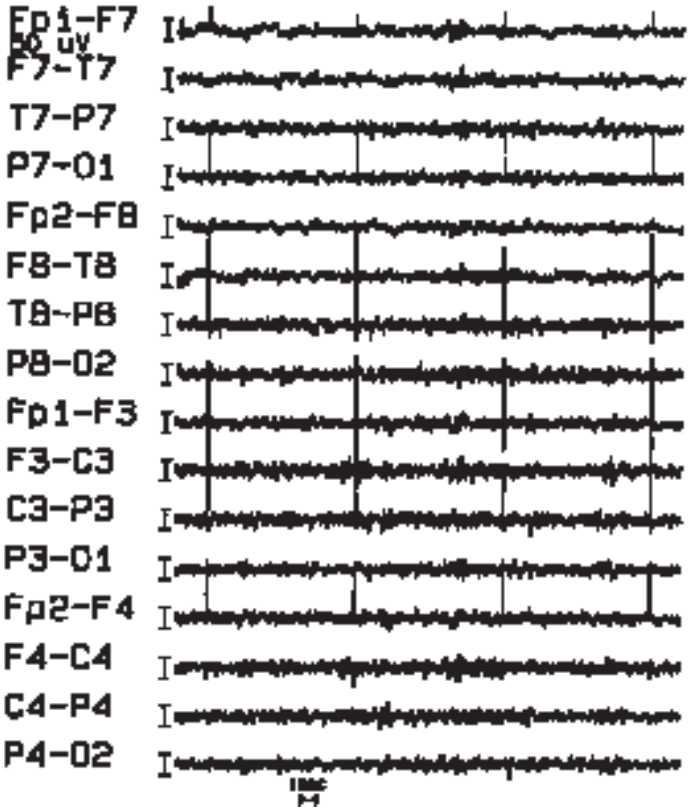

FIG. 9.11. Using the same electrostatic artifact shown in Figure 9.10, the recording has been compressed to show regularity and distribution of the artifact, which allows for easier recognition and identification by the technologist.

high resistance, a broken wire, or changes in the lead–scalp interface, usually caused by a change in the electrolytic gel used to complete this interface (7,8). In the latter case, an artifact may result from the electrolyte drying, or a change in potential related to an air bubble under the electrode causing a discharge. A good general rule when dealing with an electrode artifact is to note it the first time it occurs, determine the source of the artifact the second time it occurs, and replace the electrode or at least reapply it on the third occurrence (Figs. 9.12 and 9.13).

Environmental

Of all the artifacts typically seen in any EEG recording, the most troublesome by far are those classified as environmental. They are troublesome for a variety of reasons, but perhaps primarily because they are not easily controlled by the EEG technologist. Thus, although many of them can be identified, and some of them can be monitored, they may be difficult to eliminate. This adds an additional degree of complexity to the interpretation of recordings in which they are present. Some of these are generated by radiofrequency waves, a high-frequency signal that may be continuous or intermittent and can affect only a few or all channels of the recording. The source may be a microwave oven in a kitchen or lounge located anywhere within the vicinity of the EEG recording location. Clues to the origin of this artifact include the specific time of the day during which it occurs (i.e., lunchtime for microwaves). Another possible source is activity occurring in adjacent rooms. For example, while the technologist is recording an EEG in one operating room, high-frequency cautery may be in use in any of the adjacent rooms producing interference in the EEG recording (14). Occasionally radiofrequency artifact can be reduced or even eliminated by changing the position or orientation of the recording equipment relative to the patient.

Other environmental artifacts include line isolation scanners. These devices, which are common to intensive care units and operating rooms, often generate a particular frequency while scanning electrical outlets for leakage currents. These signals commonly produce a very low-voltage output that can be detected using the increased EEG sensitivity settings often required in these areas. Multiple ground artifacts (60-cycle artifacts) have been discussed above, but one must be aware that the interference recorded may not be from the EEG instrument, but derive instead from another electrical device connected to the patient. There are many other sources of environmental artifacts, too numerous to mention here. A good technologist will be aware of the environment and other equipment in use within the area, and must be cognizant of the fact that they all may be potential sources of extraneous signals contaminating the EEG recording.

Digital

Digital artifacts are unique to the system in use. The term *digital artifacts* is, in fact, misleading, because these artifacts are commonly related not to digital technology, but to failure of various components used in the acquisi-

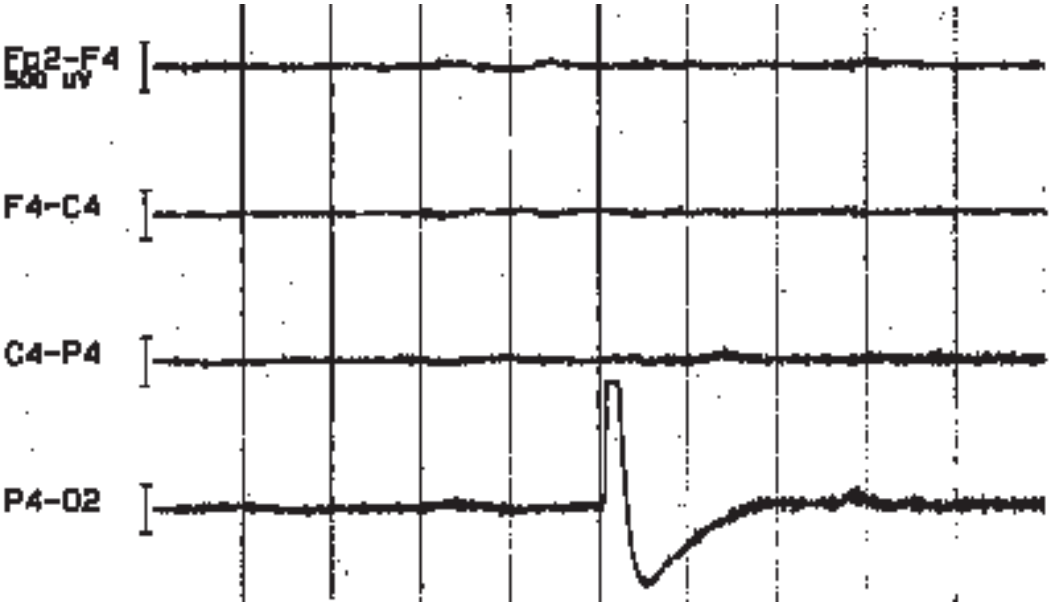

FIG. 9.12. Electrode "pop" artifact. In addition to demonstrating one of the most common artifacts seen in EEGs, this recording demonstrates that the high-voltage deflection actually exceeds the limits of the individual channel sensitivity recording capabilities and blocks or "squares off" at the top.

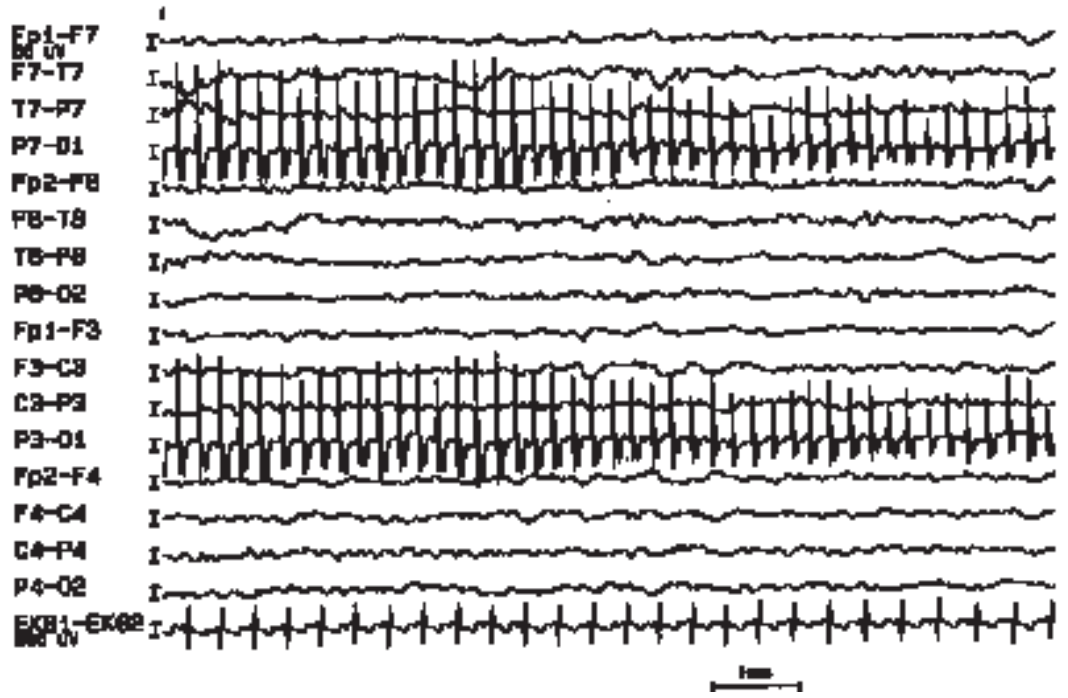

FIG. 9.13. Electrode artifact at the O1 electrode. The frequency of the discharge mimics the ECG signal on the last channel. The artifact and the ECG signal are not time locked, as they should be if the artifact were related to the heart. The technologist noted that the mother of the patient was patting the baby's back during the recording.

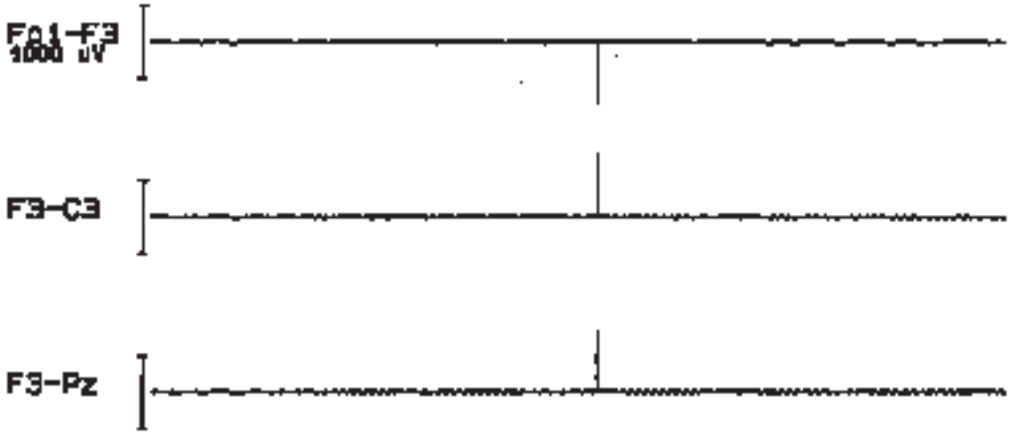

FIG. 9.14. Digital artifact produced at electrode F3 is a result of missed sampling of one data point in the channel recording F3-P3.

tion of EEG data (5,14). For example, failure of the analog-to-digital converter to accurately sample data points on a regular basis may produce something called a "sticky bit," which will result in a display like that seen in Figure 9.14. This represents a true digital artifact.

Similarly, artifacts related to aliasing (sampling at a rate that is less than twice the frequency of the high-frequency filter) will result in an error in the actual display of the acquired data. Because most commercial digital EEG instruments sample at a rate of at least 200 samples per channel per second, and most sample at a higher rate, it is uncommon to see aliasing artifacts in routine EEGs. However, the recorded photic stimulus signal often is composed of a much higher frequency, and aliasing may be present on the channel displaying the input stimulus, as seen in Figure 9.15.

Multiplexing artifacts may be seen in any type of amplifier used in digital EEG, but they are more common in amplifiers with 64 or even 128 channels. An example is seen in Figure 9.16, where the amplifier recorded 32 channels and the sampling was done in groups of 16 channels. Notice that the first 16 channels were switched with the second group of 16 channels, which was clearly seen by observing the position of the ECG monitoring channel. Digital artifacts, like other nonphysiological artifacts, often produce recordings that do not make sense. They will always lack a logical distribution of recorded activity.

In most instances, digital EEG has made it easier for the technologist to record EEG. With the ability to make changes in sensitivity, filtering, and remontaging off line, improper montages are eliminated, because the electroencephalographer can always modify the montage. Pen blocking is never a problem during high-voltage 3-Hz spike-and-wave discharges, as the display can always be changed to reduce high-voltage discharges after the recording is complete. Filtering also can always be changed after the

FIG. 9.15. Effect of aliasing caused by inadequate sampling rate. This sine wave recording sweeps through a frequency range of 0–50 Hz at a constant voltage and a sampling rate of 50 Hz. Notice the effect on the 25-Hz frequency.

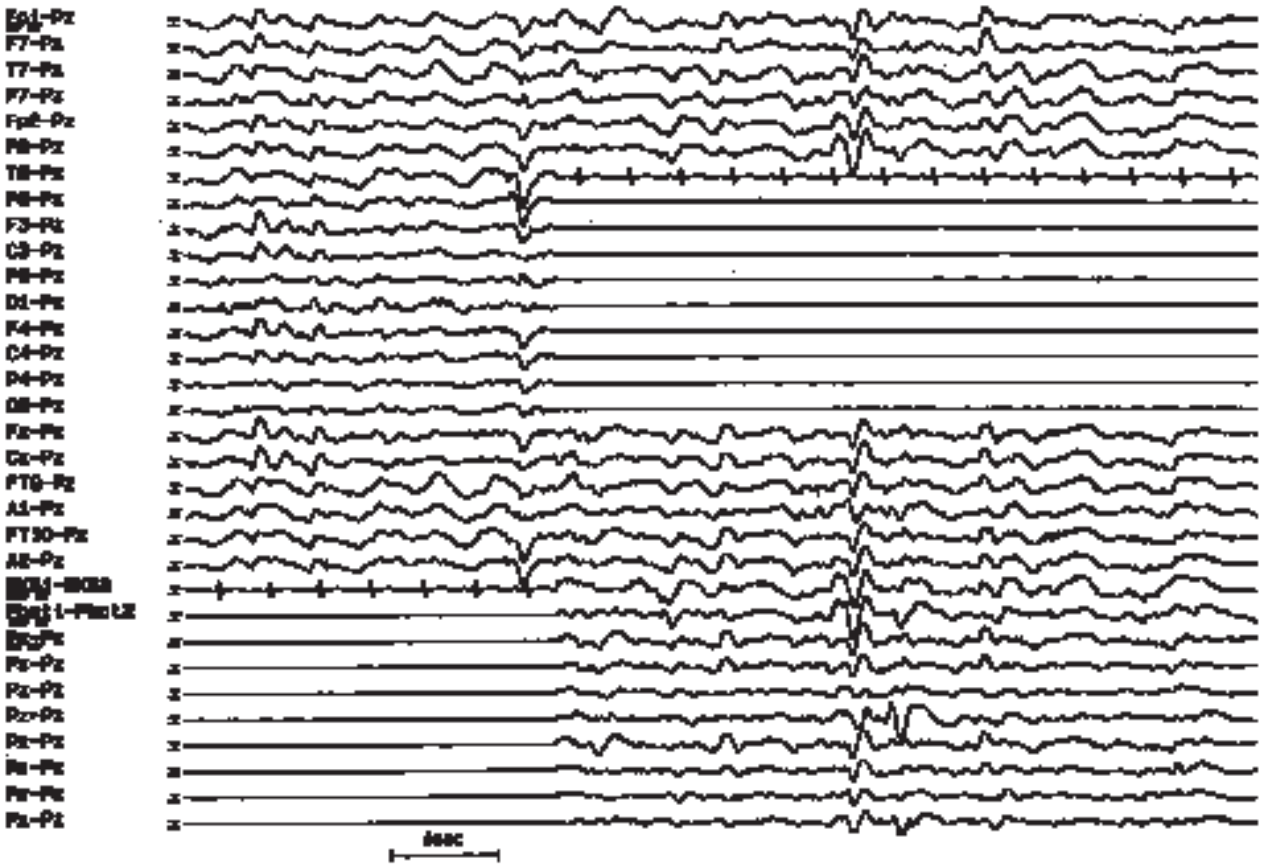

FIG. 9.16. This multiplexing artifact results when sampling is done on 16 channels at a time instead of sampling the entire 32-channel amplifier simultaneously. A timing error occurs and the groups of 16 channels invert. This is clearly seen by observing the position of the ECG monitoring channel.

recording is complete. Digital EEG does not eliminate ar tifacts, however, and the technologist, as well as the electroencephalographer, must still be aware of the variety of known physiological and nonphysiological artifacts that may be present in any recording. It has always been the technologist's responsibility to recognize artifacts, identify them with monitoring, and eliminate them whenever possible. Digital EEG has not altered this in any way; it has created an entirely new collection of artifacts that must be recognized.

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Chapter 10

An Orderly Approach to the Abnormal Electroencephalogram

Benjamin G. Zifkin and Roger Q. Cracco

Abnormal Changes in Normal Rhythms
Abnormal Alpha Rhythms
Abnormal Delta Rhythms
Abnormal Beta Rhythms
Other Abnormal Rhythms
Abnormal Slow Activity
Localized Arrhythmic Delta Activity
Diffuse and/Bilateral Arrhythmic Delta Activity
Intermittent Rhythmic Delta Activity
Other Distinctive Abnormal Patterns
Pseudoperiodic Patterns
Unusual Asymmetrical Abnormal Activity and Dysplastic Brain Lesions
Interictal and Ictal Abnormalities
Interictal Epileptiform Activities
Distinguishing Nonepileptiform from Epileptiform Discharges
Epileptiform Discharges and Seizures
Ictal Patterns
Conclusion
References

It is an obvious but important truism that the electroencephalogram (EEG) evaluates brain function, not structure. Although many different pathological processes disturb brain function, the repertoire of resulting EEG abnormalities is limited. As with other physiological tests, EEG abnormalities, although reliable indicators of brain dysfunction, cannot, except in rare instances, distinguish etiology or pathology. Advances in neuroimaging have fortunately reduced dependence on the EEG for information that it cannot reliably provide, while new methods of data processing have led to further development of its usefulness in examining brain physiology (see Chapters 4, 22, 23, and 24).

In this chapter we present a systematic approach to visual analysis of the abnormal EEG, complementing that of Chapter 5. As when analyzing a normal EEG, the electroencephalographer must (a) see abnormalities in the recording; (b) systematically characterize them in terms of morphology, topography, temporal characteristics, reactivity, and state sensitivity; and (c) retain these characteristics in mind while composing the description and interpretation. The electroencephalographer must describe abnormalities accurately, fully, and succinctly. The glossary of the Committee on Terminology of the International Federation of Societies for Electroen-

cephalography and Clinical Neurophysiology (7) provides a common vocabulary and helps us to avoid errors of logic (e.g., referring to interictal spikes as "spike seizure discharges") and jargon (e.g., referring to triphasic waves as "liver waves"). Consistently used, this approach will sharpen the electroencephalographer's powers of observation and ensure that no abnormality goes unmentioned in the report.

This approach additionally benefits the electroencephalographer by providing a framework for evaluating articles and reports on EEG. Anyone who regularly reads journal articles inevitably encounters some that lack illustrations and whose texts contain undefined terms ("a slight to moderate degree of diffuse slow-wave activity") or empty sentences ("slow tracings contained activity below 8 cps in sufficient quantities to warrant positive interpretation"). Such style should immediately alert the reader's critical faculties and lead to judicious appraisal before acceptance of any conclusions made by the author(s). Even more troubling are articles in which illustrations and text are discrepant, not a rare occurrence. An electroencephalographer whose "eye" has been sharpened by systematic analysis will quickly recognize such discrepancies and draw his or her own conclusions.

We divide our discussion into the following topics:

1. Abnormal changes in normal rhythms
2. Abnormal slow activity
3. Distinctive abnormal patterns (e.g., pseudoperiodic patterns)
4. Interictal and ictal abnormalities

Although the notion of abnormality is, strictly speaking, a statistical concept, in clinical practice an abnormal EEG is one that contains some feature known to be associated with cerebral dysfunction. An EEG may be abnormal if normal patterns are altered or if certain abnormal patterns occur. Very often, both types of abnormality are seen in the same recording, as shown in Figures 10.1 and 10.4 later in this chapter. Certain waveforms are unusual, and their appearance may be striking; however, they are seen as often in the EEGs of asymptomatic subjects as in those of patients. Accurate visual assessment of the EEG requires a systematic approach that incorporates (a) knowledge of the age and state of the subject and (b) critical assessment of voltage, frequency, rhythmicity, distribution, reactivity, and persistence of waveforms. In abnormal EEGs, each of these may be altered alone or in combination, and these changes may be localized, lateralized, or diffuse.

ABNORMAL CHANGES IN NORMAL RHYTHMS

Abnormal Alpha Rhythms

Absent or scanty posterior alpha rhythm may be due to eye opening, attention, anxiety, or drowsiness. Some asymptomatic individuals normally have little or no alpha rhythm, perhaps on a genetic basis. These factors must be considered before concluding that an apparent bilateral absence of alpha activity is abnormal. Absence of alpha rhythm, therefore, cannot be regarded necessarily as abnormal. In patients with brain pathology, bilateral absence of alpha rhythm is usually accompanied by other bilateral abnormalities, such as widespread voltage attenuation or diffuse slow activity. Clinically, such cases usually represent diffuse encephalopathies. In stupor or coma, the alpha rhythm is absent, and other rhythmic activities can be reduced or lost. This loss can be reversible (e.g., with severe barbiturate intoxication) or irreversible (e.g., with hypoxia). The prognostic value of a single EEG is therefore small, but serial recordings are helpful in evaluating improvement or deterioration.

Some asymmetry of alpha and beta rhythms, not caused by technical factors, is common and may be due to differences in skull thickness (36). Alpha activity is statistically more likely to be of higher voltage over the right side. Asymmetry of the alpha rhythm of more than 20% (expressed as a percentage of the higher side) is unusual in normal adults (40), and a consistent asymmetry of 50% or more should be regarded as clinically significant. In view of the common and normal slight right-sided predominance, asymmetries of 35%–50% may be significant and considered abnormal when the lower voltage is on the right side (33).

Localized or lateralized relative flattening or obliteration of alpha activity (Fig. 10.1) can occur ipsilateral to cortical lesions, a finding confirmed by electrocorticography (43). When this is observed in the scalp EEG, local abnormal slow activity or other localized abnormalities should be sought. This combination over the same hemisphere is a reliable sign of a focal cerebral lesion (1). Ipsilateral reduction in the amount of alpha rhythm has also been reported with unilateral thalamic tumors (32) and in a case of unilateral thalamic infarction involving predominantly the anterior and lateral thalamus (24). The presence of particular associated abnormalities such as focal paroxysmal or slow activity may help to determine (a) the severity and extent of a unilateral disturbance of alpha activity and (b) the structures most likely to be involved (see below).

Drowsiness must be excluded before attributing pathological significance to a slow background rhythm, especially in children, whose dominant occipital rhythm may slow before drowsiness is clinically evident. Alerting tasks given by the technologist (counting, repeating phrases) will be helpful. The

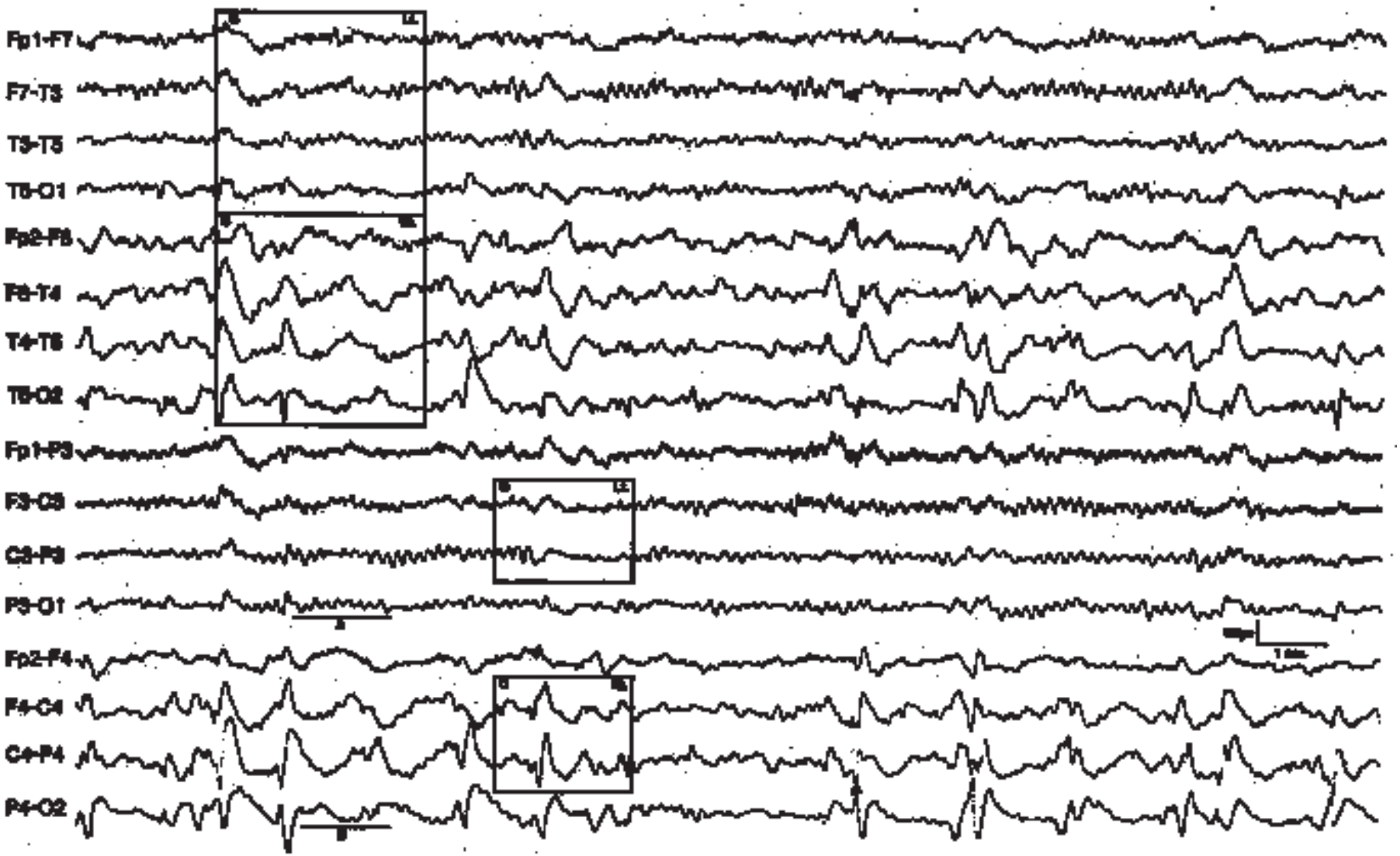

FIG. 10.1. Waking EEG of a 19-year-old man with chronic left hemiparesis, seizures, and developmental delay. Careful examination of this apparently complex recording can resolve it into its component abnormalities. **A** and **B:** Background rhythm is abnormally slow over the right occipital region; moreover, there is a significant asymmetry, with the background rhythm over the right occipital region being scanty or absent. **C:** Rhythmic activity is significantly reduced over the right hemisphere compared to the left, and right-sided arrhythmic delta activity is almost continuous. The *asterisk* indicates localized epileptiform activity over the right parietal region. (This localization must be confirmed by recording with other montages.)

frequency of the alpha rhythm does not fall below normal limits in normal aging. Slowing below 8–8.5 Hz (see Chapter 5) is a sensitive but nonspecific indication of disturbed cerebral activity. Indeed, normative studies in adults suggest that an alpha frequency of 8 Hz is more likely to be slowed from some faster frequency than to be a normal constitutional finding (33). Reduced cerebral blood flow reduces alpha frequency (49); moreover, slowed dominant occipital rhythm, often in the theta band, is seen early in many toxic and metabolic encephalopathies, including anticonvulsant drug toxicity. This finding is etiologically nonspecific but is functionally and clinically significant.

Focal slowing of alpha activity is a rare finding in cases of localized disturbances such as tumor or head trauma. A persistent difference of at least 1.5 Hz should be interpreted as being significant. Serial studies may be useful, because this abnormality may be transient and can be followed by a local amplitude asymmetry.

Whereas the normal alpha rhythm is predominant posteriorly and reacts with attenuation in response to eye opening or alerting, nonreactive monorhythmic diffuse activity in the alpha frequency band occurs in some cases of severe encephalopathy with coma, a pattern called "alpha coma" (55). When caused by hypoxia, the alpha coma pattern has been associated with a poor neurological prognosis, although this has been disputed (2). Alpha coma has been reported with good outcomes in a few cases of drug overdose (6), but this cause can usually be distinguished by the greater admixture of faster frequencies and less underlying delta activity in such cases.

The rare Bancaud's phenomenon (3) is a unilateral failure of alpha rhythm to attenuate with bilateral eye opening. The abnormal hemisphere is the one over which the alpha rhythm does not attenuate. A pattern of higher amplitude alpha rhythm and reduced reactivity over an affected hemisphere is also rare and of similar significance (25). Unilateral eye opening does not normally affect alpha rhythm, but may produce contralateral attenuation in patients with albinism, possibly as a result of misrouting of visual pathways (48).

Abnormal Delta Rhythms

Children normally develop sleep spindles in the first 6–8 weeks of postterm life, and well-formed spindles are bilaterally synchronous before the age of 2 years (Fig. 10.2*B*). Although bilateral absence of sleep spindles indicates a cerebral disturbance (31), the interpreter must be certain that the patient is in the appropriate stage of sleep for spindle occurrence (29). This is especially true for children and the elderly, in whom state changes may be rapid, frequent, and clinically hard to detect.

Stage 2 sleep in children from 6 months to 6 years of age is normally marked by high-voltage occipital delta activity. Voltage predominance often shifts from side to side, but an anterior–posterior voltage gradient should be evident (47). Delay or failure of this pattern to develop, or bilateral loss of this normal sleep-related occipital delta activity, is a sensitive but nonspecific indicator of cerebral dysfunction in early childhood.

A lateralized but shifting asymmetry of sleep spindles can occur in normal subjects. Persisting asymmetries of more than 50%, especially if the amplitude of other rhythms is also reduced on the same side, should suggest an abnormality affecting thalamocortical pathways ipsilateral to the side of the lower voltage. Coexisting localized arrhythmic delta activity (see below) indicates, moreover, that thalamocortical white matter is also involved. The normal posterior slow waves of sleep in children can be deceiving and should not be mistaken for abnormal delta activity. If significantly asymmetrical, the abnormal side is that of the lower voltage if craniotomy flaps or other bone defects are excluded. Transient asymmetries of vertex sharp waves are common and normal, especially in children and near the beginning of sleep, when these waves may be grouped and very prominent (Fig. 10.3*A*). An asymmetry that persists throughout sleep is abnormal and suggests a cerebral disturbance lateralized to the side of the lower voltage.

Bilateral spindles characteristic of slow-wave sleep may occur in the diurnal EEGs of some comatose patients. In these cases, spindles persist without reactivity and without being part of a periodic sleep cycle (9). This pattern has been called "spindle coma." Its prognostic value is unclear, but some EEG change after arousal stimuli (such as pain or loud sound) is believed to be a favorable prognostic sign in such patients.

High-voltage, exaggerated sleep spindles ("extreme spindles") were described by Gibbs and Gibbs (20) as a common abnormality in mentally retarded persons (see Fig. 10.2*A*). Our own experience agrees with this. The pattern consists of 100- to 400- μV spindles of 8- to 15-Hz activity over anterior head regions that are more continuous than normal spindles. In more severely retarded subjects, this pattern is often present in both wakefulness and sleep. It is not associated with epilepsy. Extreme spindles must be distinguished from fast activity of early sleep (see Fig. 10.3*A*), which is part of the normal sleep EEG in children, and from the expected increase in beta activity seen with certain psychoactive drugs, especially barbiturates and benzodiazepines. Extreme spindles indicate a marked diffuse cerebral disturbance but are not specific, and other abnormalities suggesting a diffuse encephalopathy would be expected in an EEG showing this pattern.

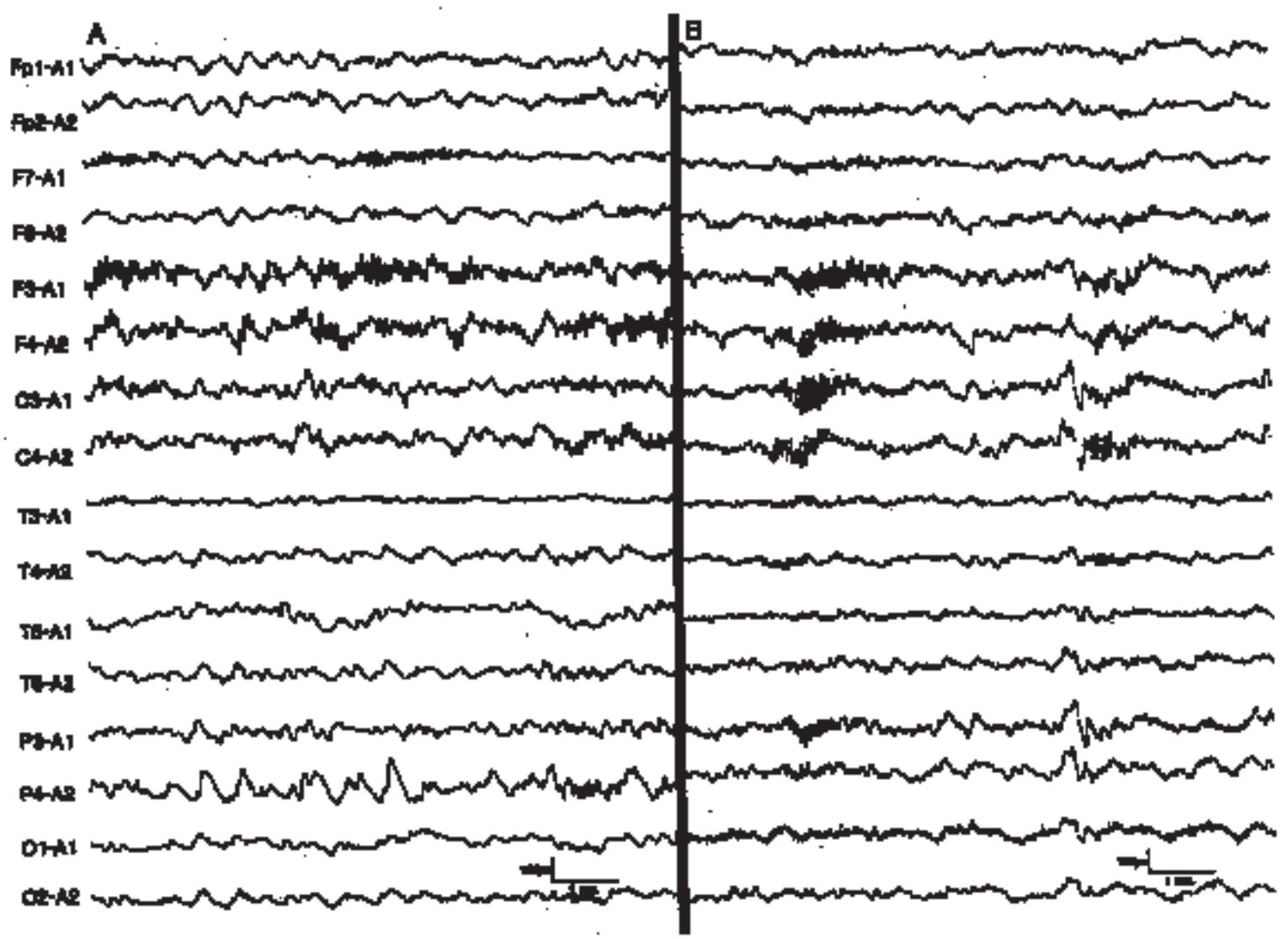

FIG. 10.2. A: Sleep recording in an 8.5-year-old mentally retarded boy. High-amplitude anterior spindles are virtually continuous throughout the EEG and do not form part of a normal sleep cycle (extreme spindles). **B:** Normal sleep recording in a 2-year-old girl. High-amplitude spindles may be seen at this age, but they are not continuous and are usually frontocentral. They form part of a pattern of cycling sleep stages as seen later in this recording.

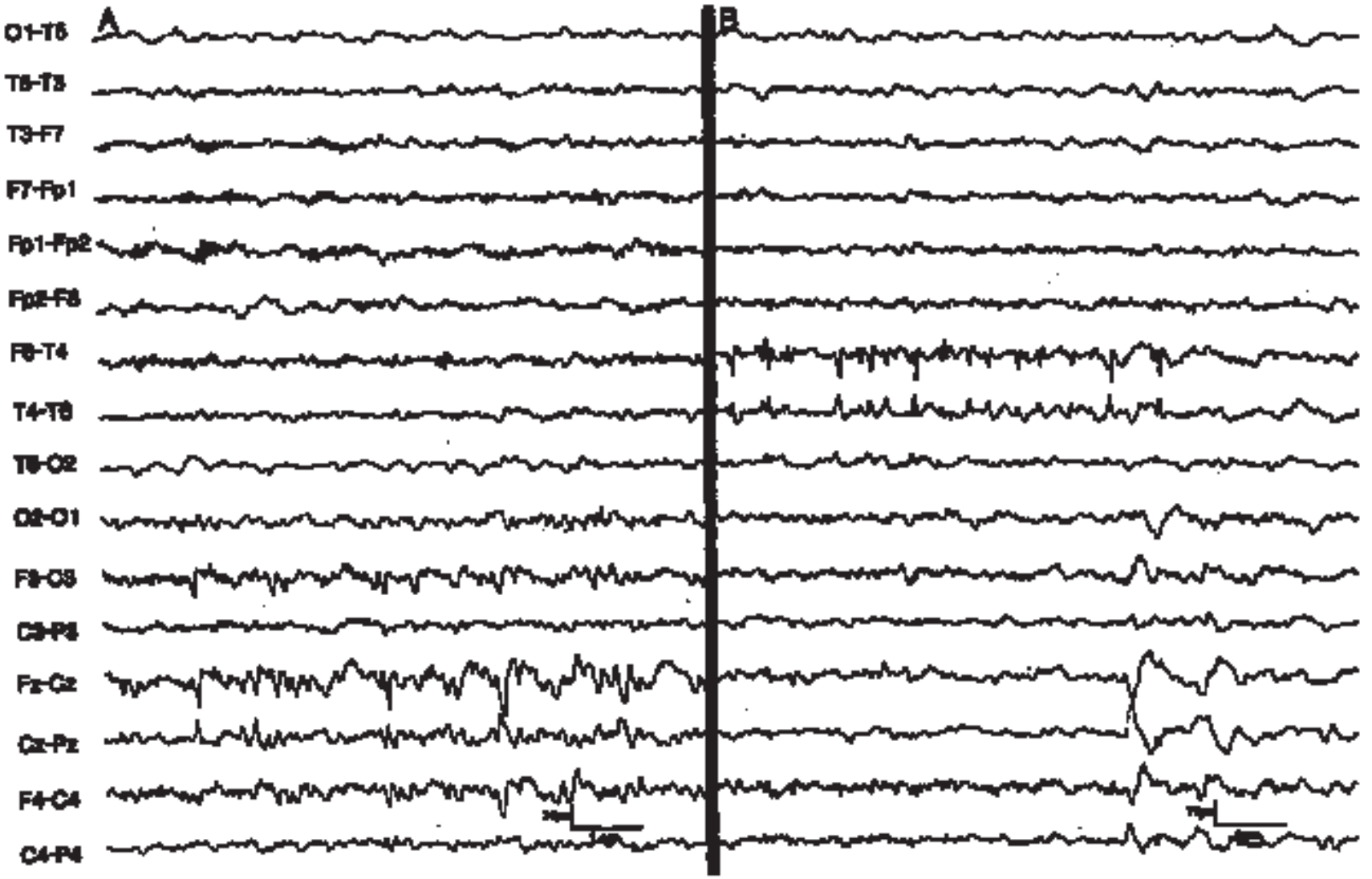

FIG. 10.3. A: Early sleep in a 9-year-old boy. Fast activity of early sleep is seen over both anterior head regions. Vertex sharp waves (channels 13 and 14) are prominent and repetitive and must be distinguished from epileptiform potentials. **B:** Later in the same recording, localized spikes are seen (channels 7 and 8) over the right temporal region, with a vertex sharp wave recorded in the sixth second of this segment.

Abnormal Beta Rhythms

The occurrence of unusually abundant symmetrical beta activity in an otherwise normal EEG is of little clinical value except to raise the question of possible sedative, hypnotic or anxiolytic drug use. It should not be interpreted as an abnormality. Rhythmic activity that is unusually fast for the subject's age, and often of unusually high amplitude in routine bipolar montages, has been reported with a variety of dysplastic cortical lesions. Localized or regional abnormal fast rhythmic activity has been reported with regional dysplastic lesions. Diffuse abnormal fast rhythmic activity is seen with diffuse lesions such as agyria (lissencephaly) or pachygyria. This may not be beta activity at first: Sustained rhythmic theta or alpha activity is abnormal in the neonate. Unusual high-amplitude, unreactive anterior or diffuse alpha and later beta activity typically develops in these children over several months (12,16).

Beta activity in normal controls may be up to 35% lower on one side, but a greater asymmetry, especially if combined with other abnormalities, is a sensitive indicator of cortical injury underlying the region of lower amplitude (see Fig. 10.1). Such an asymmetry may localize a lesion even if the associated abnormalities are more widespread. A transient localized or lateralized reduction in beta activity may also be seen following a partial seizure with or without secondary generalization.

Other Abnormal Rhythms

Rarely, patients with hemisphere lesions may have increased voltage of alpha rhythm or local beta activity on the side of the lesion (1). Green and Wilson (22) found locally diminished beta activity in patients with stroke but noted increased beta activity over some tumors.

Localized or lateralized voltage asymmetries of normal cerebral activity must be carefully evaluated before concluding that they are abnormal. Technical factors, including calibration errors, must be excluded. The technician should examine the scalp for local swelling and should check interelectrode distances, noting these procedures on the EEG. Voltage asymmetries in bipolar montages should be confirmed by referential recording using special care to select a reference electrode that is not near the region in question.

Asymmetries of lambda waves, positive occipital sharp transients of sleep (POSTS), positive slow waves of youth, and mu rhythm are common and should not be interpreted as being abnormal in the absence of associated abnormalities.

Probably the most common reason for an asymmetrical regional increase in EEG voltage is the presence of a skull defect. This is seen in scalp EEGs performed before replacement of a bone flap, but it often persists after replacement of the flap and healing of the scalp. Voltage increases may also be observed at or near isolated bur holes. The patient's history and the technician's observation of the scalp during preparation for recording should reveal such a defect, and a sketch of the location of bur holes and craniotomy scars should form part of the technician's report. "Breach rhythm" is typically a sharply contoured central or midtemporal patter n often resembling a high-voltage mu rhythm, mixed with prominent beta activity and attenuated by actual or intended movement of the contralateral hand. Breach rhythm indicates that the subject has a bone defect, but its occurrence seems to be purely the result of physical effects of the skull changes on the recording of cortical potentials rather than the result of changes in the underlying brain, though other theories have been proposed (11,15,18,30) (see also Chapter 7). The asymmetry is usually persistent, but it may be reduced after cranioplasty with bone or acrylic. After craniotomy, high-voltage regional activity that is otherwise normal should not be reported as abnormal. Because the waveforms near skull defects or bur holes are usually very sharp or "spiky," interpretation of possible spikes should be exceptionally conservative. If there is underlying brain pathology, abnormal local patterns may coexist (26). Progression of a lesion beneath the flap or bur hole should be suspected if serial EEGs show (a) attenuation of preexisting high-amplitude rhythm and/or (b) the presence of local slow waves.

ABNORMAL SLOW ACTIVITY

Delta activity was first recognized and named by Walter (56) because of its association with *d*isease, *d*egeneration, and *d*eath. Arrhythmic or polymorphic delta activity consists of delta waves that are irregular in shape and have a variable duration and frequency without a stable predominant frequency. Rhythmic delta activity consists of delta waves that are regular in shape and have a fairly constant duration and stable predominant frequency. The description and subsequent interpretation of abnormal slow activity requires study of its frequency, distribution over the scalp, temporal features, abundance, and reactivity. A single recording may contain two or more different abnormal delta activities, each with its own characteristics.

Thus delta activity may be localized, unilateral with or without focal predominance, or generalized, sometimes with a varying degree of localized or lateralized predominance. It may be continuous or intermittent. Intermittent delta activity may be random or may occur in bursts (paroxysmally); moreover, it may be bilaterally synchronous or independent over each hemisphere or homologous scalp regions. The amplitude and amount of delta activity must also be considered, as well as whether or not it reacts to external stimuli.

Delta activity can be seen with localized, lateralized, or diffuse encephalopathies and is a very significant, but nonspecific, sign of disturbed cerebral activity. It has been found empirically that qualitative differences in delta activity are clinically significant, especially in serial recordings from a single patient. Lower frequency, higher amplitude, and greater abundance are all signs of a more acute or severe abnormality, and they are consistent in serial recordings with a progressing disturbance. A reversal of these trends indicates improvement.

Localized Arrhythmic Delta Activity

The original definition of delta activity included activity slower than 8 Hz; indeed, focal arrhythmic theta activity has the same significance as delta activity but suggests a less severe or less acute disturbance. Localized arrhythmic delta activity (ADA) is characteristic of supratentorial hemispheric lesions involving white matter (21,41). It commonly occurs with other EEG indications of localized cortical disturbance, such as reductions in amplitude and amount of faster rhythmic activity (see Fig. 10.1). As a sign of locally disordered cerebral function, localized ADA is not confined to gross structural lesions. It can be seen transiently as a postictal phenomenon and in disorders such as complicated migraine (27) and head trauma. The potential field of localized ADA may be quite extensive and is typically larger than the underlying lesion as judged by computed tomography. This can be due to other functional changes assessed by the EEG, such as local reduced blood flow, or to the shallow, broad potential gradient characteristic of a deep-seated lesion. Arfel and Fischgold (1) found that the most reliable EEG localization of cerebral tumors was indicated by lower voltage delta activity without intermixed faster frequencies.

Diffuse and/Bilateral Arrhythmic Delta Activity

Diffuse ADA, or generalized slow activity, reflects a diffuse but etiologically nonspecific disturbance of cerebral activity. It is seen most commonly with various metabolic and toxic encephalopathies and varies with the severity of the underlying disorder. Assessing bilateral arrhythmic slow activity requires (a) analyzing frequency, amplitude, distribution, persistence, and reactivity; and (b) searching for associated findings that may indicate an underlying lateralized or localized disturbance. Because these characteristics are related to the severity of the encephalopathy, which may itself evolve, serial studies usually prove to be more valuable than a single recording. Initially, or in mild disturbances, slowing of the dominant occipital rhythm occurs, perhaps mixed with some bilateral irregular theta activity. It may be difficult to distinguish this pattern from that of drowsiness, especially in children. The technologist may help by noting the EEG response to state changes or arousal stimuli. With more severe encephalopathies, the amount of diffuse slow activity increases, the frequency slows, and the amplitude increases. Reactivity, demonstrated by attenuation of the slow activity following arousal stimuli, disappears with progressive obtundation and the onset of coma. Bilateral diffuse ADA may also be seen with thalamic or midbrain dysfunction caused by bilateral lesions or compression from herniation.

The most common metabolic disorders producing diffuse ADA are hypoglycemia, hypoxia or global cerebral ischemia, uremia or hepatic disease, and disordered osmolarity. A common toxic etiology is drug toxicity or overdose, in which diffuse beta activity mixed with the slow waves may suggest sedative drugs as the cause. Diffuse white matter encephalopathies such as leukodystrophies (21) can produce this pattern, as can encephalitis, meningitis, and subarachnoid hemorrhage.

Bilateral ADA may be so prominent as to mask focal EEG abnormalities that would indicate a lateralized hemisphere lesion as the underlying cause of the diffuse encephalopathy. Such ADA therefore should not be interpreted as excluding a lateralized lesion. One example of this is an expanding supratentorial mass compressing the thalamus and midbrain.

Intermittent Rhythmic Delta Activity

Cobb (10) was the first to describe bilaterally synchronous delta or theta activity, usually with anterior predominance, as an abnormal pattern in the waking adult EEG. It consists of regular delta waves with a relatively constant frequency in any one EEG. Van der Drift and Magnus (52) named it "frontal intermittent rhythmic delta activity" (FIRDA). Intermittent rhythmic delta activity (IRDA) need not be confined to the frontal regions, and indeed it is often more diffuse. Sometimes the bursts may include theta activity (Fig. 10.4). IRDA may be asymmetrical, lateralized, or even unilateral. Its onset is abrupt, and it is clearly distinguished from the surrounding EEG activity. Although bifrontal predominance is typical in adults, occipital predominance is usual in children; this seems to be related to maturation rather than to any morphological abnormality (14).

Vertical eye blinks may be distinguished from FIRDA by recording simultaneously from infraorbital and frontal scalp electrodes connected to a common reference (see Chapter 9). The electrooculogram will be 180 degrees out of phase, whereas FIRDA will be in phase, in recordings taken from

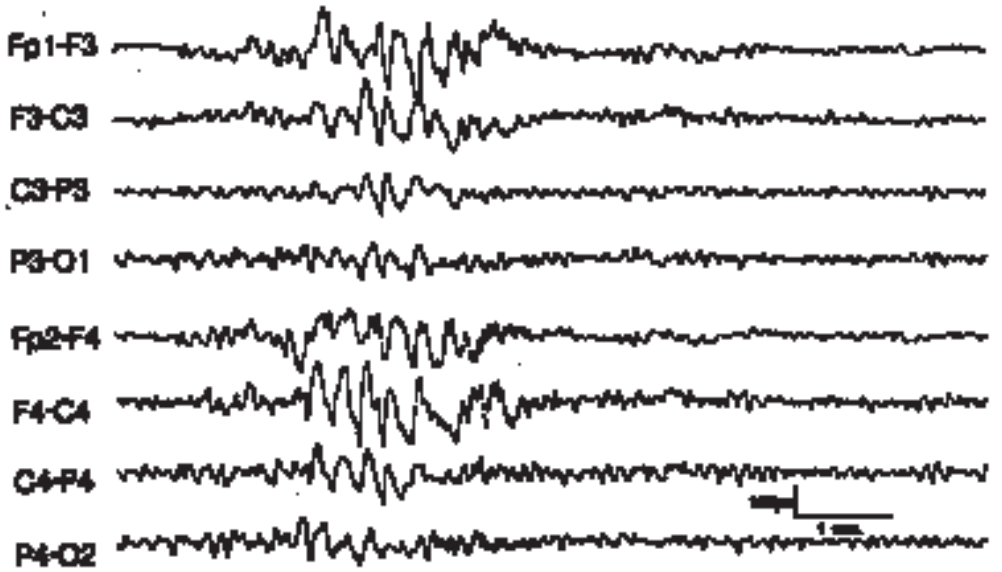

FIG. 10.4. EEG of a 26-year-old man. Bilateral intermittent rhythmic delta activity can be mixed with other frequencies and associated with other abnormalities. Background rhythm is also somewhat slow in this subject with Down's syndrome, without any evidence of a midline lesion or increased intracranial pressure.

above and below the eye. The normal response to hyperventilation, as well as the paroxysmal pattern of drowsiness in childhood (hypnagogic hypersynchrony), can be very striking and must be differentiated from abnormal bursts of rhythmic waves. Sleep-deprived normal adults may show occasional bilateral paroxysmal slow activity (42) of no clinical importance except as evidence of sleep deprivation. The pattern may also occur occasionally in the EEG of an asymptomatic elderly subject (50).

IRDA is clearly abnormal in adults and is observed with many types of cerebral dysfunction. Although paroxysmal, it is not epileptiform or predictive of epilepsy. Although IRDA may be seen with structural brain lesions (13,53), it is more often associated with diffuse encephalopathies as a nonspecific finding. IRDA is commonly a temporary pattern in the course of a cerebral disturbance. When it occurs alone in an otherwise normal EEG, it suggests a mild to moderate, diffuse, nonspecific disturbance of brain function (44,45). In metabolic encephalopathies, a common setting in which these bursts occur, background rhythm is usually abnormal as well, and consciousness is often altered (28). FIRDA is more commonly seen with anterior hemispheric lesions than with posterior ones (53). Focal EEG abnormalities such as localized ADA must be carefully sought as more reliable clues to a possible localized lesion responsible for the FIRDA.

Interpretation of this pattern should be based on its lack of specificity. It does not necessarily indicate the presence of a subcortical lesion, increased intracranial pressure, or a deep midline lesion, although these correlations have been made. Although a diffuse encephalopathy is most likely, the electroencephalographer must identify and comment on any lateralized or localized EEG signs as clues to an underlying localized lesion.

OTHER DISTINCTIVE ABNORMAL PATTERNS

Pseudoperiodic Patterns

EEG patterns consisting of spikes, sharp waves, and slow waves, or combinations of these that repeat regularly (or nearly so), are called "periodic" or, more strictly, "pseudoperiodic." They are paroxysmal, standing out from the surrounding EEG activity. Barring general anesthesia or barbiturate coma, they occur with a variety of severe encephalopathies. Other abnormalities are also found in such EEGs. Routine visual analysis of such patterns requires knowledge of the age and state of the patient. The electroencephalographer must then evaluate the pattern in terms of (a) its form; (b) its distribution over the scalp; (c) its relation to wakefulness, sleep, or pathologically altered consciousness; and (d) its reactivity to external stimuli. EEG activity between the

pseudoperiodic events must also be assessed. Any association between the paroxysmal activity and possible clinical manifestations, at times helpful in differential diagnosis, should be noted by the technologist and scrutinized by the interpreter. Additional electrodes or other devices, such as an accelerometer to document myoclonic jerks, may be helpful.

Such a systematic approach to visual analysis of these transients will usually lead to clear differentiation among them. This is important because several of these patterns have strong and diagnostically important clinical correlations. Their salient characteristics are summarized in Table 10.1.

TABLE 10.1. *Periodic and pseudoperiodic abnormal EEG patterns, along with EEG characteristics and clinical correlation*

Pattern	Form	Scalp distribution	Interparoxysm interval	Relation to state	Interburst EEG	Clinical correlation	Chapter to see
Pseudoperiodic generalized sharp waves	Diphasic or triphasic sharp waves or spikes	Generalized: may be lateralized in early stages	<2.5 s; shortens with progression sof disease; usually <1 s	In wakefulness and/or sleep	Relatively featureless	Creutzfeldt-Jakob disease; eventually seen in almost all patients	12, 13
Pseudoperiodic bilaterally synchronous and–slow sharp-wave discharges	Irregular high-voltage slow waves or sharp-and–slow wave complexes	Diffuse, bilaterally synchronous	5–10 s; very regular in a single recording	May be evoked with hyperventilation or sleep in early stages	Diffuse, lower voltage delta activity	Subacute sclerosing panencephalitis; almost always seen except early or late in the disease	12
Pseudoperiodic lateralized epileptiform discharges (PLEDS)	Biphasic or triphasic sharp waves, spikes, or polyspikes	Hemispheric; lateralization may shift	1–2 s	Consciousness often impaired, except in children; PLEDS persist in sleep	Diffuse, abnormal slow activity; may be locally predominant	Early, acute, severe lateralized encephalopathy; may correlate with focal seizurest; transient in adults, may persist in children	11
Pseudoperiodic slow complexes with temporal predominance	Sharp or triphasic waves mixed with paroxysmal slow activity; may resemble PLEDS	Unilateral temporal predominance	1–4 s	Consciousness impaired	Localized or diffuse slow activity	Herpes simplex encephalitis; may occur before abnormality on computed tomography scan	11
Burst-suppression	Brief bursts of mixed spikes, slow waves, and sharp waves, interrupted by longer periods of relative EEG flattening	Bilateral; may be synchronous and/or asymmetrical	Variable	Coma; pattern not reactive to applied stimuli; does not form part of sleep cycle	Diffuse relative flattening	Severe diffuse encephalopathy, often anoxic; may be reversible (e.g.,with drug intoxication); distinct from neonatal quiet sleep	14, 15
Triphasic waves	High-amplitude deflections, typically negative–positive–negative	Bilaterally synchronous; anterior predominance with anterior–posterior lag of 25–140 ms in bipolar EEG	Groups or runs of 1.5- to 2.5-Hz waves	Impairment of consciousness	Slowed background rhythms	Toxic or metabolic encephalopathy, especially hepatic	12, 15

Unusual Asymmetrical Abnormal Activity and Dysplastic Brain Lesions

Patients with extensive unilateral dysplastic brain lesions may have characteristic interictal EEG findings. In particular, hemimegalencephaly is associated with typical interictal abnormalities lateralized to the abnormal side (54). Their morphology depends on the age of the subject: A newborn may have unilateral burst suppression, but unilateral hypsarrhythmia may be recorded several months later. The EEG over the affected hemisphere is also asymmetrical later, with higher amplitude and frequency in wakefulness and sleep, an asymmetry that may also be found with less evident lateralized malformations. EEG electrodes must be carefully placed to avoid false lateralizations resulting from the abnormal hemisphere that extends across the midline. Hemimegalencephaly often occurs with abundant interictal epileptiform activity and very frequent lateralized ictal patterns and clinical seizures from the neonatal period. Although the diagnosis must be made by neuroimaging, magnetic resonance imaging may be impractical in the critically ill newborn and is not rapidly available in many areas outside the United States. These EEG patterns are thus useful in diagnosis.

INTERICTAL AND ICTAL ABNORMALITIES

Interictal Epileptiform Activities

Epileptiform pattern, an interpretative term, refers to "distinctive waves or complexes, distinguished from background activity, and resembling those recorded in a proportion of human subjects suffering from epileptic disorders."(7). The "distinctive waves" are spikes or sharp waves, and distinguishing these specific epileptiform transients from sharply contoured waves of normal or abnormal background activity is critical but sometimes difficult. Several criteria are used in making this distinction (for a review, see ref. 39), including the form of the transient and the surrounding activity from which it arises, but the sharpness of the wave at its peak seems to provide the best differentiation. Expressing this concept in mathematical terms of a second-order differential equation underlies attempts at computerized analysis of epileptiform activity (see Chapter 22). In everyday visual analysis, in order to extract maximal information, the electroencephalographer must systematically analyze and describe epileptiform activity in terms of temporal features, morphology, and topography.

Distinguishing spikes from sharp waves is ultimately arbitrary and of limited physiological utility. By convention, spikes last more than 20 milliseconds and less than 70 milliseconds, and sharp waves last more than 70 milliseconds and less than 200 milliseconds. The transient may occur alone, but more often a slow wave follows, forming a spike-and–slow wave complex (subsequently in this discussion, "spike" and "sharp wave" are used interchangeably). The slow wave comprises the major temporal component of spike-and–slow wave complexes, lasting from 150 to 350 milliseconds (Fig. 10.5*A*). Spikes or complexes may occur once or repetitively. With repetitive complexes, the repetition rate carries important information. The electroencephalographer must determine if one complex immediately succeeds another (rhythmic burst), or if complexes recur at intervals that are constant (periodic discharges) or slightly varying (pseudoperiodic discharges).

If epileptiform discharges occur widely over the head, particularly over the left and right sides, the electroencephalographer must determine if the discharges are simultaneous and bisynchronous, or so temporally separated as to be considered independent and asynchronous (see Fig. 10.5). Because the potential field of a single large generator may extend across the midline, only transverse montages can distinguish such a generator from two discrete, but bisynchronous, generators. Two generators sometimes occur within one hemisphere and also produce asynchronous discharges.

"Morphology" describes the very brief temporal characteristics of a spike. The discharge (Fig. 10.5*B*) may abruptly leave the baseline and return (monophasic); cross the baseline and retum (biphasic); or cross, recross, and return (triphasic), after which counting ceases (polyphasic). The polarity of a spike has equal importance. In most instances the predominant component is surface negative (see Fig. 10.3*B*). The voltage topography of spikes on the scalp reflects a dipole-like source (see Chapters 2 and 23). For cortical generators with a radial orientation, the negative EEG field maximum is directly above the source, and it is of much higher amplitude than the positive field maximum on the opposite side of the head. For spike generators with a tangential orientation, field maxima on the scalp are displaced on either side of the source, and they may be of nearly the same amplitude. Spikes with voltage fields suggesting a tangential dipole generator have most commonly been associated with benign rolandic epilepsy of childhood (23) (see Chapters 16 and 17), but now these are known to occur commonly in other focal seizure disorders (see Chapter 23). Correctly assessing the location and orientation of spike sources requires an appreciation for how different montages display scalp voltage fields, in particular how the choice of reference can alter this display (see Chapters 2 and 4). Surface-positive spikes rarely occur in patients with epilepsy but can occur in healthy persons as a "benign" normal variant, 14- and 6-Hz positive bursts (see Chapter 7).

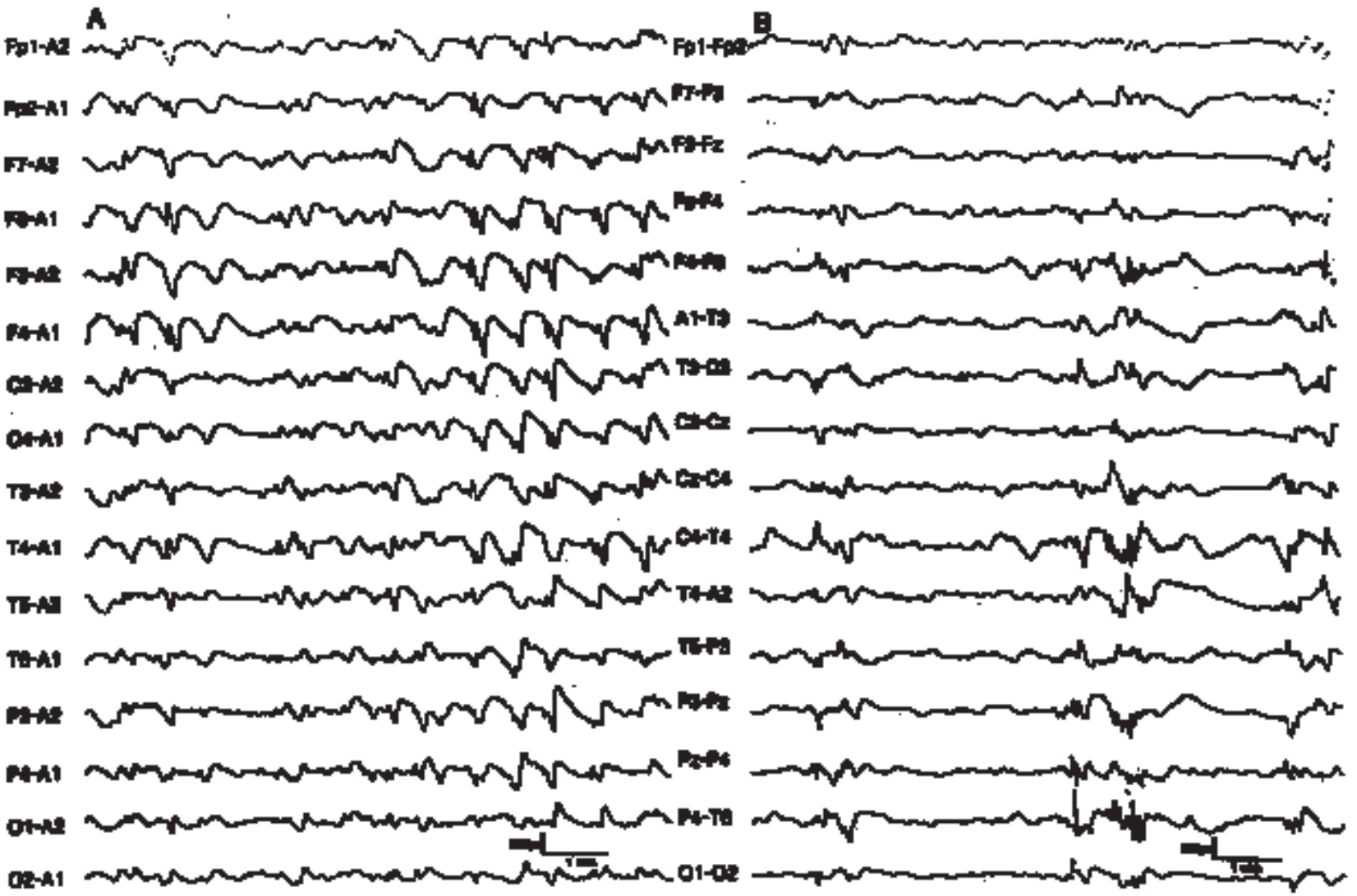

FIG. 10.5. Sedated sleep tracing of a 1-year-old girl with a diffuse encephalopathy. Many different epileptiform patterns can be recorded in a single EEG when recordings are of adequate length. **A:** Sharp waves and repetitive spike-and–slow wave complexes. The right-sided predominance of the epileptiform activity is difficult to appreciate easily in this montage. **B:** Later, spikes of varying morphology are seen, including triphasic and polyphasic spikes. The right-sided predominance is more evident.

Aftercoming slow waves are surface negative and may represent prolonged hyperpolarization caused by secondary inhibition in a large neuronal population (see Chapter 1).

As with other abnormalities, epileptiform discharges may be (a) localized (at times exquisitely so); (b) unilateral with or without focal preponderance (e.g., periodic lateralized epileptiform discharges); (c) multifocal and, usually, asynchronous; (d) generalized with shifting lateralization (e.g., 2.5-Hz sharp-and–slow wave discharges), or (e) generalized and symmetrical (e.g., 3-Hz spike-and–slow wave discharges). Particularly in children, the topography of focal spikes varies over time, appearing in serial EEGS in three or more locations (51). The bisynchronous spike components of 3-Hz spike-and–slow wave complexes typically show maximal negativity at F3 and F4; however, during non–rapid-eye-movement (NREM) sleep, isolated complexes may occur with maximal negativity over one or the other frontal region. Thus one should not assume that spikes unvaryingly arise immediately subjacent to a scalp electrode or, even less, that they signify local pathological changes. Indeed, it is common for fragments of a generalized spike-and-wave discharge to appear transiently "focal" or "asymmetrical".

Distinguishing Nonepileptiform from Epileptiform Discharges

Because a strong, but not absolute, correlation exists between epileptiform discharges in the EEG and epilepsy, certain normal bioelectrical potentials must not be confused with epileptiform discharges. Mu rhythms have asymmetrical waveforms, perhaps as a result of intermixing with quasi-harmonic beta rhythms; the negative half of the wave changes voltage more rapidly, giving it a sharp or "spiky" appearance in contrast with the sinusoidal positive half. Mu rhythms are readily distinguished from spikes by (a) a consistent frequency of 8–10 Hz, (b) voltage modulation in spindles, and (c) reactivity to contralateral actual or imagined motor acts (see Chapter 5).

In younger children (see Fig. 10.3), vertex sharp transients appearing in stage 2 NREM sleep have surprisingly high amplitudes, exhibit sharp peaks, and occur repetitively; however, their ascending and descending limbs are more symmetrical than those of spikes, their duration is somewhat longer, and they lack an aftercoming slow wave. POSTS occur at the occipital pole, appear in stage 1 NREM sleep, and disappear on arousal; these features readily distinguish them from the usual surface-negative epileptogenic occipital spikes.

"Lateral rectus spikes" are single motor unit potentials, best detected in F7 and F8 electrodes during lateral deviation of the eyes. They ride on the slower potential caused by movement of the globe (see Chapter 9). These normal rhythms are best recognized by "the company they keep": location, physiological state, reactivity, and age of the patient.

Finally, one must remember that electrode artifact can simulate most types of electrocerebral activity, both normal and abnormal. If undetected and uncorrected, it usually ultimately reveals itself by (a) abrupt discontinuities, (b) "pops," and (c) other bizarre, clearly noncerebral features.

Epileptiform Discharges and Seizures

In carefully screened populations of healthy persons, a very small percentage will have EEGs with epileptiform discharges. There is thus a strong, but not absolute, correlation between epileptiform discharges and seizures, and EEG reports should recognize this. Nonetheless, having carefully analyzed and described the discharges in terms of morphological, temporal, and topographic features, the electroencephalographer can integrate these with the clinical data and interpret them in terms of known "electroclinical" associations.

A few examples suffice (Chapter 17 provides extended discussions). In children, the topography of focal spikes correlates with their epileptogenicity: 91% of children with anterior temporal spikes have seizures, whereas only 38% of children with rolandic spikes have seizures (34). Children whose EEGs show 3-Hz spike-and–slow wave bursts and independent bursts of occipital intermittent rhythmic delta activity (OIRDA) have a better than 50% chance of spontaneous remission within 10 years and are unlikely to develop tonic–clonic seizures. In contrast, if the EEG lacks OIRDA but shows photoparoxysmal responses, such children are more likely to develop tonic–clonic seizures, and only 6% will have spontaneous remission (38).

Ictal Patterns

In the ordinary course of events, EEG laboratories infrequently record seizures, except for those laboratories associated with epilepsy centers. Those seizures that do occur are likely to overrepresent a narrow band (e.g., absence seizures) in the broader spectrum of seizures. Consequently, many electroencephalographers are relatively unfamiliar with the widely varying types of transition from interictal to ictal patterns. The simplest transition is persistent, repetitive interictal epileptiform discharges. A burst may contain a single complex or repeating complexes; if the burst persists long enough, behavioral changes appear (see Chapter 17 for fur-

ther discussion). In a meticulous study of focal seizures, Blume et al. (4) found that slightly less than one-half began with repetitive spikes or sharp waves; the remainder began with rhythmic, sinusoidal waves. Thus, in focal seizures, "prolongation" of the interictal epileptiform discharge is not the most common transition.

Furthermore, in the study of Blume et al. (4), when clinically apparent seizures occurred, two-thirds began with rhythmic waves. Geiger and Harner (19) have reported similar findings in a more heterogeneous population of patients with seizures, of whom only 40% had long-standing epilepsy. Rhythmic discharges are the hallmark of ictal transition in certain generalized epilepsies. Chatrian et al. (8) reported the EEGs of 35 patients with tonic–autonomic seizures; 28 had Lennox-Gastaut syndrome: "The most characteristic feature of our patients' electrical seizures was ... bilaterally synchronous generalized rhythmic discharge." The discharges were usually of high frequency, faster than 15 Hz in 85% of patients. With focal seizures, Geiger and Harner (19) have noted similar findings, with seizures being initiated by rhythmic discharges that were faster than 13 Hz in 50% of patients. Seizures beginning with frequencies in the alpha range, sometimes referred to as the "epileptic recruiting rhythm" (17), occurred less often, ranging from 8% (4) to 16% (8). In patients with tonic seizures, rhythms slower than 8 Hz did not occur; however, in patients with focal seizures, rhythms of 4–7 Hz appeared in 46%, whereas those of less than 4 Hz appeared in 20%.

Seizures may begin with "attenuation," a sudden diminution of voltage. Sporadic interictal epileptiform discharges may abruptly cease several seconds before attenuation occurs. Blume et al. (4) noted attenuation in 10% of focal seizures; Chatrian et al. (8) found a similar incidence in patients with tonic–autonomic seizures. Attenuation occurs so commonly as a part of infantile spasms that some have called them "electrodecremental" seizures. In a study of ictal EEG patterns in 5,042 infantile spasms, Kellaway et al. (35) found attenuation as part of the seizure in 71% and as the sole manifestation in 12%.

Finally, seizures may begin in cortical regions not readily accessible to scalp electrodes. Studies using simultaneous recordings from scalp and depth electrodes have clearly documented this for seizures arising in the medial temporal lobe (37). However, if the seizure evolves to altered awareness and automatism, the scalp EEG usually alters (see Chapters 17 and 18 for further discussion).

Although suddenly appearing seizure patterns may alert the EEG technologist, determining whether the seizure is purely an electrical event ("subclinical seizure") or a behavioral event ("clinical seizure") poses significant problems in the laboratory (see also Chapters 17 and 18). In research laboratories, studies of children with absence seizures have shown that reaction time reliably alters within 0.5 seconds after onset of a 3-Hz spike-and–slow wave burst (5). Comparable evidence suggests that, with focal spikes, altered responses may occur during the aftercoming slow wave with intervals as short as 200 milliseconds (46). Obviously, in the usual laboratory setting, epileptic patterns of brief duration may elude adequate behavioral testing. Conversely, certain paroxysmal patterns that seemingly qualify as ictal patterns may show no evidence whatsoever for behavioral change (e.g., subclinical rhythmic EEG discharge of adults) (see Chapter 7).

CONCLUSION

Visual assessment of the abnormal EEG requires a knowledge of normal patterns, their range of variation, and the abnormalities that altered normal patterns may represent. Other abnormal patterns may coexist with these or may appear alone. A systematic approach to the abnormal EEG requires examination of (a) the type or types of abnormality, (b) their distribution in time and space, (c) reactivity, and (d) associated findings. Assessment of the course of an abnormality in serial recordings can be particularly valuable. This approach permits interpretation that is useful and clinically relevant. Although EEG abnormalities are usually etiologically nonspecific, competent and prudent EEG interpretation can provide information of differential diagnostic value.

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Chapter 11

Focal Electroencephalographic Abnormalities

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HISTORICAL BACKGROUND

Before the introduction of modern brain imaging methods, electroencephalography (EEG) was routinely used to identify and localize intracranial pathology. In 1936, Walter (178) first described localized delta activity with tumors of the cerebral hemispheres, and EEG quickly became a standard test for localization of focal cerebral lesions. Theta rhythm was subsequently associated with subcortical abnormalities (179); focal attenuation of background activity as a feature of tumors was reported in 1944 (94). Over the ensuing decades, electroencephalographers refined these findings and became adept at using them to localize superficial cerebral lesions. EEG remained of limited utility for deeply located lesions, especially those located in the posterior fossa, because findings in such cases were typically nonspecific and diffuse.

In recent years, of course, computed tomography (CT) and magnetic resonance imaging (MRI) have replaced EEG as diagnostic tests of choice for detecting and localizing cerebral lesions. Both are superior to EEG for these indications, and also provide useful information about etiology. EEG, however, is still useful and can be complementary to imaging studies. Unlike CT and MRI, EEG provides information about the physiological function of the brain. Such information can be important in estimating the extent of *functional* (not anatomical) impairment, recognizing a coexisting metabolic or

toxic encephalopathy, and indicating the lesion's epileptogenic potential. Occasionally, as in acute ischemia, EEG changes may precede or outlast imaging abnormalities. Combining imaging studies and EEG, therefore, will often give a more complete pathophysiological picture than will either study alone.

In this chapter, we discuss specific focal EEG abnormalities. The emphasis is on nonepileptiform abnormalities; epileptiform patterns are discussed in detail in Chapter 17. The description of each type of focal finding is illustrated by a discussion of specific neurological conditions that may be associated with the EEG abnormality. Keep in mind, however, that many neurological conditions are accompanied by several EEG findings. For example, focal slowing may be seen with attenuation of fast-frequency activity and absence of the alpha rhythm. In this chapter, conditions are discussed under the most prevalent EEG abnormality noted in each. The final section of the chapter briefly discusses the use of EEG in the intensive care unit (ICU) and operating room to identify focal abnormalities of brain function.

NON-EPILEPTIFORM ABNORMALITIES

Changes in the EEG produced by focal brain lesions may be categorized as either epileptiform or nonepileptiform. Epileptiform abnormalities include spikes, sharp waves, spike-and-wave or sharp-and–slow wave discharges, and periodic discharges (see Chapter 17 for further discussion of epileptiform patterns). Nonepileptiform abnormalities are of several types. First, localized slow activity is the most prevalent abnormality associated with focal brain lesions; the slowing is further classified as arrhythmic (polymorphic) or rhythmic (e.g., frontal intermittent rhythmic delta activity [FIRDA]). Second, there can be alteration in normally present cerebral rhythms such as frontal beta activity or the alpha rhythm. Third, background activity can be attenuated locally. Finally, widespread or diffuse abnormalities also occur with focal lesions, especially those located in the subfrontal regions or thalamus or that produce hydrocephalus.

Changes in Normal Rhythms

A complex mixture of different background rhythms and frequencies are present in the EEGs of normal individuals. These include beta frequencies (typically most prominent over the frontal regions), alpha rhythm and other posterior-dominant rhythms, mu rhythm, and normal features of sleep such as spindles and vertex waves. These different activities are evaluated routinely in terms of voltage, frequency, persistence, symmetry, and reactivity. Because the characteristics and normal variability of these patterns in healthy individuals are well established, changes in any of the foregoing measures are useful in identifying focal or regional abnormalities. Voltage asymmetries alone, however, are common in normal persons and should be interpreted conservatively—or even ignored—in the absence of other, more specific findings indicating an abnormality. (See Chapter 5 for detailed descriptions of normal EEG patterns and their variations.)

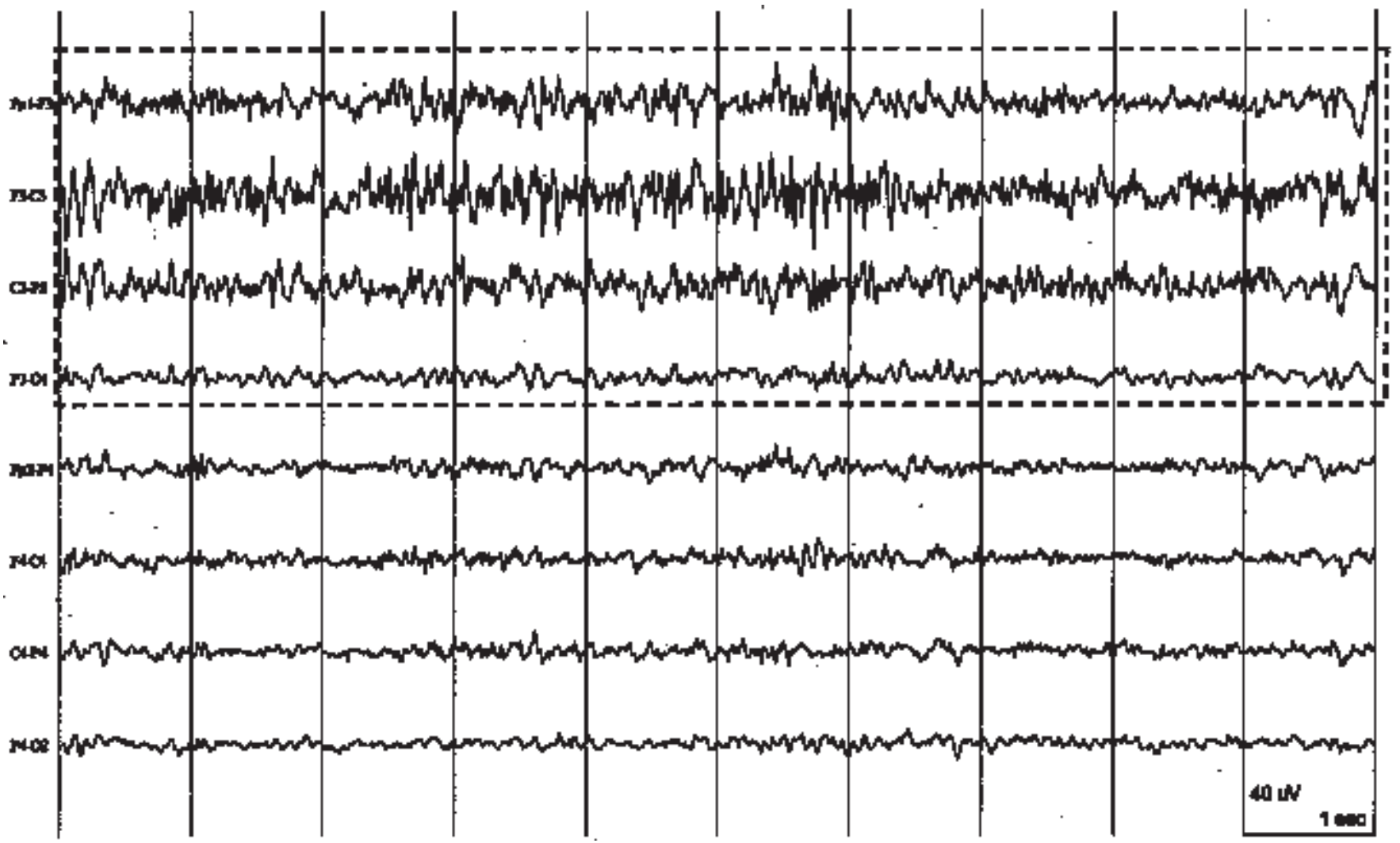
Focal Enhancement of Beta Activity

Anterior beta activity is normal in healthy adults (121), and it can be enhanced in voltage, rhythmicity, and quantity by many sedative, tranquilizing, or hypnotic medications, including benzodiazepines, barbiturates, and chloral hydrate (9,10,58). These drugs are frequently used by patients referred to EEG laboratories for treatment of epilepsy or other nervous disorders, or as sedation for the test itself. In such cases, fast activity is enhanced symmetrically. This bilateral and usually diffuse increase in normal beta activity should not be interpreted as abnormal; rather, it should be considered as being consistent with a clinically insignificant medication effect. Occasionally, prominent rhythmic beta activity recorded in the absence of known therapeutic drug use raises the possibility of illicit drug use.

Persistent asymmetry of beta activity indicates focal cortical dysfunction, which is often due to a cerebral lesion. The most common cause of focally enhanced beta activity is the "breach rhythm" (Fig. 11.1). This is usually the consequence of intracranial surgery requiring a craniotomy or burr hole. Less often, the breach rhythm results from a skull fracture. Skull defects enhance the voltage of frontal fast rhythms as much as threefold (28,80). This is most evident at C3/4 or T3/4 electrode sites because of their proximity to underlying mu rhythms or temporal rhythmic activity in the alpha frequency range. Although the enhanced beta activity is maximal nearest a burr hole or craniotomy margin, there is typically a broad voltage distribution.

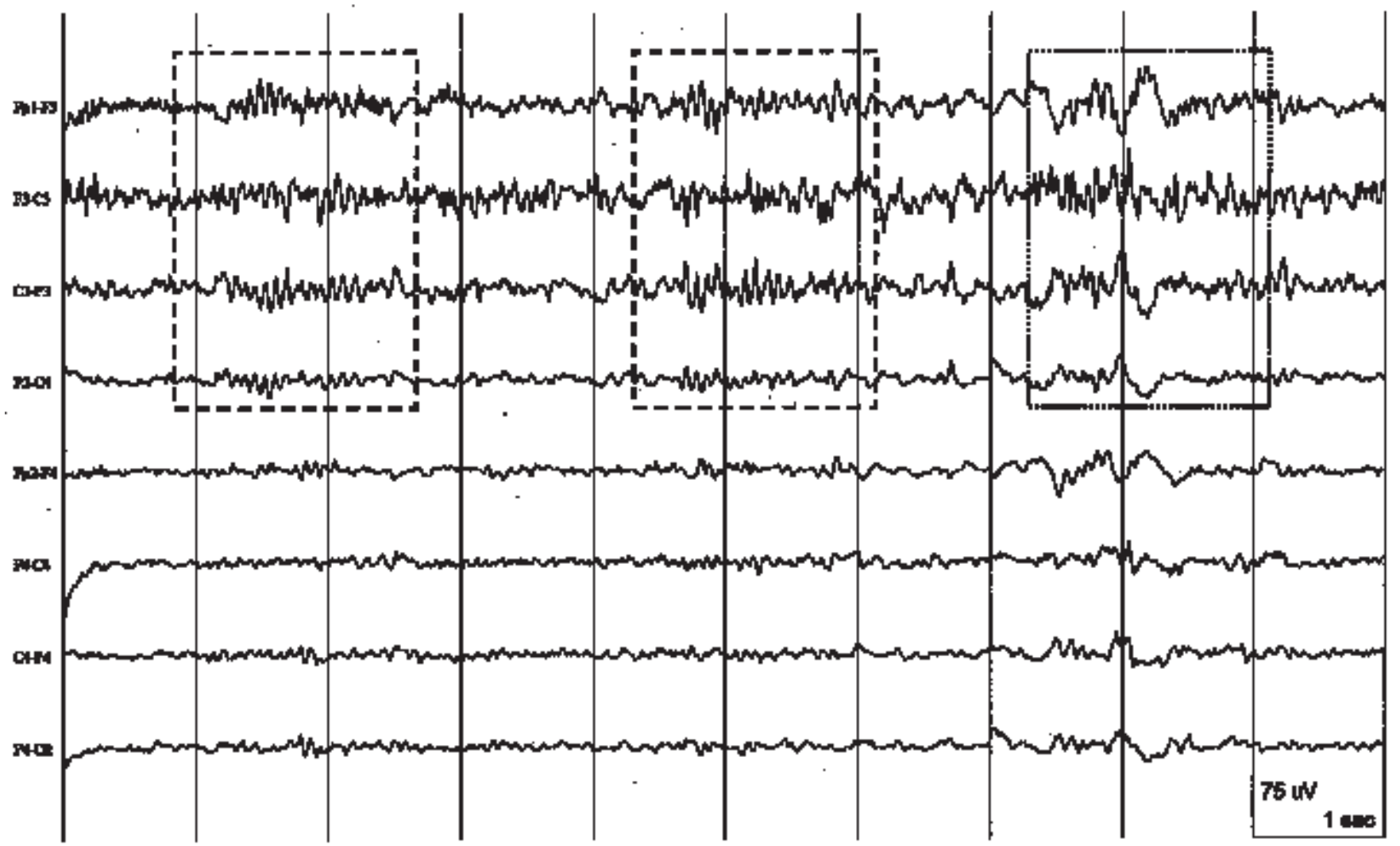
Focally enhanced beta activity is rare in other circumstances. It has been described with brain abscess (139,175), stroke, arteriovenous malformations, tumors (13,68,80), and focal cortical dysplasia (142,145). Localized *attenuation* of beta activity is much more common in these conditions than enhancement.

Normal beta activity that has a predominant rhythmic frequency has a waxing and waning quality but remains more or less constant in a given state and over the course of the recording. Paroxysmal beta activity (also referred



A

FIG. 11.1. EEGs of a 79-year-old man who had had a left subdural hematoma evacuated. **A:** Waking EEG demonstrates a breach rhythm in the left parasagittal region and focal polymorphic mixed theta and delta activity. (*Figure continues.*)



B

FIG. 11.1. *Continued*. **B:** Sample from stage 2 sleep illustrating higher voltage K complexes and sleep spindles (*boxed areas*) in the region of the skull defect.

to as paroxysmal fast activity), in contrast, is typically seen in epileptic encephalopathies, such as Lennox-Gastaut syndrome, where it is often an ictal pattern that accompanies tonic seizures (see also Chapter 17). Nealis and Duffy (125) reported nine patients with focal paroxysmal beta activity, all of whom had epilepsy. Most also had other focal EEG findings, such as sharp waves or slow-frequency activity, in the same area as the paroxysmal fast activity (Fig. 11.2).

Focal Attenuation of Beta Activity

Asymmetrical beta activity should be considered abnormal if there is a persistent voltage difference of 35% or more between homologous areas of the two sides. Frontal beta activity tends to occur out of phase on the left and right sides, and a voltage asymmetry can therefore be enhanced using bipolar montages that connect homologous areas. Focal attenuation of beta activity is a reliable sign of a cortical abnormality.

Focal attenuation of beta activity is seen in a number of conditions, including brain abscess (139,175), stroke (68), arteriovenous malformations (78), and brain tumors (13,68). Green and Wilson concluded that beta activity seems to be diminished with vascular lesions and enhanced by tumors (68). Barbiturates have been used to bring out a beta asymmetry, because focal structural lesions often diminish the usual enhancing effect of such drugs (134,135).

Beta activity is also attenuated by subdural, epidural, or subgaleal fluid collections (96). These selectively suppress higher frequency activity, much like a fast-frequency filter. Focal slowing usually accompanies parenchymal lesions but not fluid collections, a point that is sometimes helpful for interpretation. However, when extraaxial blood or cerebrospinal fluid results from a head injury, the underlying cortex is often injured as well, invalidating this distinction.

Abnormalities of the Alpha Rhythm and Photic Driving Response

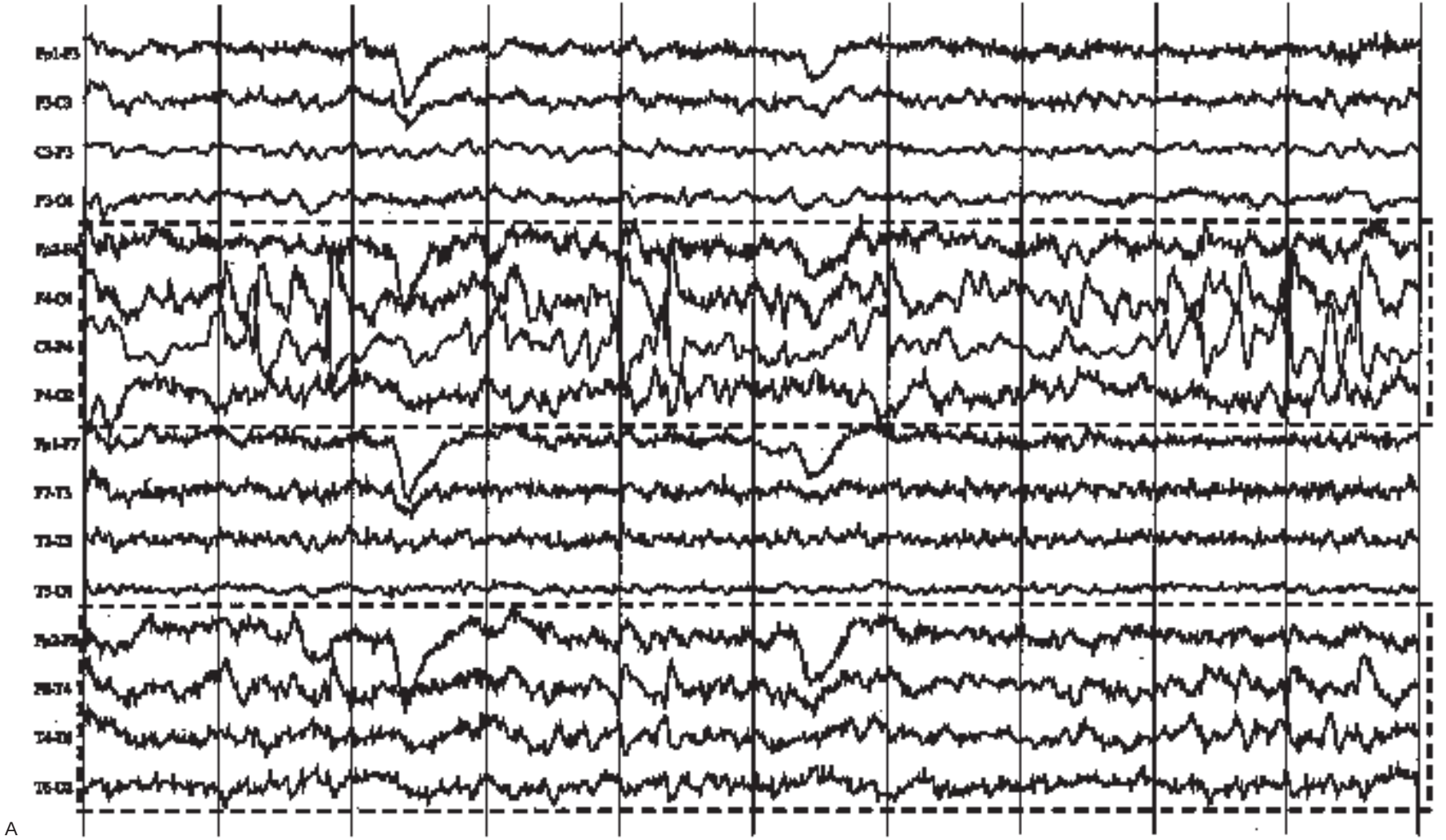
Focal cerebral lesions can alter the alpha rhythm, even when they do not directly involve the occipital lobes and adjacent posterior brain regions (Fig. 11.3). Changes that can result from focal lesions include unilateral (a) slowing of frequency (1 Hz or more difference between the sides); (b) loss of reactivity; (c) loss of modulation; and (d) voltage attenuation. Unilateral attenuation or absence of alpha rhythm usually occurs with lesions of the occipital cortex and anteroventral thalamus (83). Unilateral failure of the alpha rhythm to attenuate with eye opening (Bancaud's phenomenon) occurs with posterior subcortical lesions (3). Voltage asymmetry, by itself, is only rarely an indication of focal abnormality. In contrast, asymmetries of frequency and reactivity are abnormal and reliably indicate the side of the lesion.

Skull defects result in higher voltage alpha rhythm, a difference that can be two to three times that of the normal side (28). Rarely, the alpha rhythm is higher on the side of a brain tumor (38,89), but in such cases the alpha rhythm is also usually less reactive and poorly modulated.

Asymmetries in the response to intermittent photic stimulation may result from lesions on the side of lower voltage, but responses can also be consistently lateralized in some normal individuals (31). Therefore, voltage asymmetries in photic driving should not be interpreted as abnormal in the absence of corroborative findings such as focal slowing or localized attenuation of background rhythms on the same side. Rarely, epileptogenic lesions result in responses to photic stimulation that are of higher voltage on the side of the lesion (Fig. 11.4).

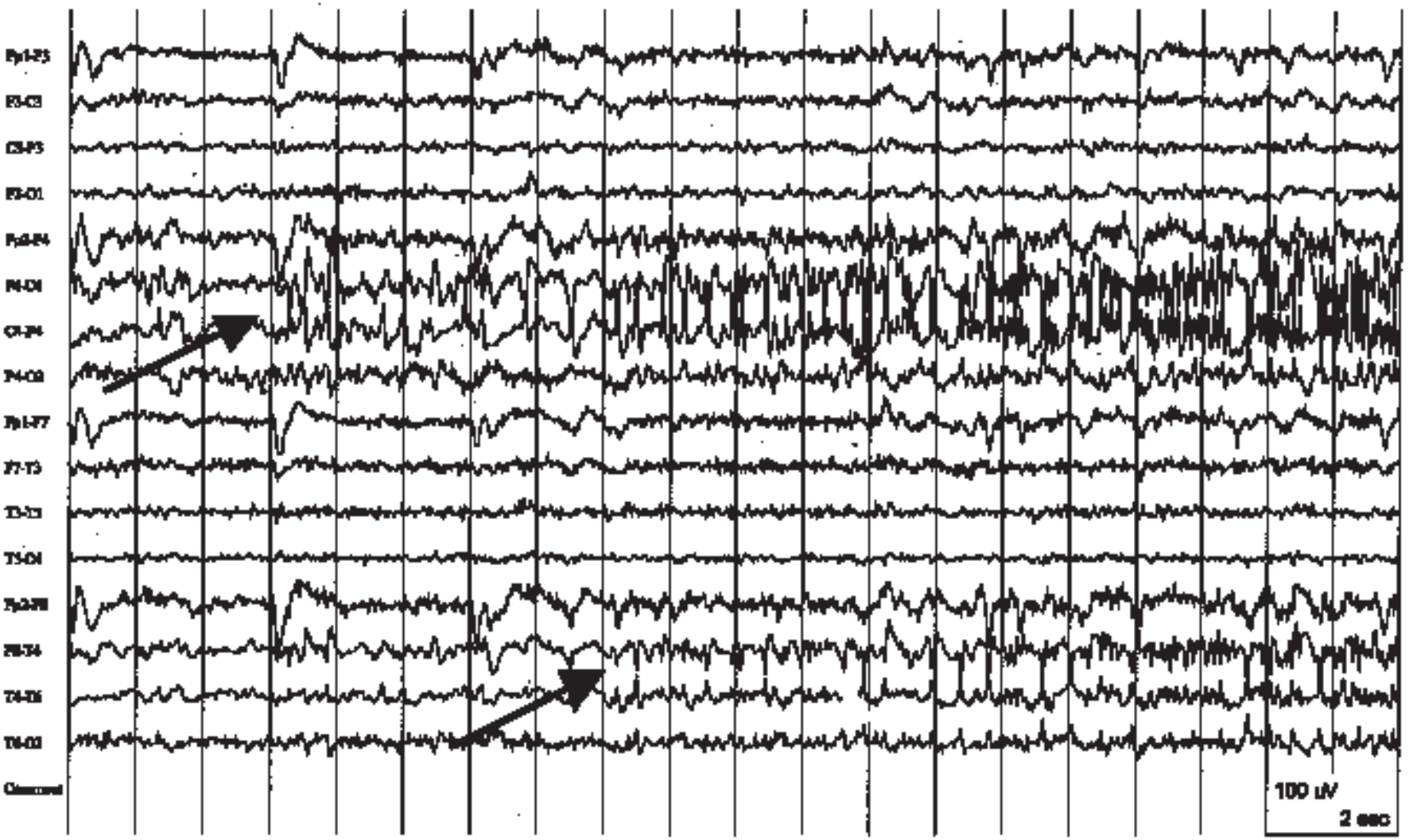
Changes in Other Normal Rhythms

A unique precentral alpha-frequency rhythm was first recognized by Jasper and Andrews (82) and later characterized by Gastaut and coworkers (55) as "*le rythme rolandique en arceau*." They described a 7- to 11-Hz arch-shaped rhythm over one or both rolandic areas that was unaltered by eye opening but attenuated with contralateral sensory stimuli or movement, either passive or active. The "parietal focal theta rhythm" described by Cobb (27) was probably similar activity. Fishgold et al. (47) first reported on the effects of bone defects on EEG activity. These investigators concluded that bone defects resulted in higher voltage alpha rhythm, but they were probably describing the effect on mu rhythm (28). Cobb and colleagues (28) recorded EEGs from 33 patients before and after replacement of a bone flap. Electrode location was controlled by radiography. Most recordings with the bone absent showed asymmetrical 6- to 11-Hz waves that were maximal over the rolandic region (usually C3/4) and blocked by fist clenching. They termed this a "breach rhythm." Although it usually had a limited field, the breach rhythm could be identified several centimeters from the bone edge. In most patients, replacing the bone flap either attenuated the breach rhythm significantly or eliminated it completely. The breach rhythm is mu activity made especially prominent (long duration, high voltage, and sharp contour) by a skull defect (see Fig. 11.1). Like all mu activity, it attenuates with real



A

FIG. 11.2. EEGs of a 47-year-old man who had a right parietal intracerebral hemorrhage evacuated recently. Afterward, he developed confusional episodes secondary to frequent nonconvulsive seizures. **A:** There is focal polymorphic delta activity, attenuation of faster organized frequencies, and epileptiform discharges over the right central-parietal region. Rhythmic theta activity is higher voltage on the right because of the craniotomy. *(Figure continues.)*



B

FIG. 11.2. *Continued.* **B:** Interictal–ictal transition in the right central epileptogenic brain region. Note that individual epileptiform discharges first increase in frequency (*higher arrow* on left) and then evolve into an ictal pattern consisting of rhythmic 12- to 14-Hz waves that spread to involve the adjacent right temporal area (*lower arrow* on right).

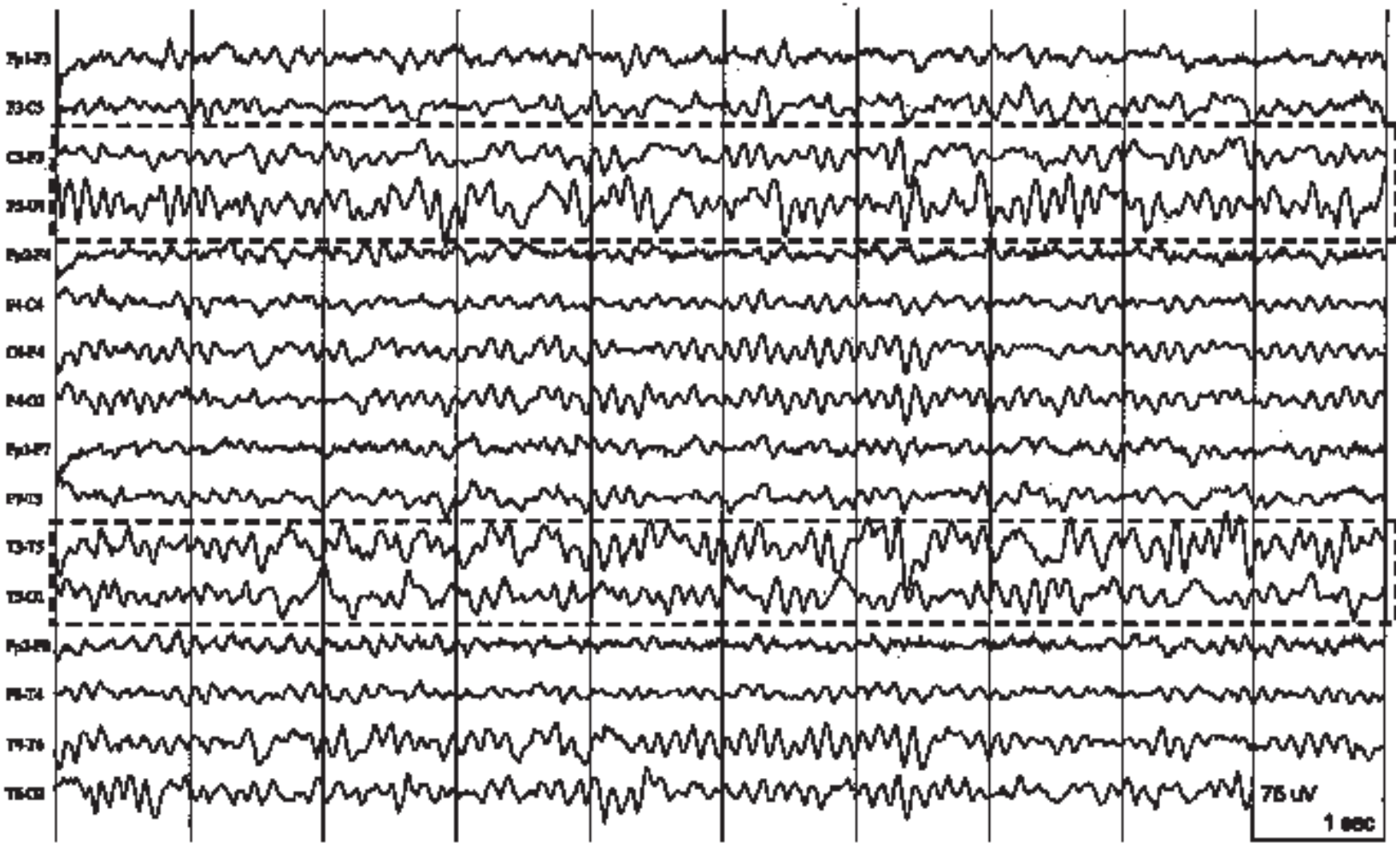
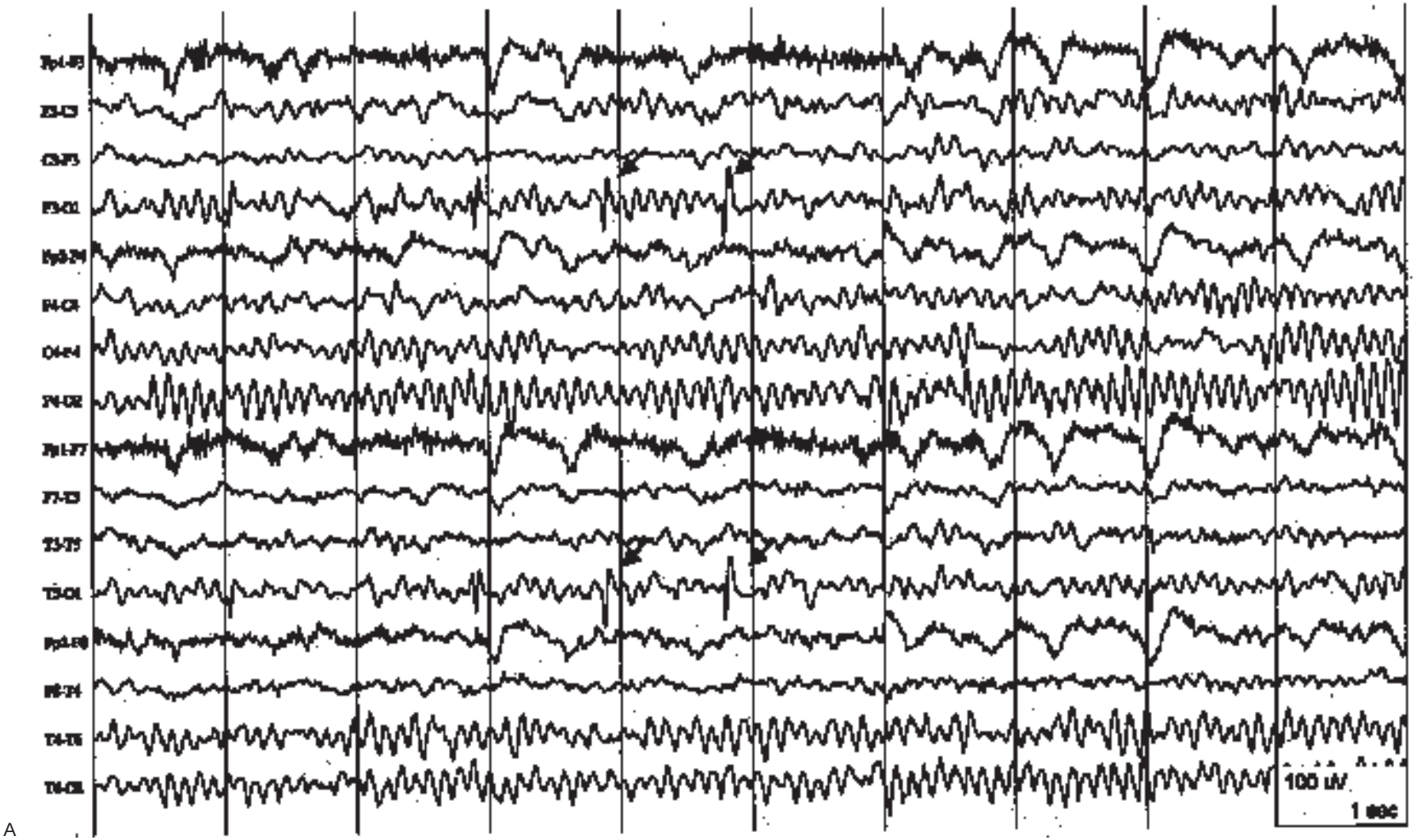
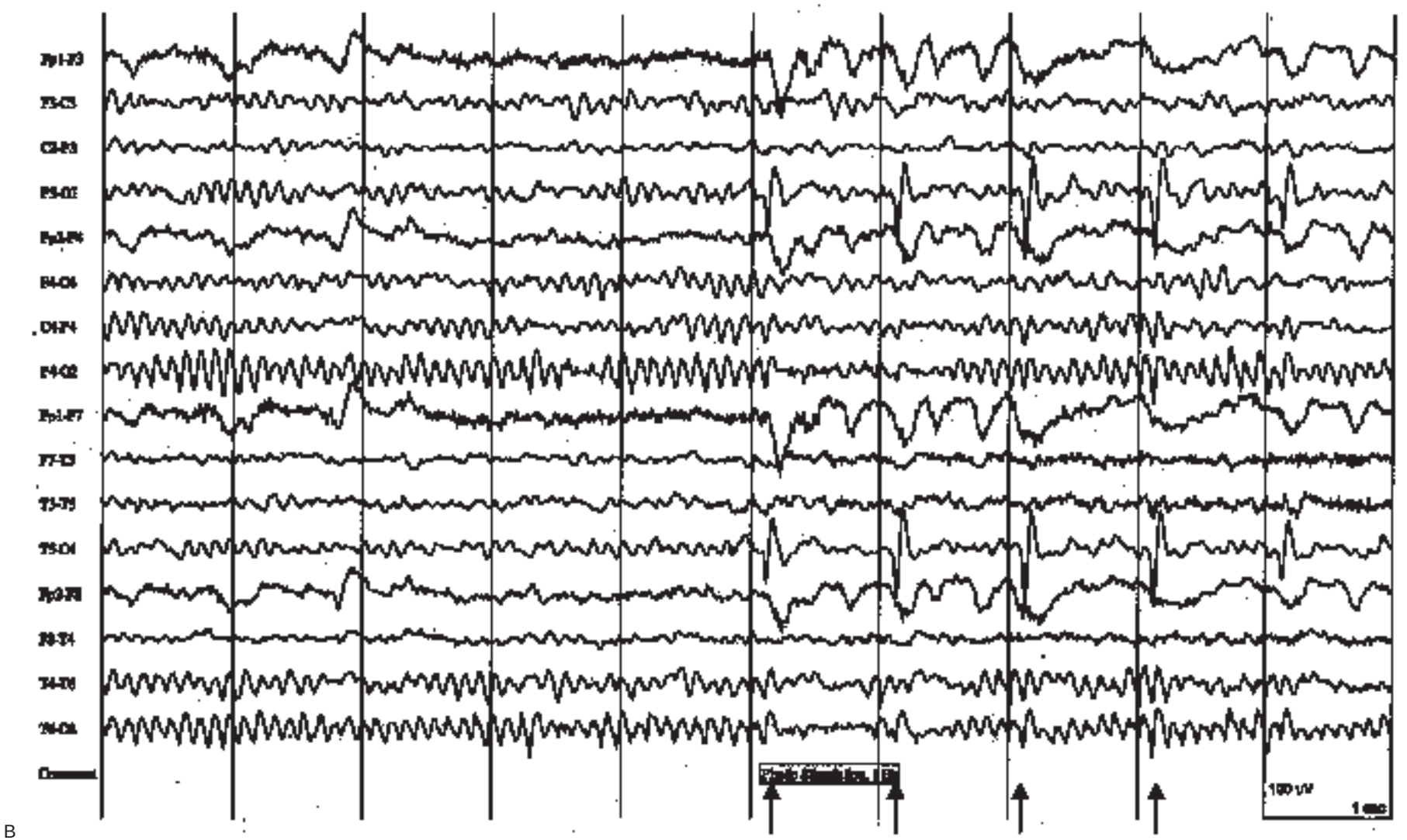


FIG. 11.3. EEG of a 31-year-old man with a left occipital arteriovenous malformation. There is continuous focal polymorphic delta activity over the left parieto-occipital–posterior temporal areas. The alpha rhythm on the left is 1–1.5 Hz slower and paradoxically of higher voltage on the left.



A

FIG. 11.4. EEGs of a 6-year-old boy with intractable epilepsy and left occipital cortical dysplasia on MRI scan. **A:** Asymmetry of the alpha rhythm, which is normal on the right but greatly attenuated and poorly regulated on the left. There are frequent left occipital (O1) epileptiform discharges (*arrows*). *(Figure continues.)*



B

FIG. 11.4. *Continued.* **B:** Paradoxical enhancement of photic responses to 1-Hz light flashes on the left (*arrows* indicate typical examples in channels 4[P3-01] and 12[T5-01]).

or imagined movement of the contralateral hand. It probably results primarily from physical factors related to removing a portion of high-impedance calvarium. Development of adhesions that act as low-impedance bridges between cortex and dura or skull may also play a role (47). A postoperative mu or breach rhythm has no clinical implications, and one must exercise caution in not overinterpreting sharply contoured fragments of such activity as epileptiform.

Although both the unilateral appearance and absence of mu activity were at one time thought to indicate focal cerebral pathology (15,155), this has not been substantiated. It is now recognized that asymmetries of mu rhythm are common (mu is unilateral in about 30% of normal people) and of no clinical significance.

Normal sleep patterns, especially sleep spindles and vertex waves, can be affected by cerebral lesions. Once stage 2 sleep is well established, persistent asymmetry of spindles indicates an abnormality on the side of lower voltage. Lesions of the parietal lobe or thalamus can attenuate sleep spindles (17,34). Thalamic lesions can also result in interhemispheric asynchrony of spindles, affect regulation of spindle frequency, or, rarely, lead to the appearance of spindle-like rhythms during the waking state (75). Skull defects enhance the scalp-recorded voltage of sleep spindles and vertex waves (see Fig. 11.1).

Focal Slow-Wave Activity

Slow-wave activity is classified as rhythmic or arrhythmic, intermittent or continuous, and focal or generalized. Focal polymorphic (arrhythmic) delta activity is slow-frequency activity (< 4 Hz) that lacks sustained rhythmicity; it is characterized by a constantly changing morphology, frequency, and voltage. Continuous focal polymorphic delta activity is highly correlated with a localized structural lesion (149,178), such as a tumor, stroke, abscess, intraparenchymal hematoma, or contusion (Fig. 11.5). Such delta activity usually persists during changes in physiological state. The clinical correlations of intermittent polymorphic slow-wave activity are less well defined, as are those of delta waves that attenuate with eye opening (or other alerting maneuvers) or disappear with sleep. Voltage of focal polymorphic delta activity is usually higher than ongoing background activity, but it can vary, depending in large part on the proximity of the lesion to the cortical surface and recording electrodes. Typical voltage of focal polymorphic delta activity is 100–150 μV in adults and up to 500 μV in children.

Focal polymorphic delta activity is often, but by no means always, maximal over the lesion. If sufficient destruction of the cortex and adjacent white matter has occurred, however, the voltage of the delta activity is actually reduced over the area of maximal cerebral involvement by the lesion (3). It is particularly important to pay attention to areas of relative inactivity ("flat" or "smooth" polymorphic delta activity), in which the voltage of both slow waves and faster background rhythms is depressed. In these cases, the voltage will be higher in the areas bordering the lesion (64).The localizing value of focal polymorphic delta activity is greatest when it is topographically discrete and associated with depression of superimposed faster background frequencies (3,64). Superficial lesions tend to produce more restricted EEG changes, whereas deep cerebral lesions can result in hemispheric, or even bilateral, delta activity. Focal delta activity associated with lesions of the frontal lobe typically spreads to homologous contralateral areas, where it typically is of lower voltage and has a smaller field than slowing ipsilateral to the lesion. Lesions involving the posterior frontal and parietal lobes often produce delta activity that is falsely localized to the temporal areas.

Clinical (63,127) and experimental (62) data indicate that polymorphic delta activity results primarily from lesions affecting cerebral white matter. Involvement of superficial cortex is not essential; indeed, lesions restricted to the cortical mantle do not generally produce significant focal delta activity. Cerebral edema, by itself, does not make a substantial contribution to production of delta waves (56,62,127). Brain tumors, abscesses, and areas of infarction are electrically silent (48,153). The EEG changes produced by these lesions, therefore, probably reflect alterations in cortical electrogenesis caused (a) directly by anatomic disruption of neurons and their local networks or by locally impaired blood flow, cellular metabolism, and the microenvironment; and (b) indirectly by modifying input onto cortical neurons. EEG is generally not useful in distinguishing among different types of brain lesions. This is largely because there are only a limited number of ways the brain can react to injury; therefore, a few electrographic changes are seen with a wide variety of conditions affecting the central nervous system.

Although experimental, clinical, and brain imaging studies have demonstrated the strong correlation between localized anatomical pathology and focal polymorphic delta activity, they also illustrate that delta activity can occur in the absence of a demonstrable lesion (60). This is most likely to occur when the polymorphic slowing is intermittent and contains substantial amounts of intermixed theta activity (Fig. 11.6). In these cases, the underlying cerebral dysfunction is often reversible. Examples include migraine, trauma, encephalitis, and postictal dysfunction. Focal arrhythmic theta activity can be seen early in the course of benign or well-differentiated brain tumors and during resolution of acute lesions caused by stroke or head trauma.

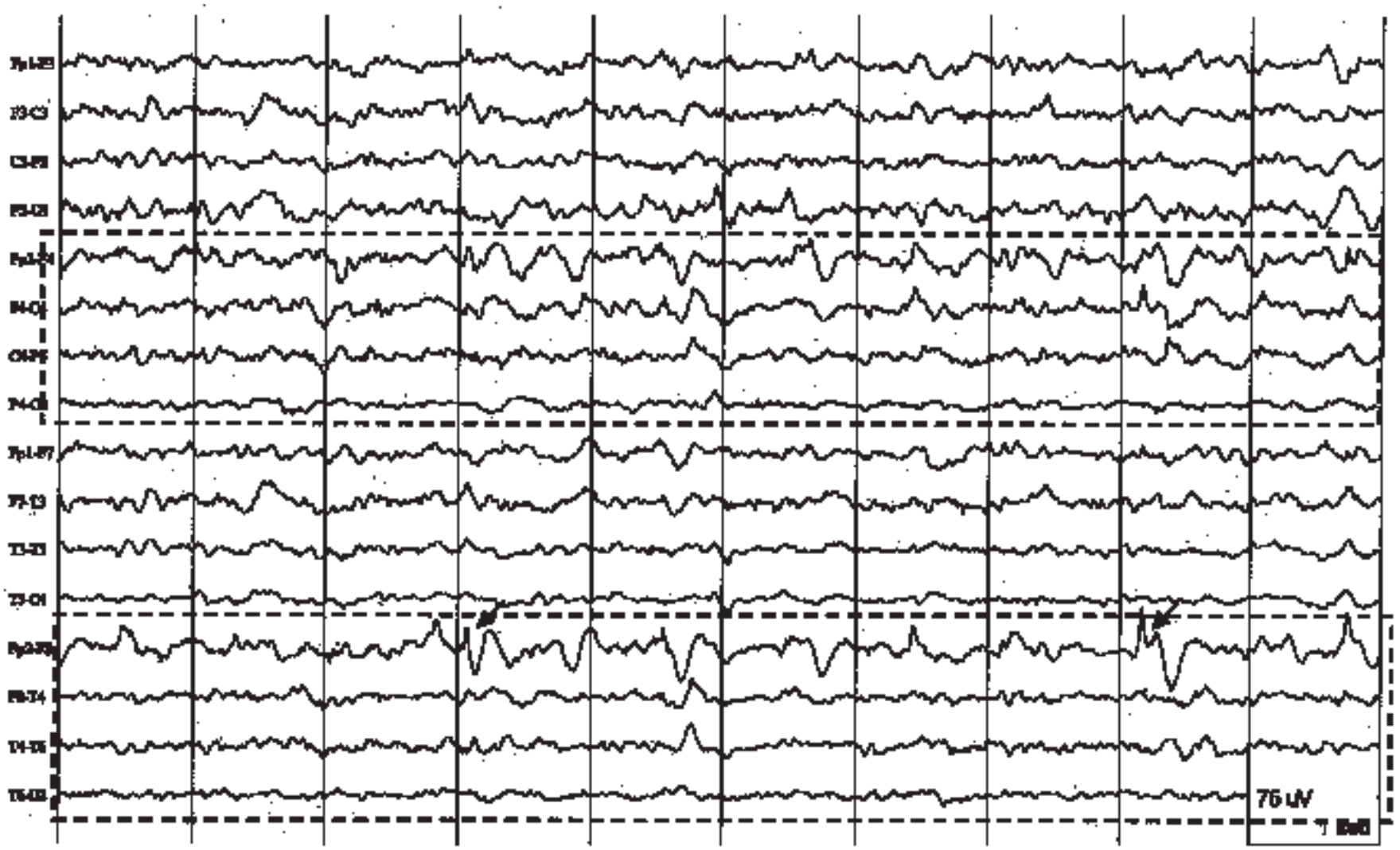


FIG. 11.5. EEG of a 79-year-old man with focal seizures secondary to multiple right hemisphere infarcts (frontal gyrus rectus, thalamus, and occipital lobe). There is continuous right frontal polymorphic delta activity, which spreads to the left frontal areas intermittently. There are also right frontal polar epileptiform discharges (*arrows*). Background activity is diffusely slowed and poorly differentiated.

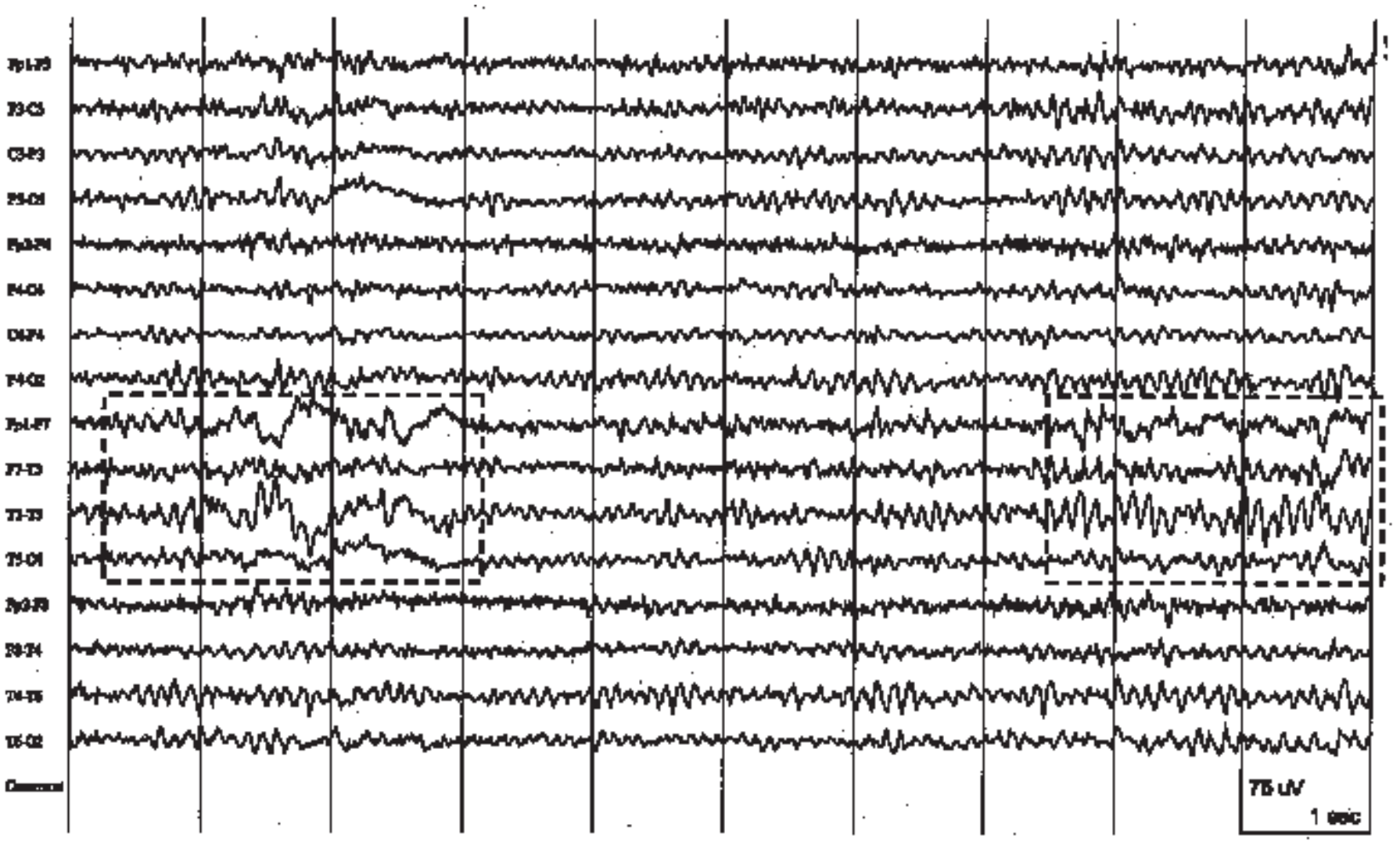


FIG. 11.6. EEG of a 57-year-old woman with a left temporal subcortical lesion and aphasia secondary to neurosarcoidosis. There is intermittent focal polymorphic delta activity in the left temporal area (*boxed channels*) that is relatively isopotential in the F7-T3 channel. Note that faster frequencies are preserved, riding on the delta waves.

Focal Voltage Attenuation

The value of voltage attenuation was referred to in the foregoing section. Berger (9) first described localized areas of low voltage in the EEG. These indicate either loss of normal cortical electrical activity (as with cerebral atrophy, invasion by tumor, or ischemia) or signal attenuation by fluid collections such as subdural hematoma (2).

Hemispheric voltage attenuation occurs with congenital lesions (e.g., infantile hemiplegia syndrome resulting from cerebral infarction), porencephaly, or Sturge-Weber disease (Fig. 11.7). Focal voltage attenuation occurs most often in combination with focal polymorphic delta activity, as described in the foregoing section of this chapter. Attenuation results from injury to, or destruction of, cortex as well as the subjacent white matter, as occurs with large cerebral infarctions and malignant brain tumors. Subdural hematoma, subgaleal fluid accumulation, and parasagittal meningioma also attenuate faster frequency activity, because they act as high-frequency filters. EEG alone cannot reliably distinguish among these possibilities.

Intermittent Rhythmic Delta Activity

Intermittent rhythmic delta activity (IRDA) was first described by Cobb (27) and later by Jasper and Van Buren (83) and Daly et al. (33). Although intermittent rhythmic theta activity also occurs, most studies and textbooks have emphasized IRDA that is maximal over the frontal regions (FIRDA). For many years, electroencephalographers tried to correlate IRDA with lesions involving deep midline or posterior fossa structures. It is now clear that most bilateral rhythmic slow-wave patterns are not reliably associated with localized structural pathology or specific anatomical locations.

IRDA is characterized by bursts and runs of high-voltage, bisynchronous, well-formed slow waves of relatively fixed frequency (about 2.5 Hz) and waveform. It usually increases with hyperventilation and during drowsiness, attenuates with eye opening, and disappears during stage 2 and deeper sleep (34). Interestingly, IRDA can reappear during rapid-eye-movement sleep (158). In children under the age of 15 years, IRDA appears most prominently over the occipital areas (OIRDA) (34). This age-related variability in voltage field is most likely the result of maturational factors, not differences in etiology of the IRDA.

The pathophysiology of IRDA is not well understood. The final common pathway may be abnormal thalamocortical interactions (62,64,83). However, it is likely that generation of IRDA requires pathological dysfunction, not complete disruption, of thalamocortical connections. This is supported by the observation of spindle-like rhythms seen both experimentally after isolated thalamic lesions (62) and clinically (but only rarely) in children with thalamic brain tumors (75). The dorsal medial nucleus of the thalamus has been implicated as being particularly important in generating IRDA, because rhythmic slow waves are seen when this nucleus is partially, but not completely, destroyed (30,83). IRDA occurs in a wide variety of neurological disorders with both structural and physiological etiologies (43,150). Historically, subfrontal, diencephalic, or infratentorial lesions have all been associated with IRDA. Schaul and co workers (154) reviewed EEGs from 154 patients with diencephalic or posterior fossa lesions. Only 12% of those with diencephalic lesions had normal EEGs, whereas 60% of patients with lower brainstem and 73% of patients with cerebellar pathology had normal EEGs. Lateralized IRDA has a high correlation with ipsilateral deep lesions (Fig. 11.8). When IRDA occurs in patients with posterior fossa lesions, it is most often due to obstructive hydrocephalus. In fact, FIRDA and OIRDA are relatively nonspecific in regard to etiology. In a general EEG laboratory's referral population, FIRDA is seen much more often in the setting of metabolic disorders or other diffuse encephalopathies and idiopathic epilepsy than with focal lesions, regardless of location. OIRDA is especially common in children ages 6–10 years who have absence seizures (32).

Temporal intermittent rhythmic delta activity (TIRDA) (Fig. 11.9) is associated with complex partial seizures and temporal lobe epilepsy (147) (see Chapter 17). Like FIRDA, zeta waves are more prominent during drowsiness and light sleep.

Finally, Magnus and Van der Holst (106) described an unusual form of rhythmic delta slowing in which the waveform is characterized by an initial negativity followed by a steep positivity crossing the baseline, then a slow return to baseline. They designated these waveforms as *zeta waves* because of their appearance. Zeta waves have been associated with particularly severe brain lesions, especially those due to trauma, but not stroke.

Activating Techniques

This topic is covered extensively in Chapter 8. We discuss it here only as it relates to focal abnormalities. Hyperventilation is useful in accentuating focal slowing that is low voltage and intermittent at baseline. Intermittent photic stimulation has no effect on focal slowing. The effect of sleep on focal polymorphic delta activity relates to the severity of the abnormality. Sleep has little effect on continuous polymorphic delta activity. Its effect on intermittent polymorphic delta activity is more variable. When slowing is caused by a structural

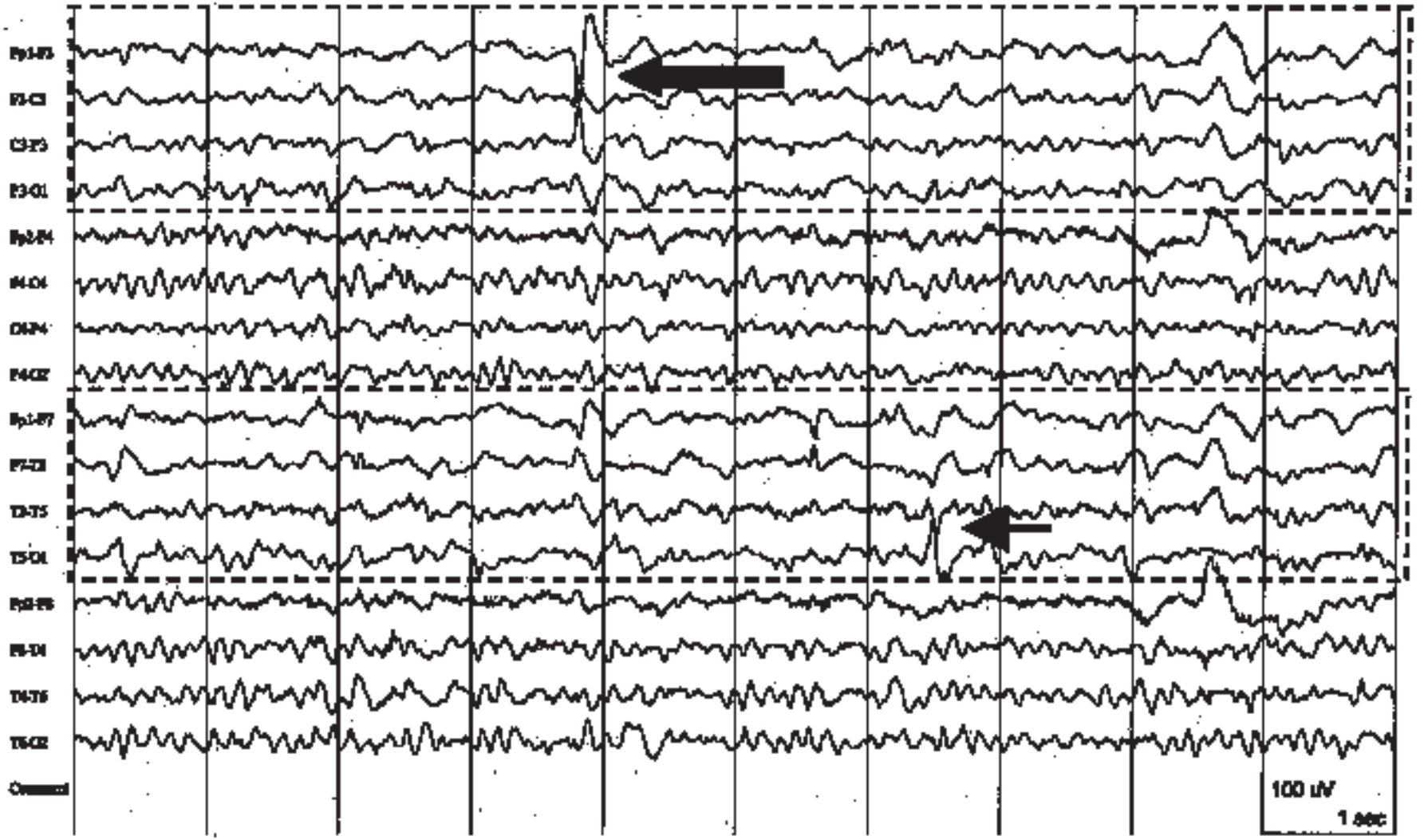


FIG. 11.7. EEG of a 40-year-old woman with right hemiparesis and intractable epilepsy secondary to a congenital left hemisphere stroke. There is continuous polymorphic delta activity over the entire left hemisphere, with attenuation of faster frequencies and nearly complete loss of the alpha rhythm. There are multifocal epileptiform sharp waves (left frontal and left posterior temporal discharges are indicated by *arrows*).

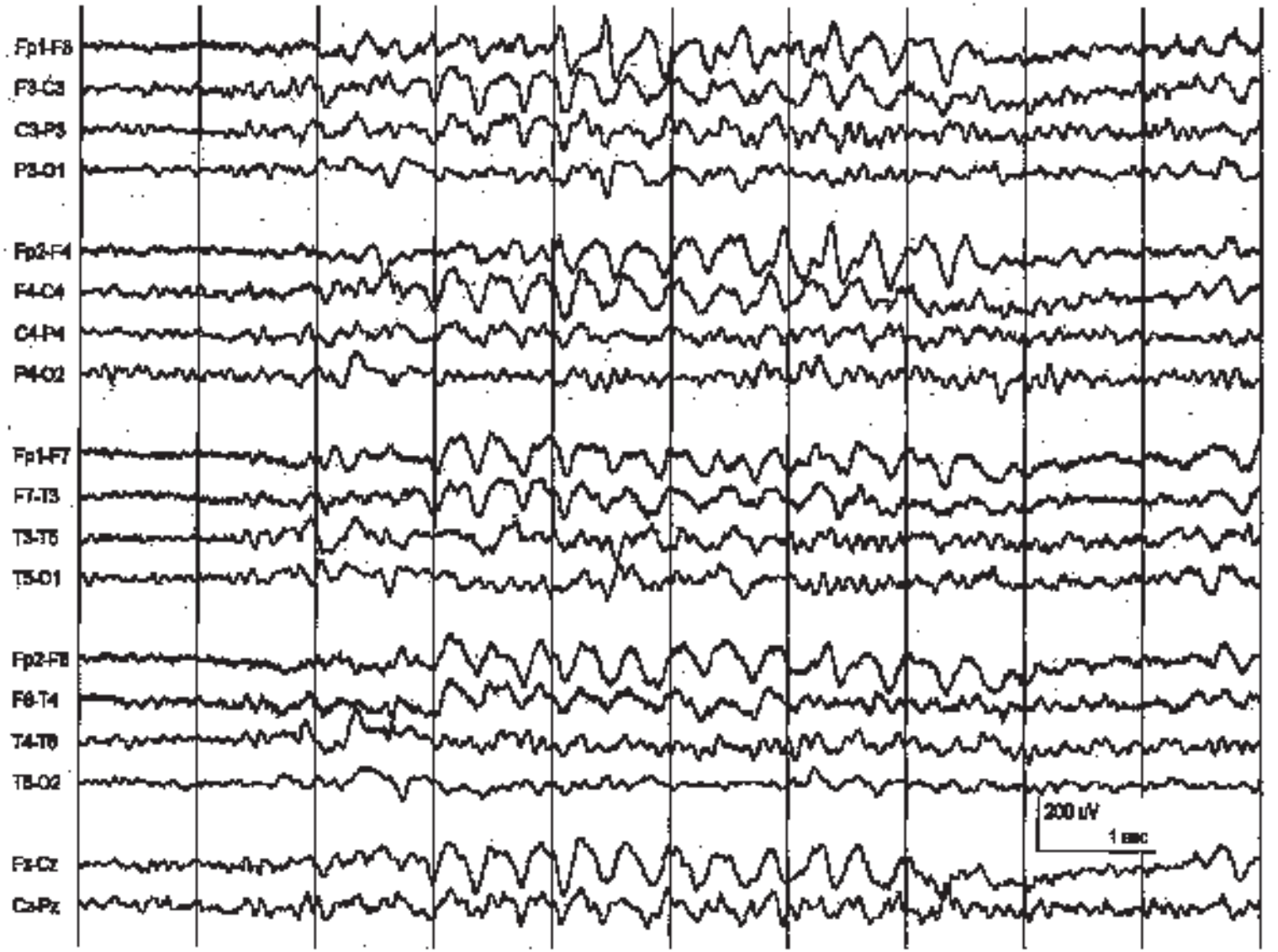


FIG. 11.8. EEG of a 67-year-old woman with bilateral thalamic and basal ganglia infarcts. Note runs of rhythmic 2.5 Hz activity, seen maximally in the frontal region bilaterally (FIRDA). The intervening background shows only mild diffuse theta frequency slowing.

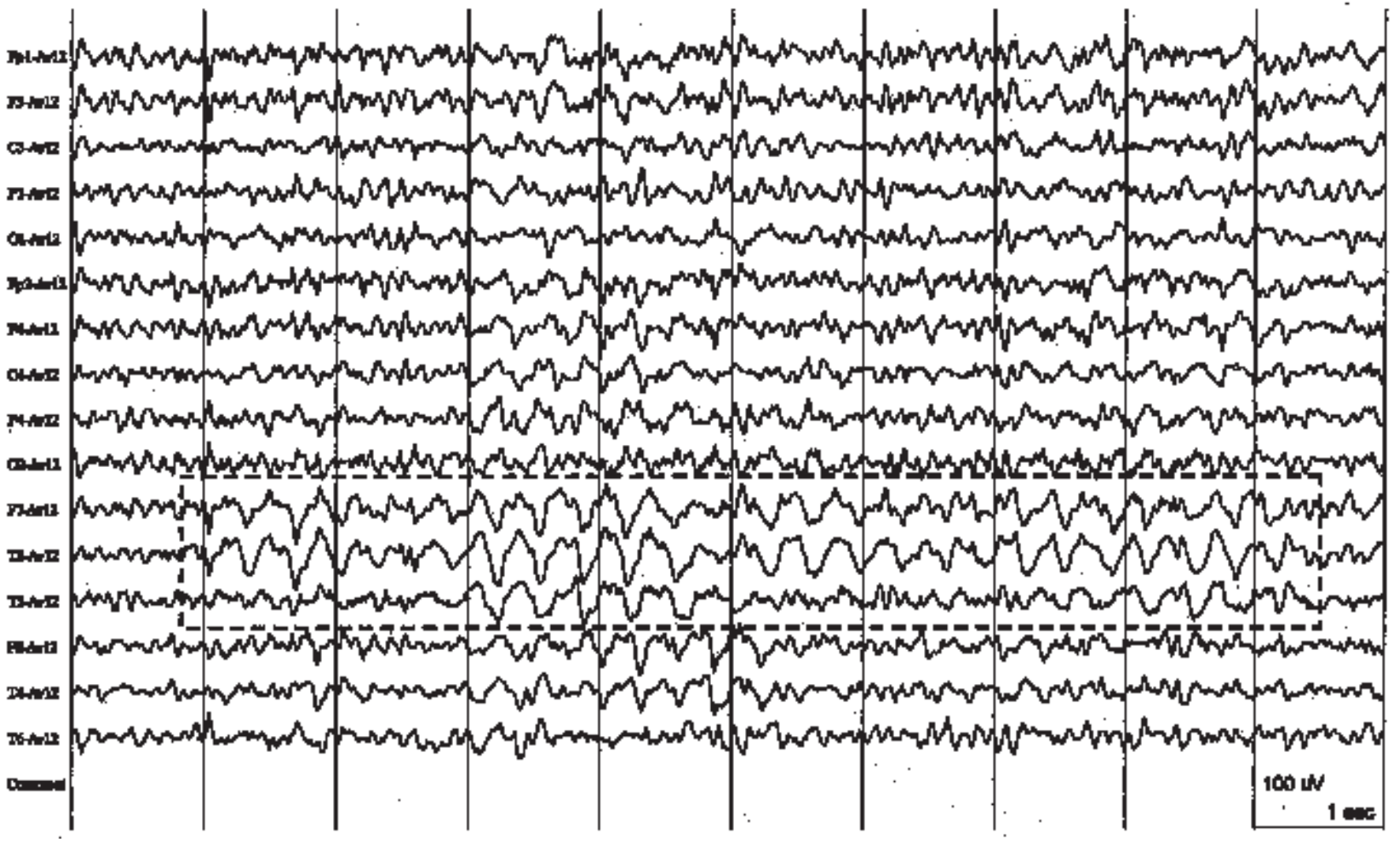


FIG. 11.9. EEG of a 44-year-old man with paroxysmal atrial fibrillation and new-onset seizures. There are frequent runs of intermittent rhythmic temporal delta activity (TIRDA) (*boxed channels*) that are not associated with epileptiform discharges.

brain lesion, sleep has little effect. However, with reversible, nonstructural etiologies, sleep may attenuate focal intermittent slowing. Hypoglycemia activates slowing associated with structural lesions (6,113) and epilepsy (67,155). In areas where the blood–brain barrier has been compromised, high doses of intravenous penicillin can activate focal epileptiform activity (148).

EPILEPTIFORM ABNORMALITIES

Seizures are a common symptom of chronic or slowly progressive focal lesions, so it should not be surprising that interictal epileptiform discharges are frequently present in the EEGs of such patients (see Fig. 11.7) (91). Epileptiform activity (spikes or sharp waves) is common in EEGs of patients with well-differentiated glioma, traumatic cicatrix, brain abscess, medial temporal sclerosis, and cortical dysplasia. In patients with benign or very slowly progressive tumors, focal epileptiform discharges sometimes antedate the appearance of focal slow-wave activity by months or years (72). In general, however, patients with brain tumors usually have other EEG abnormalities (focal slowing, voltage attenuation) in addition to spikes or sharp waves (14). Epileptiform discharges are less common with acute cerebral infarction or hemorrhage. Although these typically occur ipsilateral to the infarct, they can be seen rarely contralateral to an acute stroke (173). A complete discussion of epileptiform abnormalities is provided in Chapter 17.

Acute destructive lesions such as stroke, tumor, abscess, and viral (especially herpes simplex) encephalitis can result in periodic lateralized epileptiform discharges (PLEDs) (23,35,36,98,108,143,157,164,177) (Fig. 11.10). Although the most common cause of PLEDs is stroke, their occurrence in this condition is infrequent (90). PLEDs have also been reported early in the course of Creutzfeldt-Jakob disease (50) and in patients with subdural hematoma (26), MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) (49), nonketotic hyperglycemia (160), and, occasionally, chronic lesions, especially in the presence of a superimposed metabolic abnormality. Electrolyte abnormalities and nonketotic hyperglycemia have also been postulated as factors that contribute to PLEDs appearing after acute stroke (126). Specific etiologies associated with epileptiform activity are described in the following sections.

SPECIFIC ETIOLOGIES

Trauma

Routine EEG has little role to play in management of acute head injury. Following closed head trauma with concussion, the EEG most often shows diffuse, nonspecific slow-wave activity. The degree of slowing and the extent to which normal background rhythms are lost (e.g., loss or slowing of the posterior dominant rhythm) are proportional to the severity of trauma and the patient's level of consciousness at the time the EEG is recorded. Focal abnormalities indicate cerebral contusion or hemorrhage. Sometimes focal changes are present and persist even in the absence of abnormalities on brain imaging, indicating that functional injury can occur without identifiable anatomical changes. Transient focal changes are often multifocal.

Brain Tumors

Tumors are a common cause of focal slow-wave activity in the EEG (Figs. 11.11 and 11.12). Among EEGs showing focal polymorphic delta activity, tumors account for 13% (60) to 40% (180) depending on the laboratory's referral population. The character and distribution of EEG changes produced by a tumor, as with any focal lesion, depend on its size, its distance from the cortical surface, and the anatomical structures involved. With brain tumors, the degree of malignancy, reflected in rapidity of growth and acute or subacute mass effect, is an additional factor. Tumors having substantial mass effect that results in shift of midline structures, compression of the lateral ventricle, and downward pressure on the thalamus and upper brainstem produce IRDA and bilateral arrhythmic slowing as well as focal slowing. When severe, these secondary bilateral and diffuse features may partially obscure focal indicators of the underlying lesion.

The EEG is normal in up to 40% of brain tumors (11), but this statement must be qualified. Normal EEGs actually occur in only about 5% of hemispheric tumors, which account for the majority of brain tumors in adults. In contrast, EEGs are normal in at least 25% of deep midline, basal, and infratentorial tumors (33,72,111), and this figure is undoubtedly higher in the absence of obstructive hydrocephalus and increased intracranial pressure. Unlike supratentorial intraparenchymal tumors, parasagittal meningiomas may be relatively silent electrically (92,170). Early on, they tend to produce localized attenuation of beta activity and focal spikes or sharp waves, but focal polymorphic delta activity is not usually prominent until there is sufficient tumor bulk to compress the underlying cortex and adjacent white matter. Rarely, hemispheric brain tumors produce focal enhancement of alpha (38) or beta (74) activity. Thus brain tumors can be associated with any or all of the EEG abnormalities seen with focal lesions.

Isolated spikes and sharp waves are rare as the sole electrographic manifestation of a neoplasm (11). Sharp waves are said to be more common than

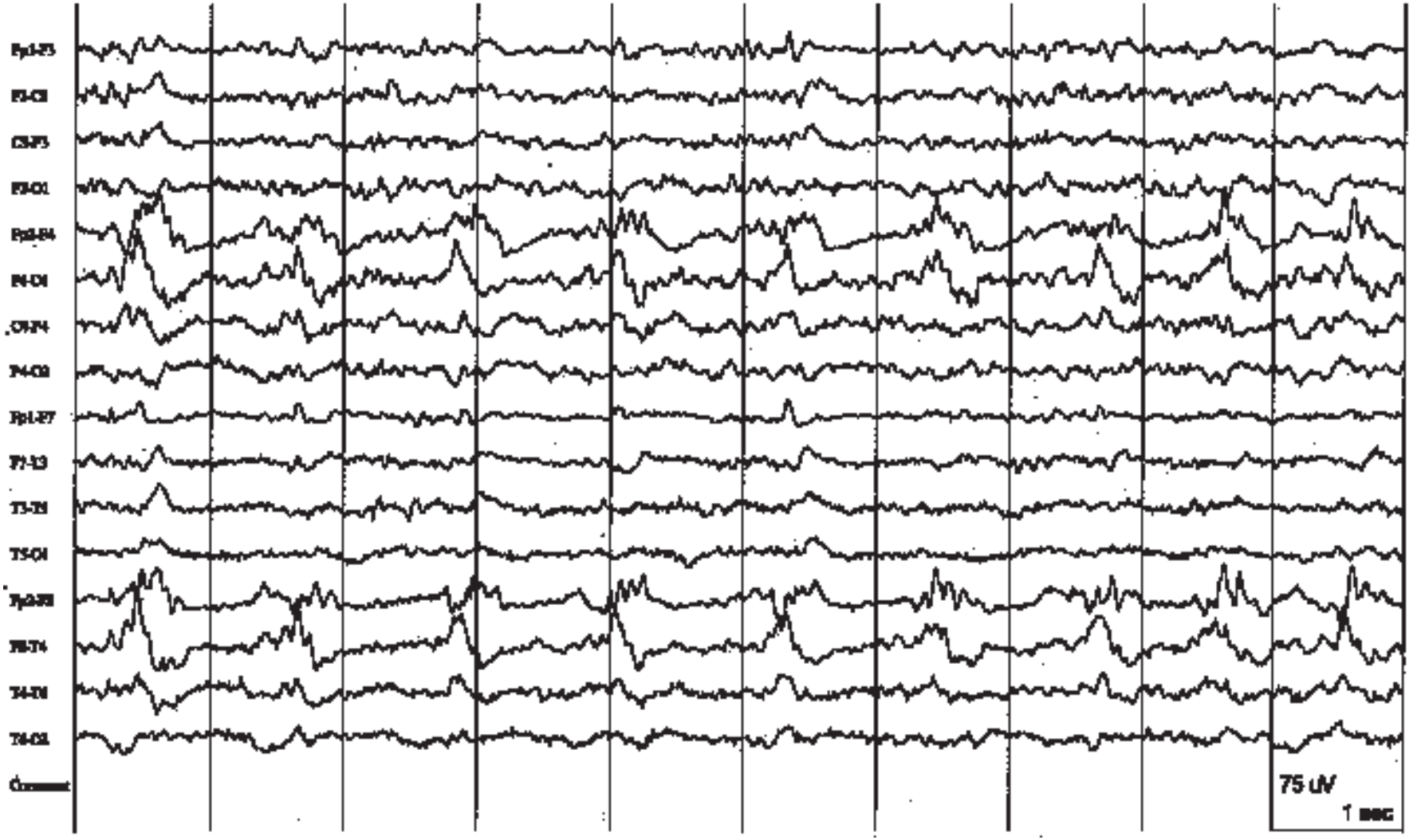


FIG. 11.10. EEG of a 90-year-old man with acute infarcts involving right anterior and middle cerebral artery territories. There are right frontal–temporal PLEDS occurring with a repetition rate of about 1.5 Hz. Note associated diffuse slowing of background rhythms, which is continuous and generally more pronounced on the right.

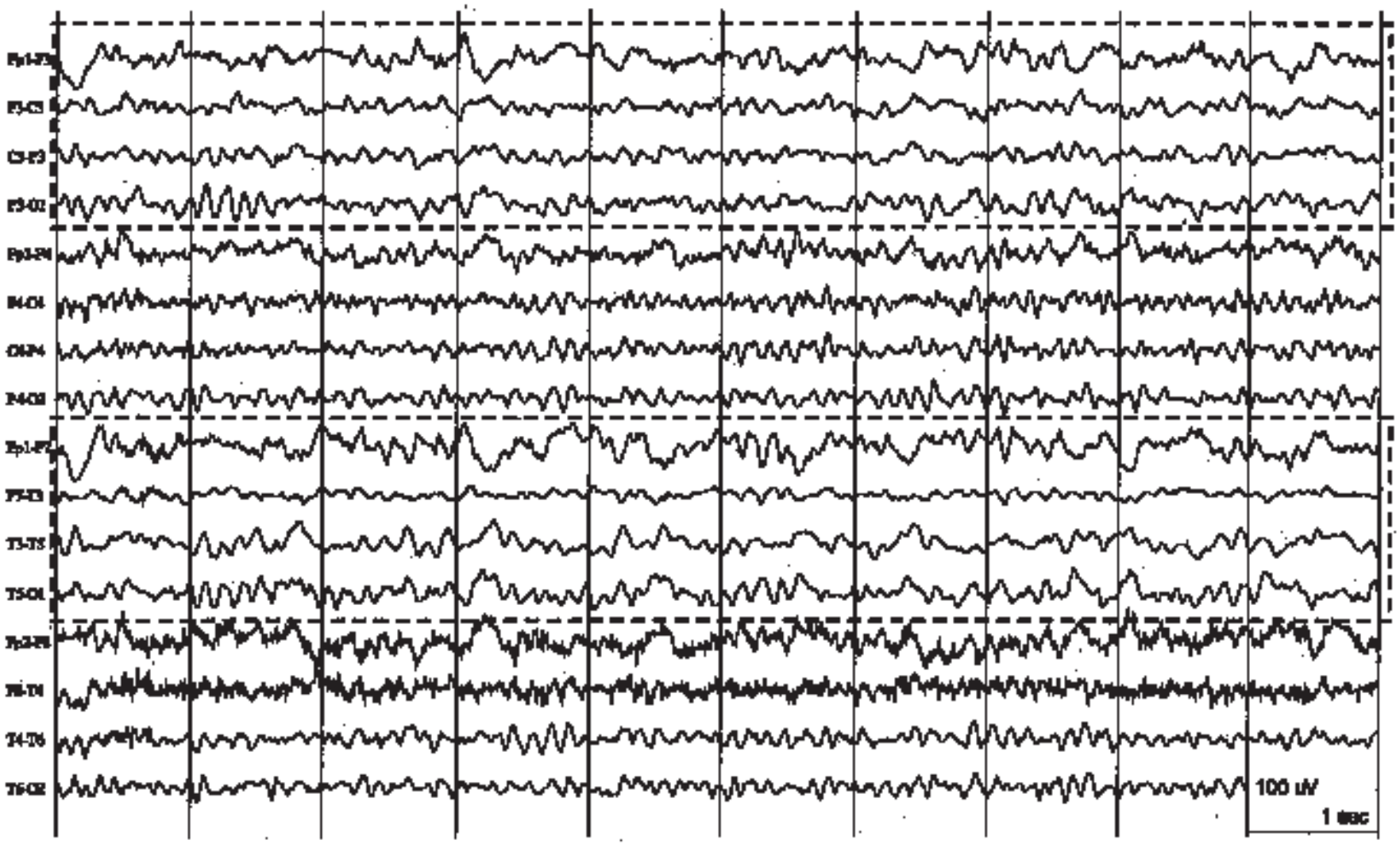


FIG. 11.11. EEG of a 44-year-old man with a large suprasellar meningioma extending mainly to the left, compressing subfrontal and temporal regions. There is widespread polymorphic delta activity over the left hemisphere with attenuation of faster background frequencies. In this bipolar montage, the slowing is isopotential in the F7-T3 channel.

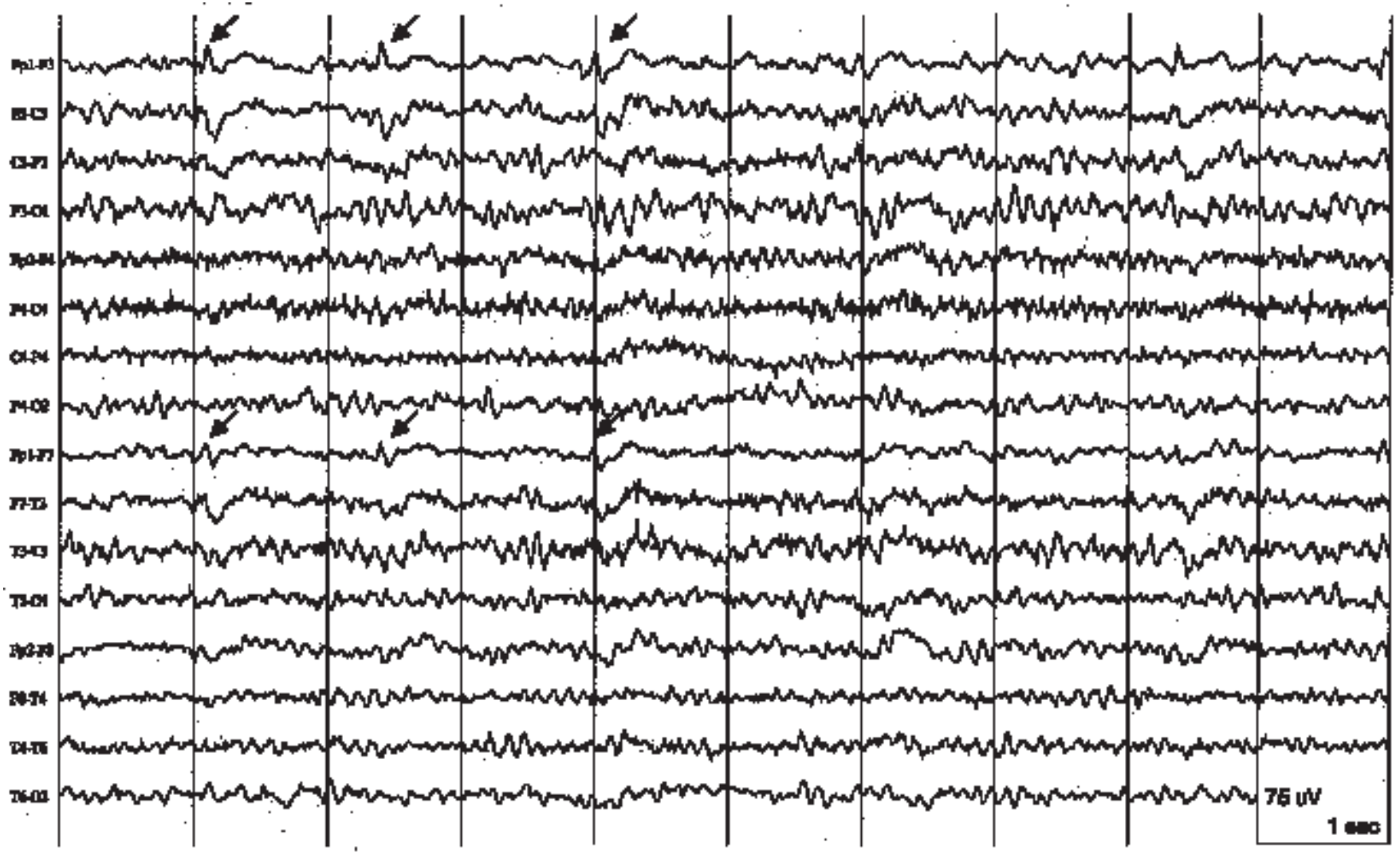


FIG. 11.12. This 80-year-old woman has esophageal carcinoma and new-onset twitching of right facial muscles, dysarthria, and confusion secondary to metastasis involving the left frontal calvarium with infiltration of the underlying meninges and cortex. The EEG shows left frontal polymorphic delta activity, which spreads intermittently to the right frontal area, attenuation of fast-frequency activity over the left frontal region, and left frontal epileptiform discharges (*arrows*).

spikes with oligodendroglioma and astrocytoma, but they do not correlate with clinical seizures (89,91). FIRDA is historically associated with subcortical tumors (27,169), but this statement must be qualified, as discussed above in the section on "Intermittent Rhythmic Delta Activity."

Although EEG can usually lateralize tumors accurately, more precise localization is often not possible (see Fig. 11.12). In addition to factors that produce more widespread changes in the EEG, such as mass effect and hydrocephalus, it has long been recognized empirically that EEG abnormalities are often "displaced" in relation to the tumor's anatomical location. Thus maximal delta activity may be more anterior, and the effect on alpha rhythm more posterior, than the lesion itself (46,85). In addition, abnormalities may have a temporal emphasis regardless of tumor location (166).

It is obviously not possible to determine the type of tumor by EEG, but several generic observations provide useful guidelines. Slow-growing extraaxial lesions, such as meningiomas, usually produce the least changes in the EEG. Rapidly growing intraparenchymal lesions, such as glioblastomas and malignant gliomas, result in the most pronounced abnormalities in terms of focal continuous polymorphic delta activity and localized attenuation of background rhythms (81). Bilateral but lateralized slow-wave activity is characteristic of frontal lobe tumors. Subfrontal and diencephalic tumors are most likely to produce bilateral but asymmetrical IRDA. Bilateral arrhythmic slowing with bursts of IRDA reflects hydrocephalus or mass effect with shift. Parasellar and hypothalamic tumors do not cause EEG changes unless they obstruct the third ventricle or extend into the temporal lobe on one side (124).

Gastaut and colleagues (56) studied 127 cases of brain tumor using both CT and EEG. They included both malignant and benign tumors. Intermittent or continuous focal delta activity occurred in 62% of the EEGs. The presence of surrounding edema, even when extensive, did not affect EEG findings. Other investigators have also found that cerebral edema does not contribute significantly to EEG findings (62,127). More recent studies using quantitative EEG analysis provide further evidence that vasogenic edema does not contribute to delta activity (44,45).

Intracranial Hemorrhage

Subdural hematomas that are not associated with significant compression or shift of the underlying brain produce little effect on the EEG. As with meningiomas, large subdural collections produce ipsilateral voltage attenuation, especially for faster frequency activity and variable amounts of arrhythmic slow-frequency activity (103) (Fig. 11.13). Very large lesions produce bilateral, sometimes generalized findings that are most pronounced on the side of the subdural hematoma (171).

EEG changes with acute subarachnoid hemorrhage (SAH) generally parallel the Hunter and Hess grading scale: grade I SAH may not be associated with any EEG abnormalities, whereas grade IV or V SAH produces severe, bilateral delta activity consistent with the patient's stupor or coma. Focal slow-wave activity indicates parenchymal extension of the hemorrhage or onset of vasospasm with ischemia corresponding to the affected vascular territory (117,172).

Acute intracerebral hemorrhage into the basal ganglia or centrum semiovale results in ipsilateral hemispheric polymorphic delta activity with more localized voltage attenuation and loss of faster frequencies over the hematoma (Fig. 11.14) (172). With large hemorrhages that produce midline shift and compression of diencephalic structures, there is bilateral slowing and bursts of ipsilateral IRDA (76). EEG effects of thalamic hemorrhages depend very much on lesion size. Small hemorrhages produce restricted or more widespread ipsilateral slowing depending on their location within the thalamus. Involvement of the ventrobasal thalamus attenuates sleep spindles and sometimes affects their frequency regulation. Lesions affecting the anteromedial thalamus attenuate the ipsilateral alpha activity (83) and usually produce frontotemporal delta activity as well. EEG findings with brainstem hemorrhage also depend on size and location, but tend to be similar to the range of effects described below for ischemic stroke.

Stroke

Because of its incidence and prevalence, stroke is the most common cause of continuous focal polymorphic delta activity (60,84).

Transient Ischemic Attacks

The EEG is usually normal in patients with transient ischemic attacks (41). However, if the EEG is performed at, or in close proximity to, the time a patient is symptomatic, there will often be focal slowing in the appropriate vascular territory, even though CT or routine MRI scans are likely to be normal (105,110). Chronic ischemia within the middle cerebral artery (MCA) territory is associated with intermittent, low-voltage delta or theta activity, mainly over the temporal areas (19,54). When focal

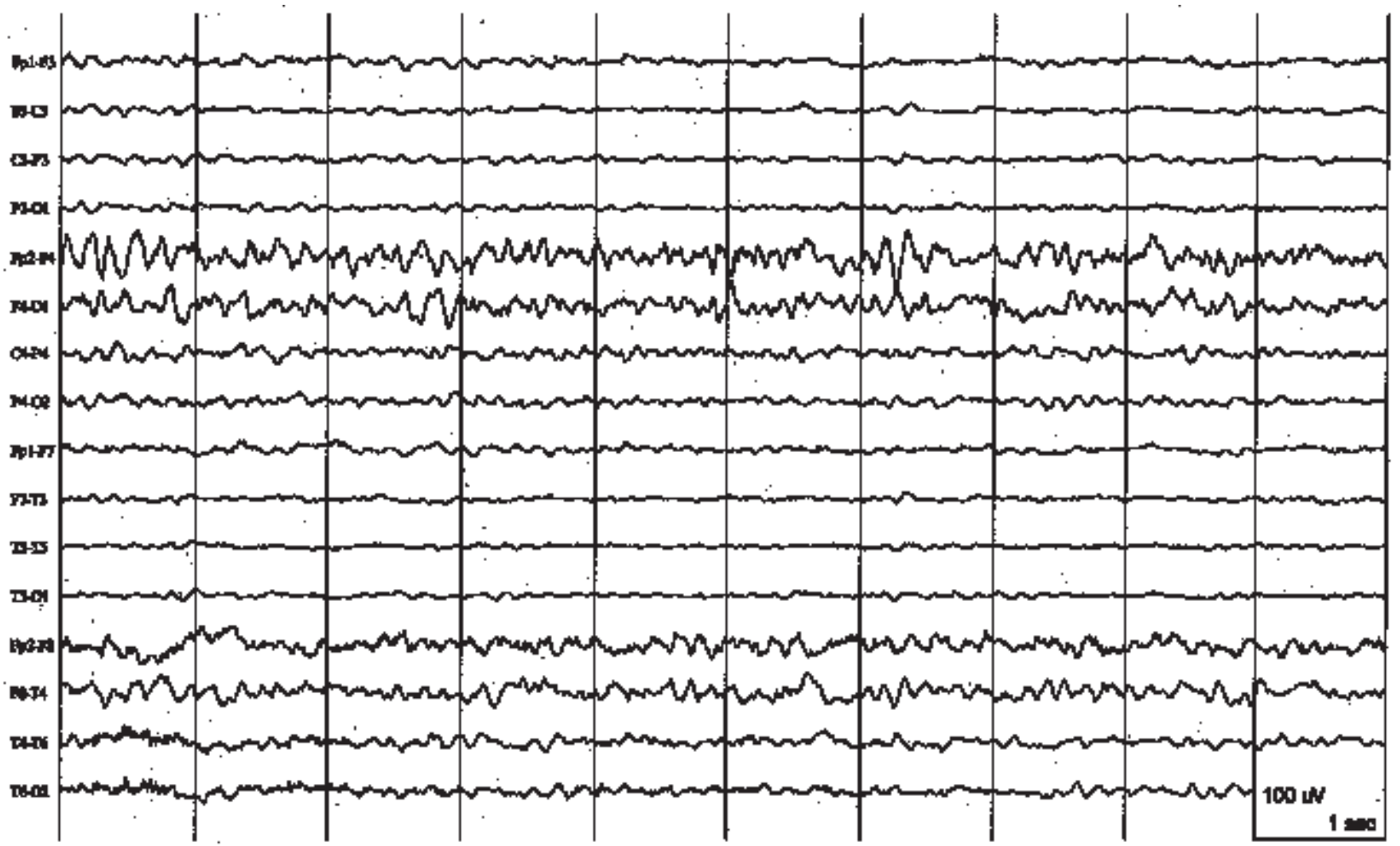


FIG. 11.13. EEG of an 81-year-old man following evacuation of a right subdural hematoma, who then developed an acute left-sided subdural hematoma. There is marked voltage attenuation and loss of faster frequency activity over the entire left hemisphere. There is continuous rhythmic and arrhythmic slowing over the right frontal region accompanied by enhanced voltage of both 6-Hz rhythmic activity and mixed-frequency beta activity in the same area. The increased voltage on the right is a postcraniotomy effect (breach rhythm).

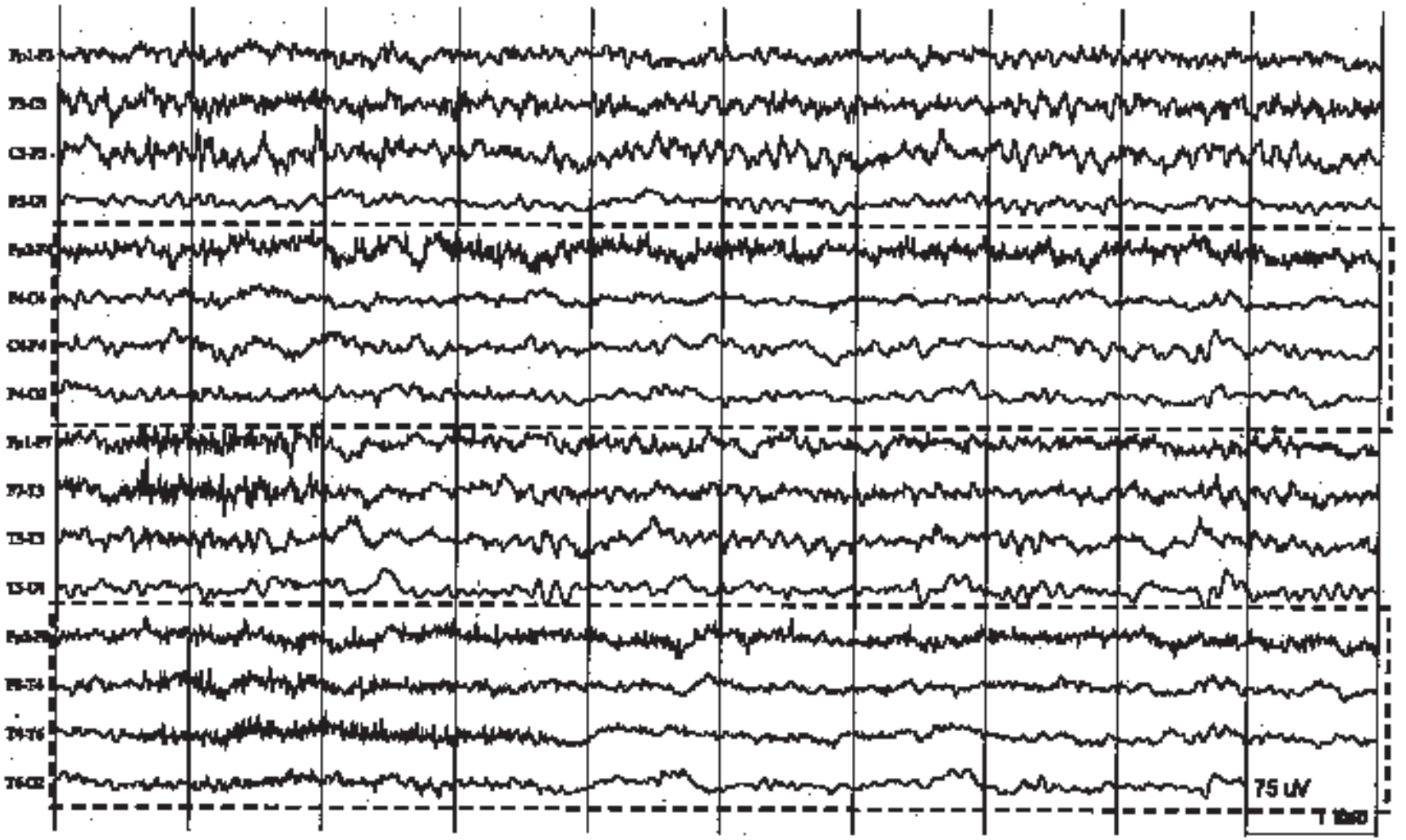


FIG. 11.14. EEG of a 67-year-old man with an acute hemorrhage into the right frontal lobe. Head CT showed the hemorrhage with a small right-to-left midline shift. There is nearly continuous arrhythmic delta activity over the right frontal and temporal regions with marked voltage attenuation of faster frequencies, especially in the right temporal area (*boxed channels*). There is also procedure slowing over the right hemisphere, but overall background activity is better preserved. The more rhythmic delta waves on the right spread to homologous regions on the left side.

or lateralized slow-wave activity is pronounced and of new onset, but the patient has no symptoms or signs, there is risk of vascular occlusion and impending infarction (182).

Ischemic Stroke: Large Infarcts

The major cause of ischemic stroke is occlusion of the internal carotid artery (ICA), the MCA, or one of its branches. Following acute occlusion of the ICA or MCA, there is widespread attenuation of all EEG activity for the first few hours (171). Polymorphic delta activity appears that is maximal over the anterior and midtemporal regions and, to a somewhat lesser extent, over the frontal area (Fig. 11.15). The alpha rhythm may be attenuated or show decreased reactivity on the side of the stroke. FIRDA is common, and this may paradoxically be of higher voltage contralaterally because of voltage attenuation on the ischemic side (171). Large infarcts are accompanied by cerebral edema and mass effect, which increase over the first 72 hours. PLEDs (see Fig. 11.10) and other epileptiform discharges occur in a minority of patients. These acute changes diminish and evolve over the next few weeks (171) (Fig. 11.16). Polymorphic slow activity becomes intermittent, and more theta frequencies appear as the amount of delta activity decreases. Faster frequencies and the overall complexity of background activity reappear to the extent that viable cortex remains. PLEDs are always a transient phenomenon and, if present, disappear over 2–3 weeks.

Strokes involving the anterior cerebral artery are less common than those involving the MCA. The EEG in such cases demonstrates delta activity over the ipsilateral frontal area, usually with attenuation of faster background frequencies. Infarctions within the territory supplied by the posterior cerebral artery produce focal slowing that is maximal over the ipsilateral posterior temporal, parietal, and occipital regions. There is usually complete loss or marked disruption of the alpha rhythm on the same side.

Uncomplicated strokes or other lesions of the lower pons and medulla (e.g., Wallenberg's syndrome) are not accompanied by EEG abnormalities. Lesions of the rostral pons and midbrain have variable effects on the EEG, largely dependent on the extent to which the reticular activating system is damaged. For example, patients with infarcts that affect the ventral pons but spare the pontine tegmentum produce the "locked-in syndrome," in which the patient is mute and quadriplegic because of disruption of descending motor pathways but fully conscious with a normal EEG because the reticular activating system is spared (71,107). When the reticular activating system in the rostral pons, midbrain, or thalamus is involved, patients are comatose, and their EEGs show various types of diffuse background abnormalities, including both rhythmic and arrhythmic frequencies, widespread paroxysmal theta and delta waves, and abnormal or absent reactivity to various stimuli (Fig. 11.17) (154). Rarely, lesions of the rostral brainstem show diffuse, monorhythmic alpha frequency activity that is a variation of the "alpha coma" pattern (181).

Frequency analysis and topographic EEG mapping may be superior to routine EEG in detecting and localizing focal abnormalities following stroke (129). These methods also seem to correlate more closely with regional cerebral blood flow (122,123,167).

Ischemic Strokes: Lacunar Infarction

Single lacunae or other discrete, small subcortical lesions usually produce little or no change in the EEG acutely: only 9% (104) to 13% (138) of lacunar infarctions are accompanied by ipsilateral slow-wave activity. Although 53% of patients with lacunar infarcts will have mild EEG abnormalities, most of these reflect previous strokes or are unexplained (86,138).

Role of the EEG in Stroke

Today, EEG plays only a limited role in management of patients with stroke. In the first 48–72 hours, the degree of focal slowing generally correlates with the clinical deficit. Clinical worsening as a result of stroke progression or the consequences of developing edema and mass effect is accompanied, and sometimes preceded, by deterioration in EEG activity. Marked hemispheric slowing following a transient ischemic attack, especially when routine head CT or brain MRI is normal, likely indicates marginal perfusion and chronic ischemia. This finding adds urgency to the evaluation and to the consideration of surgical or endovascular intervention. EEG monitoring during carotid endarterectomy can be helpful, because EEG changes (attenuation of cortical faster frequencies, with or without focal polymorphic delta activity) appear before irreversible ischemic injury occurs. If prolonged or severe, such changes are strongly associated with postoperative clinical deficits (29). EEG monitoring can help distinguish epileptic from ischemic causes of episodic neurological dysfunction. Epileptiform discharges, including PLEDs, are highly correlated with clinical seizures occurring during the first few weeks following a stroke (77). Finally, EEG is essential to identify patients who, although completely paralyzed and unable to speak, are conscious and aware (the locked-in syndrome).

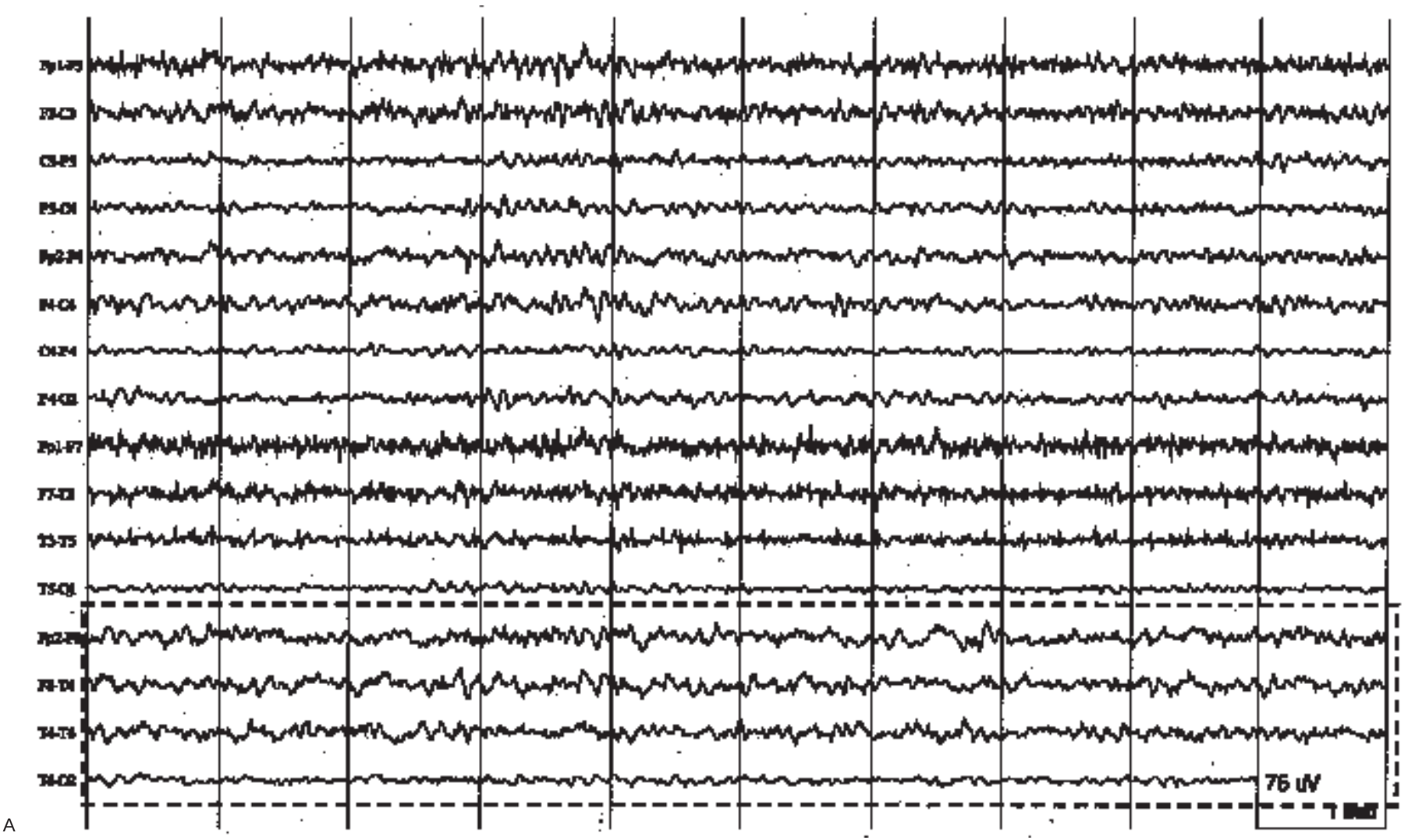
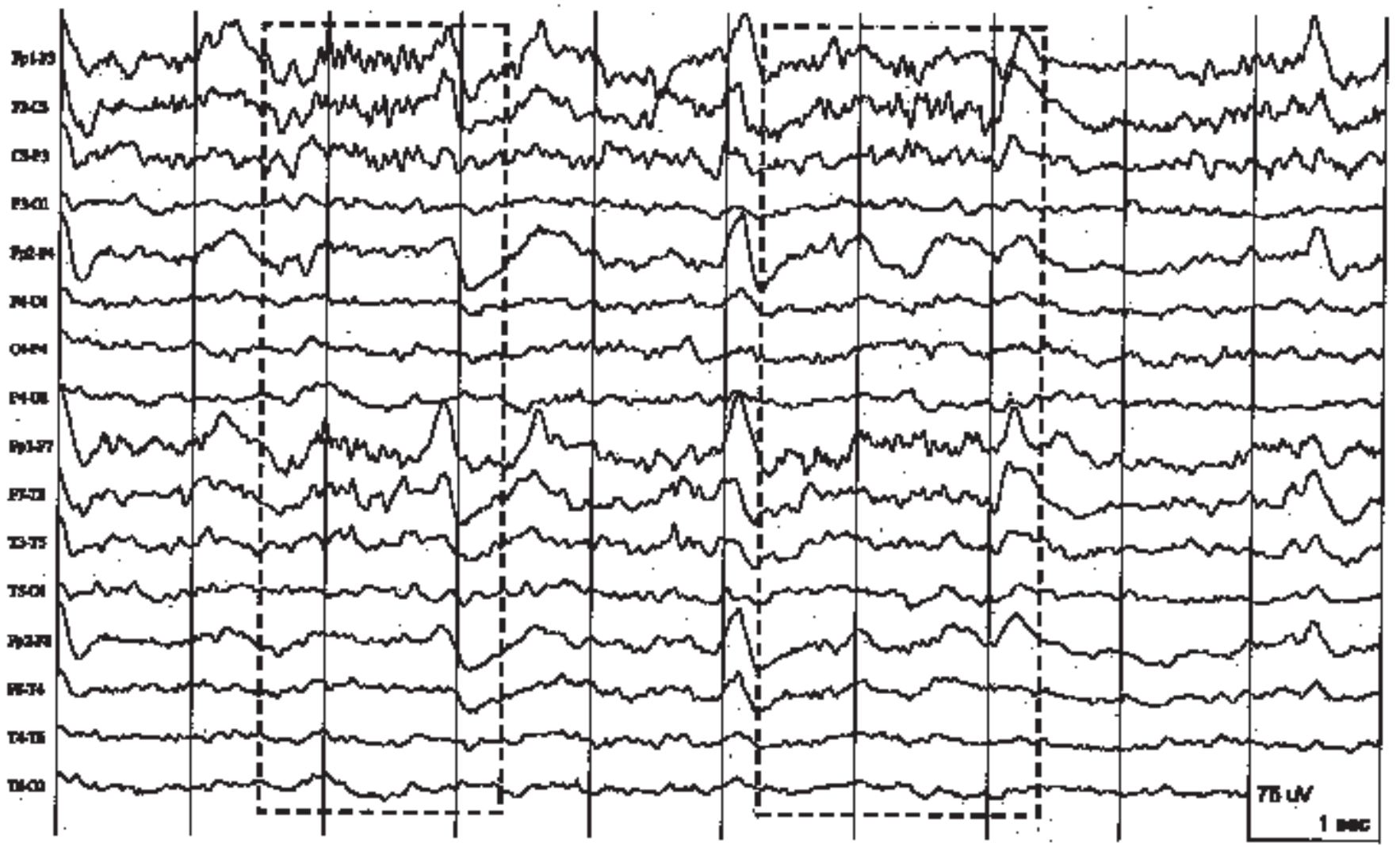


FIG. 11.15. EEGs of an 82-year-old woman with subacute infarction involving the right middle cerebral artery territory. **A:** With the patient awake, there is continuous polymorphic delta activity with voltage attenuation of all frequencies over the right hemisphere. **B:** With the patient asleep, note absence of sleep spindles over the right hemisphere. (*Figure continues.*)



B

FIG. 11.15. *Continued.*

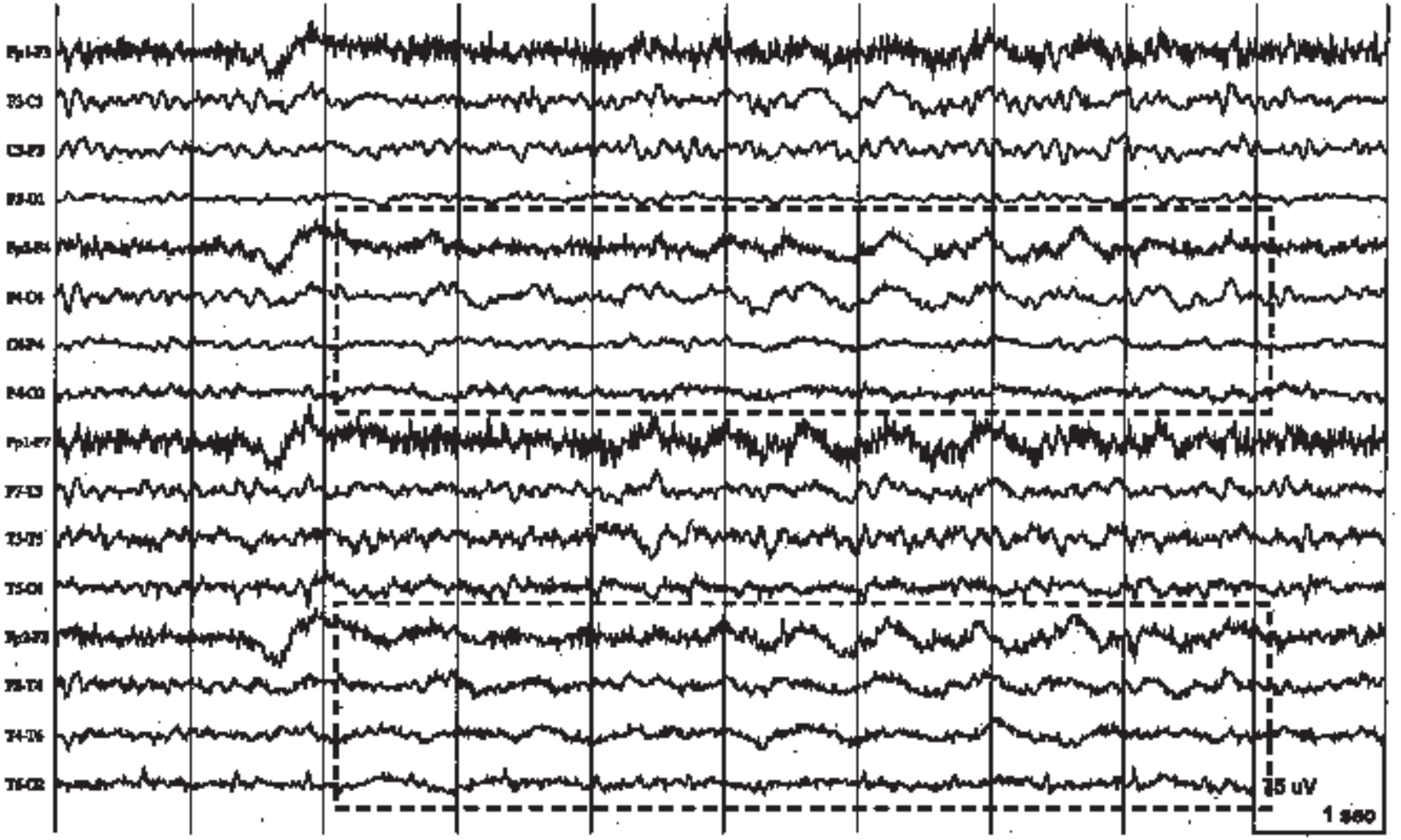


FIG. 11.16. EEG of an 82-year-old woman with an old right middle cerebral artery stroke. There is continuous focal polymorphic delta activity over the right temporal region.

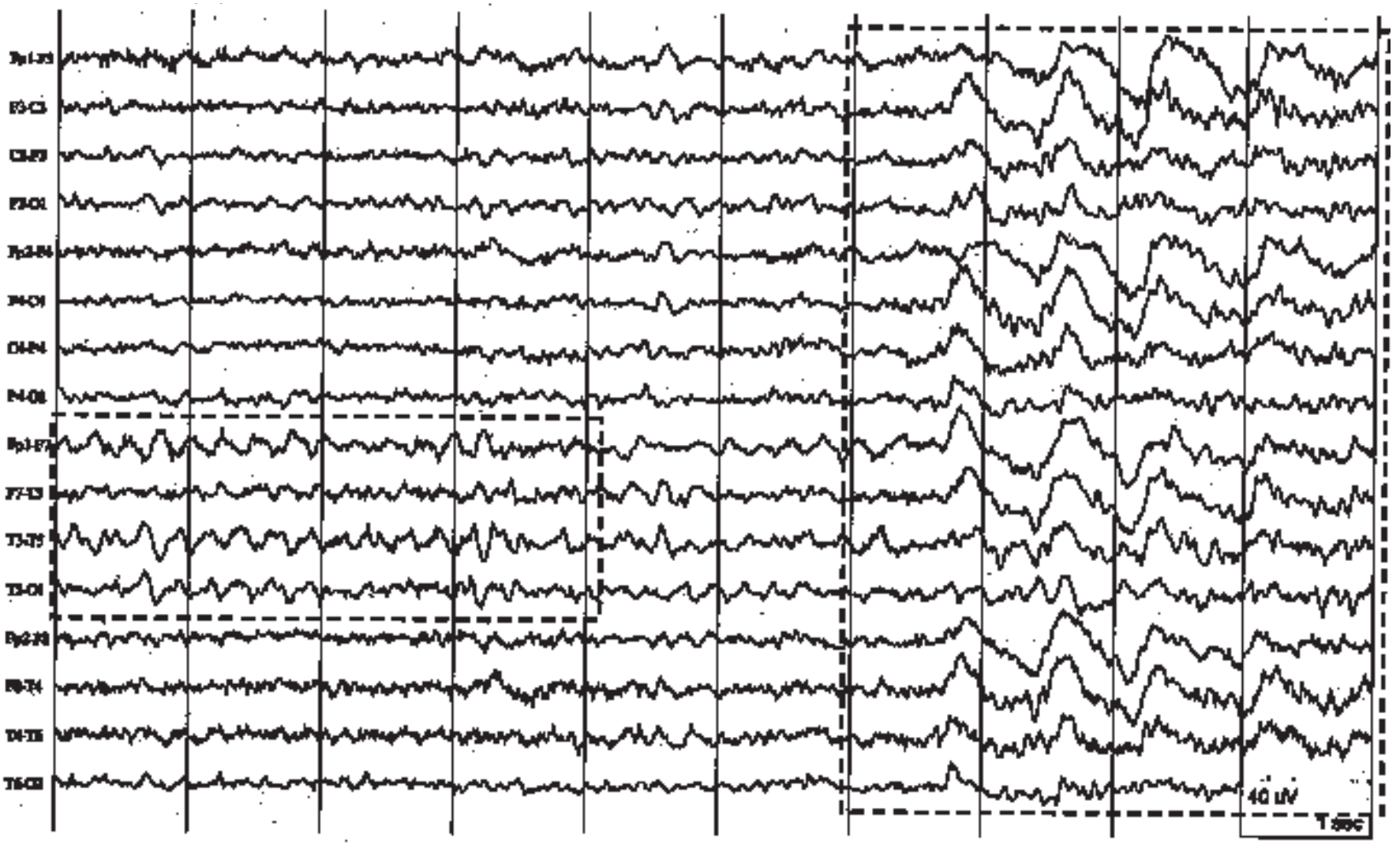


FIG. 11.17. This 70-year-old man has acute infarcts of the left basal ganglia and right thalamus. An EEG with the patient drowsy shows runs of intermittent rhythmic 4- to 5-Hz activity over the left temporal region (*left boxed area*) and bursts of 1.5- to 2-Hz FIRDA (*right boxed area*).

Brain Abscess

EEG findings caused by cerebral abscess are similar to those seen with brain tumors (Fig. 11.18). Focal polymorphic delta activity is the most common finding (5,37,114,139,184), and this tends to be both very slow (0.5–2 Hz) and of high voltage (140). As with tumors, EEG changes are related not just to the lesion itself, but also to mass effects that may be present. Edema, per se, does not play a significant role (114). Epileptiform discharges occur frequently and are often abundant around bacterial abscesses, and seizures occur in nearly three-fourths of patients. PLEDs occur but are rare (114). Epileptiform activity at the time of diagnosis and treatment does not predict later epilepsy (101). Most EEG changes disappear following surgery, although residual focal slow-wave activity will persist, declining over several years following treatment (101).

Focal Cortical Dysplasia

Focal cortical dysplasia is a common cause of epilepsy, especially in children. Raymond et al. (146) studied 22 patients with localized cortical dysgenesis and seizures beginning in childhood (age 3 weeks to 10 years). The main EEG findings were (a) generally preserved, age-appropriate background rhythms; (b) localized slow-wave activity in half of the patients; and (c) epileptiform discharges in 20 of 22 patients. A distinctive feature of the epileptiform activity was that it was either continuous or nearly so. Other reports have also emphasized the presence of focal polymorphic delta activity (15) and rhythmic epileptiform discharges (51,145) in these patients. A minority of patients have had abnormal focal fast-frequency activity (142,145) (Fig. 11.19).

Epilepsy

Focal slowing is frequently present in patients with localization-related epilepsy; it occurs both with and without associated sharp waves (Fig. 11.20). Epilepsy is the most common cause of continuous focal polymorphic delta activity in patients with nonlesional brain imaging studies (60,110). In the great majority of cases, focal delta activity is ipsilateral to the epileptogenic brain area, although rarely the delta activity is maximal on the contralateral side (128,137). Intermittent focal polymorphic delta activity localized to the temporal region is a common finding in patents with medial temporal lobe epilepsy and hippocampal sclerosis (95,137). Such slowing most likely reflects multiple factors, including microscopic changes in the epileptogenic tissue (neuron loss, abnormal neuron morphology, gliosis) and nonepileptic physiological dysfunction within the epileptogenic cortex. When the scalp-recorded delta activity is rhythmic, chronically implanted depth electrodes occasionally reveal ictal discharges restricted to deep structures.

Migraine

A variety of abnormalities have been reported in migraine, including generalized or focal slowing, exaggerated responses to hyperventilation and photic stimulation, excessive fast activity, changes in the alpha rhythm, and epileptiform discharges. These have been reviewed by Gronseth and Greenberg (69). However, much of this literature is difficult to interpret because control groups were usually not included, definitions of "normal" and "abnormal" have changed, and recording techniques were inconsistent (69,156). During classical visual auras, the EEG can be normal, show posterior delta activity, or demonstrate loss of the normal alpha rhythm (8,152). Enhanced photic driving is frequently cited as being typical of migraine (161,163), but there is, in fact, little convincing evidence to support significant differences in photic responses between migraineurs and healthy individuals without migraine (65). Beaumanoir and Jekiel (8) described repetitive spike discharges that disappeared with onset of headache. There does appear to be a slightly increased incidence of nonspecific abnormalities such as intermittent focal (usually temporal) or generalized slow-frequency activity during and after common or classical migraine attacks, but these are the exception, not the rule (66).

During hemiplegic migraine, there is contralateral delta activity, which is sometimes accompanied by attenuation of beta activity (57,73,183). EEGs obtained during attacks of basilar migraine, which can present as a confusional state in children, sometimes show generalized slow-frequency activity and extended runs of high-voltage rhythmic delta waves over the posterior head regions (52,100). Occipital spikes have been reported in some patients with basilar migraine (121,136), and Gastaut (53) found that about one-third of children with benign focal epilepsy of childhood with occipital spikes had migraine-like headaches (see Chapter 17 for further discussion). Migraine is common, however, and its coexistence with other disorders (e.g., epilepsy) or epileptiform EEG findings (12,61) should not be unexpected (7,109).

Because there are no EEG findings that are diagnostic of migraine or that distinguish different types of headache, there is little justification for obtaining EEGs routinely as part of the evaluation of patients with headache. The exception to this is the small subgroup of patients with atypical headache, and in whom the differential diagnosis includes both migraine and epilepsy (69,141). In such cases, EEG may aid in making a diagnosis of epilepsy.

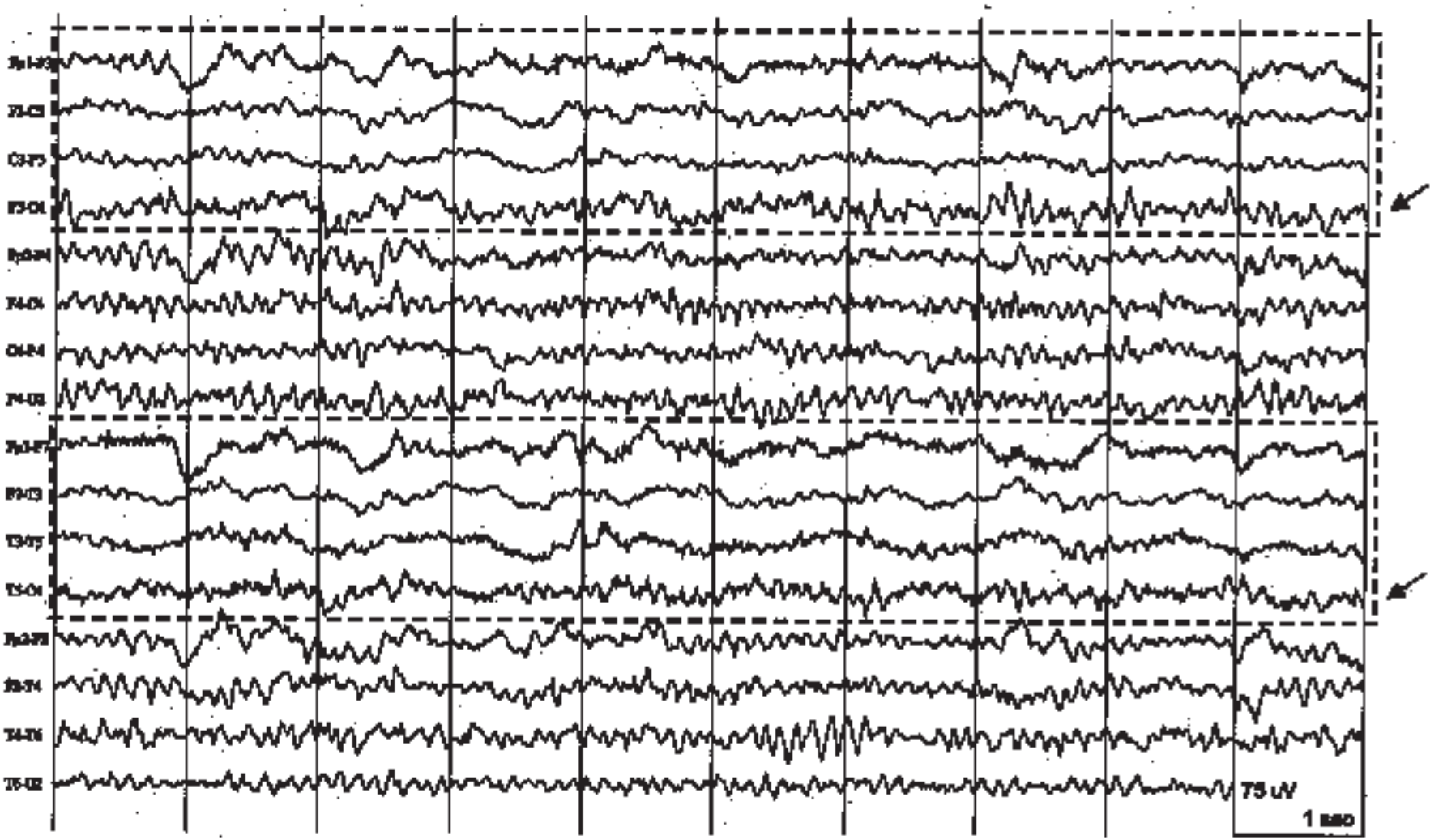
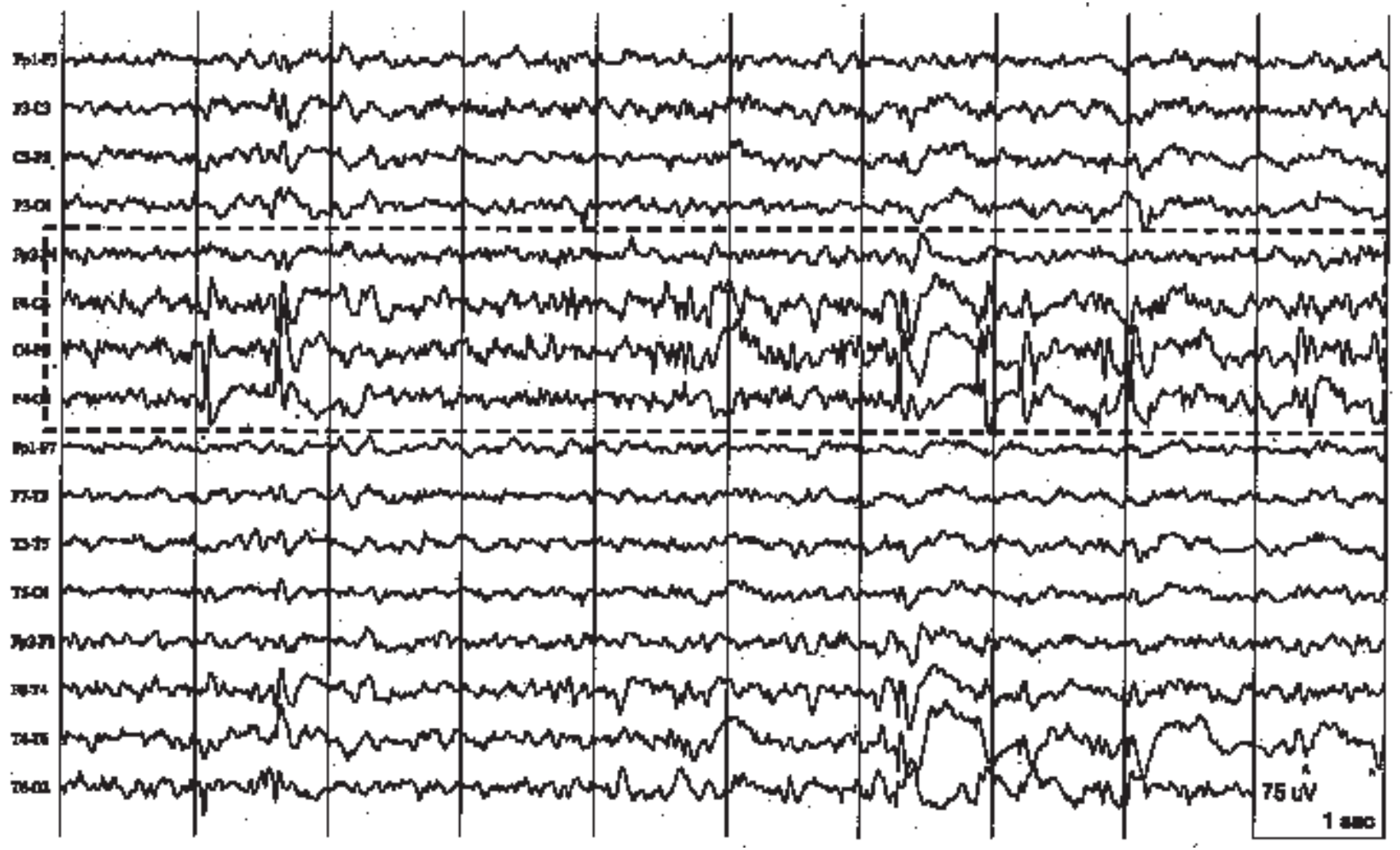
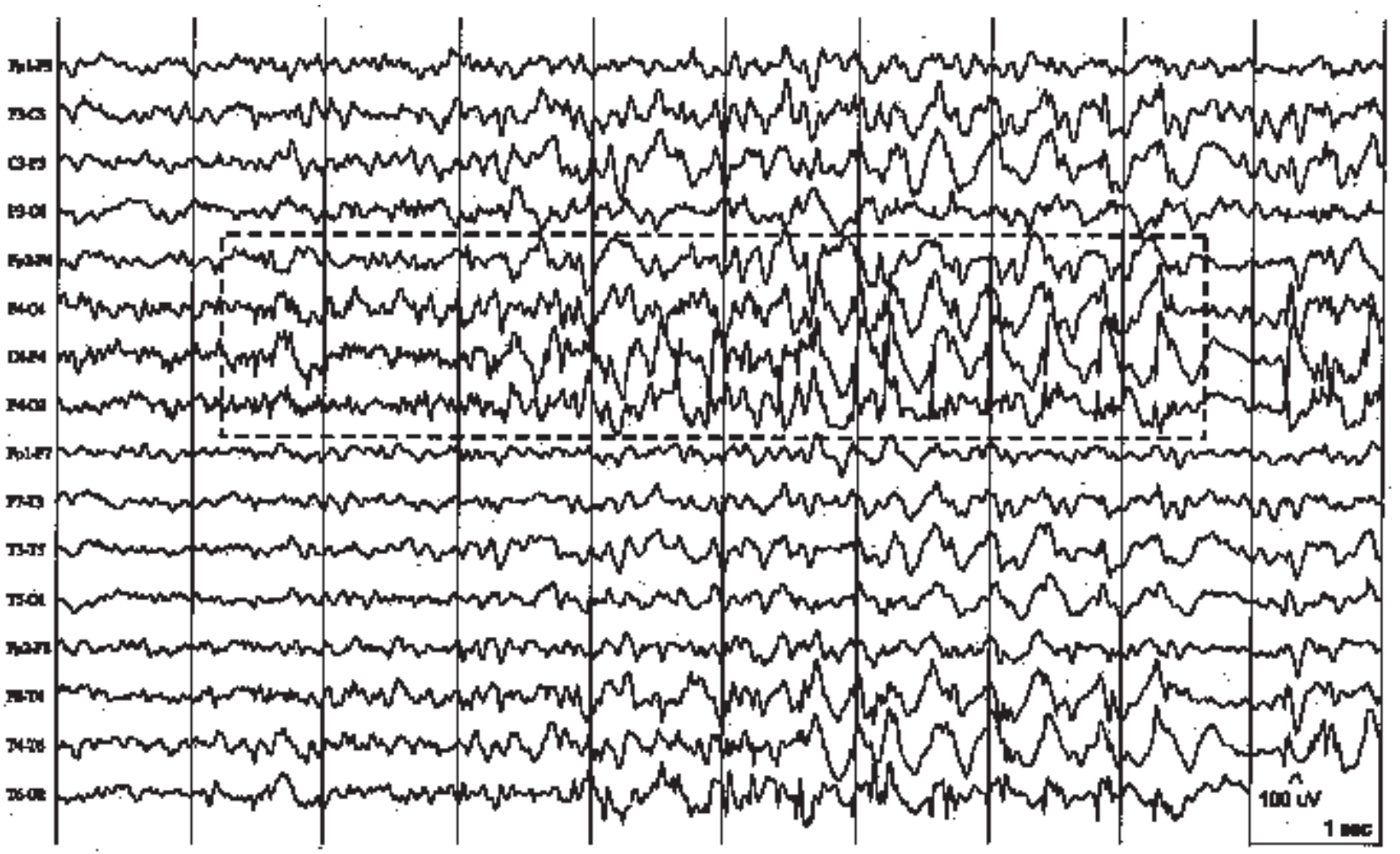


FIG. 11.18. EEG of a 36-year-old woman with a history of ulcerative colitis and abscesses involving the left frontal lobe. She has a right hemiparesis and aphasia. Note continuous arrhythmic delta activity over the left temporal and frontal areas. Faster frequencies are attenuated in the same region. The parieto-occipital regions are relatively uninvolved, although the alpha rhythm is disorganized and poorly modulated on the left.



A

FIG. 11.19. EEGs of a 12-year-old girl with intractable nocturnal secondarily generalized seizures and cortical dysplasia involving the right parietal lobe. **A:** There are frequent spikes in the right parietal region that also involve the posterior temporal and occipital areas on that side. (*Figure continues.*)



B

FIG. 11.19. *Continued.* **B:** A brief ictal episode arising from the right parietal region with buildup of spikes and rhythmic 5-Hz activity that slows to 2.5-Hz activity. There is contralateral spread. There were no clinical manifestations. (*Figure continues.*)

C

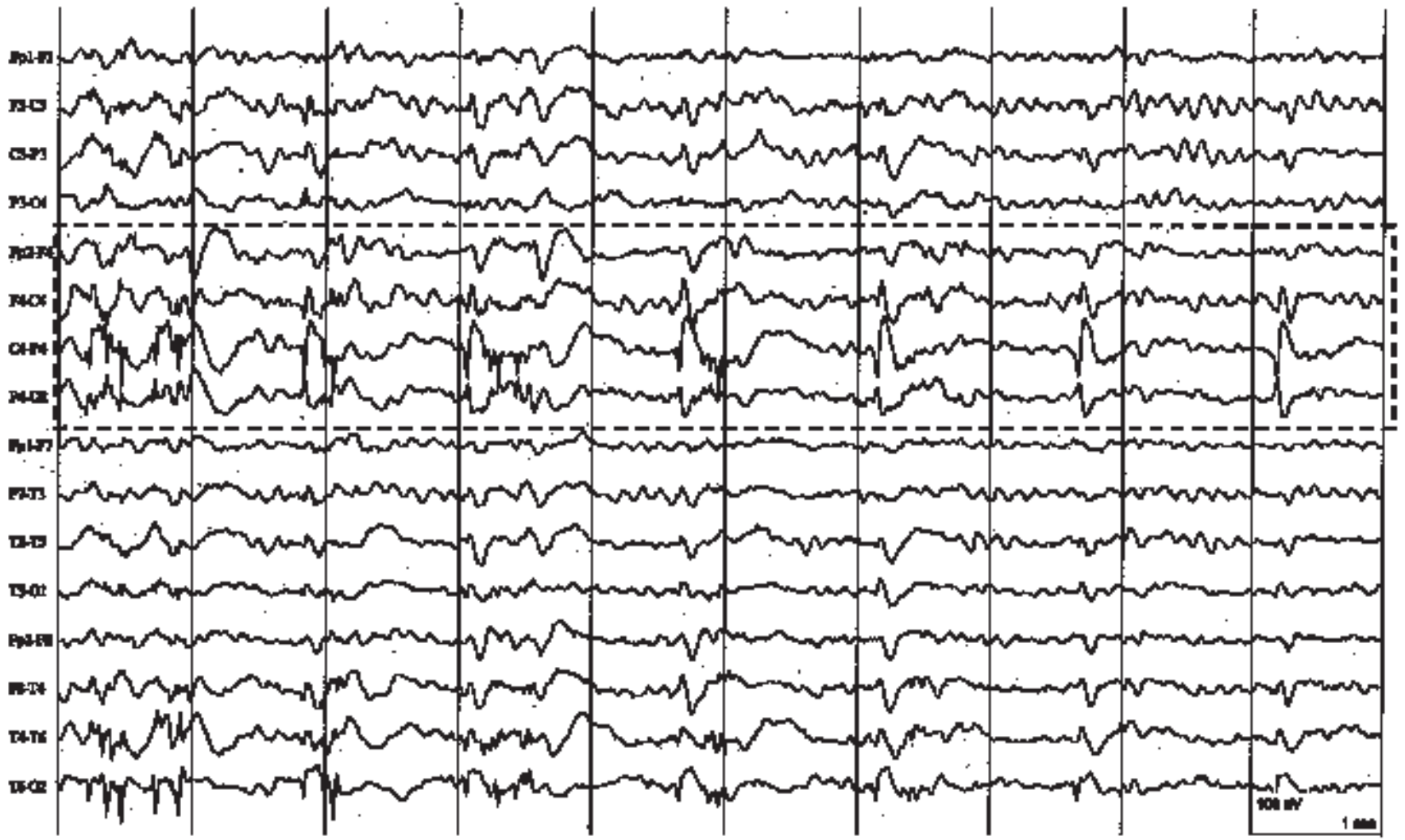
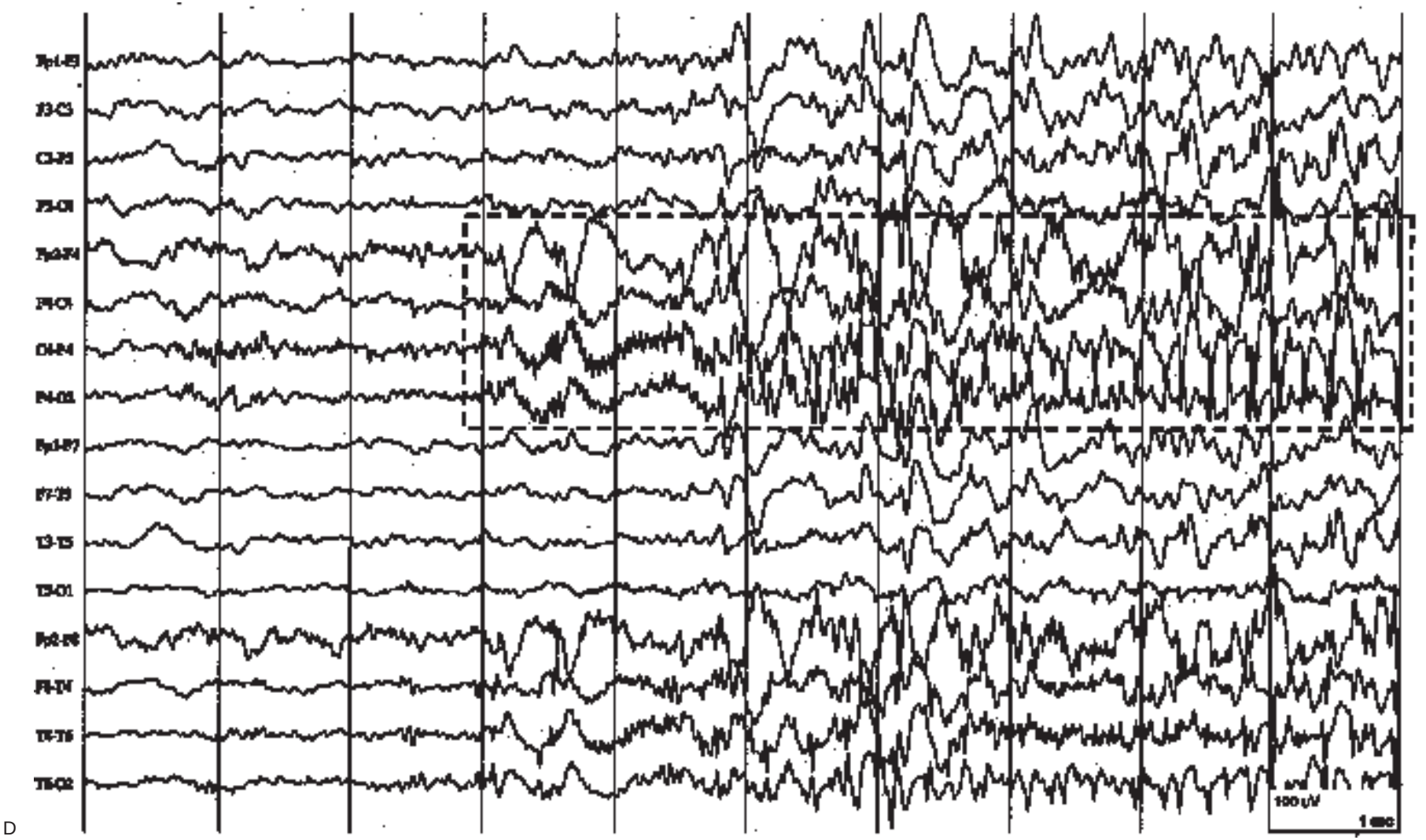
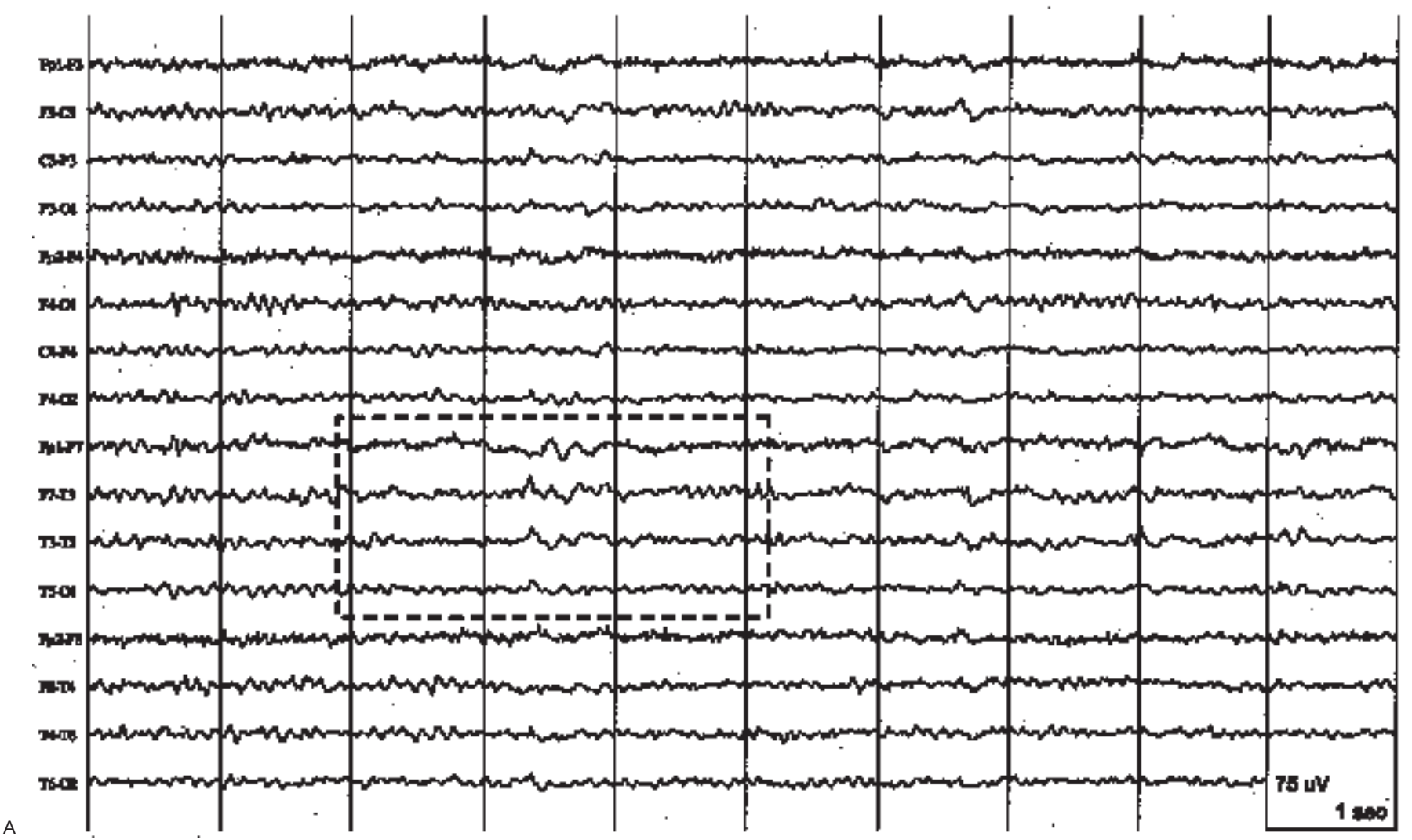


FIG. 11.19. *Continued.* **C:** This subclinical seizure ends with bursts of semirhythmic spikes and multiple spikes associated with voltage attenuation of background activity. (*Figure continues.*)



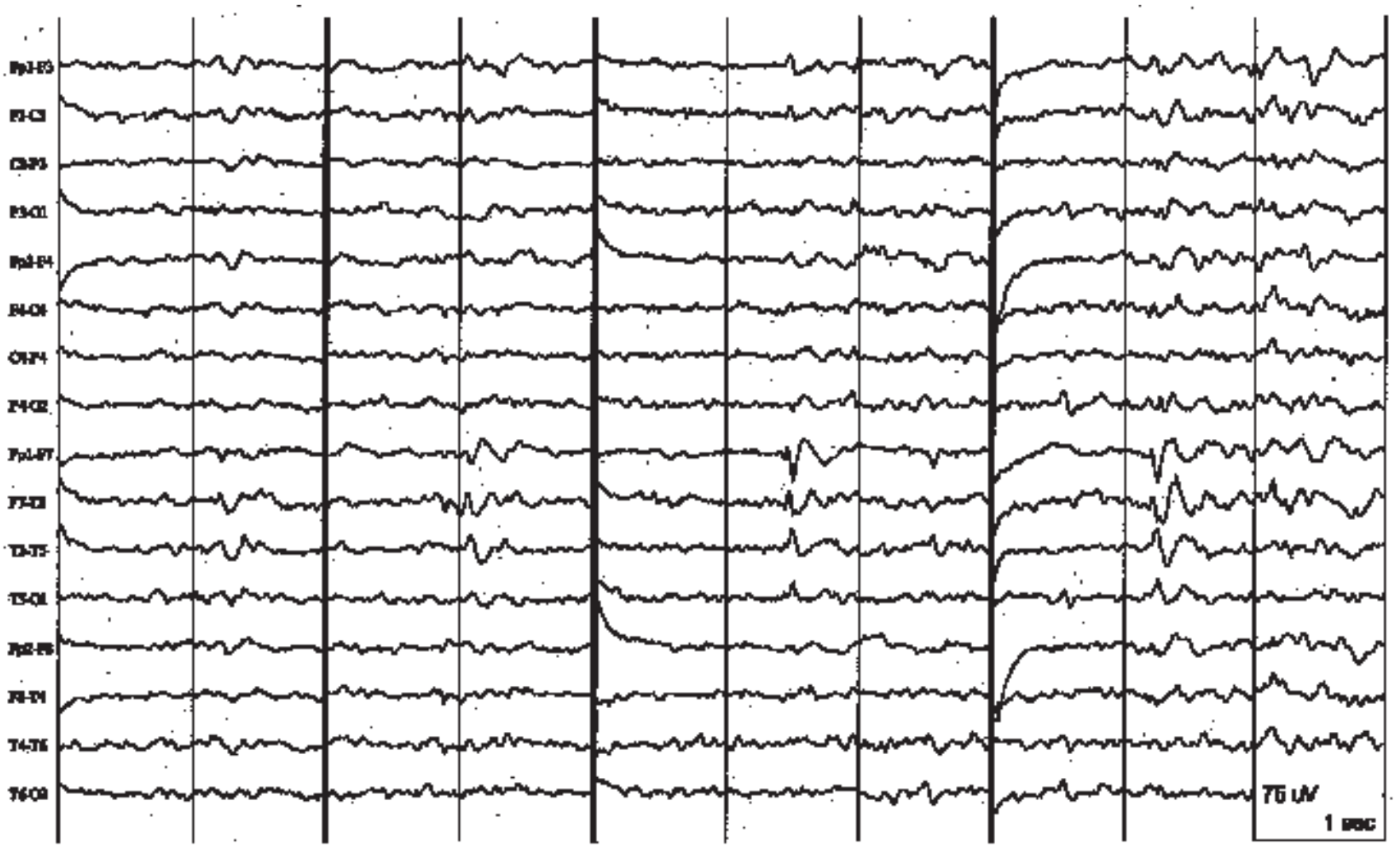
D

FIG. 11.19. *Continued.* **D:** A clinical seizure begins with paroxysmal beta activity in the right parietal region followed by rhythmic 6- to 8-Hz spikes at P4 that gradually slow to about 5 Hz in the last 3 seconds of the page. There is spread of rhythmic slow waves to the left side, and intermittent spikes occur at P3 and T5.



A

FIG. 11.20. EEGs of a 66-year-old man with a 10-year history of episodes he characterized as “loss of time.” **A:** There is intermittent arrhythmic slowing over the left temporal region during drowsiness (*boxed channels*). (*Figure continues.*)



B

FIG. 11.20. *Continued*. **B:** During stage 2 sleep, there are frequent spikes and sharp waves in the same area.

Temporal Slowing in the Elderly

The amount of both diffuse and focal slow-frequency activity increases with age, and the degree of these changes correlates with impaired cognition and decreased longevity (120,159). This correlation is best for moderate or severe changes, because mild slowing of EEG activity does not preclude normal intellectual function (130,131). Focal theta and delta activity is common over the temporal regions, especially the left, in persons over the age of 60 (93,132,159). In a study of 424 volunteers of all ages, Busse and Obrist (20) found that 20% of people between the ages of 40 and 59 years had focal theta activity over the temporal areas; this was maximal on the left in 80% of cases. In persons between 60 and 79 years of age, focal theta and delta activity was seen in 40%. Kooi and colleagues (93) studied 218 "neurologically intact" adults; 37 of these were over 60 years of age. Two-thirds of this group had temporal theta activity, and one-third had temporal delta activity. The slowing was enhanced by drowsiness. There was no medical or other historical explanation for the slow-frequency activity.

Some earlier investigators had argued that these changes indicate subclinical pathology and should not be attributed to "normal aging" (130). Subsequent studies of carefully selected neurologically and psychologically normal elderly persons supported this view. Katz and Horowitz (87) studied healthy septuagenarians and found that focal slow-wave activity in the theta range occurred in only 17% of EEG records and, when present, occupied no more than 1% of waking background activity. Delta activity was rare and consisted only of random, single transients. In studying normal subjects 65 years of age and older, Visser and coworkers (176) reported that temporal delta activity correlated with decreased performance on a verbal fluency test consistent with temporal lobe dysfunction.

What conclusions can be drawn from these observations, and how should they affect interpretation of focal slow-wave activity in elderly individuals? First, there are people over 60–65 years of age who have few of the EEG findings traditionally attributed to normal aging. Second, focal slow-wave activity over one or both temporal regions is nonetheless common in older persons who are functioning normally at home and in their communities, and whose routine neurological examinations are normal. Third, the more prominent the focal slowing in terms of frequency (delta), voltage, and persistence, the more likely it is to be associated with focal dysfunction and symptoms. Finally, it is useful to define, for practical clinical purposes, focal slow-wave activity that is "benign" and of little use in drawing inferences that are helpful in diagnosis or management. Such benign focal slow-wave activity of the elderly is temporal in location, predominantly in the theta frequency range, intermittent, and either rhythmic or arrhythmic. It occurs mainly in drowsiness, but sometimes appears when patients are alert. Focal slowing that meets these criteria should be interpreted conservatively and not considered strongly indicative of structural pathology.

Viral Encephalitis

EEG findings are particularly important in the diagnosis of encephalitis caused by herpes simplex virus, type 1 (HSV-1), and some reports have suggested that a normal EEG excludes the diagnosis (1,39,99). Many types of abnormalities have been described, including focal or diffuse slow-wave activity, focal epileptiform discharges, electrical seizure patterns, localized attenuation of background activity, and PLEDs (1,24,70, 79,116,168). Because HSV-1 causes severe hemorrhagic necrosis mainly of the inferior and medial parts of the temporal lobes and the orbital frontal regions, focal or lateralized findings that are maximal in these areas are highly suggestive of herpes encephalitis and can also be helpful in determining the best site for brain biopsy (24,99) (Fig. 11.21). The acute destructive nature of the lesions probably accounts for the frequency with which PLEDs are seen. PLEDs appear in the acute phase of the illness, usually between the fifth and twelfth day after onset of neurological symptoms (99). They consist of 100- to 500- μV sharply contoured slow waves or polyphasic spikes that typically recur at 1.5- to 2.5-second intervals, although both slower and faster rates can be seen (1,22,99,116,144, 170). The periodic complexes are usually unilateral, but they can be bilateral and occur either independently or time locked on the two sides (162). PLEDs usually appear before changes on head CT (18,42,88) but not before abnormalities on brain MRI.

Although the periodic pattern is usually seen in adults with herpes simplex encephalitis, it has been reported in infants and children (22,162). Some authors have reported that periodic complexes are associated with increased mortality (24,40), whereas others have disputed this (79,99).

Herpes simplex virus, type 2, causes encephalitis in neonates, and this is also associated with a distinctive periodic EEG pattern (115,118,151). The periodic discharges are not restricted to the temporal areas and are often multifocal. Each site of discharge has its own morphology and periodic interval. Focal spikes and seizures are also common. Other forms of focal encephalitis cause focal slowing and spikes, but PLEDs are rare.

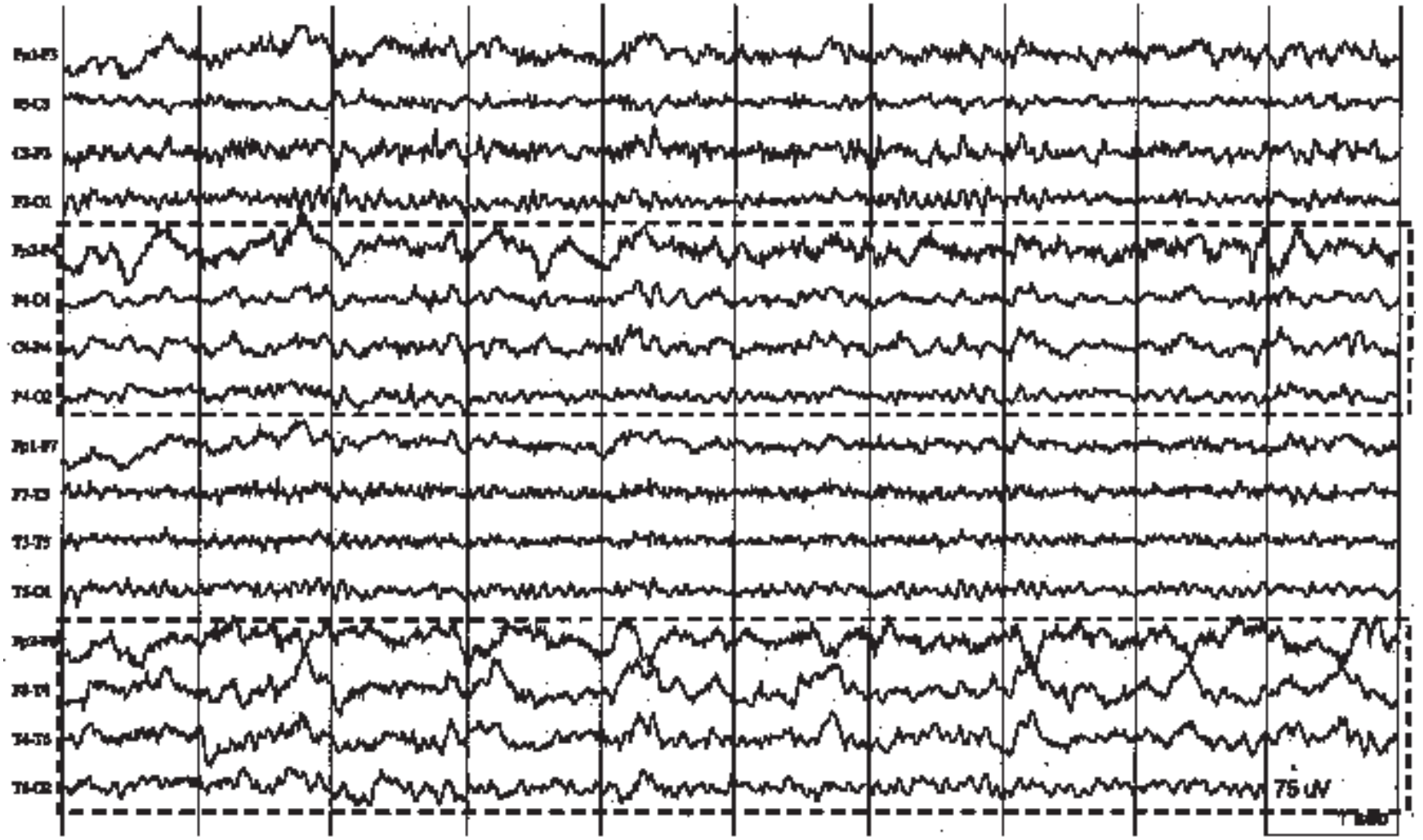


FIG. 11.21. EEG of a 64-year-old woman with herpes simplex encephalitis affecting mainly the right temporal lobe and orbital region of the right frontal lobe. There is continuous arrhythmic and semirhythmic delta activity of medium to high amplitude over the right temporal, frontal, and frontal-polar regions. Lower voltage polymorphic delta and theta activity are seen over the entire right hemisphere, and the alpha rhythm is largely absent on that side. Although the right frontal slow activity spreads to contralateral homologous regions, left hemisphere activity is otherwise relatively well preserved.

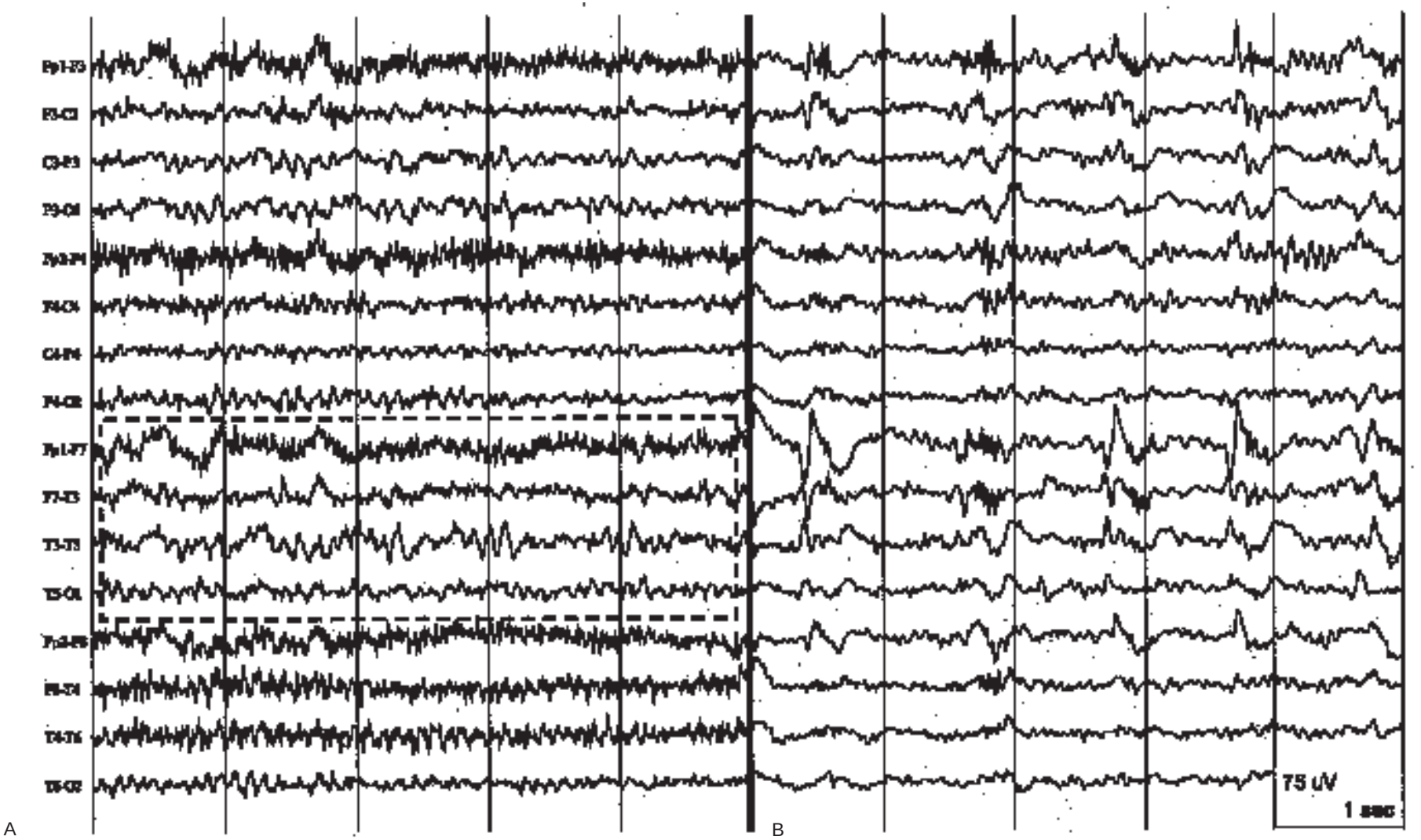


FIG. 11.22. EEGs of a 47-year-old man with neurocysticercosis and new-onset seizures. MRI demonstrated multiple ring-enhancing lesions, with the largest involving the left posterior hippocampus and adjacent cortex. **A:** Awake EEG. There is intermittent polymorphic delta activity over the left temporal region (*boxed area*) with spread to the suprasylvian and parasagittal areas. **B:** Sleep EEG. There are periodic complexes over the left midtemporal region consisting of a sharp wave followed by paroxysmal fast activity lasting 200–400 milliseconds. The paroxysmal fast activity spreads to the frontopolar region.

Other Conditions

EEG abnormalities are common in multiple sclerosis, especially as the disease progresses (59). All are nonspecific and include focal and diffuse slow-wave activity, and voltage attenuation (102). Sturge-Weber syndrome, which includes "tramline" calcification within layers of the parieto-occipital cortex, is associated with focal voltage attenuation and epileptiform discharges (17). In cysticercosis, there are focal or multifocal spikes accompanied by focal or multifocal delta activity (112) (Fig. 11.22). Generalized slow-wave activity also occurs. Cerebral arteriovenous malformations may have no effect on the EEG, but, if large or associated with ischemia or hemorrhage, they produce focal polymorphic delta activity, often accompanied by localized voltage attenuation (133) (see Fig. 11.3).

USE OF EEG IN THE ICU AND OPERATING ROOM

The sensitivity of EEG to acute focal brain dysfunction makes it a useful tool to monitor cerebral physiological function. Scalp EEG has been used for this purpose during carotid endarterectomy to make decisions about the need for shunting (25,97,119). Arnold and others (4) used EEG and transcranial Doppler ultrasound to monitor 82 patients undergoing carotid endarterectomy. EEG had a high correlation with decreased velocity of blood flow, but there were many false positives. Consequently, these authors concluded that EEG did not add additional useful information in these cases. Others, however, disagree with this conclusion (see Chapter 31 for a full discussion). EEG has also been used during endovascular embolization of arteriovenous malformations. The procedure generally used is to inject low doses of sodium amobarbital through an intra-arterial catheter into the feeding artery(ies). Neurological and EEG assessment during this reversible period of anesthesia is used to predict the functional effects of permanently occluding the feeding artery(ies). When embolization has been performed despite EEG changes during a preceding amobarbital test, clinically important deficits have resulted (133).

Continuous EEG monitoring is increasingly used in the neonatal ICU to detect ischemic changes caused by vasospasm following subarachnoid hemorrhage (174) and to identify subclinical seizures. Because of the large volume of acquired data, the use of compressed spectral array (CSA) can aid in detecting clinically significant changes. CSA uses power spectra to summarize data over time and indicate trends related to improvement or deterioration in focal, hemispheric, or bilateral cerebral function. CSA can never fully replace raw EEG. Conventional displays of EEG activity must be available for each patient to determine the meaning of CSA patterns. A complete discussion of ICU monitoring is contained in Chapter 25.

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Chapter 12

Metabolic, Infectious, and Hereditary Encephalopathies

Akio Ikeda, George H. Klem, and Hans O. Lüders

Abnormal EEG Patterns Frequently Seen in Diffuse Encephalopathies
- Background Slow Activity
- Diffuse Intermittent Slow Activity
- Diffuse Intermittent Rhythmic Slow Activity
- Diffuse Continuous Slow Activity
- Periodic Patterns
- Triphasic Waves
- Burst-Suppression
- Diffuse Background Attenuation
- Special EEG Patterns Seen in Patients in Coma
- Electrocerebral Inactivity

Metabolic Encephalopathies
- Hepatic Encephalopathy
- Uremic Encephalopathies
- Encephalopathies Related to Alterations of Glucose Metabolism
- Encephalopathies Related to Electrolyte and Fluid Balance Alterations
- Encephalopathies Related to Alterations in Body Temperature
- Acute Intermittent Porphyria
- Eclampsia

Anoxic Encephalopathy

Endocrine Encephalopathies
- Thyroid Disorders
- Calcium Abnormalities
- Adrenal Gland Abnormalities
- Pituitary Gland Abnormalities

Nutritional Deficiency Encephalopathies

Infectious and Inflammatory Encephalopathies
- Meningitis
- Acute Encephalitis
- Subacute and Chronic Encephalitis
- Transmissible Spongiform Encephalopathies (Prion Diseases)
- AIDS and Human Immunodeficiency Virus Infection
- Multiple Sclerosis and Other Autoimmune Diseases
- Celiac Disease

Hypertensive Encephalopathy

Neurodegenerative and Hereditary Diseases
- PME Syndromes
- Leukodystrophies of Adult Onset
- Other Inherited Metabolic Diseases of Adult Onset

Acknowledgments

References

TABLE 12.1. *Types of diffuse encephalopathies*

Metabolic encephalopathies
Anoxic encephalopathies
Endocrine encephalopathies
Nutritional deficiencies
Infectious and inflammatory encephalopathies
Hypertensive encephalopathies
Neurodegenerative and hereditary diseases (adult onset only)
Progressive myoclonic epilepsy syndromes
Leukodystrophies of adult onset
Mucopolysaccharidoses
Niemann-Pick disease
MELAS

TABLE 12.2. *EEG abnormalities frequently seen in diffuse encephalopathies*

Background slow activity
Diffuse intermittent slow activity
Diffuse intermittent rhythmic slow activity
Diffuse continuous slow activity
Periodic patterns and PLEDs/ BiPLEDs
Triphasic waves
Burst suppression
Diffuse background suppression
Special EEG patterns seen in patients in coma
Alpha coma
Spindle coma
Beta coma
Delta/theta coma
Electrocerebral inactivity

Electroencephalography (EEG) is a sensitive and reliable test to assess cerebral dysfunctions, and occasionally it can detect abnormalities even before clinical symptoms appear. The degree of EEG abnormality usually parallels the severity of the brain damage, and can therefore provide an objective measurement of the severity of a diffuse encephalopathy. Most encephalopathies produce nonspecific EEG abnormalities, but there are selected exceptions, such as Creutzfeldt-Jakob disease (CJD), that are associated with highly specific EEG patterns. The EEG usually cannot differentiate between acute and chronic states of diffuse encephalopathies even if acute insults in general tend to produce relatively more severe EEG abnormalities for any given insult. In this chapter, we describe EEG findings of diffuse encephalopathies caused by various etiologies as listed in Table 12.1. Drug effects and toxic encephalopathy, specific progressive pediatric syndromes, and EEG changes with organic brain syndrome are described elsewhere in this book.

ABNORMAL EEG PATTERNS FREQUENTLY SEEN IN DIFFUSE ENCEPHALOPATHIES

This section provides a description of the EEG abnormalities most commonly seen in diffuse encephalopathies (81) (Table 12.2). Most of these EEG patterns are nonspecific but, as mentioned above, tend to reflect the severity of cerebral dysfunction. The abnormalities described below are listed according to degree of EEG abnormality, starting with the least abnormal patterns.

Background Slow Activity

Background slow activity is defined as slowing of the main rhythmical posterior background activity (Fig. 12.1). It is a very sensitive index of a nonspecific diffuse encephalopathy, and occurs in almost all diffuse encephalopathies of mild or moderate degree. The degree of background slowing is also a function of the degree of cerebral dysfunction. Background slow activity frequently also occurs in association with some of the other abnormal EEG findings listed below.

Diffuse Intermittent Slow Activity

Diffuse intermittent slow (IS) activity is defined as excessive slow activity (exceeding the physiological slowing) that appears in an intermittent fashion (Fig. 12.2). The posterior dominant background rhythms are usually well preserved but may be abnormally slow (background slow activity). When occurring in isolation, diffuse IS activity usually reflects a mild, diffuse, and nonspecific cortical or subcortical dysfunction.

Diffuse Intermittent Rhythmic Slow Activity

Diffuse intermittent rhythmic slow (IRS) activity is a subclass of diffuse IS activity in which the slow waves appear grouped in bursts and consist of

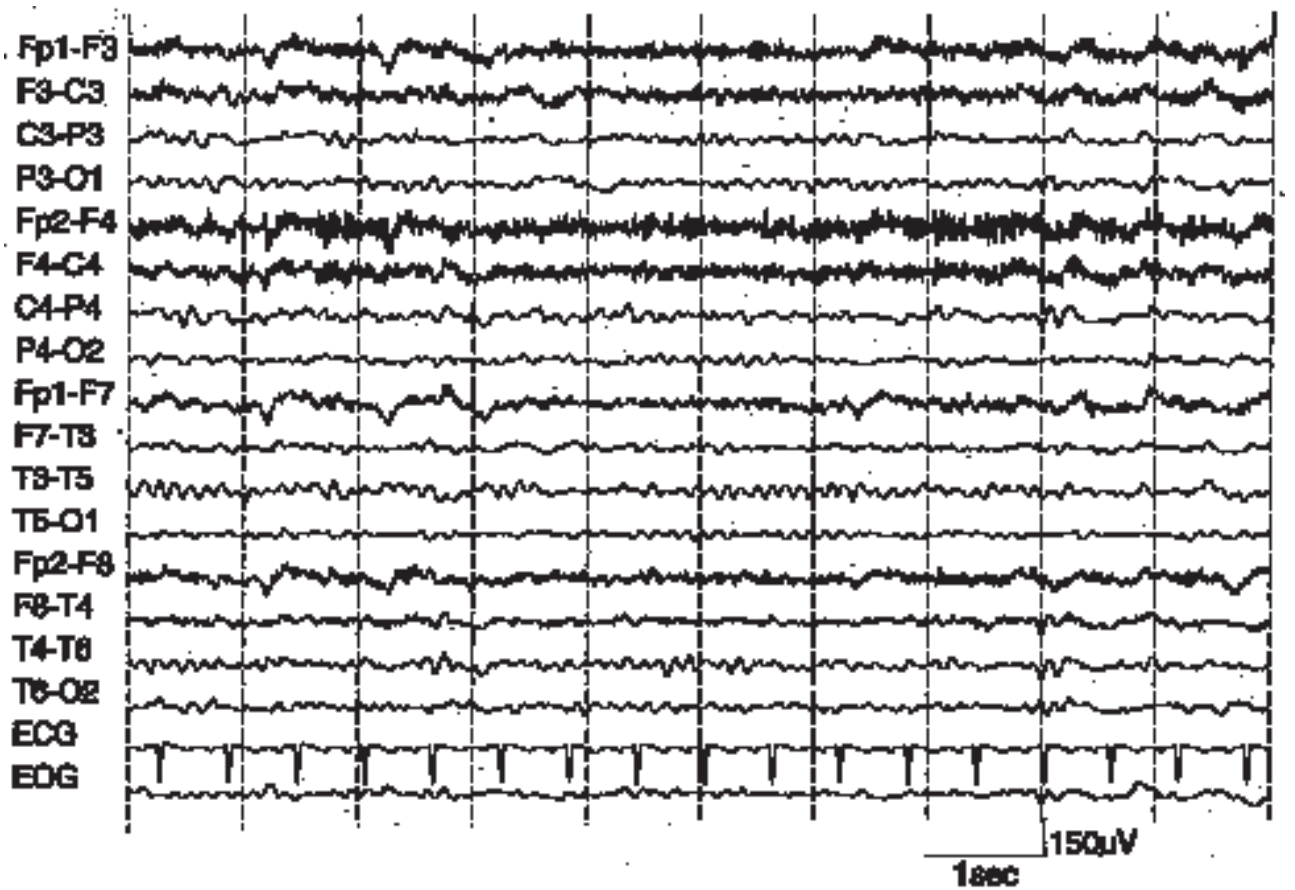

FIG. 12.1. Background slow activity in an 84-year-old man with dementia and confabulation 1 month after subarachnoid hemorrhage. The alpha rhythm is about 7 Hz, and there is also a diffuse, low-amplitude delta activity.

relatively rhythmic waves. Diffuse IRS activity is usually maximal over the anterior head regions in adults (frontal intermittent rhythmic delta activity [FIRDA]) (Fig. 12.3) and over the posterior head regions in children below 10 years (occipital intermittent rhythmic delta activity, or OIRDA).

It often shows shifting asymmetries, and not infrequently is associated with background slow and/or diffuse continuous slow (CS) activity as described below. It is usually an expression of a nonspecific, diffuse encephalopathy of any cause. Less frequently it occurs in patients with mesial frontoparietal cortical lesions or focal subcortical gray matter lesions (destructive processes involving subcortical gray matter structures, such as third ventricle tumors or increased intraventricular pressure).

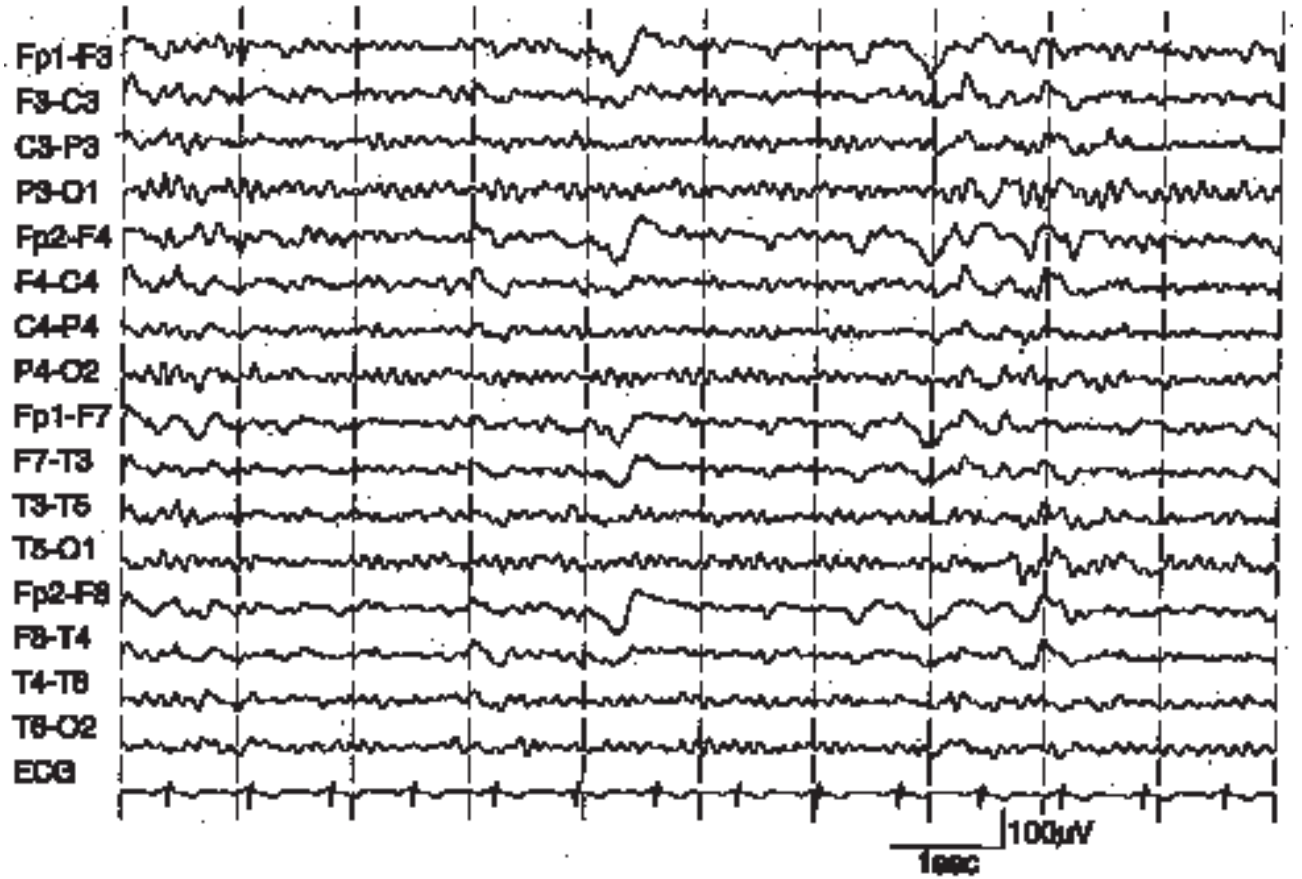

FIG. 12.2. Diffuse intermittent slow activity in a 26-year-old man with acute viral encephalitis.

Diffuse Continuous Slow Activity

Diffuse continuous slow (CS) activity consists of continuous, nonrhythmic, irregular (polymorphic) slow activity that is nonreactive to external stimuli, and exceeds the amount of CS activity that is physiologically appropriate for the age of the patient (Fig. 12.4). Variable degrees of disturbance of interneuronal connections or the biochemical environment of cortical neurons lead to diffuse CS. Gloor et al. (44) observed that polymorphic delta activity (PDA) was less common in pure cortical and subcortical gray matter disease in which white matter was relatively preserved. Their studies suggest that cortical deafferentation is an important cause of diffuse CS activity. The degree of slowing and its amount tend to be a function of the

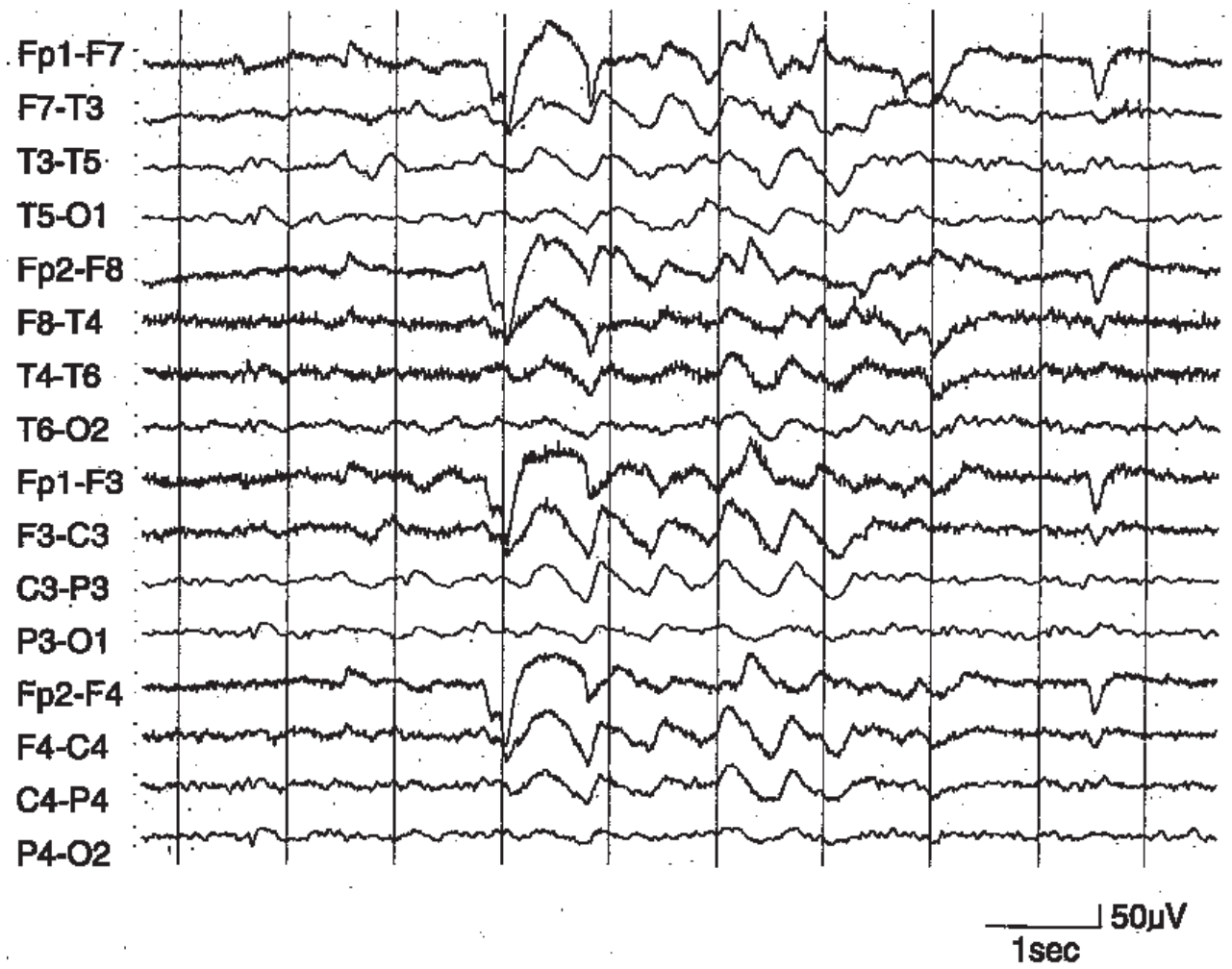

FIG. 12.3. Diffuse intermittent rhythmic slow activity maximal in the frontal areas. This is also termed frontal intermittent rhythmic delta activity (FIRDA).

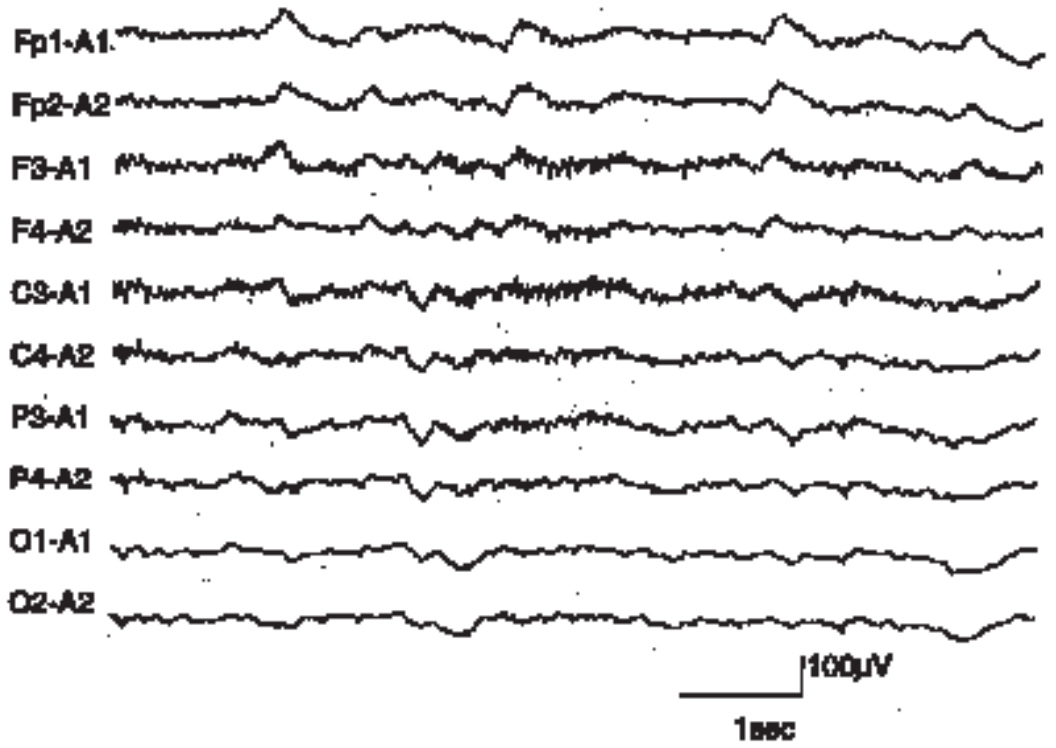

FIG. 12.4. Diffuse continuous slow activity in a 54-year-old man in stupor from acute meningoencephalitis and acute renal failure.

severity of diffuse encephalopathy. However, diffuse CS activity occurring with no remaining rhythmic background activity is usually an expression of a severe diffuse encephalopathy, such as that in patients with stupor or coma. Moderate or even mild degrees of CS activity may occur when rhythmic background activity is still preserved.

Periodic Patterns

Periodic patterns consist of relatively stereotyped waveforms (frequently sharp waves) that appear in a periodic or quasiperiodic fashion. They are usually indicative of an acute or subacute, severe, diffuse encephalopathy. The repetition rate and waveform of the periodic complexes are relatively characteristic for encephalopathies of different etiologies. A repetition rate of more than once every 2 seconds is most frequently seen in CJD in adults and in lipidosis in infants and children. Periodic patterns with a much slower repetition rate, from 4 to 10 seconds, characteristic of subacute sclerosing panencephalitis (SSPE) (18) (Fig. 12.5).

As one of the nondiffuse periodic patterns, periodic lateralized epileptiform discharges (PLEDs) are defined as sharp transients, including sharp waves or spikes, that have a lateralized distribution and appear in a periodic or quasiperiodic fashion (Fig. 12.6). They may be unilateral (PLEDs) or may have a bilateral distribution (bilateral periodic lateralized epileptiform discharges [BiPLEDs]) (26) (Fig. 12.7). These patterns are seen in (a) acute or subacute,

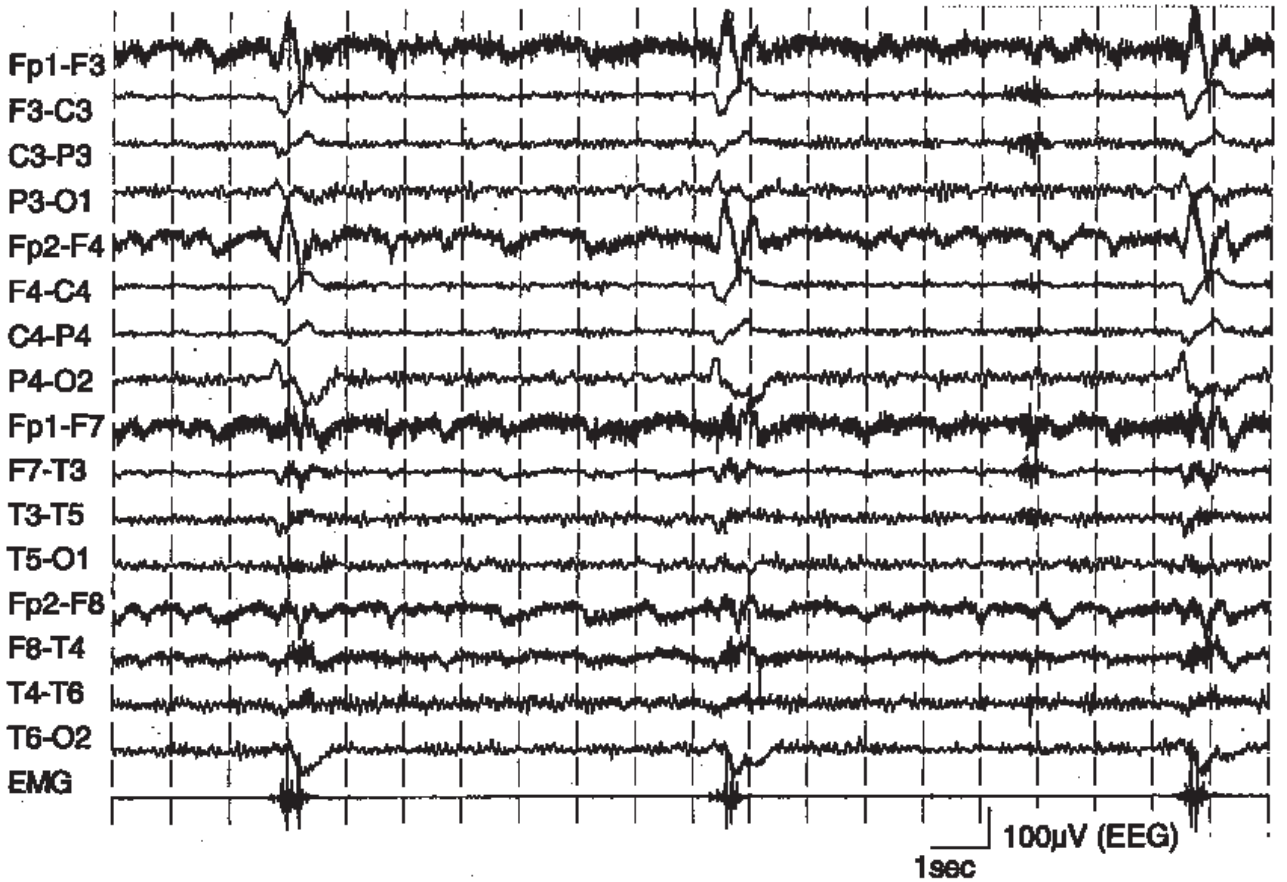

FIG. 12.5. Diffuse periodic discharges every 7–8 seconds in a 19-year-old woman with the early stage of SSPE. Posterior dominant rhythms of 9 Hz are well preserved. Electromyogram of the right extensor carpi radialis is shown in the last channel.

severe, focal destructive lesions (most often acute hemorrhagic infarcts, fast-growing tumors, or herpes simplex encephalitis); or (b) focal epileptogenic lesions not necessarily associated with an acute underlying structural pathology. In both conditions, focal pathology is frequently associated with a diffuse encephalopathy. PLEDs may occur in patients with diffuse encephalopathies with focal manifestation, such as herpes simplex encephalitis.

Triphasic Waves

Triphasic waves consist of high-voltage (> 70 μV), positive sharp transients that are preceded and followed by negative waves of relatively lower amplitude (Fig. 12.8). They have a diffuse, usually anterior-dominant, distribution and a periodic repetition rate of approximately 1–2 Hz (16).

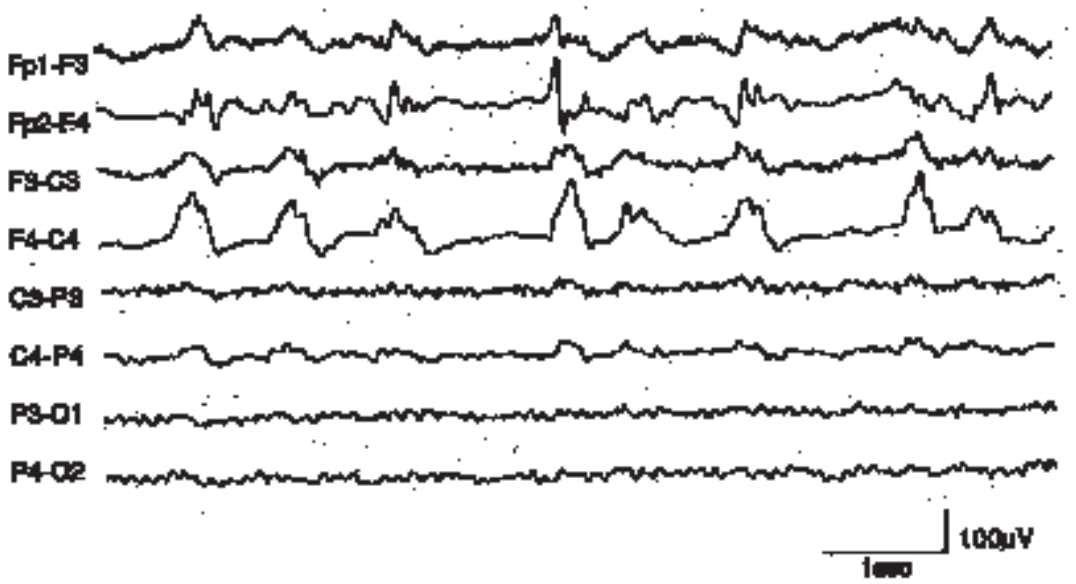

FIG. 12.6. PLEDs in a 52-year-old woman with acute onset of delirium who had a liver transplant 6 months ago.

Triphasic waves are usually due to a metabolic encephalopathy, and although they are particularly frequent in hepatic encephalopathy, they may be seen in other toxic/metabolic conditions, such as uremia, severe hyponatremia, and lithium toxicity. Triphasic waves usually occur in patients with a mild alteration of consciousness but not in conditions as severe as stupor or coma. Occasionally, triphasic waves and generalized slow spike-and-wave epileptiform discharges are difficult to distinguish (35).

Burst-Suppression

Burst-suppression constitutes a subgroup of periodic patterns in which the activity between the complexes (spikes and sharp waves mixed with nonspecific waves of variable amplitude, frequency, and waveform) is almost completely attenuated (less than 10 μV) (Fig. 12.9). Generalized burst-suppression EEGs occur in patients with a severe degree of toxic or anoxic encephalopathy and constitute the EEG pattern that immediately precedes electrocerebral inactivity (ECI) in patients who are deteriorating progressively. Patients who show diffuse burst-suppression in their EEGs are always in coma.

Diffuse Background Attenuation

This pattern is defined as absence of electrical brain activity greater than 10 μV. It is seen in patients in coma or deep stupor, and it is always indicative of a severe diffuse encephalopathy. However, some normal individuals have EEG activity that may not exceed 10 μV. Therefore, this pattern should only be considered abnormal if the patient is in stupor or coma (1).

Special EEG Patterns Seen in Patients in Coma

For a more detailed discussion of EEG changes in coma and brain death, see Chapter 14.

Alpha Coma

Alpha coma refers to by an EEG in which the predominant rhythmic activity is in the alpha range and occurs in patients who are in coma. The alpha activity most frequently has a diffuse distribution with frontal pre-

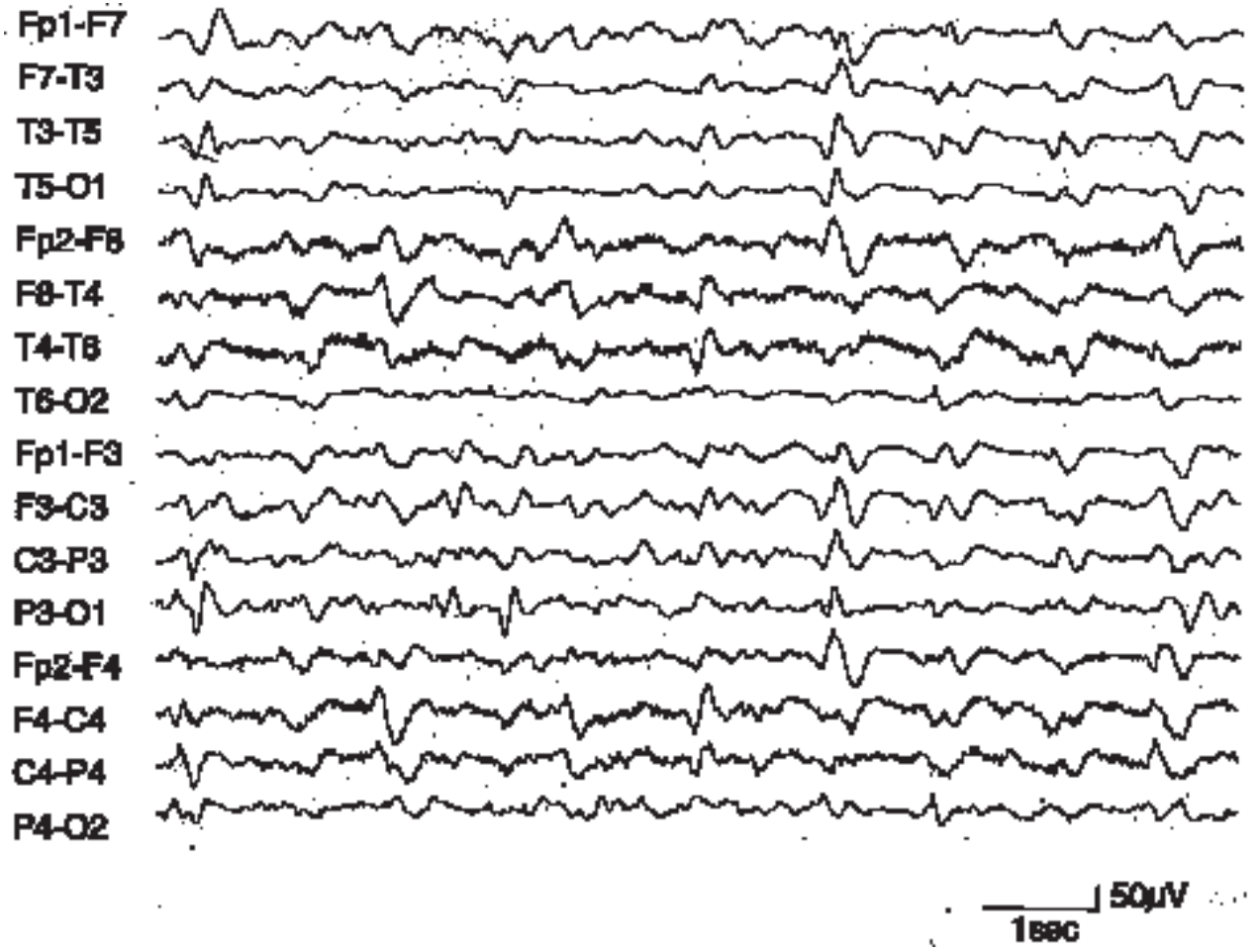

FIG. 12.7. BiPLEDs in a 74-year-old woman with encephalitis.

dominance and is nonreacti ve to external stimuli. This EEG patter n is most frequently seen in se vere anoxic encephalopathy and is associated with an extremely poor prognosis. Less frequently, this pattern is seen in patients with more limited lesions at the pontomesencephalic le vel. It has been reported that patients with alpha coma resulting from ano xia due to respiratory arrest and high-voltage electrical injur y tend to ha ve a better outcome than those with alpha coma occur ring after cardiac ar rest (45,46).

Spindle Coma

Spindle coma is a ter m used when diurnal EEG acti vity in comatose patients contain features of stage 2 sleep, including prominent spindle-lik e activity (73). It can occur in patients with nonprogressive conditions such as a posttraumatic or postencephalitic encephalopathy, but most frequently it is an expression of a high mesencephalic lesion. This EEG pattern usually carries a good prognosis.

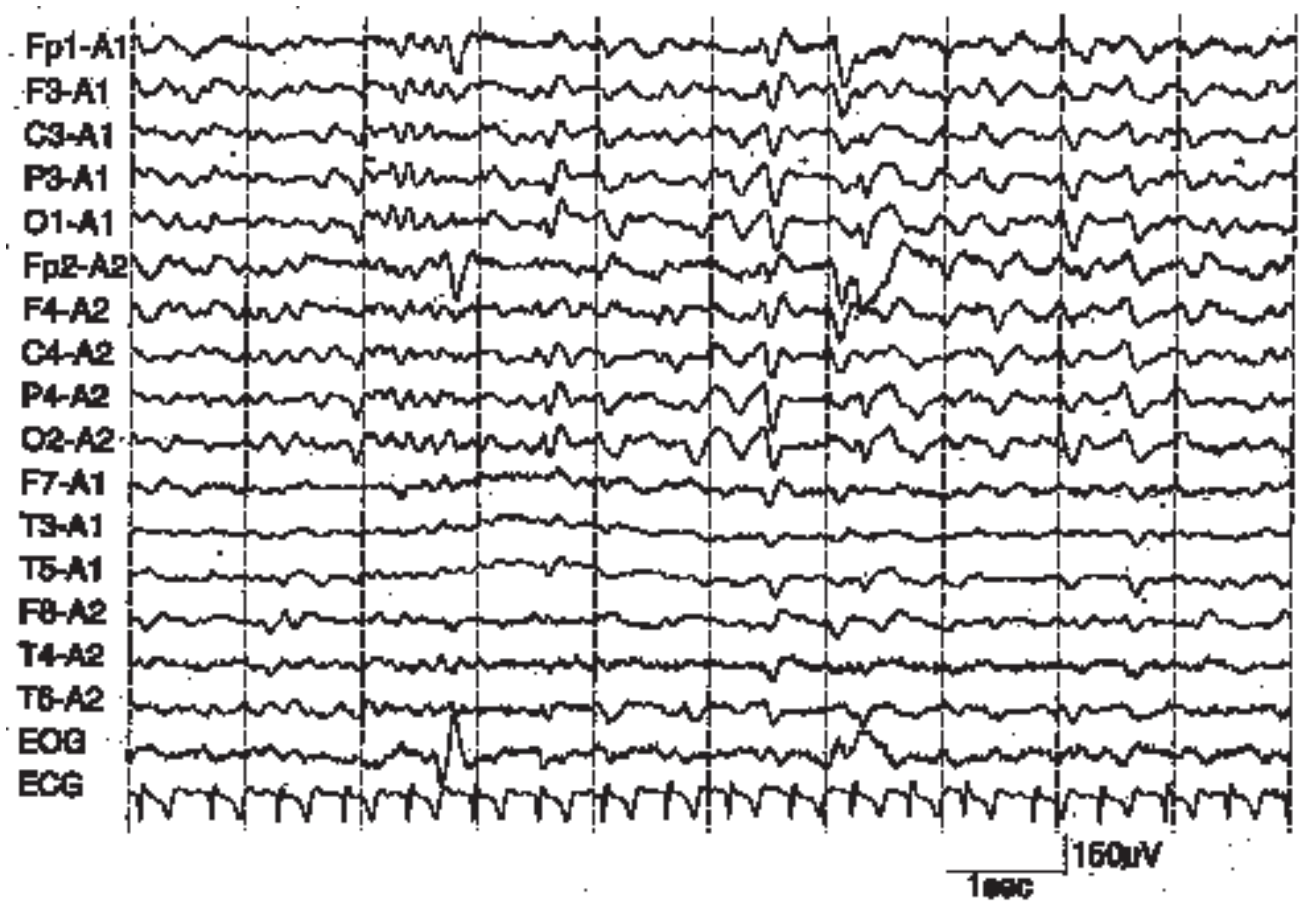

FIG. 12.8. Triphasic waves in a 61-year-old woman with hepatic encephalopathy.

Beta Coma

Beta coma EEGs consist of high-amplitude beta activity (usually > 30 μV) in patients who are in coma. It is usually seen in diffuse encephalopathies caused by drug intoxication, and therefore represents a potentially reversible EEG abnormality. It may also occur in acute brainstem lesions (98).

Delta/Theta Coma

Delta/theta coma EEGs show delta or theta activity as the predominant background activity in patients who are in coma. It is seen in patients with diffuse encephalopathies of diverse etiologies, and is a potentially reversible EEG pattern. The prognosis depends mainly on the reversibility of the underlying cause(s) of the encephalopathy (19).

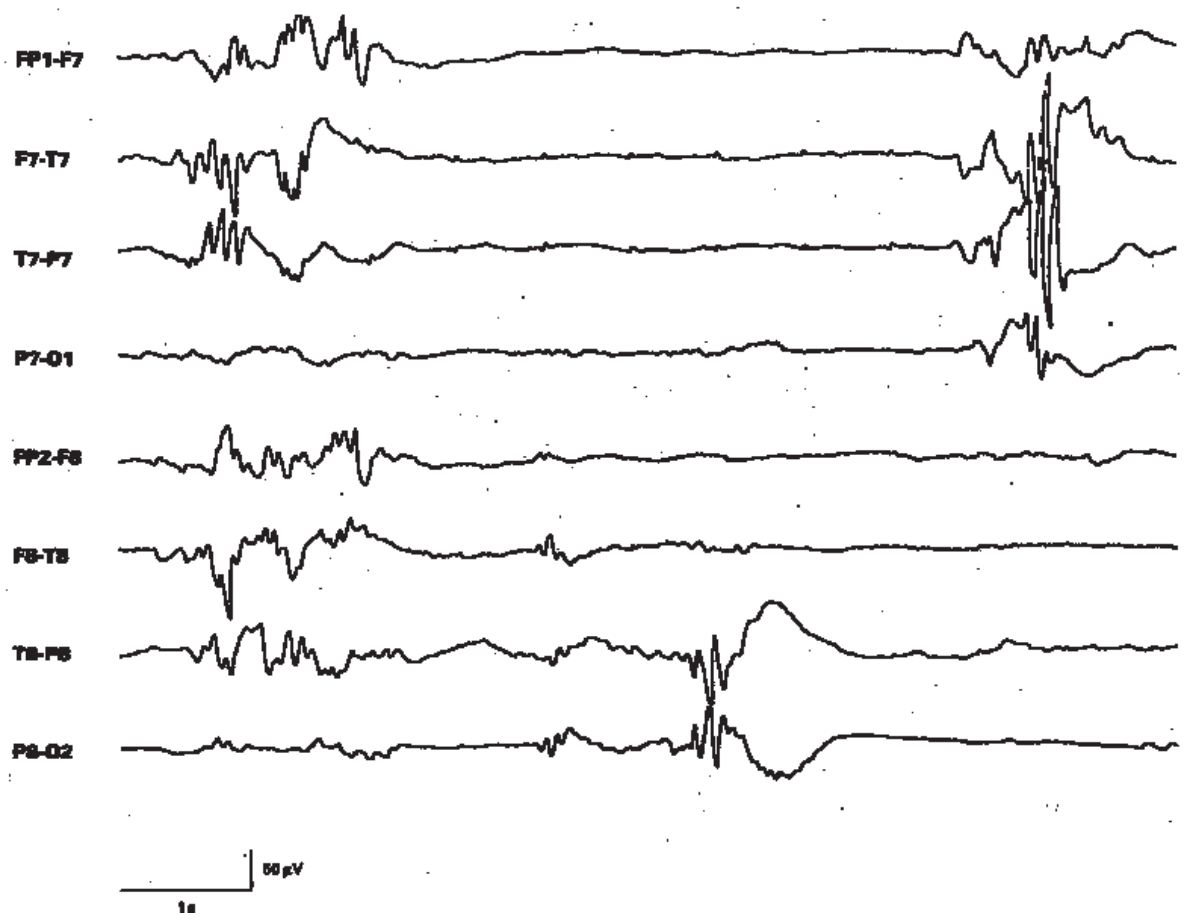

FIG. 12.9. Burst-suppression in a 3-year-old boy with severe anoxic encephalopathy. (From Lüders HO, Noachtar S. *Atlas and classification of electroencephalography*. Philadelphia: WB Saunders, 1999, with permission.)

Electrocerebral Inactivity

ECI is defined as no electrical brain activity exceeding 2 µV in EEGs recorded from scalp electrodes following the minimal technical standards proposed by the American Electroencephalographic Society (2) (Fig. 12.10). With very few exception it is an expression of brain death.

Encephalopathies involving mainly cortical regions are associated with seizures with generalized epileptiform discharges, changes in background rhythms, and amplitude attenuation of background activity, whereas those mainly involving white matter are correlated with arrhythmic, polymorphic slow activity in the theta and delta frequencies. Most diffuse encephalopathies, however, affect both the gray and white matter, and lead to all the EEG abnormalities listed above. Fluctuations of the EEG pattern over time, such as normal sleep-wave changes and reactivity to external stimuli, indicate less severe brain dysfunction than when no variability or reactivity is present. In contrast, the presence of a constant EEG pattern that does not change over time and does not react to external stimuli indicates a more severe disturbance. Serial EEG recordings are useful because the evolution

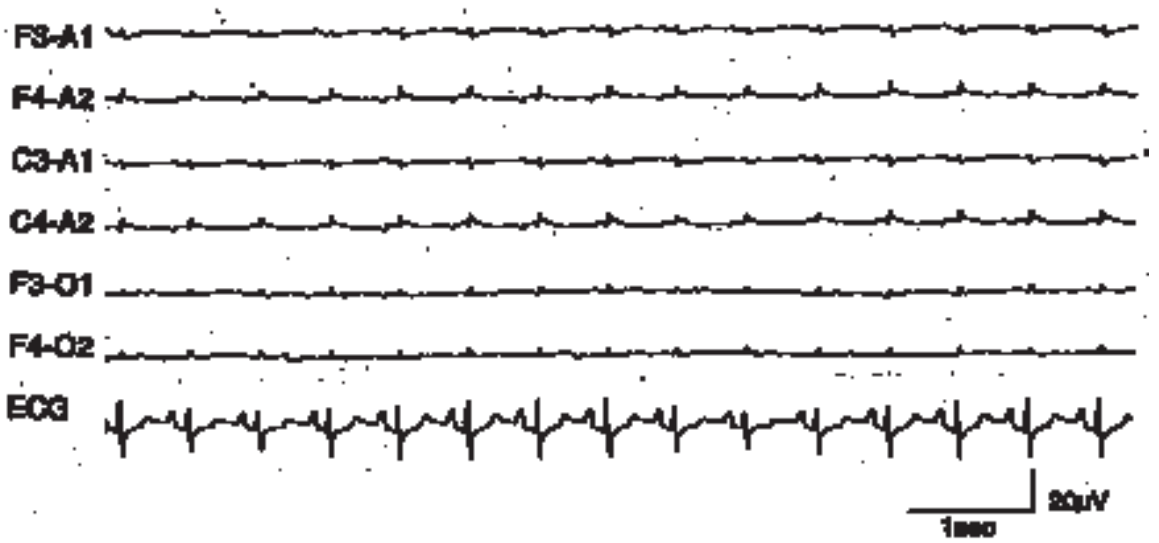

FIG. 12.10. Electrocerebral inactivity in a 19-year-old woman who 6 days ago had suffered a severe head injury in a traffic accident.

of the EEG pattern not infrequently allows more precise evaluation of the prognosis of a diffuse encephalopathy.

METABOLIC ENCEPHALOPATHIES

Hepatic Encephalopathy

EEG changes in hepatic encephalopathy vary from mild abnormalities such as background slow and diffuse IRS activity to severe, diffuse CS activity, seen usually in patients who are in coma. Triphasic waves are seen in moderate stages of encephalopathy usually associated with somnolence and mild stupor (see Fig. 12.8). Triphasic waves resemble spike-and-wave complexes in morphology, as earlier suggested by Foley et al. (35), who identified them as "blunt spike-wave" discharges. Triphasic waves are no longer regarded as a specific EEG abnormality for hepatic encephalopathy, as they can be seen in a variety of other metabolic encephalopathies such as renal failure, anoxia, hyperosmolar state, hypoglycemia, hyponatremia, hypercalcemia, and hyperthyroidism. However, there are reports suggesting that triphasic waves occur relatively more commonly in hepatic encephalopathy than in metabolic encephalopathies of other causes (34).

Triphasic waves can be classified into "typical" (bilaterally symmetrical and synchronous, anterior predominance, fronto-occipital time lag, occurrence in groups or runs) and "atypical" (lack of at least one of the four features specified for typical triphasic waves). According to Reiher (106), typical triphasic waves occur almost exclusively in patients with hepatic encephalopathy, although this has been disputed by Fisch and Klass (34).

In patients who undergo liver transplantation, the frequency of the posterior background activity tends to increase significantly (31). This improvement is apparently correlated with changes in cerebral blood flow in the frontal areas (25). It has also been reported that survival at 18 months after liver transplantation is strongly associated with higher frequencies of the background activity at baseline (31). Epileptiform abnormalities in EEGs from patients after orthotopic liver transplantation have been associated with serious, often irreversible brain damage, and most probably are the result of metabolic, electrolyte, and toxic alterations superimposed on structural brain changes (138).

In patients under age 20, triphasic waves do not accompany hepatic encephalopathy (29). In children with Reye's syndrome (acute childhood toxic encephalopathy), which is always associated with hepatic dysfunction of varying severity, EEG findings range from minimal background slow

activity to burst-suppression or background attenuation. Triphasic waves, however, are extremely rare. Interestingly, 14- and 6-Hz positive spikes are seen not infrequently. Focal or multifocal epileptiform discharges and EEG seizure activity can be seen in the later stages of the disease (4).

Uremic Encephalopathies

Acute renal failure is more frequently associated with clinical encephalopathy than is chronic renal failure, and epileptic seizures are seen in more than 30% of patients with acute renal failure. This is a significantly higher incidence than in other metabolic encephalopathies (80). In milder degrees of uremic encephalopathy, only background slow or diffuse IRS activity occurs, whereas triphasic waves and diffuse CS activity occur in more severe stages. Myoclonus (labeled as polymyoclonus because of its multifocal character), asterixis (negative myoclonus), and generalized seizures are frequent. Focal seizures may also occur, most often in patients with previous focal brain lesions. Epileptiform discharges are rare, but photic stimulation often elicits photoparoxysmal and photomyoclonic responses (63). These observations are consistent with animal experiments in which urea infusion can produce myoclonus that rapidly progresses into uncontrollable generalized tonic–clonic convulsions (92,142). The myoclonus observed in these animal experiments most probably arises from the brainstem reticular formation, and it has been suggested that it is mediated by glycine (23).

In chronic renal failure, the EEG tends to be less abnormal than in acute renal failure. However, generalized epileptiform discharges have been reported in 8%–9% of patients (58). In "dialysis dysequilibrium syndrome," patients may deteriorate and even have seizures during or immediately after hemodialysis. The symptoms of dialysis dysequilibrium syndrome are due to a sudden normalization of some major biochemical blood abnormalities. The EEG in this syndrome shows diffuse IRS activity (69). The syndrome is rare with modern dialysis methods.

"Dialysis dementia" (also called progressive dialysis encephalopathy) is seen in patients who have been on hemodialysis for 3–4 years and is characterized by dysarthria, myoclonus, dementia, and eventually seizures and death. Sudden onset of hesitant, nonfluent speech is the most common characteristic and usually the earliest sign. The EEGs are more abnormal than would be expected from the clinical findings, showing high-voltage spike-and-wave patterns intermixed with abundant slow activity. This combination of clinical and EEG features is virtually pathognomonic (79). Aluminum intoxication is probably a major contributor to this syndrome. It was prevalent during the 1970s, but it is now extremely infrequent, most probably as a result of the use of an aluminum-free dialysate (20).

Encephalopathies Related to Alterations of Glucose Metabolism

Hypoglycemia

Level of consciousness and blood sugar levels do not necessarily parallel each other. However, the degree of EEG changes (background slow, diffuse IS, diffuse CS activity) in hypoglycemia tends to correlate closely with the severity of cerebral dysfunction. Epileptiform activity can be associated with diffuse slowing (94), and patients may clinically show confusion, stupor, coma, and even generalized convulsions.

Hyperglycemia

In diabetic coma, which is usually associated with acidosis and electrolyte imbalance, the EEG usually shows diffuse CS activity. In nonketotic hyperglycemia, localized epileptic phenomena such as PLEDs occur in association with partial seizures or epilepsia partialis continua (51,84). Ketotic hyperglycemia, in contrast, is much less frequently associated with seizures, most probably because of the antiepileptic effects of ketosis (67).

Encephalopathies Related to Electrolyte and Fluid Balance Alterations

Drowsiness, confusion, stupor, and coma, as well as generalized seizures and other neurological abnormalities, may occur with derangements of electrolyte or fluid balance (i.e., hypo- and hypernatremia, hypo- and hypercalcemia, hypophosphatemia, and hypomagnesemia). In these conditions, the EEG shows nonspecific, generalized slowing consistent with the degree of diffuse encephalopathy. Usually the *rate* of changes of electrolyte concentration is more important than the absolute degree of electrolyte abnormality as a factor responsible for developing clinical and EEG abnormalities, especially epileptic seizures.

Hyponatremia (usually of less than 125 mEq per liter) tends to be associated with hypo-osmolarity, which leads to cellular dehydration and brain edema. The syndrome of inappropriate antidiuretic hormone secretion is a frequent cause of hyponatremia that complicates many neurological disorders such as head trauma, meningitis, encephalitis, subarachnoid hemorrhage, and neoplasm. In this syndrome, alpha activity is replaced by high-

voltage slow waves. These EEG abnormalities tend to persist even after correcting the hyponatremia, most probably because of a delay in equilibration of extracellular and intracellular water and electrolytes or because of acute cellular damage (97). Hypernatremia is associated with brain volume reduction, and the EEG usually only shows mild, nonspecific slowing.

Hypomagnesemia (less than 1.4 mEq per liter) can be caused by reduced intestinal absorption of magnesium (malabsorption syndrome, bowel resection, etc.) and excessive use of diuretics. No detailed studies of the EEG changes in hypomagnesemia have been reported. Magnesium deficiency has an inhibitory effect on the parathyroid gland, leading to secondary hypocalcemia. Hypomagnesemia produces generalized or partial seizures together with neuromuscular irritability (action or intention tremor, myoclonic jerks, startle response). A direct correlation between low plasma magnesium concentrations and seizure frequency has been demonstrated (10). Hypo- and hypercalcemia are described in the section on "Endocrine Encephalopathies" further on.

Encephalopathies Related to Alterations in Body Temperature

With hypothermia, depending on its severity, EEG changes can vary from diffuse slowing to burst-suppression and ECI. Burst-suppression occurs at 20–22°C, and ECI appears with body temperatures below 18°C (103). During cooling for open-heart surgery, sporadic spikes and periodic patterns may occur. In assessing ECI, especially at body temperatures below 32.2°C (90°F), potentially reversible EEG abnormalities produced by hypothermia should be considered (131). A mean increase in background frequency from 9 to 13 Hz has been described when the body temperature rises by 3.5°C (55), whereas relatively low-voltage and slow EEGs occur with temperature elevation to 42°C (107).

Acute Intermittent Porphyria

This autosomal dominant disease is characterized by attacks of abdominal pain, acute polyneuropathy, and cerebral dysfunction (confusion, delirium, visual defects, and seizures). The EEG in severe states of acute intermittent porphyria shows nonspecific diffuse slowing and epileptiform discharges (28).

Eclampsia

Eclampsia is a multisystem disorder associated with hypertension, proteinuria, edema, hemoconcentration, hypoalbuminemia, and diffuse encephalopathy with generalized, and occasionally also partial, seizures. These symptoms are most likely due to an extensive vasculopathy or vasospasm secondary to an exaggerated vascular responsiveness to circulating angiotensin II and catecholamines. Brain computed tomography and magnetic resonance imaging (MRI) show cerebral edema in the white matter mainly in posterior brain areas. EEG findings include diffuse slow activity and epileptiform discharges (126). These abnormalities disappear relatively quickly after clinical recovery. The EEG, clinical, and imaging findings in eclampsia are similar to those seen in hypertensive encephalopathy (118,127).

ANOXIC ENCEPHALOPATHY

During complete interruption of cerebral blood flow, predictable sequential EEG changes occur (39,88). No clinical or EEG changes occur in the first 6 seconds. Between 7 and 13 seconds, diffuse CS activity or FIRDA is recorded as consciousness is lost. When the arrest of circulation is prolonged, background attenuation occurs. Total cerebral anoxia of more than 5 minutes in a normothermic subject causes irreversible cerebral damage.

The EEG patterns that Prior (103) and Hockaday et al. (56) observed after a cardiopulmonary arrest can be subdivided into the following five grades:

Grade 1: dominant alpha activity (with or without scattered theta activity)
Grade 2: dominant theta activity (with rare alpha activity and diffuse IS activity of delta frequency)
Grade 3: diffuse CS activity, with little activity of faster frequency; spontaneous variability and reactivity of the EEG to stimuli are present
Grade 4: low-amplitude unreactive diffuse CS activity of delta frequency
Grade 5: background attenuation, burst-suppression, or ECI

Grade 1 indicates an excellent prognosis for recovery, whereas grades 4 and 5 are usually associated with a permanent neurovegetative state or death. Patients with EEGs of grades 2 and 3 show more variable outcomes. However, patients with ECI in the first hour after cardiopulmonary arrest may recover. Therefore, for prognostic purposes, it is recommended to obtain an EEG 5–6 hours after the time of cardiopulmonary arrest (99,103). Serial EEGs showing progressive deterioration or progression toward normalization are of great value for correct prognosis.

In addition to the above nonspecific EEG findings, several special EEG patterns can be seen in patients who have suffered from cardiopulmonary arrest. The following EEG patterns occur in patients who are comatose and carry a bad prognosis:

1. Generalized periodic spikes or sharp waves, at intervals of 0.5–2 seconds (75). Clinically these patients have bilateral, multifocal or generalized status myoclonicus (21), and at times electrographic status epilepticus in the absence of conspicuous somatic motor manifestations (119,120). The EEGs in these patients resemble triphasic waves and occasionally resemble those seen in patients with CJD.
2. Bilateral PLEDs consisting of periodically repetitive sharp-wave discharges occurring asynchronously over the two hemispheres.
3. Alpha coma pattern.

Patients with apallic syndrome show marked EEG attenuation during the day when they are "active" (Fig. 12.11), and at night two EEG patterns, suggesting rapid-eye-movement (REM) and non-REM sleep, can be distinguished (86). Normal slow-wave sleep is absent.

Postanoxic myoclonus is an action or intention myoclonus frequently associated with other neurological symptoms, including cerebellar ataxia, gait disturbance, postural lapse, and generalized seizures (Lance-Adams syndrome) (78). This myoclonus is of cortical origin and is associated with epileptiform discharges that, when not observed by direct visual analysis,

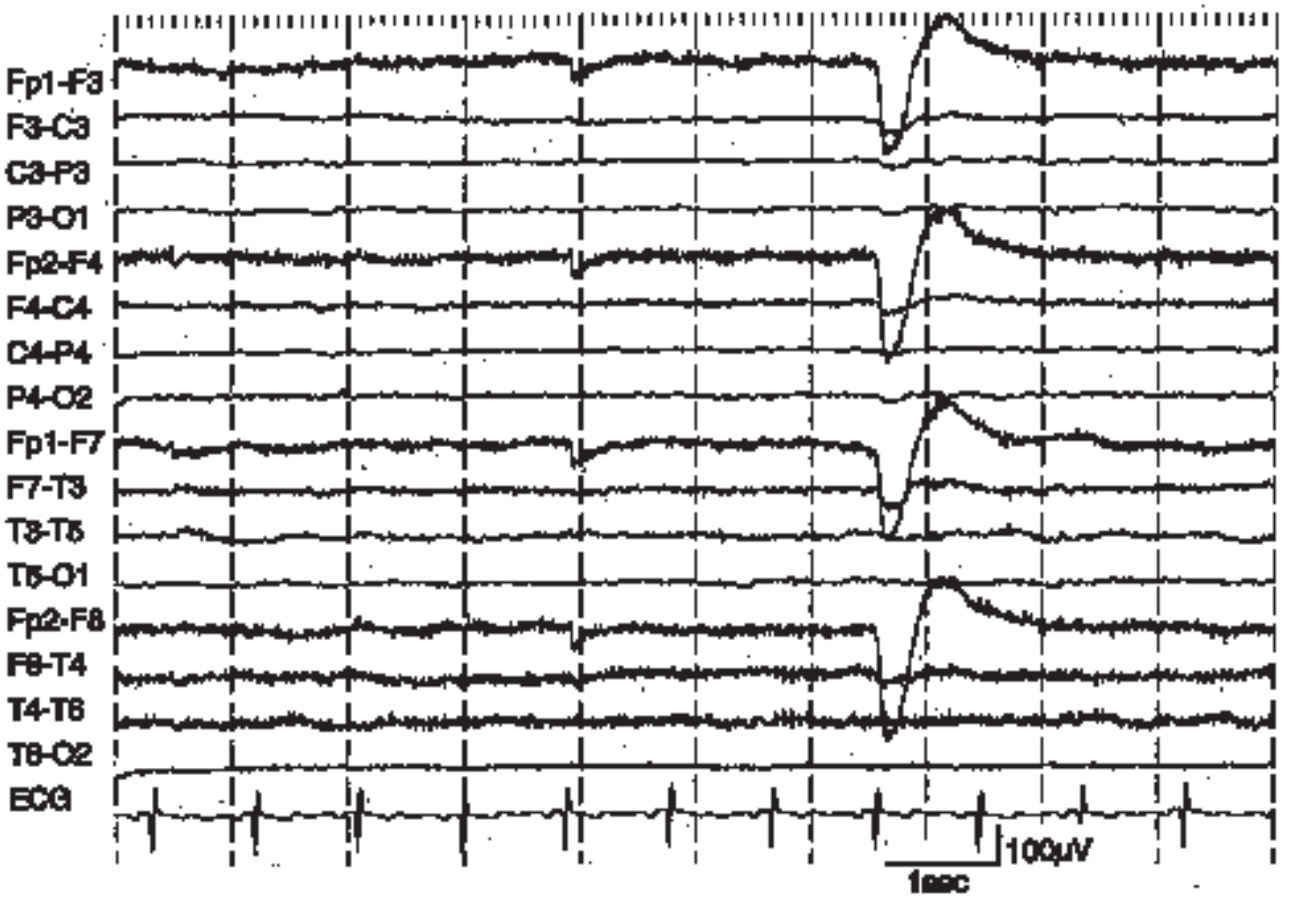

FIG. 12.11. Low-voltage EEG in a 54-year-old man who had a severe anoxic encephalopathy 6 months ago and now has severe cognitive deficits.

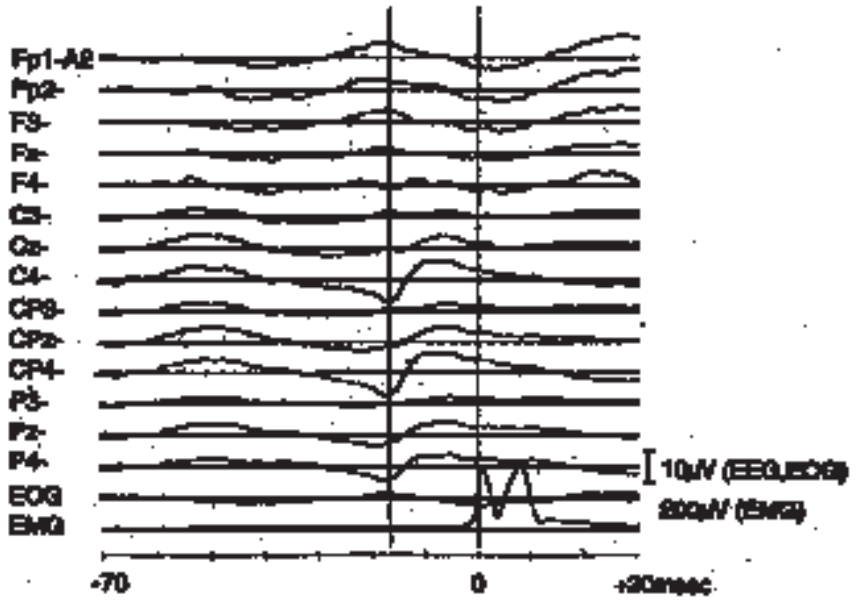

FIG. 12.12. Jerk-locked back-averaging in an 18-year-old man with severe action myoclonus (Lance-Adams syndrome). A positive potential maximum at C4 and CP4 preceding the action myoclonus at the left extensor carpi radialis by 16.7 milliseconds (shown by the left vertical line) can be distinguished by the back-averaging. Average of 250 trials. EEG recording referential to A2.

can be uncovered by jerk-locked back-averaging technique (112) (Fig. 12.12).

ENDOCRINE ENCEPHALOPATHIES

Thyroid Disorders

Hyperthyroidism is associated with a slight acceleration of alpha rhythm, enhancement of fast activity, and augmentation of rolandic mu rhythms (137). Bursts of epileptiform discharges and clinical seizures can occur, and epilepsy patients with hyperthyroidism respond poorly to anticonvulsants. In thyrotoxicosis and Hashimoto's encephalopathy, which is most likely caused by an immune-mediated cerebral vasculitis, diffuse slowing, FIRDA, sharp waves, and occasional triphasic waves have been reported (50,102).

Hypothyroidism in adults is associated with low-amplitude and diffusely slowed EEGs, and an absent or poor alpha blocking response. As expected, the EEG slowing becomes much more prominent in myxedematous coma. Seizures in hypothyroidism are associated with prolonged postictal recovery (32). In myxedematous infants, a EEG development, especially of sleep spindles, may be delayed (111).

Calcium Abnormalities

Hypocalcemia increases Na^+ conductance, which leads to membrane depolarization and repetitive neuron firing. This produces tetanic manifestations of peripheral origin. Hypocalcemia with calcium levels of 5–6 mg/dL also produces epileptic seizures of both generalized and partial origin, and epileptiform activity in the EEG. In addition, the EEG also shows irregular high-voltage delta activity that is enhanced by hyperventilation (43).

In hypercalcemia, epileptic activities usually do not occur. However, EEG changes consisting of diffuse slowing, diffuse IS activity, and sometimes triphasic waves appear when the calcium level reaches 13 mg/dL (57).

Adrenal Gland Abnormalities

Adrenocortical insufficiency (Addison's disease) can be associated with background slow, diffuse IS, and CS activity, depending on the severity of the disease. In severe cases, loss of reactivity to eye opening, increased sensitivity to hyperventilation, and decreased beta activity also appear (131). Usually no epileptic activity is seen.

EEG changes in adrenal cortical hyperfunction (Cushing's syndrome) tend to be less prominent than in Addison's disease. There are isolated reports that therapeutic dosages of adrenocorticotropic hormone (ACTH) may produce enhanced seizure susceptibility (101). This is in contrast to the well-recognized antiepileptic effect of ACTH in children with infantile spasms and hypsarrhythmia (108).

Pheochromocytomas produce extremely high blood pressure values, but the EEG shows no or little change except for those cases in which hypertensive encephalopathy occurs.

Pituitary Gland Abnormalities

Hypopituitarism, as seen in patients with postpartum necrosis of the anterior lobe of the pituitary gland (Sheehan's syndrome) is associated with diffuse IS or CS activity accompanied by alteration of consciousness. These clinical and EEG changes are most probably due to secondary hypofunction of the adrenal cortex (70). Pituitary adenomas may also cause similar EEG dysfunction secondary to hypopituitarism. In these patients, seizures may

also occur related to an extension of the tumor to the uncinate gyrus and the mesial temporal region (5).

NUTRITIONAL DEFICIENCY ENCEPHALOPATHIES

Thiamine (vitamin B_1) deficiency gives rise to Wernicke's syndrome (disturbance of consciousness, gaze palsy, cerebellar ataxia, nystagmus) with or without Korsakoff's psychosis (amnestic–confabulatory encephalopathy). EEG findings parallel the severity of the neurological symptoms, and epileptiform discharges occur in severe cases (37).

Pellagra (nicotinic acid deficiency) manifests with dermatitis, diarrhea, depression, and dementia, and the EEG shows only nonspecific diffuse slowing (122).

Pyridoxine (vitamin B_6) deficiency can cause polyneuropathy and seizures. Seizures are particularly severe in neonates and infants with vitamin B_6 deficiency. Pyridoxine dependency is a rare, autosomal recessive, vitamin-responsive aminoacidopathy. It is characterized by early onset of convulsions (even *in utero*), failure to thrive, hypertonia–hyperkinesia, irritability, tremulous movements, and exaggerated auditory startle response, and leads to irreversible psychomotor retardation if not treated. There are decreased levels of pyridoxal 5-phosphate and γ-aminobutyric acid in the brain, and daily oral supplement of pyridoxine controls the symptomatology and permits normal development. The EEG in infants shows paroxysmal and epileptiform patterns consisting of generalized bursts of bilateral, asynchronous, high-amplitude, 1- to 4-Hz waves intermixed with spikes similar to the hypsarrhythmia pattern (89).

In vitamin B_{12} deficiency (pernicious anemia), besides subacute combined degeneration of the spinal cord and polyneuropathy, mental signs (irritability, apathy, somnolence, confusion, depressive psychosis, intellectual deterioration) and visual impairment (centrocecal scotoma and optic atrophy) occur in a minority of patients. Diffuse EEG slowing and focal epileptiform discharges occur frequently (71,132). These neurological and EEG findings are not secondary effects of anemia but are rather directly related to the effects of vitamin B_{12} deficiency on the central and peripheral nervous systems.

INFECTIOUS AND INFLAMMATORY ENCEPHALOPATHIES

Meningitis

In patients with meningitis, the EEG shows various degrees of slow activity depending on the type of meningitis and the associated degree of involvement of the brain parenchyma. In aseptic meningitis, the EEG shows no or little slowing, and any EEG changes return to normal in days to a few weeks. In meningitis associated with infectious mononucleosis, the EEG shows mild to moderate slowing. In acute purulent meningitis, moderate to severe diffuse slowing occurs, but with effective treatment resolves in several weeks (134). *Haemophilus influenzae* type B used to be the most frequent cause of acute purulent meningitis in children, but after introduction of conjugate vaccine for this bacterium in the United States, five other pathogens (*Streptococcus pneumoniae, Neisseria meningitidis*, group B streptococcus, *Listeria monocytogenes*, and *H. influenzae*) have become the major causes of meningitis in the United States (110). In tuberculous meningitis, severe inflammation with proliferative changes and vasculitis can lead to clinical symptoms such as level of consciousness disturbance ranging from stupor to coma, cranial nerve involvement, hydrocephalus, hemiplegia, and epileptic seizures. The EEG shows at least moderate diffuse slowing with or without focal findings and epileptiform discharges, depending on the severity of the clinical symptoms. The mortality rate is more than 50% in patients with tuberculosis meningitis who present with stupor or coma (76).

Acute Encephalitis

In acute encephalitis, the EEG is always abnormal because the inflammatory process predominantly affects the brain parenchyma. The degree of EEG abnormality is more pronounced than in meningitis (see Fig. 12.2).

In acute viral encephalitis, both diffuse abnormalities (generalized convulsions, delirium, stupor, coma, etc.) and focal findings (aphasia, mutism, hemiparesis, focal seizures, ataxia) occur. The EEG is always abnormal, showing at least diffuse slowing. Leukoencephalitides caused by non-neurotropic viruses (e.g., measles, rubella) and the postvaccinal state are associated with more severe EEG changes than those encephalitides caused by neurotropic viruses (e.g., mumps, equine encephalomyelitis, St. Louis encephalitis), which affect predominantly the gray matter (71). This is consistent with the experimental observation (44) that polymorphic delta activity is primarily produced by dysfunction of the white matter. During the acute stage of uncomplicated childhood viral infections such as measles, mumps, rubella, chickenpox, and scarlet fever, diffuse EEG slowing can be observed even when there was no clinically overt evidence of nervous system involvement (42). Acute bacterial encephalitides (e.g., those caused by *Mycoplasma pneumonia, L. monocytogenes*, and *Legionella pneumophila*) also show similar nonspecific diffuse slowing, as well as focal abnormalities if focal lesions develop.

Herpes simplex encephalitis (HSE) is frequently associated with characteristic EEG findings consisting of unilateral or bilateral periodic complexes

(PLEDs or BiPLEDs) (130). HSE usually gives rise to intense hemorrhagic necrosis of the inferior and mesial parts of the temporal lobes and the orbital parts of the frontal lobes. The earliest changes in HSE consist of background slow and irregular slow activity appearing in a focal or lateralized fashion with predominance over the involved temporal areas (Fig. 12.13). Focal or lateralized sharp- and/or slow-wave complexes then appear over the temporal regions, and rapidly evolve to periodic patterns occurring every 1–3 seconds (PLEDs or BiPLEDs). Background activity between periodic discharges is usually attenuated (see Fig. 12.7). The periodic patterns tend to develop within several days after the clinical onset, frequently as BiPLEDs occurring synchronously, either in a bilateral time-locked relationship with one another or independently (77). The periodic patterns are generally transient, lasting only 3–4 days, and almost always disappearing in a week regardless of whether there is clinical deterioration or improvement. EEGs in neonates with HSE also show periodic or quasiperiodic complexes, electrical seizures, slowing, and attenuation of background rhythms (91). As already mentioned, PLEDs reflect acute destructive cortical lesions and, therefore, are not pathognomonic for the diagnosis of HSE. However, the presence of this EEG pattern in combination with clinical findings suggesting HSE strongly supports the diagnosis.

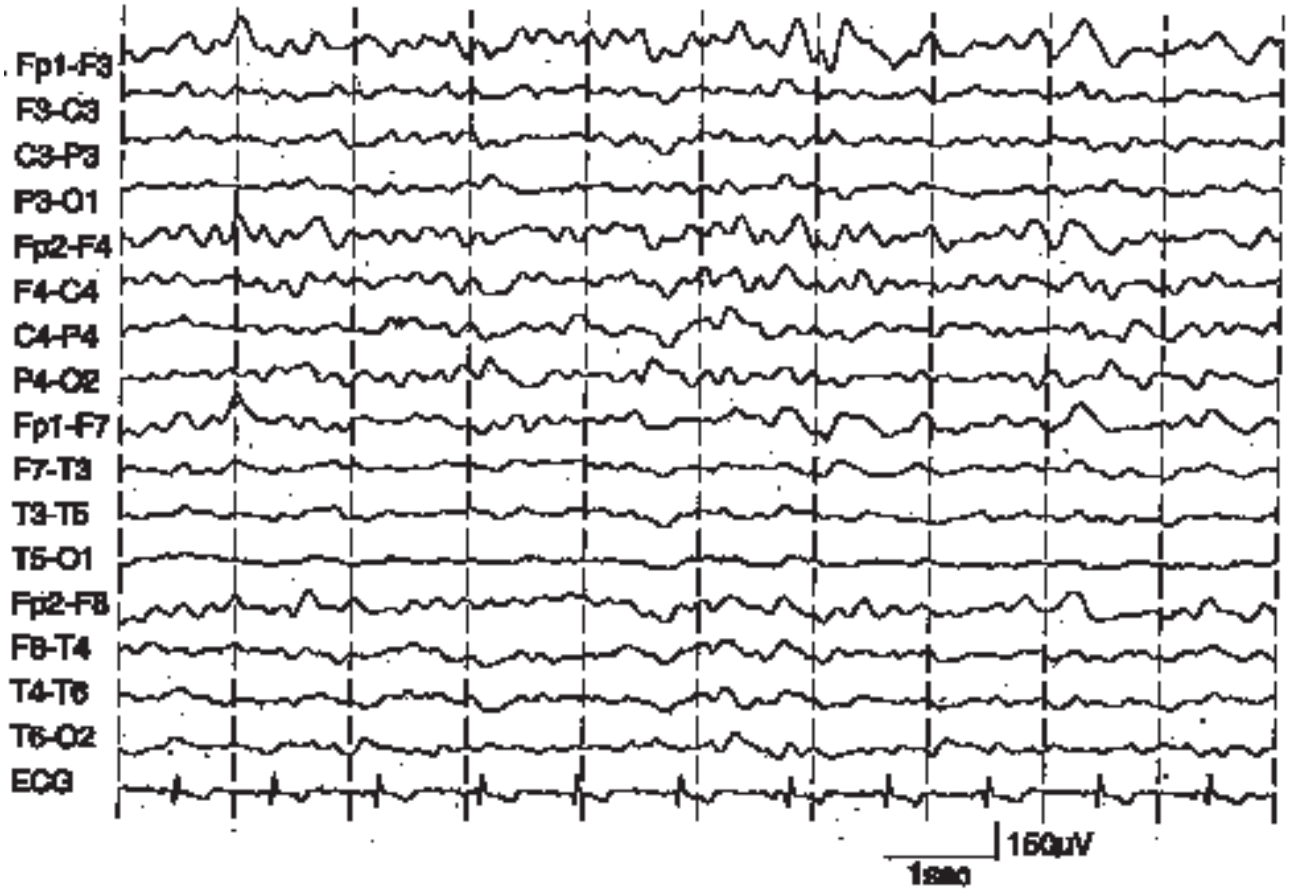

FIG. 12.13. Diffuse continuous slow activity, more on the right, in a 16-year-old boy with dementia and frequent generalized seizures who had herpes simplex encephalitis 1 year ago.

Subacute and Chronic Encephalitis

SSPE is a chronic measles infection that has almost disappeared in countries where routine measles vaccination has been introduced. The EEG pattern in SSPE is one of the most characteristic and specific in EEG (24). The pathology of SSPE involves the cerebral cortex and white matter of both hemispheres and also the brainstem. Clinically, several stages can be identified (62):

Stage I: personality changes and intellectual disturbance
Stage II: progressive intellectual deterioration with convulsions, myoclonus, and ataxia
Stage III: rigidity, hyperactive reflexes
Stage IV: decorticate state

High-voltage (300–1,500 μV) repetitive polyspike- and sharp-and–slow wave complexes of 0.5–2 seconds in duration, recurring every 4–15 seconds, occur in stage I or II. Initially this periodic pattern can be seen with normal background activity, and the complexes recur at irregular intervals (see Fig. 12.5). At this stage, EEG complexes can often be evoked by external stimuli. Later, however, the complexes occur at regular intervals and are no longer influenced by external stimuli (24). These periodic EEG complexes are usually associated with slow myoclonic jerks or dystonic myoclonus. During sleep, the periodic EEG discharges remain, although clinical myoclonus disappears. In the later stages, background activity between the periodic discharges becomes slow, and there is shortening of the intervals between the complexes. In the final stage, background activity is greatly attenuated and periodic discharges disappear (85).

Subacute measles encephalitis usually occurs in patients with defective cellular immunity, such as those with acquired immunodeficiency syndrome (AIDS). Symptoms (seizures, myoclonus, stupor, and coma) occur 1–10 months after measles, and epileptic discharges have been observed. Periodic EEG patterns, like as those with SSPE, have not been reported (40).

Progressive rubella encephalitis is very rare, and may appear as long as 10 years after exposure to rubella or in congenital rubella. Dementia, ataxia, and myoclonic seizures occur. The clinical picture is similar to that of SSPE, but EEG abnormalities and myoclonus are not as prominent as in SSPE (133).

Progressive multifocal leukoencephalopathy, caused by JC virus, is almost always a complication of chronic immunosuppression. It is characterized by widespread demyelinating lesions of the cerebral hemispheres, as well as the brainstem and cerebellum. Diffuse delta activity, most prominent in the posterior head regions, is common; epileptiform discharges with seizures and myoclonus are rare (33).

Transmissible Spongiform Encephalopathies (Prion Diseases)

CJD (sporadic and familial types), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia, and the new variant of CJD are classified as prion diseases transmissible between humans (49,65). Because these diseases do not cause an immune response, they simulate degenerative diseases.

CJD usually occurs in persons after the age of 50 years, and clinically is characterized by progressive dementia, myoclonic jerks, and various focal neurological deficits (e.g., ataxia, aphasia, visual loss, amyotrophy). The disease progresses to akinetic mutism, and at the later stages even the myoclonic jerking subsides. Early in the disease the EEG can be normal or show only mild non-specific slowing. As the disease progresses, typical periodic complexes appear (Fig. 12.14). For the diagnosis of CJD, these periodic complexes have a specificity and sensitivity of 67% and 86%, respectively (123). However, if repeated EEGs are obtained, more than 90% of patients show the characteristic periodic pattern (22). Myoclonic jerks are frequently, but not always, time-locked to the periodic EEG discharges, suggesting that there are both cortical and subcortical generator mechanisms for the myoclonic jerks (116). The periodic EEG pattern may disappear in the terminal phase, when the myoclonus also subsides (see Chapter 13 for further details).

GSS is usually a familial, slowly progressive disorder characterized by cerebellar ataxia, dysarthria, diminished tendon reflexes, and dementia, a phenotype similar to hereditary ataxia. Usually myoclonic jerks are absent and no periodic EEG pattern occurs (36), although a patient with sporadic GSS, confirmed by prion protein gene analysis (Pro102Leu mutation), was reported to show a periodic EEG pattern (60).

Fatal familial insomnia is characterized by progressive insomnia, hypovigilance, attention deficits, dysautonomia (tachycardia, sweating, hypertension), focal motor signs, and cognitive decline. The main pathological changes occur in the thalamus. Patients with fatal familial insomnia cannot generate a normal sleep pattern, and the awake EEG shows diffuse slowing (82,83).

A "new variant" of CJD in humans was reported in 1996 in the United Kingdom. This has been attributed to transmission from diseased cattle with bovine spongiform encephalopathy (mad cow disease). The new variant of CJD differs from sporadic CJD in several ways: (a) patients are young, with a mean age of 29 years; (b) the initial symptoms are often behavioral changes, ataxia, and peripheral sensory disturbances; and (c) the EEG abnormality is not periodic. In this prion disease, the EEG only shows nonspecific diffuse slowing (136,141).

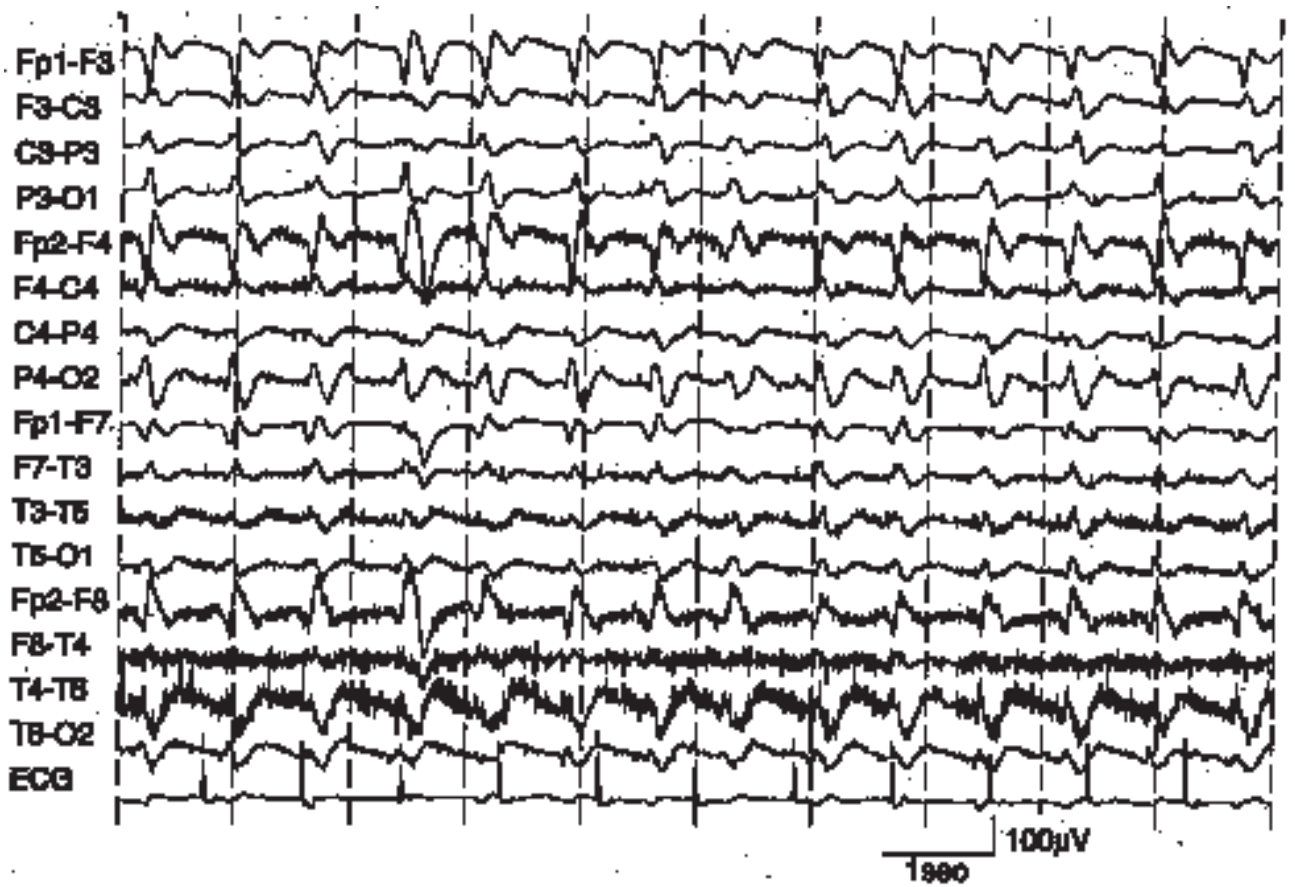

FIG. 12.14. Diffuse periodic pattern clearly dominant in the right hemisphere in a 72-year-old woman with CJD. The periodic discharges have a repetition rate of slightly more than 1 Hz.

AIDS and Human Immunodeficiency Virus Infection

Acute neurological manifestations of human immunodef iciency virus (HIV) infection may take the form of a meningoencephalitis, myelopathy, or neuropathy. Most patients recover from the acute illness, which usually precedes seroconversion. After seroconversion, as immunodef iciency appears and worsens, patients become vulnerable to opportunistic infections causing focal (brain abscess, toxoplasmosis, neurosyphilis, tuberculoma) as well as non-focal (cytomegalovirus, varicella-zoster virus, herpes simplex virus) brain disease, primary central nervous system (CNS) lymphoma, and AIDS dementia complex (subacute chronic HIV encephalitis). Neurolo gical abnormalities occur in one-third of patients with AIDS, although at autopsy, the nervous system is affected in nearly all patients.

EEGs in HIV symptomatic infection and AIDS usually show nonspecific abnormalities; epileptiform discharges are rare (38,48). Epileptic seizures occur in less than 5% of the HIV-infected population at any stage of the disease (76) b ut may affect 10% of more of those with adv anced disease (131a). Quantitative EEG analysis studies also sho w no significant EEG

abnormalities in patients with asymptomatic HIV infection (93,96). There is an isolated report of action myoclonus of cortical origin demonstrated by JLA technique in HIV-positive patients (68). In AIDS dementia complex, low-avoltage slow activity (47) and myoclonic jerks associated with triphasic waves (125) have been reported. Over time, there is further voltage attenuation and de-differentiation of EEG activity (47).

Multiple Sclerosis and Other Autoimmune Diseases

The incidence of EEG abnormalities in multiple sclerosis (MS) varies from 20% to 50%, depending on the location, size, and number of lesions, the duration and stage of the disease, and the rate of progression (71). EEG abnormalities consist most often of diffuse irregular slow activity; some patients also show diffuse rhythmic slowing. Focal EEG abnormalities may correlate with the area of maximal cerebral involvement, but more often, there is little correlation between EEG findings and clinical signs or symptoms (61,71). Epileptiform discharges are rarely observed, consistent with the low incidence of seizures (less than 2%) in MS (41).

In acute disseminated encephalomyelitis (ADEM), convulsions, confusion, stupor, and myoclonus occurs. The EEG in ADEM shows non-specific, diffuse, high-voltage slowing with epileptiform discharges; and focal slow activity can also occur. Spindle coma and alternating patterns may occur in patients who recover (17).

Miller-Fisher syndrome, characterized by acute ophthalmoplegia, ataxia, and areflexia, usually has a good outcome. It is associated with anti-GQ1b Iqg antibodies (94,136a). Non-specific EEG abnormalities (diffuse slow activity) may occur transiently in the acute stage of the disease (9,114). Coma has been reported in one patient (85a).

Systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and polyarteritis nodosa can produce EEG abnormalities resulting from cerebral vasculitis or immune-complex neuronal dysfunction. The EEG is abnormal in 50% of patients with SLE, including those without symptomatic cerebral involvement, and both diffuse and focal slow activity, as well as epileptiform discharges, may occur (52). Seizures are most commonly seen in patients with SLE and with primary granulomatous angiitis of the brain (74).

Celiac Disease

Celiac disease is primarily a gastrointestinal disease with gluten-sensitive enteropathy and malabsorption. In about 10% of cases, neurological symptoms appear several years after the onset of enteropathy in the absence of vitamin E deficiency. Neurological manifestations include peripheral neuropathy, myelopathy, encephalopathy, cerebellar ataxia, progressive multifocal leukoencephalopathy, cerebral atrophy, and dementia. Seizures and polymyoclonus of cortical origin may occur (15), and, in these patients, the EEG usually shows multifocal epileptiform discharges (72). From a clinical standpoint, these cases may be regarded as a form of progressive myoclonic epilepsy or progressive myoclonic ataxia.

HYPERTENSIVE ENCEPHALOPATHY

Encephalopathy can complicate hypertension of any cause, such as chronic renal disease, acute glomerulonephritis, pheochromocytoma, and Cushing's disease but it is most often caused by rapid worsening of essential hypertension. Eclampsia is thought by some to share pathophysiological mechanisms similar to those of hypertensive encephalopathy. The symptoms, caused by rapid development of malignant hypertension, consist of headache, nausea, vomiting, visual disturbances, convulsions, and, in advanced stages, stupor and coma. MRI shows increased T2-weighted signal abnormalities in the white matter, usually in the posterior hemispheres. This is not due to infarction but is the result of fluid accumulation with little or no mass effect. Scattered, punctate lesions occur in a watershed distribution. This clinical picture has been labeled as reversible posterior leukoencephalopathy syndrome (53), because the MRI changes disappear with clinical recovery. Focal occipital seizures may be the main symptomatology in mild cases (6). The EEG shows diffuse slow activity with or without focal abnormalities in the occipital areas. Patients with profound slow activity in the EEG tend to have more grand mal seizures and more prolonged disturbance in consciousness than those with less amount of slow activity (139).

NEURODEGENERATIVE AND HEREDITARY DISEASES

Many progressive neurological diseases once thought to be neurodegenerative in nature are now known to be genetically determined. The specific diagnosis in a given condition is made by testing for an enzyme defect, a gene mutation or abnormal protein product, a biochemical marker, or a pathognomonic pathological abnormality. In diseases affecting primarily white matter, such as leukodystrophies, the most prominent clinical and EEG features are due to the dysfunction and interruption of white matter tracts (corticospinal, corticobulbar, cerebellar peduncle, sensory, medial longitudinal fasciculi, and visual pathways). Seizures, myoclonus, and epileptiform discharges are less frequently initial manifestations, whereas

diffuse polymorphic and rhythmic slow activity tends to be prominent (44). In diseases affecting mainly cerebral gray matter (poliodystrophies), as in the progressive myoclonic epilepsy (PME) syndromes, seizures, myoclonus, chorea, dystonia, ataxia, and tremor occur frequentl y. In these cases, the EEG is characterized by epileptiform discharges (hypsarrhythmia in infants or children) in addition to dif fuse irregular slow activity. However, in advanced stages, white and gray matter diseases are difficult to differentiate, and both evolve to an undifferentiated, attenuated pattern.

PME Syndromes

PME syndromes are familial disorders characterized by cortical myoclonus (mainly action and intention types), epileptic seizures (generalized tonic–clonic, myoclonic, or absence seizures), and pro gressive neurological deterioration (usually dementia and ataxia) (11,12,14,112,113). Specif ic disorders manifesting as PME syndrome are listed in Table 12.3. Common EEG findings consist of (a) background slowing with diffuse IS activity; (b) gener-

TABLE 12.3. *Age of onset, mode of inheritance, and causes of progressive myoclonic epilepsy syndromes*

	Age at onset (yr)	Mode of inheritance[c]	Diagnosis or causes
Common			
Unverricht-Lundborg disease	10–20	AR	Gene for cystatin B
Lafora body disease	10–20	AR	Mutation of *EPM2A*
Neuronal ceroid lipofuscinoses		AR	
Late infantile classical (Jansky-Bielschowsky disease)	1.5–4		*CLN2* gene (lysosomal pepstatin-sensitive protease)
Late infantile variant	2–7		*CLN5, -6, -7* genes
Juvenile (Spielmeyer-Vogt-Sjögren disease)	5–10		*CLN3* gene
Progressive epilepsy with mental retardation	5–10		*CLN8* gene
Adult (Kufs' disease)	10–40	(AD also)	*CLN4* gene
Sialidosis	7–20	AR	
Type I (cherry-red spot myoclonus syndrome)			α-*N*-Acetylneuraminidase deficiency
Type II (galactosialidosis)[a]			Neuraminidase & β-galactosidase deficiency
Myoclonic epilepsy with ragged red fibers (MERRF)	10–40	Sporadic or familial	Point mutation of mitochondrial DNA
Rare			
G_{M2} gangliosidosis		AR	β-*N*-Acetylhexosaminidase subunits
Tay-Sachs disease	6 mo		
Juvenile	1–4		
Adult variant	15–20		
Gaucher's disease (noninfantile form)	10–40	AR	β-Glucocerebrosidase
Juvenile neuroaxonal dystrophy	9–10	AR	Axon spheroid in peripheral and central nerves
Action myoclonus-renal failure syndrome[b]	19	AR	
Dentatorubral-pallidoluysian atrophy[a]	5–60	AD	DNA triplet (CAG) repeat expansion
Familial cortical myoclonic tremor[a]	30–50	AD	
Celiac disease		nh	Gluten-sensitive enteropathy

[a]Mainly reported in Japan.
[b]Mainly reported in Canada.
[c]AD, autosomal dominant; AR, autosomal recessive; nh, nonhereditary.
Modified from Berkovic et al. (12), Shibasaki (112), and Bate and Cardiner (7).

alized polyspikes and spike-wave complexes and focal (particularly occipital), at times multifocal, independent epileptiform discharges; (c) photoparoxysmal responses (Fig. 12.15); and (d) enhanced cortical components of short latency evoked potentials such as "giant" somatosensory evoked potentials (SEPs) (Fig. 12.16). Action or intention myoclonus is often associated with clear epileptiform discharges in the EEG, and jerk-locked back-averaging techniques consistently reveal spikes over the sensorimotor area in the contralateral hemisphere. These precede the jerk by 15–20 milliseconds, even in patients who do not show spikes in a single EEG record. This finding supports a cortical origin for the myoclonus (115). Patients with PME frequently have enhanced long-loop reflexes with giant SEPs, also suggesting a cortical "reflex" myoclonus (117) (Fig. 12.16).

Unverricht-Lundborg disease (ULD), common in Finland, is also found sporadically worldwide. In ULD, myoclonus is very severe and generalized

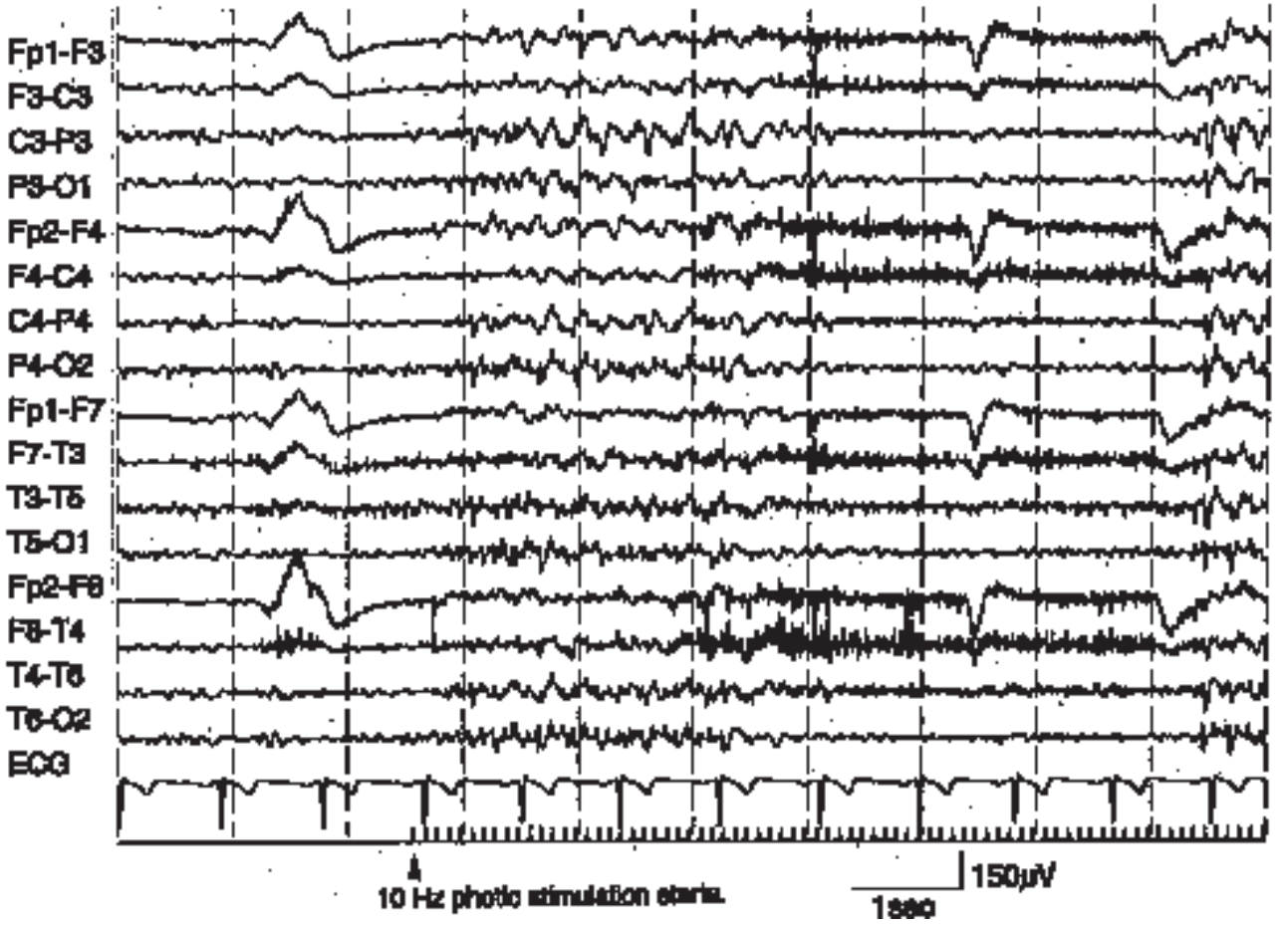

FIG. 12.15. High-amplitude, widespread photoparoxysmal responses in a 38-year-old man with familial cortical myoclonic tremor.

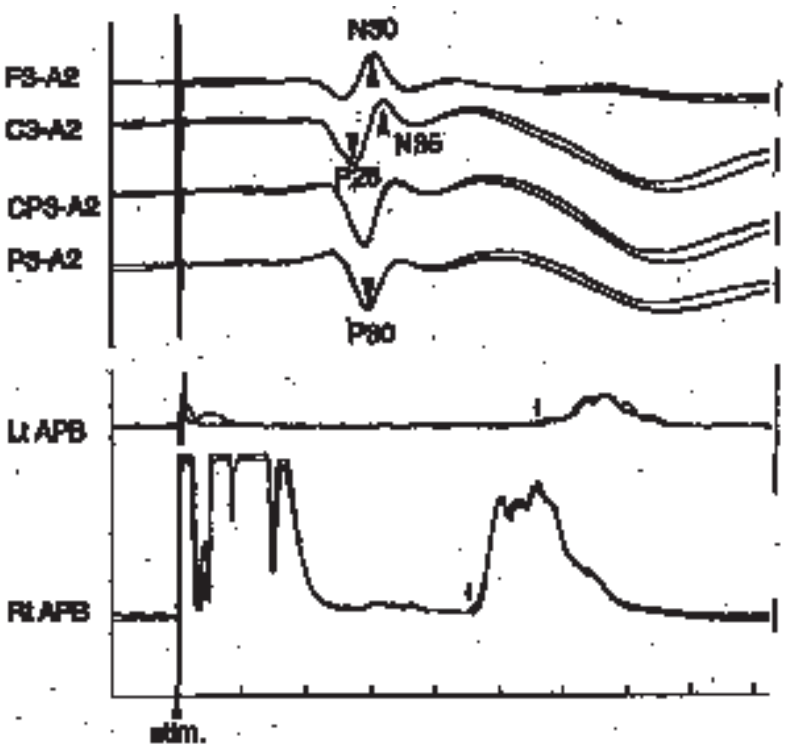

FIG. 12.16. Giant SEPs (P25, N30, P30, N35) (the peaks shown by *large arrows*) and enhanced C reflexes (the onsets shown by *small arrows*) in response to electric stimulation of the right median nerve at the wrist in a 74-year-old woman with familial cortical myoclonic tremor. *APB*, abductor pollicis brevis muscle. Vertical bars correspond to 20 μV, and one horizontal division corresponds to 10 milliseconds. (Modified from Terada K, Ikeda A, Mima T, et al. Familial cortical myoclonic tremor as a unique form of cortical reflex myoclonus. *Mov Disord* 1997;12:370–377.)

seizures may be difficult to control, but progression of ataxia and dementia is relatively mild. The EEG shows progressive background slow activity, generalized spike-wave complexes, generalized polyspike-wave complexes, and focal occipital spikes.

Lafora disease, which used to be reported mainly in Southern Europe, is now found worldwide. Partial seizures, particularly of occipital origin, rather mild myoclonus, and relatively severe dementia are characteristic clinical features. The EEG findings are similar to the ones described in ULD. Focal spikes in Lafora disease are also particularly frequent in the occipital areas (128) (Fig. 12.17). Spike-wave complexes are not enhanced during sleep in Lafora disease (14).

Neuronal ceroid lipofuscinoses occur worldwide and are divided into at least five forms; all are characterized by the accumulation of abnormal lipopigment in the lysosomes. The late infantile type of lipofuscinosis (Jansky-Bielschowsky disease; *CLN2* gene) is characterized by seizures, ataxia, psychomotor regression, visual failure, and progressive spasticity. EEG photosensitivity is characteristic, and visual evoked potentials (VEPs) are of high voltage (135). A late infantile variant of lipofuscinosis is similar to the classical infantile form, except that the onset is later and progression occurs earlier. Abnormally large VEPs are also similar, but tend to decrease in amplitude as the disease progresses (109). In juvenile lipofuscinosis (Spielmeyer-Vogt-Sjögren disease; *CLN3* gene), visual failure occurs early, followed by dementia and extrapyramidal signs. Seizures are a relatively minor symptom. Photosensitivity is not present, and VEPs are of low voltage (100,135). Adult lipofuscinosis (Kufs' disease; *CLN4* gene) is very rare, and characterized clinically by dementia and extrapyramidal and cerebellar signs. Blindness does not occur. EEG shows polyspike-wave complexes with marked photosensitivity (13).

Sialidosis is divided into type I (occurring mainly in Italy) and type II (occurring mainly in Japan). Type I sialidosis (cherry-red spot myoclonus syndrome) is characterized by severe myoclonus, gradual visual loss, ataxia, and typical retinal cherry-red spots. There is no dementia (105). Type II sialidosis (galactosialidosis) includes, in addition to the clinical features characteristic of type I sialidosis, gargoyle-like facial features, hearing loss, vertebral dysplasia, corneal opacity, and limited intellect (129). In both type I and type II sialidosis, EEG background activity shows low-amplitude fast activity and trains of vertex-positive, 10- to 20-Hz, small spikes associated with myoclonic EMG discharges. Generalized spike-wave complexes are not observed (30).

Myoclonic epilepsy with ragged red fibers (MERRF) is probably the most common form of PME today. It is characterized by myoclonus and myopathy with ragged red fibers on skeletal muscle biopsy. Generalized tonic–clonic seizures, dementia, and ataxia are also common. Less often, there is neuropathy, deafness, and optic atrophy. The EEG shows progressive background slowing, generalized spike-wave or polyspike-wave complexes, and sporadic focal spikes. VEPs are usually normal (121).

In non-infantile Gaucher's disease, apraxia of horizontal eye movements and splenomegaly are present in addition to other clinical features of PME.

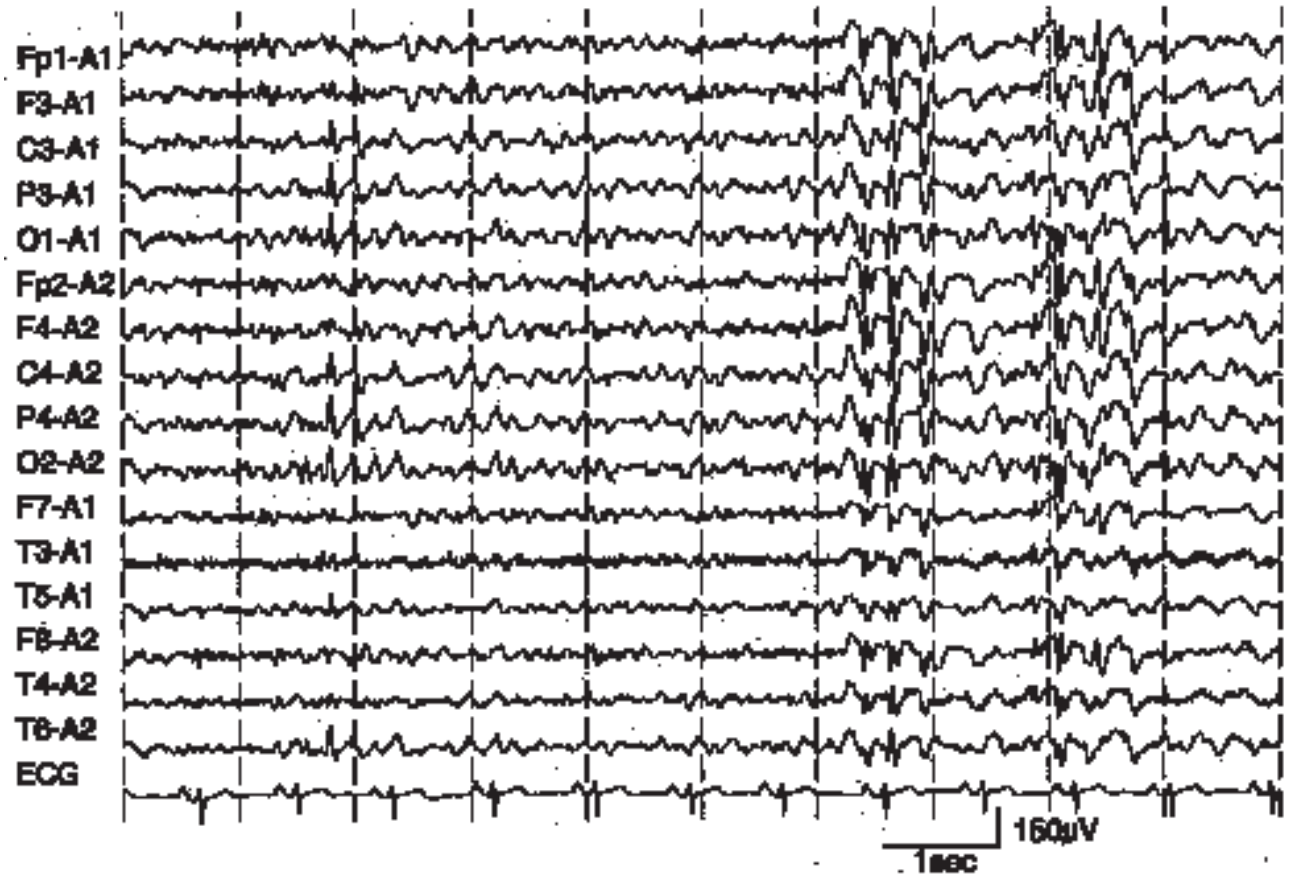

FIG. 12.17. Generalized spike-and-wave complexes with regional spike-and-wave complexes maximal either anteriorly or posteriorly in a 19-year-old man with Lafora disease.

The EEG shows generalized spike-wave complexes and bursts of 6- to 9-Hz spikes or sharp waves over the central and posterior head regions (95).

Juvenile neuroaxonal dystrophy manifests as chorea and peripheral neuropathy in addition to the clinical features of PME. The EEG shows generalized polyspikes and polyspike-wave discharges. Sporadic and induced occipital spikes are often seen (27).

Action myoclonus–renal failure syndrome is characterized by tremor, action myoclonus, generalized seizures, and proteinuria associated with progressive renal failure; dementia does not occur (3). The EEG shows the typical features of PME with marked photosensitivity (87). In this syndrome, CNS dysfunction progresses even if renal failure is controlled by dialysis or transplantation.

Dentatorubral-pallidoluysian atrophy (DRPLA), mainly reported in Japan, has a variety of clinical phenotypes (PME, ataxic choreoathetosis, choreo-dementia). The EEG in PME-type DRPLA shows slowing of background activity, frequent generalized polyspike-wave complexes, and multifocal spikes. Photosensitivity is prominent. However, the SEP amplitude is always relatively small in spite of the giant VEPs, frequent myoclonus, and

generalized seizures. The photosensitivity is most likely due to a severe disturbance in the afferent pathways above the lemniscus medialis (90).

Familial cortical myoclonic tremor (124), called also cortical tremor (59) or benign adult familial myoclonic epilepsy (140), is a frequent cause of PME in adults in Japan, where it has been reported exclusively. It is characterized by rhythmic postural and action myoclonus involving distal limbs (thus resembling essential tremor), absence of ataxia and dementia, rare generalized tonic–clonic seizures, and no or only minimal progression. The EEG usually shows normal background activity with only occasional epileptiform discharges. Photosensitivity is seen in some patients (see Fig. 12.15). In addition, giant SEPs and, by back-averaging, spikes preceding the tremor-like EMG discharges can be observed (see Fig. 12.16). Familial cortical myoclonic tremor should be differentiated from familial essential myoclonus, which has similar clinical characteristics except for the absence of epileptic seizures and no evidence of cortical hyperexcitability either on EEG or SEPs (104).

Leukodystrophies of Adult Onset

Leukodystrophies of adult onset include metachromatic leukodystrophy (MLD) (an autosomal recessive, sphingolipid storage disease caused by arylsulfatase deficiency, resulting in sulfatide accumulation mainly in the white matter); globoid body leukodystrophy (Krabbe's disease) (an autosomal recessive disease caused by galactocerebrosidase deficiency, resulting in the accumulation of galactocerebroside, particularly in the white matter); and adrenoleukodystrophy (ALD) (X-linked autosomal recessive disease caused by impaired peroxisomal oxidation of very-long-chain fatty acids, leading to their accumulation in the brain and adrenal glands). Krabbe's disease usually occurs in infancy, and MLD and ALD are seen most frequently in childhood. However, all three leukodystrophies can also occur in adults. Because these diseases affect white matter primarily, the most prominent clinical signs and symptoms are due to the interruption of white matter tracts (corticospinal, corticobulbar, cerebellar peduncle, sensory, medial longitudinal fasciculi, and visual pathways). Epileptic seizures and myoclonus are infrequent. The EEG usually shows high-amplitude, continuous, polymorphic slow waves (44), which in ALD are most prominent posteriorly (8), in good agreement with the predominant involvement of the white matter in the posterior hemispheres shown by MRI and the frequent occurrence of cortical blindness. Epileptiform discharges are infrequent (Fig. 12.18).

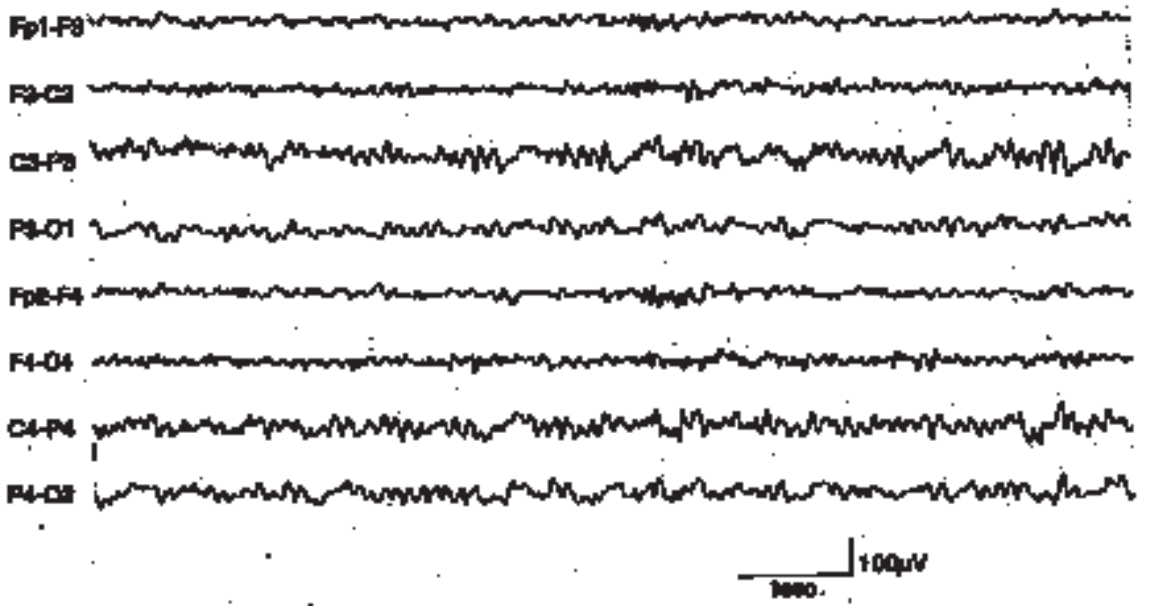

FIG. 12.18. Diffuse continuous slow activity most prominent in the posterior hemispheres in a 28-year-old man with diffuse leukodystrophy of unknown etiology.

Other Inherited Metabolic Diseases of Adult Onset

Mucopolysaccharidoses are mainly autosomal recessive diseases in which acid mucopolysaccharides (glycosaminoglycans) are degraded and accumulate within lysosomes in neurons (brain, spinal cord), connective tissues, heart, viscera, and bone because of enzyme defects. Obstructive hydrocephalus secondary to skeletal deformity and thickening of the base of the skull is a frequent complication. The EEG shows non-specific slowing consistent with the degree of impaired cerebral function.

Niemann-Pick disease (autosomal recessive disease with increased sphingomyelin due to sphingomyelinase deficiency) can occur in adolescents, and cataplexy has been described in a variant of this disease(66).

MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) is a mitochondrial disease characterized by metabolic strokes, encephalopathy (seizures, dementia), mitochondrial dysfunction with lactic acidosis, and ragged red fibers. Myopathic weakness, exercise intolerance, myoclonus, ataxia, short stature, and hearing loss are also common. The disease can be due to several types of mitochondrial DNA point mutations. Because of the metabolic strokes, the EEG most often shows focal rather than diffuse abnormalities. Focal and generalized epileptiform discharges may occur in association with, respectively, focal and generalized seizures (54). Kojewnikoff's syndrome (epilepsia partialis continua) may also be seen in patients with MELAS.

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Chapter 13

Organic Brain Syndromes and Dementias

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EEG Changes with Normal Aging
Delirium (Acute Confusional State)
Dementia
Alzheimer's Disease
Pick's Disease
Huntington's Disease
Parkinson's Disease
Progressive Supranuclear Palsy
Creutzfeldt-Jakob Disease
Acquired Immunodeficiency Syndrome
Cerebrovascular Disease
Dementia Resulting from Other Causes
Pseudodementia
Amnesic Syndromes
Transient Global Amnesia
Korsakoff's Syndrome
Conclusions
References

There has been a change in the classif ication of organic disorders characterized by cognitive or memory deficits as employed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) of the American Psychiatric Association (4). The previous edition (DSM-III) distinguished two major disorders: or ganic brain syndrome and or ganic mental disorders. The former term referred to the disorder without reference to etiolo gy (e.g., delirium, dementia, etc.), w hereas the latter designated disorder with kno wn or presumed etiolo gy (Alzheimer's disease [AD], multi-inf arct dementia [MID], etc.). In the DSM-IV, the term *organic mental disorder* has been eliminated because it incor rectly implies that "nonor ganic" mental disorders do not have a biological basis. The disorders with significant deficits in cognition or memory compared to the previous level of functioning are now placed into three subgroups: delirium, dementia, and amnesic or other cognitive disorders. *Organic brain syndrome* is a term commonly used by the medical community to refer collectively to these three subg roups. Delirium or acute confusional state refers to an acute but reversible disturbance of fluctuating consciousness. Dementia is characterized by global impairment of cognitive functions that is more or less persistent. Amnesic disorders comprise conditions with selective memory impairment in the absence of other co gnitive deficits.

Because electroencephalography (EEG) measures cortical activity, it can help in diagnosis and prognosis of organic brain syndromes. Although EEG changes are usually nonspecific (e.g., generalized slowing of background activity), EEG can play an important discriminative role in several circumstances:

1. EEG can aler t physicians to une xpected toxic-metabolic causes for changes in mental state displaying distinctive EEG patterns (e.g., tripha-

sic waves in hepatic or renal encephalopathy, or fast rhythms superimposed on slow activity in sedative-hypnotic drug ingestion).
2. EEG is indispensable in diagnosing nonconvulsive status epilepticus producing acute confusional states.
3. By demonstrating periodic discharges, EEG is often the first test to suggest certain encephalitides, such as Creutzfeldt-Jakob disease (CJD).

Selected reviews that discuss EEG in diffuse encephalopathies include those by Markand (113), Brenner (15), and Rosen (169).

EEG CHANGES WITH NORMAL AGING

Because organic brain syndromes, particularly dementias, are common in older age groups, it is essential to discuss EEG in normal elderly subjects. An important feature of the EEG is the frequency of the alpha rhythm, which in adults ranges from 8 to 13 Hz. During the seventh decade and particularly during the eighth, normal subjects show a shift to slower frequencies posteriorly compared to younger adults (84). In subsequent studies (7,93,205), the mean alpha frequency approached 10 Hz in carefully selected normal elderly subjects. A number of earlier studies, which reported slower alpha frequencies, included a variety of different subject groups, ranging from normal volunteers living in the community to institutionalized subjects, some with significant neurological and/or medical disease (212). This variation in selection criteria yielded discrepant findings of dominant alpha frequencies in elderly subjects (93). Arenas et al. (7) found that, in 42 healthy, elderly subjects who had a well-developed alpha rhythm, only 6 had frequencies less than 9.0 Hz and in no subject was the frequency less than 8.0 Hz. Pedley and Miller (148) considered an alpha frequency, while alert, of less than 8.5 Hz as abnormal. Katz and Horowitz (93) considered a dominant frequency of less than 8.0 Hz as abnormal in elderly subjects (up to 80 years of age), and this is probably true in the "old old" (> 80 years) as well (83,143).

Oken and Kaye (141) found that the posterior peak frequency (PF), determined by computerized EEG frequency analysis (which in almost all cases was within 0.5 Hz of the PF determined visually), was maintained above 8 Hz in all subjects under age 84. However, it was between 7 and 8 Hz in 5 of 22 subjects over 84. All subjects were extremely healthy and cognitively intact. Soininen and Riekkinen (185) studied 52 subjects ages 20–91 years and found that aging was not associated with slowing. Relative power of delta, theta, alpha, and beta activity did not differ across age. In addition, Brenner et al. (19) in a study of older individuals found that, although the parasagittal mean frequency decreased with age, changes were not significant when subjects were grouped by decade (ages 60–87 years).

Another finding in the elderly, long recognized (26), is that EEGs of normal elderly subjects often contain focal slowing consisting of delta and theta activity. This focal slowing in normal subjects is limited to the temporal regions and is present considerably more often over the left side (Fig. 13.1). There is enormous variation in the way electroencephalographers evaluate such activity in this age group. In addition, Torres et al. (205) reported that 52% of EEGs of asymptomatic healthy elderly individuals would be called abnormal if judged on the basis of standards usually applied to young adults. Thus there is a need to modify these standards when interpreting EEGs of the aged.

In a study of 50 carefully selected healthy elderly (60 years or greater) subjects, without evidence of neurological or psychiatric disorders, Arenas et al. (7) found that intermittent focal slowing in the temporal area during wakefulness occurred in 36% of subjects. This finding was similar to that of other studies (26–28,84). Like other investigators, Arenas et al. (7) found the slowing to be predominantly left sided (72%). The explanation for this left-sided dominance remains unclear. As regards the amount of slow (delta-theta) activity, Arenas et al. (7), found that the percentage of recording time of such activity ranged from 0.2 to 10.2; however, excluding one subject, slow activity did not exceed 1.8%. Similar results have been reported in a study of healthy septuagenarians by Katz and Horowitz (93), who found that slowing, predominantly in the delta (< 4 Hz) frequency, did not occupy more than 0.6% of the total recording time in any subject. The following is a summary of the characteristics of "benign temporal transients of the elderly" (95):

They occur chiefly at ages greater than 60 years.
They are confined to the temporal regions and, within these regions, are maximal anteriorly.
They occur more frequently on the left side.
They do not disrupt background activity and are not associated with an abnormal asymmetry of the alpha rhythm.
Their morphology is usually rounded but occasionally irregular.
Their voltage is usually greater than 60–70 μV.
They are attenuated by mental alerting and eye opening, and their prevalence is increased by drowsiness and hyperventilation.
They occur sporadically as single waves or in pairs, not in longer rhythmic trains.

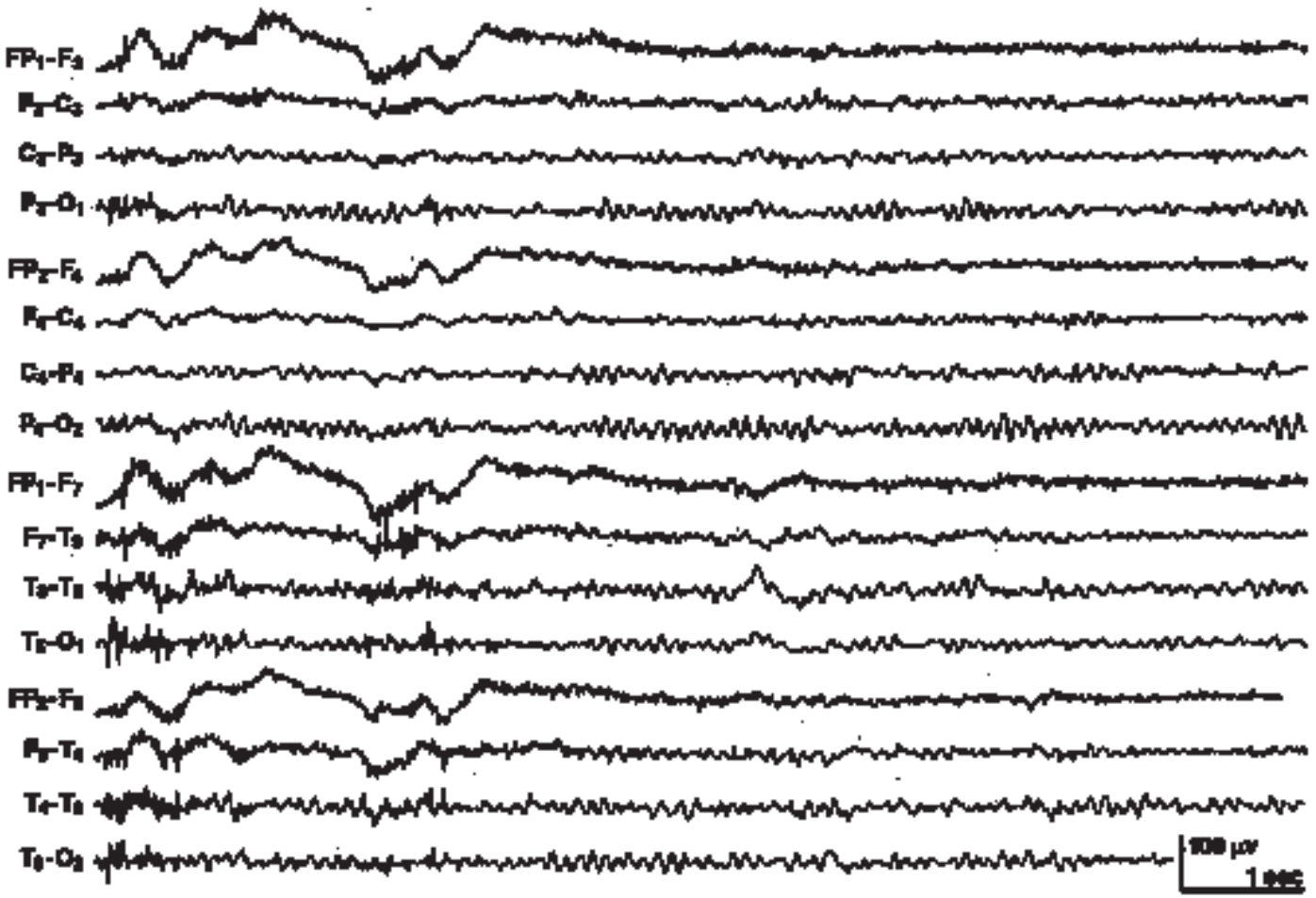

FIG. 13.1. EEG of a 78-year-old person showing intermittent slow transients in the left temporal region.

They are present for only a very small proportion (up to > 1%) of the recording time.

Temporal theta activity is also increased in the elderly and usually occupies a higher percentage of recording time than does delta activity (7,148). Pedley and Miller (148) allowed 10%–15% before considering it abnormal. Arenas et al. (7) found approximately 2%, except for one subject with approximately 10%.

The clinical significance of mild temporal slowing is uncertain, and most studies have not shown a correlation between these focal abnormalities and neurological deficits (139–141). However, one study reported that a subgroup of normal elderly subjects whose EEGs showed left temporal slowing

performed poorly on a fluency test compared to those normal elderly subjects without temporal slowing (208). The etiology of the slowing is uncertain, although vascular factors have often been invoked. Oken and Kaye (141) found intermittent temporal slowing in 17 (52%) of 33 subjects over age 65 years. Its presence was related to the presence of white matter hyperintensities on magnetic resonance imaging (MRI) but not to blood pressure or cognitive function.

State-related changes are important in the interpretation of EEGs in any age group. However, there are some findings in the elderly that are noteworthy. Aside from the slowing of the dominant rhythm (seen in all ages during drowsiness), as well as the increase of temporal slowing that accompanies drowsiness and is seen particularly in the aged, the elderly also have bursts of generalized rhythmic delta activity, maximal anteriorly, during drowsiness (Fig. 13.2). Katz and Horowitz (94) termed this pattern *sleep*

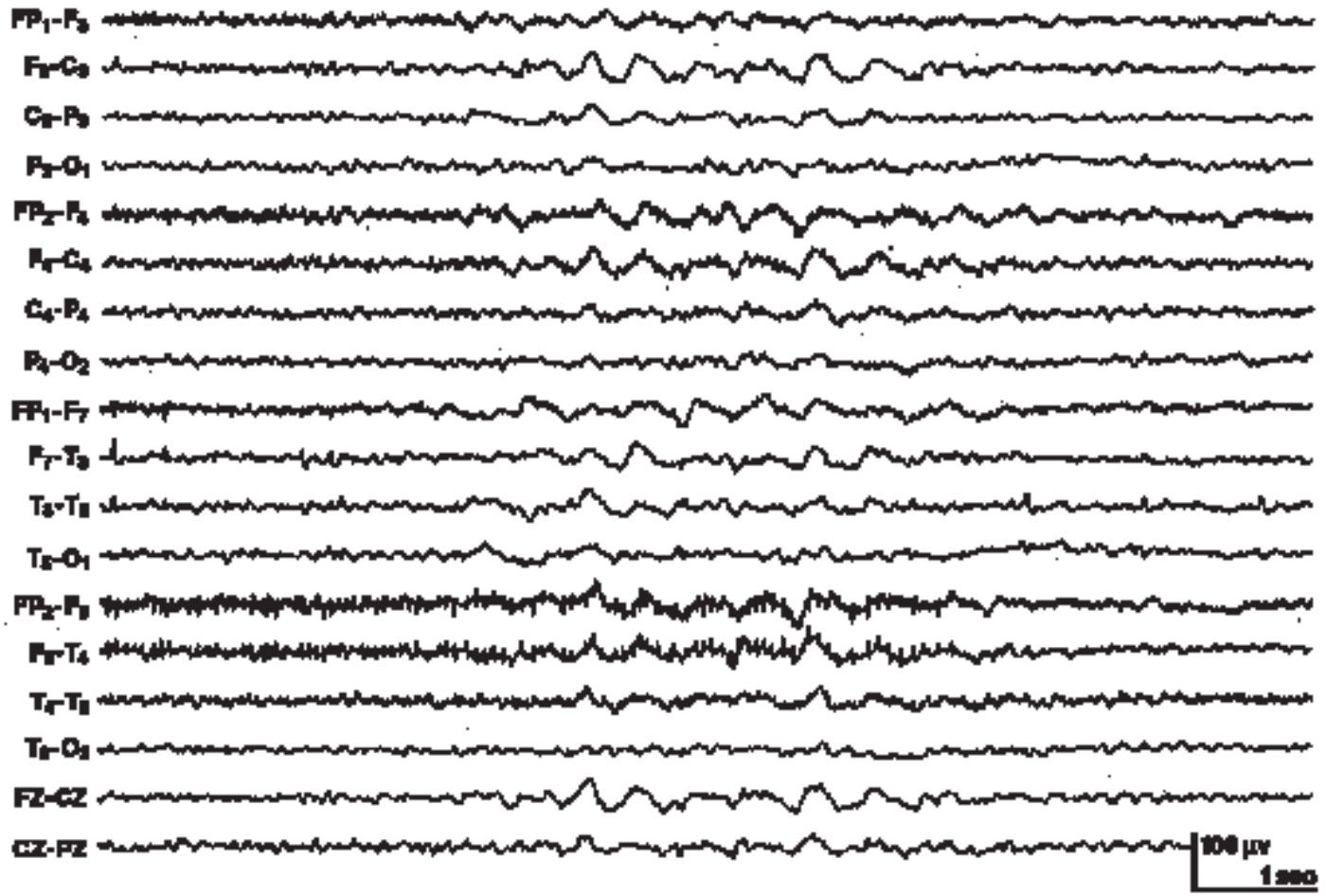

FIG. 13.2. EEG of a 66-year-old man showing frontal intermittent rhythmic delta activity at sleep onset, a normal finding in elderly subjects.

onset–FIRDA (frontal intermittent rhythmic delta activity) to help distinguish it from FIRDA that is abnormal and not limited only to drowsiness. FIRDA during wakefulness is present in a wide variety of diffuse disturbances, most often toxic-metabolic encephalopathies (172). Thus, in the interpretation of frontal delta activity on the EEG in the elderly, one has to consider whether this pattern occurs only during drowsiness and is normal, or is clearly present during wakefulness and is abnormal. Other clues to detect drowsiness include a decrease in frequency of the alpha rhythm, appearance of slow lateral eye movements, decrease in myogenic artifact, and clinical appearance of the subject. In addition, the bursts need to be distinguished from noncerebral activity such as artifacts related to vertical eye movement or tongue movement (glossokinetic potential).

DELIRIUM (ACUTE CONFUSIONAL STATE)

"Delirium" in the DSM-IV refers to an acute but transient development of altered consciousness that tends to fluctuate during the course of the day, accompanied by difficulty in sustaining/shifting attention, and one or more evidences of abnormal behavior, such as perceptual disturbance, impaired memory, incoherent speech, altered psychomotor activity (agitation or lethargy), and disturbed sleep–wake cycle. Neurologists often distinguish acute confusional state from delirium, using the former term in a generic manner and restricting the term *delirium* to a more florid confusional state with psychomotor hyperactivity (agitation, restlessness, combativeness). This difference is probably unwarranted because psychomotor activity can shift from one extreme to the other over the course of a day.

Early studies by Engel and Romano (45,168) have demonstrated that changes in EEGs paralleled degree of behavioral impairment. In early stages, slowing of alpha rhythms appeared, succeeded by medium- to high-voltage generalized slow activity in the theta-delta range. Resolution of delirium was reflected by reversal of these changes, although (particularly in the elderly) resolution lagged behind behavioral recovery.

Obrecht et al. (137) reported on the value of EEG in 95 patients with acute confusional state; 83 had abnormal EEGs, 52 with marked and 31 with mild disturbance of the background activity. Patients who had intracranial pathology often showed asymmetries of delta activity and paroxysmal discharges. Quantitative EEG (qEEG) was performed in 51 elderly delirious patients and compared to that of 19 controls in a study by Koponen et al. (96). Delirious patients showed significant reduction of alpha percentage, increased theta-delta activity, and slowing of the PF and mean frequency. The reduction in the alpha percentage and various ratio parameters correlated significantly with score on the Mini-Mental State Examination, whereas delta percentage and mean frequency correlated with the lengths of delirium and hospitalization. Similar spectral abnormalities have been reported in elderly delirious patients by Jacobson et al. (85). The paper by Brenner (15) provides a review of the utility of the EEG in delirium in the elderly.

Although excessive slowing in the theta-delta frequency and decreased to absent alpha rhythm constitute major EEG findings in the acute confusional state, low-voltage fast (beta frequency) activity may dominate the EEG in some delirious patients (159). These patients have usually been hyperactive and agitated, with apparently heightened levels of arousal (delirium tremens) often marked by fear and anxiety. Such EEGs have been most often described in patients withdrawing from sedative drugs such as alcohol. In such cases, the EEG probably cannot be labeled abnormal during delirium without establishing a significant change through serial EEG studies, because approximately 10% of normal adults may show low-amplitude tracings.

Spehr and Stemmler (186) used spectral power density analysis and Hjorth's time-domain descriptors to study 48 patients with chronic alcoholism within 2 days after cessation of delirium tremens (54%) or impending delirium (34%) and 18 days later after clinical recovery. In the acute phase after florid delirium, EEGs showed prominent beta activity and sparse amounts of relatively normal-frequency alpha rhythm. A second group showed persistent, rather slow delta activity and little beta or alpha activity. This group drank twice the amount of alcohol and had significant electrolyte disturbances, and perhaps were medically more sick.

DEMENTIA

The hallmark of dementia is global impairment of cognitive function without alteration of consciousness. Major clinical features are memory impairment, poor judgment, personality change, decreased capacity for abstraction, aphasia, agnosia, and apraxia, which lead to social and occupational disability. In the past two decades, some neurologists have attempted to distinguish between cortical and subcortical dementia. Patients with progressive supranuclear palsy (PSP), Huntington's disease, and parkinsonism were said to have "subcortical" dementia with impaired memory and learning associated with slow intellectual function, depression, and apathy but without impaired language, perception, or praxis, the latter three symptoms

putatively characterizing "cortical" dementia. The concept of subcortical dementia was further expanded to include Wilson's disease, normal-pressure hydrocephalus (NPH), and acquired immunodeficiency syndrome (AIDS) dementia. A clamorous debate has ensued regarding the validity of this subdivision. Whitehouse (215) has critically reviewed the problem and has found "little support for this classification system, although adequate systematic studies have not been performed."

The separation of dementias into subcortical and cortical types has no firm basis on either clinical or pathological grounds. The neuropathology of AD—a prototype of cortical dementia—shows subcortical involvement, and the so-called subcortical dementias have significant neuronal degeneration in the cerebral cortex. Paulsen et al. (147) demonstrated distinctive cognitive profiles in neuropsychological tests in cortical (AD) and subcortical (Huntington's disease) dementias at all levels of dementia severity. However, the clinical and pathological overlap makes the distinction between cortical and subcortical dementias less relevant.

There are numerous inadequacies in earlier studies attempting to correlate EEG changes and behavioral changes in dementia. While making obeisance to the maxim that only neuropathological examination can confirm the diagnosis of AD, most early studies (61,62,101,106,138) did not address accuracy of diagnosis. Earlier epidemiological studies of clinically diagnosed AD documented an agreement between clinical and pathological diagnosis in only 55%–70% of patients (166,195), although the accuracy of clinical diagnosis of AD has improved to 75%–100%, according to most recent reports (119,211). Also, lack of uniform psychometric testing procedures makes comparison across different studies impossible. Lack of behavioral measures of severity and rate of progression have rendered most studies a grab bag of patients having various degrees of dementia progressing at varying rates. Some well-conceived prospective studies have addressed these problems (34,35,149).

Another problem encountered in EEG investigation of dementia has been lack of an appropriate control group or the use of an ill-defined one. Criteria for what constitutes an appropriate control group for dementia have varied among studies, with relevant subject variables such as age, sex, race, and socioeconomic status all being important in defining the comparative group.

In addition to this morass of methodological problems, EEG studies have been plagued by a lack of uniformity in describing and categorizing EEG changes. Some studies lack clear descriptions of EEG criteria (183); other studies have relied on qualitative visual evaluation and used broad categories such as (a) normal, (b) excessive beta activity, (c) predominant theta activity, or (d) predominant delta activity (164). One study reporting on patients with AD, Pick's disease, and MID did not distinguish between focal and generalized slowing (89).

Finally, in analyzing the EEGs of patients with dementia, one must consider age-specific changes that occur in healthy elderly persons (*vide supra*). Quantitative EEG studies (35,57,149) have shown that changes with age in a healthy population are distinct from those seen in patients with dementia associated with AD. With these extensive caveats in mind, we now review EEGs in various types of dementia.

Alzheimer's Disease

Epidemiological studies around the world suggest that AD occurs in about 2%–6% of people age 65 years or older (166). Autopsy studies of dementia at all ages have found that 50%–60% of cases result from AD (198,204). Most patients with AD lack an obvious family history and are classified as sporadic. A small proportion of cases, particularly with early onset, have a positive family history and an autosomal dominant inheritance. Some of them have a specific genetic mutation of the amyloid precursor protein (*APP*) gene on chromosome 2 (60). Other mutations have been mapped to chromosome 14 (173) or chromosome 19 (150). In late-onset familial and sporadic AD patients, the e4 allele of the *APOE* gene has been found to manifest at a higher frequency than in controls; the frequency is 50% in late-onset familial and 36% in sporadic cases compared to 16% in controls (171,193).

The EEG changes in AD are generalized, as reported in several studies (61,62,101,106,138,183). Alpha rhythm is slow or may be absent, and diffuse low- to medium-amplitude irregular theta activity appears. Theta activity later becomes the dominant background activity, and irregular diffuse delta waves may occur randomly (Figs. 13.3 through 13.7). Runs of large-amplitude generalized, irregular or semirhythmic delta activity may also appear, often more prominently over the frontotemporal regions (88,138). Spontaneous or barbiturate-induced beta activity, normally seen over the frontocentral regions, is reduced or absent. Sleep potentials may be disorganized, with poorly developed spindles; K complexes may be difficult to evoke (101). Rarely, patients with AD may develop myoclonus, but their EEGs lack the periodic complexes characteristic of CJD. Many studies (89,106,121,164,183) have found a positive correlation between (a) the severity of intellectual impairment in demented patients and (b) abnormalities on visual inspection of the EEG.

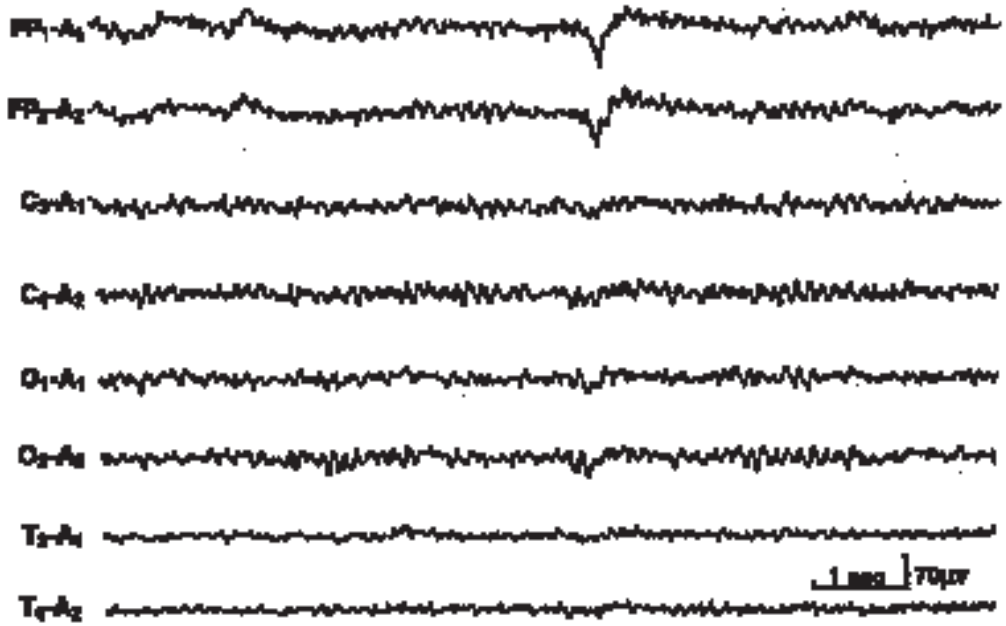

FIG. 13.3. Initial EEG of a 59-year-old woman with Alzheimer's dementia 1 year after onset of mild difficulty with memory and calculations. Alpha rhythm is at lower limit of normal frequency, 8 Hz. Note frontocentral 7-Hz theta rhythms. (From Markand ON. Electroencephalography in diffuse encephalopathies. *J Clin Neurophysiol* 1984;1:357–407, with permission).

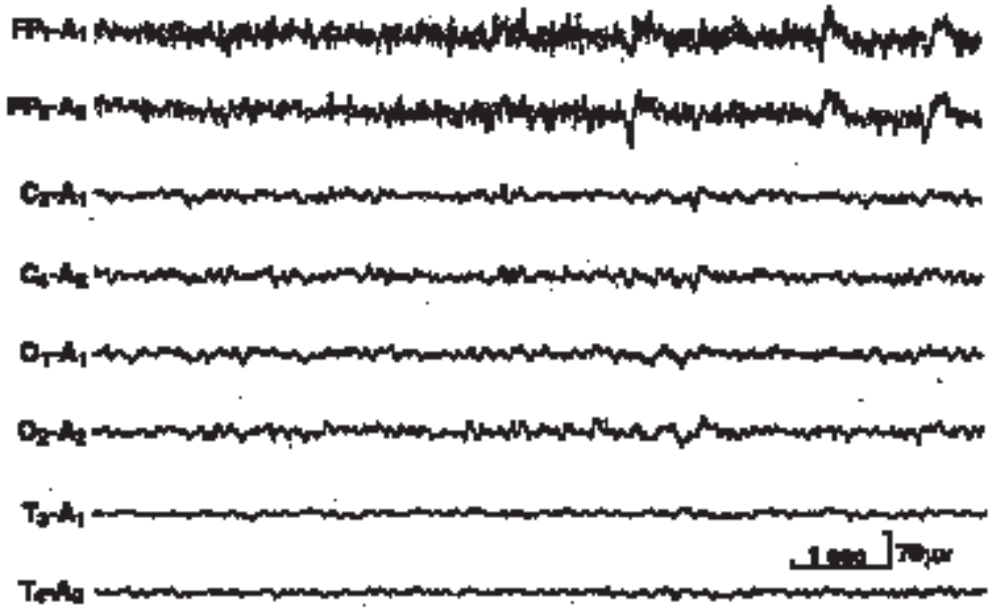

FIG. 13.4. EEG 2 years later in the same patient as in Figure 13.3 shows alpha rhythm replaced with background of low-amplitude theta and delta activity. At that time, she had moderate dementia: She was unable to prepare meals, shop, or balance her checkbook. (From Markand ON. Electroencephalography in diffuse encephalopathies. *J Clin Neurophysiol* 1984;1:357–407, with permission).

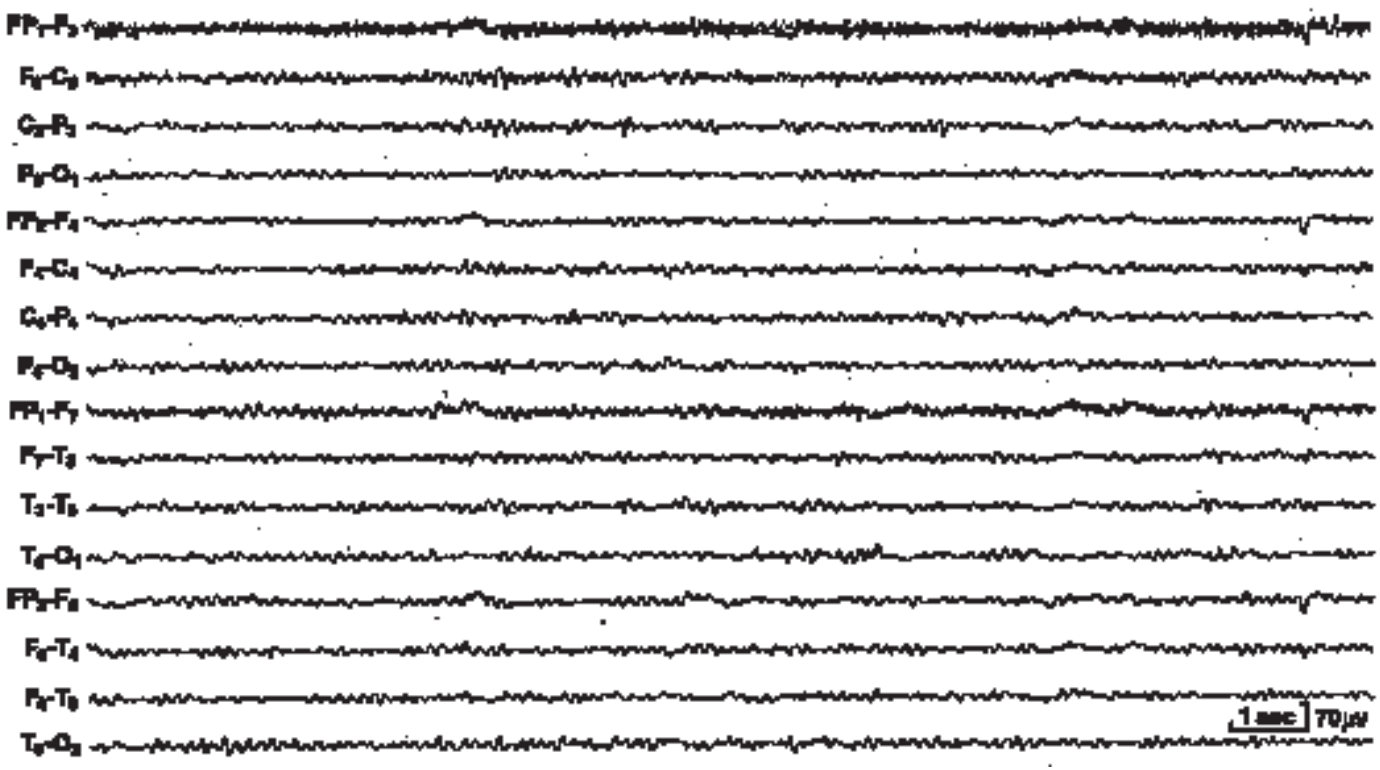

FIG. 13.5. EEG of an 80-year-old man with a history of depression, progressive intellectual impairment, and episodes of confusion for 2 years resulting from dementia. Note absence of alpha rhythm and diffuse rhythmic 6-Hz theta activity.

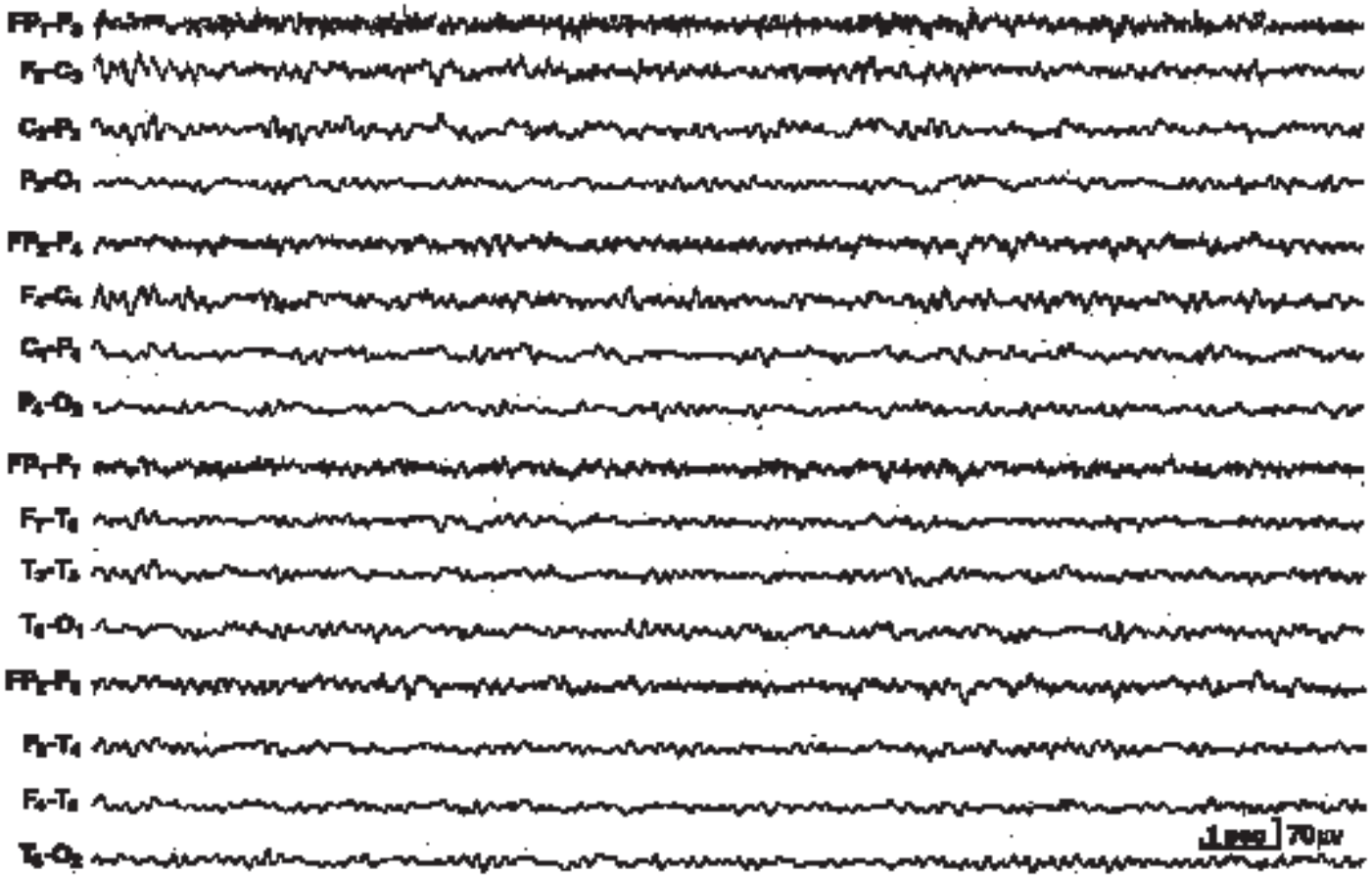

FIG. 13.6. EEG of same patient as in Figure 13.5 recorded 13 months later shows further deterioration with absence of alpha rhythm, slower (5-Hz) and higher amplitude theta rhythms, and arrhythmic centroparietal delta activity.

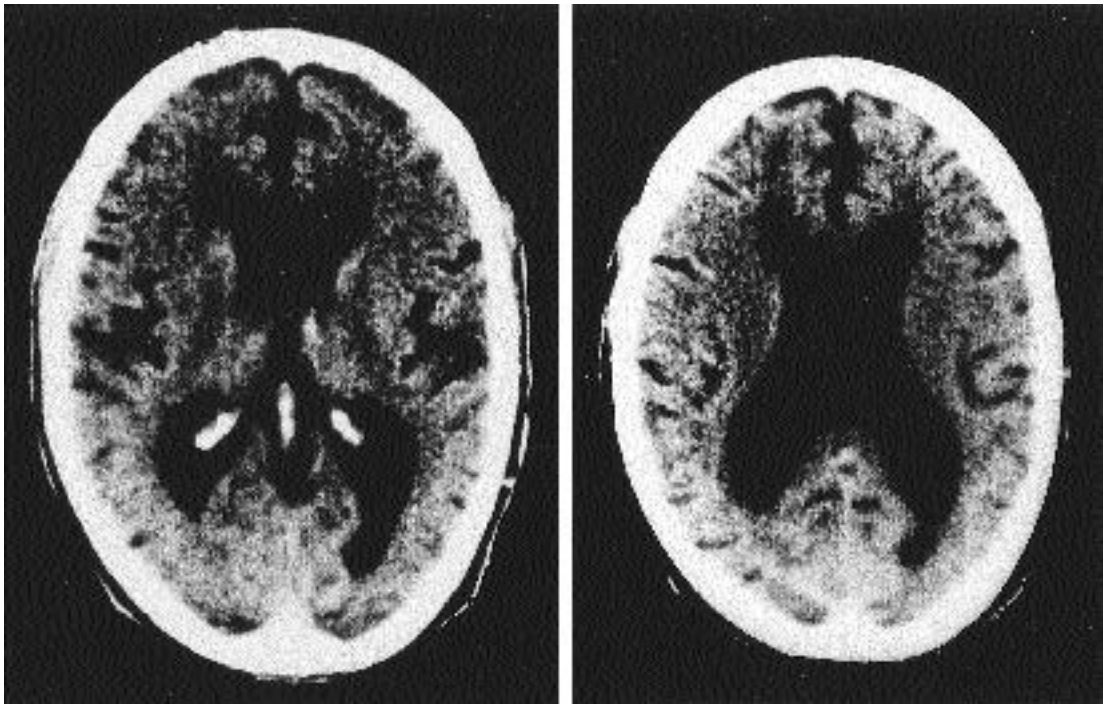

FIG. 13.7. CT scan of same patient as in Figures 13.5 and 13.6 made at time of second EEG shows dilated ventricles and prominent sulci, indicating cerebral atrophy.

Epileptiform discharges are rare even if epileptic seizures are part of the clinical picture. Muller and Kral, in 1967 (125), described sharp or triphasic waves usually occurring over posterior head regions in severely demented patients (Fig. 13.8). More recently, others (13,155,161) have reported similar waveforms in dementia. Rae-Grant et al. (161) found 15 of 268 EEGs in patients with AD, and Primavera and Traverso (155) found 15 of 114 patients with probable AD, showing triphasic waves. Triphasic waves are usually associated with a severe degree of dementia and are posterior dominant in most such patients (13,125,155), compared to their usual frontal dominance in acute metabolic encephalopathies. They may occasionally be quasiperiodic in their occurrence (13,42,155) but usually lack the persistence and regular periodicity seen in CJD (*vide infra*). Myoclonus can occur in late stages of the disease. Hallett and Wilkins (72) have described small multifocal jerks of muscles in distal parts of the extremities: "EEG was slow often with some epileptic activity that could not be readily correlated with the jerks." However, back-averaging EEG activity from myoclonic jerks revealed focal negativity in the contralateral rolandic area 20–40 milliseconds before the jerk, suggesting cortical myoclonus.

Although many authors have reported abnormal EEGs with slowing of background rhythms in almost all cases of AD (62,88,101,138), this statement is true only for those patients with moderate to severe dementia. Systematized blind interpretation of EEGs in 86 patients with AD showed abnormal findings in 87.2% at the initial examination and 92% at the follow-up (165); a normal EEG had a predictive value of 0.825 for the diagnosis of AD. In early stages, however, when cognitive difficulties first develop, EEGs may be normal, with alpha rhythms well over 8 Hz (see Fig. 13.3). Using strict criteria for EEG abnormalities (e.g., moderate diffuse slowing) such that most normal subjects are correctly classified, a high false-negative rate occurs in patients with AD, especially in the early stages (16,20).

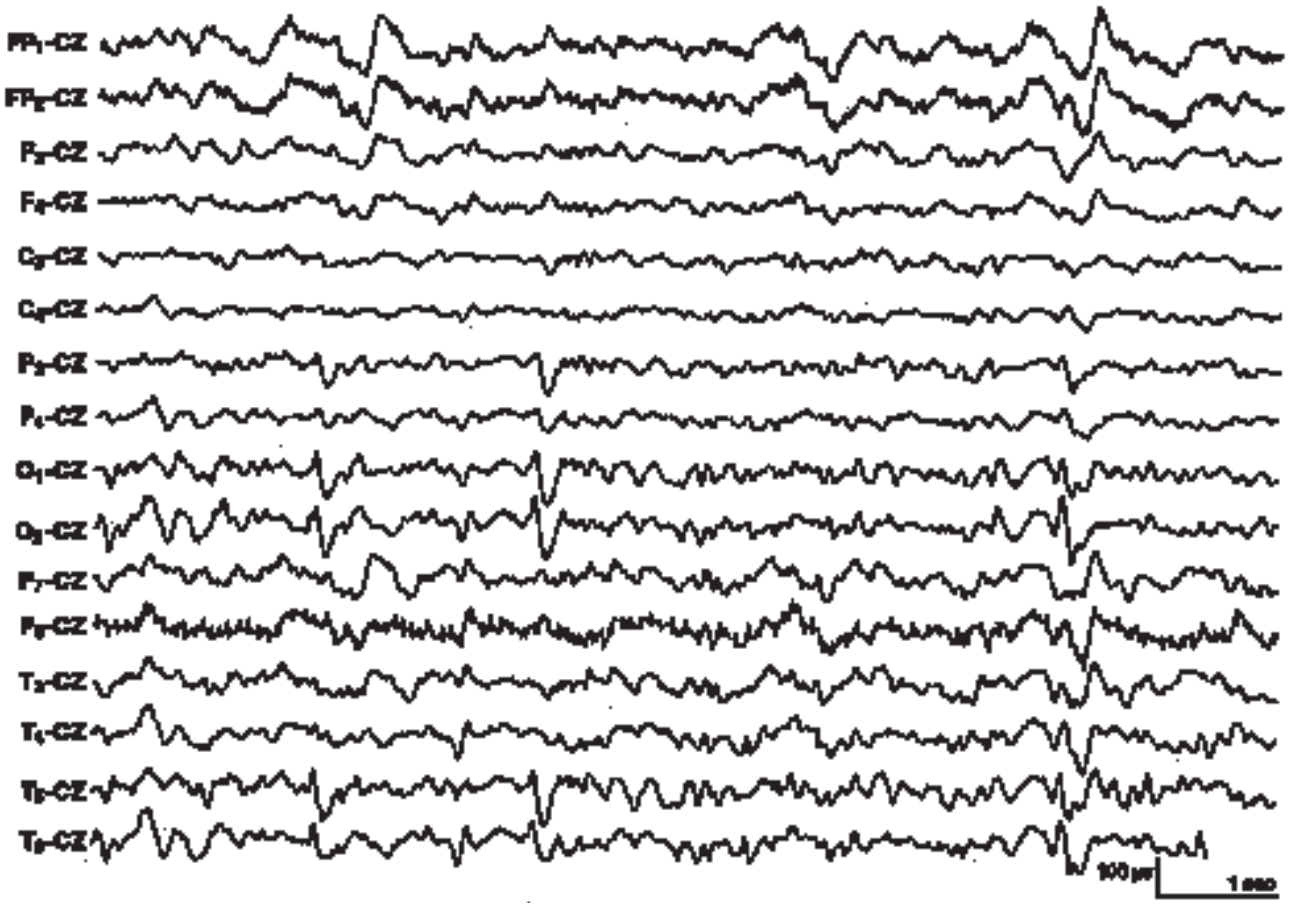

FIG. 13.8. EEG of an 82-year-old woman with advanced dementia shows diffuse slow activity and posterior hemispheric sharp (triphasic) waves.

In the hope of increasing the diagnostic value of EEG, interest has developed in computerized EEG spectral analysis, which provides more quantitative data than does conventional visual EEG analysis. Findings with spectral analysis are similar to those reported with conventional EEG analysis. Several studies (20,34,35,57,123,174,209) have shown a shift of the spectrum to slower frequencies, with an increase in theta activity and a decrease in beta activity, in patients with AD compared to normal elderly subjects. There is a correlation between spectral EEG measures, such as mean frequency and severity of dementia (20,29,39,149,179,191). In mild dementia, there is an increase in theta and a decrease in beta activity (34,35), whereas with greater severity of dementia there are also decreases in alpha and increases in delta activity (35,43,78,123,149,182,190).

In a study comparing the diagnostic efficacy of computerized spectral versus visual EEG analysis in elderly normal and AD subjects, Brenner et

al. (16) found that spectral analysis afforded only modest advantages over visual EEG analysis in differentiating AD patients from elderly controls. Because the degree of spectral and visual EEG abnormalities correlated with the severity of dementia, both tests more often correctly classified those AD patients with lower Mini-Mental State Examination (49) scores. Also, both tests identified primarily the same patients. The authors did not find the computer to be more sensitive than the eye in the identification of AD patients with mild impairment, and such patients, who are more difficult to diagnose clinically, may not be identified by EEG criteria. However, computerized spectral data were derived from only 4 channels, while 16 channels and a longer recording time were used for visual analysis. Strijers et al. (192), utilizing 19 channels for visual analysis and 12 channels for computerized data, which included both frequency analysis and coherence, also found that accuracy in identifying demented patients was comparable between visual analysis and qEEG. However, only nine AD patients were studied.

Soininen et al. (184) also thought that the value of spectral analysis of the EEG in the diagnosis of AD in its early stages had limitations. Using a T6-O2 derivation, they found that in 50% of early AD cases there were no EEG alterations or worsening at 1-year follow-up. Similarly, Coben et al. (33), using an occipital-vertex derivation, reported only modest sensitivity (about 20%) of the EEG to detect individuals with mild AD when compared to normal subjects. However, the specificity was 100%. Although Hooijer et al. (82) found a slight advantage in visual analysis over quantitative analysis, Schreiter-Gasser et al. (175) found quantitative data, particularly absolute power of delta activity, to be the best predictor of degree of dementia. Both qEEG and visual EEG analysis were highly correlated with degree of dementia, but computed tomography (CT) scans were not.

In addition to spectral analysis, qEEG studies have also evaluated coherence, which is a measure of the synchronizational neuronal activity between two cortical sites. Several studies (10,40) reported decreased coherence in AD patients, suggesting fewer neuronal connections. Whether coherence provides any useful information beyond the known frequency analysis changes per se is uncertain, because relatively few studies have been performed. Furthermore, there is not a prospective validation of the clinical utility for coherence testing in patients with dementia (135).

Currently, although both visual analysis of EEG and qEEG compare favorably to other laboratory tests, such as CT, MRI, single-photon emission CT (SPECT), and positron emission tomography, in the evaluation of dementia (76,90,165), for mild degrees of dementia the specificity and sensitivity are limited. This may be improved with further development of quantitative techniques and mathematical manipulations, such as discriminant analysis and artificial neural networks (5,11,158). At present, the clinical usefulness of qEEG in dementia is limited, because most changes can be seen in routine EEG testing (135). Unlike Jonkman (90), we do not believe that qEEG is the preferred study, and concur with Nuwer (134) that qEEG should not be employed separately from routine EEG. Furthermore, even with improvements in qEEG techniques, it is possible that in early dementia the sensitivity and specificity of these tests may be mediocre compared to other routine kinds of medical testing, such as neuropsychometric testing (134).

There have been several longitudinal EEG studies of AD patients. Coben et al. (35) found overall changes in power spectra (increases in delta and theta and decreases in beta, alpha, and mean frequencies) over a 2.5-year period. Sloan and Fenton (179) did not find significant power spectra changes in an 18-month follow-up of AD patients. Hooijer et al. (82) found visual analysis to be better for showing a progression of slowing of the EEG in AD patients than power spectral analysis. However, with progression of disease, the conventional EEG does not invariably worsen in all AD patients (161).

What is the role of the EEG as a predictor of progression in dementia? Berg et al. (9), using spectral measures, did not find this test to be predictive of progression of dementia in AD patients at a 1-year follow-up. Helkala et al. (77), using both conventional visual EEG analysis and spectral measures, found that AD patients with an abnormal EEG at an early stage of the disease had a different pattern of cognitive decline than AD patients (matched for severity of dementia) with a normal EEG. Those with deteriorating EEGs during the initial 1-year follow-up subsequently showed a greater decline in praxic functions, as well as a tendency toward a higher frequency of extrapyramidal symptoms and a greater risk of institutionalization, than AD patients with stable EEGs during the first year. Lopez et al. (107) found more marked EEG abnormalities (conventional visual and spectral analysis) in AD patients with delusions and hallucinations compared to AD patients matched for severity of dementia, but without delusions and hallucinations. Patients with these psychotic symptoms had a more rapid rate of decline as measured by the Mini-Mental State Examination (49). In a subsequent study, Lopez et al. (108) found both abnormal EEG and psychosis to be independent predictors of disease progression. Rodriguez et al. (167), in a pilot study of 31 AD patients, thought that qEEG may have prognostic relevance and be useful for clinical purposes such as predicting loss

of activities of daily living, incontinence, and death, whereas Forstl et al. (51) did not find qEEG a predictor for cognitive performance.

The magnitude of disease-related changes in ventricular size and dilation of sulci correlates roughly with cognitive deficits, particularly in advanced stages of dementia (38,121). However, most authors have found no correlation between (a) diffuse EEG abnormalities in dementia and (b) magnitude of cerebral atrophy (164,188). Because EEG reflects disordered function rather than loss of neural tissue, this lack of relationship is less surprising. The degree of background slowing correlates better with severity of cognitive impairment (89,92,154) and severity of pathological changes at autopsy (126) in demented patients. Kaszniak et al. (92) have shown further that EEG slowing better predicted mortality and related more closely to widely disrupted cognitive functions than did degree of cerebral atrophy. Therefore, the effects on both cognition and survival appear to be more severe when the brain is electrophysiologically abnormal than when there is only simple tissue loss.

A number of investigators have evaluated sleep in patients with primary degenerative dementias (156,157,162,163). Demented patients nap frequently in the daytime and awaken frequently during the night, resulting in decreased sleep efficiency as compared with normal elderly persons. Sleep architecture shows several changes: (a) decreased rapid-eye-movement (REM) sleep time and REM activity, (b) decreased amount of delta sleep, (c) normal or slightly increased latency to REM sleep, and (d) increased percentage of time awake in bed. Comparing demented patients and normal elderly subjects yields statistically significant differences only for certain variables (162). Sleep maintenance and sleep efficiency are reduced in demented patients. EEGs show poorly developed sleep spindles and K complexes; thus scoring of stage 2 non-REM sleep in dementia becomes difficult.

Although some changes of sleep overlap in demented and depressed patients, certain major differences exist. Both demented and depressed patients demonstrate diminished sleep efficiency; however, inability to maintain sleep particularly marks depressed patients, who awaken frequently and consequently have lower sleep maintenance percentage. Delta sleep diminishes in both demented and depressed patients, but REM sleep increases in elderly depressed (as compared to demented) patients. Depressed patients have also shorter REM latency, often less than 30 minutes. An interesting shift of REM sleep time and REM intensity occurs in depressed patients during the first part of the night's sleep. Duration of first REM period, as well as REM activity during this period, increases compared to that of normal elderly or demented patients. In patients with depression, the first REM period may increase to more than 18 minutes. Despite these differences in REM sleep parameters, usefulness of polysomnography in early diagnosis of dementia or in separating organic dementias from pseudodementia remains limited because of significant overlaps in abnormalities.

Pick's Disease

Pick's disease occurs less commonly and is characterized by circumscribed atrophy of the frontal and temporal lobes. It constitutes one of the subtypes under the broad category of "frontal" or "frontotemporal" dementias (128). Terry (197) has reported a ratio of 1:50 for Pick's disease compared to AD. Munoz-Garcia and Ludwin (127) have identified two subgroups among sporadic Pick's disease; the first group (classical) had predominantly cortical atrophy, whereas the second group (generalized) showed subcortical as well as cortical atrophy. Familial cases occur, although usually the disease appears sporadically. In a study of a kinship with 25 cases, EEGs in 13 patients were within normal limits in 11 while 2 patients had excessive frontoparietal theta activity, although alpha rhythm was of normal frequency (67). Similarly, only one of three patients reported by Gordon and Sim (62), two of ten patients reported by Tissot et al. (203), and three of seven patients reported by Johannesson et al. (89) had abnormalities in the EEG. More recently, Yener et al. (218) compared conventional and quantitative EEG in 26 patients with AD and 13 patients with frontotemporal dementia (all had confirming findings on SPECT studies). In the majority of patients with frontotemporal dementia, there was a well-preserved alpha rhythm, which was not the case in AD patients. Thus a majority of patients with Pick's disease or frontotemporal dementia show mild EEG abnormalities, consisting of low- to medium-amplitude slow activity over anterior hemispheric areas, while alpha rhythm may remain normal even with severe dementia (Fig. 13.9).

There have been relatively few qEEG studies in frontotemporal dementia. Like visual analysis, qEEG studies have found EEG changes to be less severe in this group of patients than in those with AD (50,218).

Huntington's Disease

This autosomal dominant disease manifests at age 20–40 years with chorea, mental disorders, and progressive dementia. The rare juvenile form

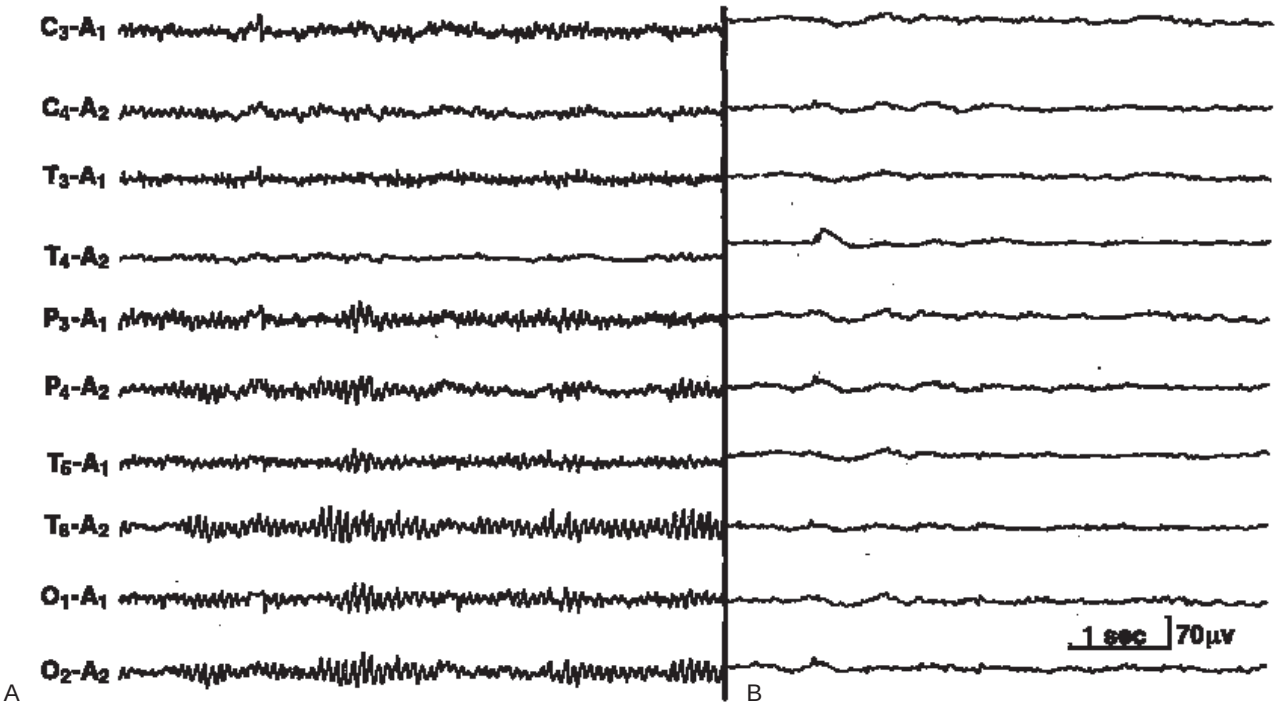

FIG. 13.9. EEGs in a 27-year-old patient with rapidly progressive Pick's disease, proven by brain biopsy. Patient had a 2-month history of aphasia, difficulty in simple calculations, memory deficits, and personality change. **A:** Initial EEG is normal, with 80–90 µV, 11-Hz alpha rhythm. **B:** Nine months later, EEG shows loss of alpha rhythm along with very low-amplitude (15 µV), irregular slow activity. By now, patient had no evident cognitive functions and led a virtually vegetative existence.

shows parkinsonian rigidity, rather than chorea, and epileptic seizures. The disorder has been demonstrated to be due to expanded trinucleotide (cytosine, adenine, and guanine) repeats involving the Huntington gene on chromosome 4. Controls have 12–36 such repeats compared to over 40 (as high as 80) in patients with Huntington's disease (69). EEGs characteristically have very low-voltage ("flat") background activity (52,79) (Fig. 13.10), a finding reported by Margerison and Scott (112) in 60% of patients; others (142) have reported a much lower incidence, particularly in early stages when diagnosis often is difficult. Adams (2) has investigated clinical correlates of "flat" EEGs, defined as alpha rhythm voltage less than 20 µV, and has found flat tracings in 10% of adults without neurological or psychiatric disorders and in 13% of various neurological and psychiatric conditions afflicting patients ages 40–70 years. He has concluded that flat EEGs lack diagnostic significance. In a detailed study of 95 patients with Huntington's disease, Scott et al. (176) have used more stringent criteria for flat EEGs, designating an EEG "positive" only if it lacked any activity exceeding 10 µV. Such tracings, not found in normal subjects, occurred in one-third of Huntington's disease patients. Hyperventilation tends to increase amplitude and persistence of rhythmic activity in normal subjects with flat EEGs, but caused no change in patients with Huntington's disease. In a more recent study of 16 patients, Sishta et al. (178) found 10 with "positive" EEGs by the criteria of Scott et al. (176); another 4 had mean amplitudes below 10 µV, although they occasionally showed activity exceeding 10 µV. Of additional interest was universally abnormal sleep patterns with diminished or absent vertex sharp waves, sleep spindles, and K complexes. Although EEGs of less than 10 µV are not peculiar to Huntington's disease, they occur infrequently with other neurological or psychiatric disorders and never occur in normal subjects.

Myoclonus is rare but has been reported as a major feature in a few families with Huntington's disease. EEG in some of them may show bisynchro-

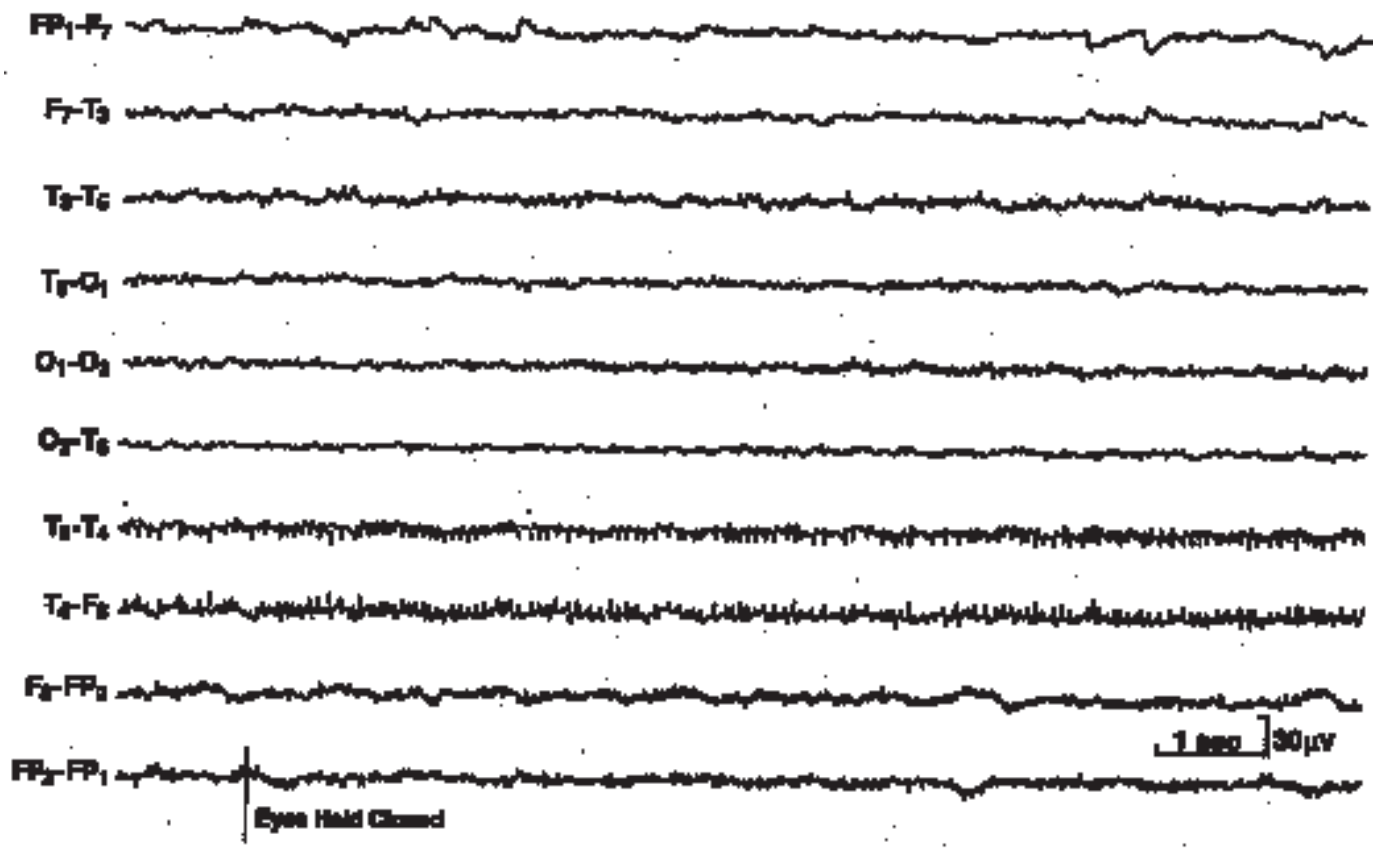

FIG. 13.10. EEG of a 53-year-old patient with Huntington's disease shows low-amplitude (10 μV) scattered theta-delta activity.

nous generalized spike-waves or polyspike-waves that may be enhanced by photic stimulation (210). Epileptiform discharges are more likely to occur in juvenile patients with seizures (12,64).

Low-amplitude tracings in Huntington's disease remain unexplained, although Scott et al. (176) have claimed a significant correlation between low-amplitude EEGs and generalized cortical atrophy.

Attempts to detect presymptomatic carriers of the gene for Huntington's disease have failed. In 26 at-risk persons from nine families with Huntington's chorea, Patterson et al. (146) had predicted, on the basis of slow-wave activity, development of the disease in 19. In 1966, Chandler (31) reported follow-up studies on 23 of the 26 individuals. Prediction based on EEG findings was correct in 11 and incorrect in 12 at-risk cohort members!

Streletz et al. (191), using computerized analysis, found increased theta and decreased alpha activity in patients with Huntington's disease; quantitatively similar changes were found in patients with AD.

Parkinson's Disease

In 1959, England et al. (46) reported abnormal EEGs in 39 of 75 patients from a clinic for Parkinson's disease, abnormalities characterized as bilat-

eral theta or mixed theta-delta activity predominantly over posterior head regions. Patients were withdrawn from drugs for only 36–48 hours before EEG, an interval not sufficient to eliminate drug effects. Ganglberger (56) reported abnormality in 34.6% of patients with parkinsonism; in most patients (32.2%), abnormality consisted of alpha rhythm of less than 8 Hz. Sirakov and Mezan (177) reported on 100 patients selected from a population of "several hundred" on the basis of "technically good records." In 64 patients, EEGs were regarded as normal; the majority of the remaining patients showed slight to moderate degrees of "diffuse slow-wave activity" (Fig. 13.11). Yeager et al. (217) have reported on EEGs of 223 patients with parkinsonism who were candidates for stereotactic surgery; subsequently, 118 underwent operation. EEGs of 142 patients were interpreted as normal; 41 showed diffuse slowing; 22, focal slowing; and 18, focal and diffuse slowing. The authors recognized sampling bias in that all patients were candidates for surgical treatment, presumably reflecting more intractable and disabling parkinsonism. From these earlier studies, one can conclude that the majority of patients with parkinsonism probably have normal EEGs. In a minority (approximately one-third) of patients, probably representing more advanced stages of parkinsonism, slowing of alpha rhythm to below 8 Hz and generalized slow activity in the theta or theta-delta range occur; some of these changes could represent drowsiness induced by drugs or could reflect direct effects of drug toxicity.

There has been increasing awareness of dementia in idiopathic Parkinson's disease, with the incidence varying in different studies from 20% to 81% (116,153). A few more recent studies have therefore compared the EEG findings (visual analysis or qEEG) in patients with and without dementia. In a study of 128 patients, Neufeld et al. (131) reported abnormal EEGs characterized by slowing of the background in 7 of 43 (16%) nondemented and 35 of 80 (44%) demented patients with Parkinson's disease, a statistically significant difference ($p < 0.005$). In this study, the EEG slowing was also related to motor disability. There was a strong suggestion that the two factors—cognitive and motor status—affected the EEG independently because, in the nondemented patients, increased motor disability correlated significantly with increased slowing of the EEG. In studies using frequency analysis on one channel (181) and on multiple channels (130) in controls, nondemented parkinsonian patients, and demented parkinsonian patients, findings have been largely similar to those of unaided visual analysis of the EEG. Parkinsonian patients without dementia showed more ampli-

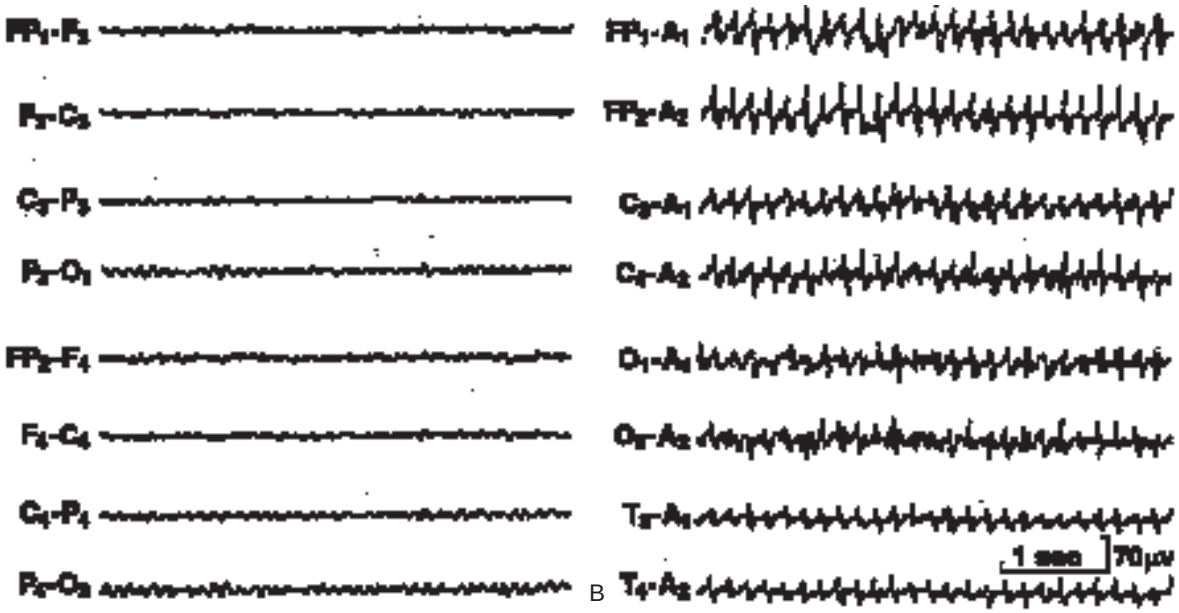

FIG. 13.11. EEG of a 57-year-old patient with Parkinson's disease shows slight slowing of the background activity **(A)** and characteristic 4- to 6-Hz, rhythmic tremor artifact **(B)**. (From Markand ON. Electroencephalography in diffuse encephalopathies. *J Clin Neurophysiol* 1984;1:357–407, with permission).

tude in the theta frequency band and diminution in the amplitude of alpha band activity. The demented patients showed a further increase in the theta and delta amplitudes compared to the nondemented patients.

Stereotactic surgery has significant, often permanent, effects on the EEG as shown by Ganglberger (56) and Yeager et al. (217). After stereotactic surgery, EEG abnormalities developed in 50% of patients even if none existed preoperatively. Postsurgical changes include diffuse or focal theta-delta slowing, or both. Focal or lateralized slowing usually occurs ipsilateral to the side of surgery. Slowing may be diffuse immediately postoperatively but later usually remains confined to the side of surgery. No relationship exists between target site (globus pallidus or lateral-ventral thalamus) or side (right or left) and severity of EEG abnormalities. Dopa therapy may improve preexisting abnormalities (63) but can also induce seizures and paroxysmal EEG abnormalities (110). Neufeld (129) described four parkinsonian patients who developed levodopa-induced encephalopathy, with their EEGs showing quasiperiodic generalized triphasic waves. The clinical condition and EEG cleared following levodopa reduction or discontinuation.

Parkinsonism–dementia syndrome occurs in endemic form among Chamorro Indians on Guam. EEGs have been abnormal in 12 patients studied (80). Alpha rhythms may be 8–9 Hz or slower. Scattered diffuse theta activity and, at times, focal arrhythmic delta activity appear in the frontotemporal regions. Severity of EEG abnormalities appears to correlate with degree of mental deterioration. Although this syndrome clinically resembles CJD, EEG findings differ in that they lack periodic complexes.

Progressive Supranuclear Palsy

Steele et al. (187) have described PSP, a heterogeneous system degeneration, and distinguished it from Parkinson's disease. Lesions are largely confined to diencephalic and brainstem nuclei. Su and Goldensohn (194) reported EEG findings in 12 patients. In the initial stages, alpha rhythms have normal frequencies. In five of eight patients, initially normal EEGs became abnormal over 3 months to 7 years. Abnormalities were varied: Focal arrhythmic delta activity occurred in three patients, whereas intermittent rhythmic delta activity occurred in five. As the illness progressed, EEGs deteriorated, showing increased slowing—and eventually disappearance—of alpha rhythm. In two series (53,111), EEGs were normal in over one-half of patients. The remainder had excessive diffuse or bitemporal theta activity, minor asymmetries of slow activity, low-voltage tracings, or frontal intermittent rhythmic delta activity.

Montplaisir et al. (124) evaluated quantitative EEG and sleep architecture in six patients with PSP and compared those findings with results in age-matched controls. qEEG demonstrated more severe slowing in the frontal region rather than temporal areas, a finding in accordance with the imaging and neuropsychological studies showing impairment of frontal lobes in PSP. These authors also confirmed the earlier reported abnormalities in the sleep architecture (68) in patients with PSP. Patients with PSP show a shorter total sleep time, lower sleep efficiency, a drastic reduction in sleep spindles, an atonic slow-wave sleep, and a marked reduction in REM sleep with reduction both in the number of REM periods and the mean duration of a REM period. REM sleep abnormalities are consistent with the known PSP-associated degeneration of the pedunculopontine tegmentum—a critical structure in REM sleep generation.

Creutzfeldt-Jakob Disease

CJD was once regarded as a neurodegenerative disorder, but it has been firmly established that it is due to a transmissible agent attributed to prior infection (160). Prion diseases can be sporadic, familial, or iatrogenic. They are characterized by abnormal metabolism of the prion protein PrP, leading to accumulation of an abnormal infectious prion protein, scrapie (PrP^{sc}), which is an isoform of normal cellular PrP. Human prion diseases include CJD, Gerstmann-Sträussler-Scheinker (GSS) syndrome, kuru, and fatal familial insomnia; CJD is the most common. Although most cases of CJD are sporadic, 5%–15% are clustered in families (23,117). The clinical picture is similar in sporadic and familial patients. Three clinical stages are recognized. The first is characterized principally by progressive dementia or a wide variety of focal symptoms indicating lesions in various parts of the brain. In the second stage, the focal features tend to disappear as a picture of progressive dementia, bilateral rigidity, pyramidal signs, and widespread myoclonus evolves. In the third stage, the patient becomes bedbound with deepening stupor, increasing rigidity, and weakness of the limbs that proceeds relentlessly to death. Markand (114) has reviewed the EEG findings in CJD.

In the first phase, EEG changes are limited to a progressive disorganization of background rhythms and increased amounts of generalized slow (theta-delta) activity (24). These changes may be more marked anteriorly or posteriorly, or over one hemisphere or part of a hemisphere (Fig. 13.12A, B). Such focal or lateralized features may suggest a tumor or even a stroke, but sooner or later EEG activity becomes bilaterally slow.

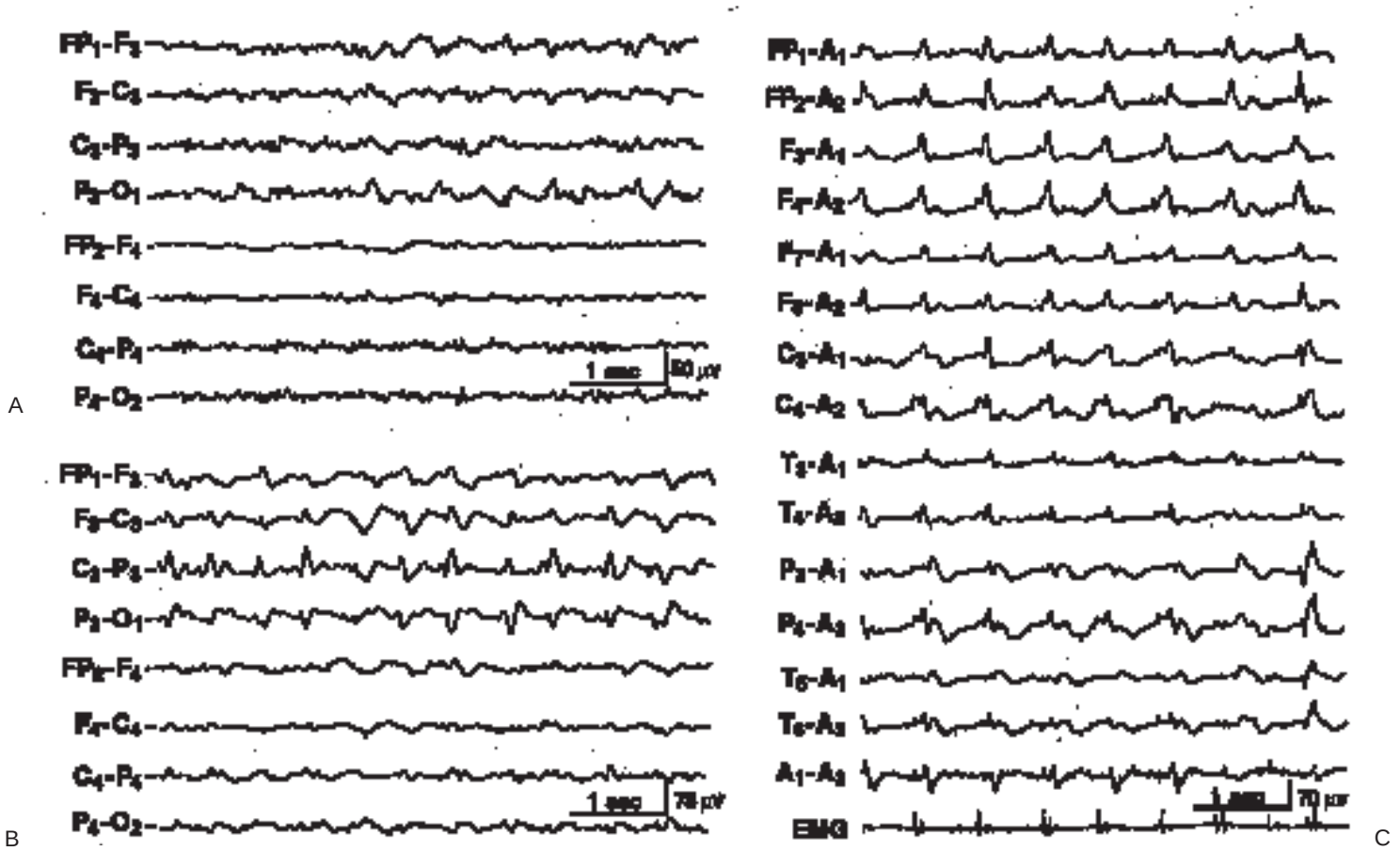

FIG. 13.12. EEGs of a 62-year-old patient with Creutzfeldt-Jakob disease. **A:** The earliest EEG, taken 2 months after the onset of dementia and right hemiparesis, shows lateralized abnormality consisting of widespread delta activity over the left hemisphere. **B:** Two weeks later, the EEG shows periodic lateral epileptiform discharges on the left side. There is more deterioration of background activity over both sides. **C:** EEG obtained 5 months after the onset of Creutzfeldt-Jakob disease shows generalized periodic sharp waves recurring every second. Patient had rhythmic jerks of the left arm, which are monitored on the last channel. The channel next to last (A1-A2) records the electrocardiogram. The periodic complexes have a close temporal relationship to the myoclonic jerks but are independent of the cardiac activity. (From Markand ON. Electroencephalography in diffuse encephalopathies. *J Clin Neurophysiol* 1984;1:357–407, with permission).

During the second phase of CJD, the EEG is characterized by periodic, bilaterally synchronous potentials (1,24). The periodic potentials take the form of diphasic or triphasic sharp waves, 200–500 milliseconds in duration and up to 300 μV in amplitude. As the disease progresses, some patients exhibit more complex discharges with multiphasic or polyspike configuration (3). The frequency of the periodic complexes is close to 1 per second; the interval between successive discharges varies from 0.5 to 1.6 seconds. There is a fairly close, but not precise, relationship between the periodic complexes and the myoclonic jerks: The jerks may occur a few milliseconds before or after the electrical event (Fig. 13.12C). The periodic sharp-wave complexes (PSWCs) in the EEG may occur without associated myoclonic jerks. This is particularly true during sleep or late in the course of the disease, when the myoclonic jerks decrease or disappear while the PSWCs persist (1).

This periodic pattern continues into the third (i.e., final) phase of CJD. Many authors (1,3,14) describe a progressive lengthening of the interval between periodic complexes with advancing disease, but others (24) have reported a remarkable consistency of the frequency even into the terminal stages. Finally, the amplitude of the background activity decreases, which results in an undifferentiated low-voltage tracing from which rhythmic discharges emerge.

The characteristic periodic pattern has been reported in 75%–94% of patients with CJD (24,32). From original data and review of the literature, Levy et al. (105) affirmed that lack of periodic abnormalities in EEGs after an illness of 12 weeks weighs strongly against CJD. However, at least a few patients with CJD, particularly those with forms considered atypical (e.g., ataxic or amyotrophic variety or with long duration), may not show periodic EEG activity at any point in the entire illness (3,22,219).

No comprehensive evaluation of EEGs has been carried out in familial cases of CJD. It appears, however, that PSWCs are less common in familial than in sporadic CJD, although the clinical characteristics are not dramatically different. Tietjen and Drury (201) reported an absence of myoclonus and PSWCs in serial EEGs of four members of a kindred with pathologically verified CJD.

In the early stages of CJD, periodic discharges may be present only for 5–10 seconds at a time or may appear only a few times in a single EEG. Also, before the periodic pattern is fully established, the EEG may show state-dependent variability.

During periods of drowsiness or sleep, the PSWCs may virtually disappear and be replaced by medium-amplitude generalized theta-delta activity. Also during this state, the myoclonic jerks often disappear, heart and respiratory rates are reduced, and periods of apnea may occur (14,91). Periodic complexes reappear during the periods when the patient is aroused and more alert. The EEG may thus show a cyclic alternating pattern, that is, alternation of the two stereotyped EEG patterns (PSWC pattern alternating with diffusely slow EEG).

Another characteristic feature of the PSWCs, particularly in the early stages, is their reactivity to alerting stimuli or to the administration of drugs. Before the PSWCs are well established, or when they occur only intermittently, acoustic or other alerting stimuli may trigger the periodic pattern when delivered during a diffusely slow EEG phase (14). In some patients, intermittent photic stimulation (IPS) may elicit tight coupling of periodic complexes to flashes, particularly when the rate of stimulation is close to that of the periodic complexes (3,14). In the terminal stages of CJD, when the PSWCs are nearly absent, IPS may be able to initiate the onset of time-locked triphasic waves coincidental to each stimulus (14). Administration of 10 mg of diazepam intravenously, in contrast, may be followed by a transient disappearance of PSWCs and myoclonus that restarts after several minutes in response to acoustic stimuli (14).

The periodic discharges of CJD are classically bilaterally symmetrical and generalized in distribution. However, focal or lateralized periodic sharp waves (i.e., a PLEDs pattern) may occur in the early stages of the disease (8,41,54), as illustrated in Figure 13.12B. With progression of the disease, the periodic events become bilaterally symmetrical.

The *Heidenhain variant of CJD* is characterized by predominant involvement of the occipital cortex, often resulting in cortical blindness early in the disease. The EEG may show slowing of the background activity and PSWCs over the posterior head region. The complexes may be focal or unilateral initially but become bilateral over the posterior regions as the disease progresses (54).

GSS disease is a rare familial variant of CJD, characterized by spinocerebellar ataxia, diminished reflexes, myoclonus, and a longer course (2–15 years) than CJD (100). The EEG is characterized by variable slowing of the background activity, but, unlike CJD, periodic complexes are absent.

The localization of the PSWCs corresponding to the site of maximum involvement (occipital cortex) in the Heidenhain variant of CJD and the absence of PSWCs in the ataxic variant of CJD with maximum cerebellar involvement suggest that cortical pathology is a critical substrate for the production of PSWCs in CJD. The pathogenesis of PSWCs, however, remains unknown. They may derive from mechanisms intrinsic to affected neurons

that become electronically coupled because of virus-induced membrane fusion (206).

Similar EEG patterns consisting of sharp waves occurring regularly every 1.0–1.5 seconds may rarely occur in other encephalopathies (cerebral anoxia, subtle status epilepticus, hepatic/renal encephalopathies, lithium and baclofen intoxication, etc.) (18,133). A few authors (42,213) have also described a similar EEG picture in rapidly progressive AD, but the resemblance was only superficial. These cases showed frequently occurring sharp waves that had random, not periodic, intervals—even when frequently repetitive. This confusion stresses the need for a more strict definition of periodicity in EEG. Note very frequently recurring paroxysmal discharge in the EEG should be called "periodic." This category should be reserved only for those discharges for which a modal value of intervals can be established at a minimal range of variation around that value (59).

ACQUIRED IMMUNODEFICIENCY SYNDROME

Markand (114) discussed EEG findings in AIDS. Infection by the human immunodeficiency virus, type 1 (HIV-1), results in a spectrum of central nervous system (CNS) complications. The best known are the opportunistic infections and neoplasia of the brain secondary to immunodeficiency. A devastating but poorly understood consequence of HIV-1 infection is a progressive encephalopathy that results in the AIDS dementia complex, HIV-1–associated cognitive–motor complex, or HIV-1 dementia. Approximately 15%–20% of all patients with AIDS will develop dementia. Although some cases of dementia are probably due to subacute encephalitis caused by HIV-1, in others the pathological changes are relatively minor. It has been suggested that neurotoxic viral proteins or the biological activities of cytokines released from HIV-activated macrophages cause CNS dysfunction (152). The pathological changes and the MRI-demonstrated atrophy involve both cortex and basal ganglia; the most severe changes occur in the basal ganglia, especially the caudate nucleus (37).

The EEG is invariably abnormal in well-established cases of HIV-1 dementia. The abnormalities include a slow or absent posterior rhythm and intermittent or continuous theta-delta slowing, which is either generalized or predominantly anterior (55,97,145,202). There is a good correlation between the severity of the EEG abnormalities and the severity of HIV-1 dementia. Some patients with advanced dementia have low-voltage (< 20 μV), slow EEGs (73), not unlike that reported in Huntington's disease (176). Periodic sharp or triphasic waves, 1.5–2.0 cycles per second, over both frontocentral regions have also been described in a patient with HIV-1 dementia similar to the characteristic EEG pattern of CJD (200). This patient had myoclonic jerks; the periodic EEG pattern and the myoclonus both responded dramatically to zidovudine therapy.

An interesting aspect of the EEG in HIV infection has been the reports of EEG abnormalities even in asymptomatic HIV-1–infected individuals (44,55,97,145). It is proposed that these EEG abnormalities (usually background slowing) provide the earliest indicator of subclinical CNS dysfunction (97) and may predict subsequent development of HIV-1–related neurological disease (144). Parisi et al. (144) reported computer-analyzed EEG abnormalities in 50 of 185 (27%) asymptomatic or lymphadenopathy-only individuals infected with HIV-1. Inclusion of intravenous drug users in the HIV-seropositive group and absence of matched seronegative controls make it difficult to ascribe EEG abnormalities specifically to the HIV infection. A well-controlled study by Nuwer et al. (136) reported no significant difference in either clinical or computer-analyzed EEG between HIV-seronegative (n = 86) and HIV-seropositive (n = 114) asymptomatic men. They found that 22% of the seropositive and 26% of the seronegative men showed abnormal or borderline EEGs; rates were higher in both groups (45% in seronegative and 36% in seropositive men) when neuropsychological abnormalities coexisted. The incidence of EEG abnormalities thus failed to correlate with the serostatus but correlated with an impaired neuropsychological status in HIV-infected patients as well as controls. If risk factors such as intravenous drug abuse (which increases the incidence of EEG abnormalities) are excluded, the incidence of EEG abnormalities among the asymptomatic HIV-infected group is probably less than 7%, a rate comparable to that of uninfected controls (132).

CEREBROVASCULAR DISEASE

Hachinski et al. (71) introduced the term *multi-infarct dementia* to characterize relatively global cognitive impairments resulting from multiple infarcts (none of which alone would cause dementia) and to emphasize that the dementia reflects cumulative effects of multiple infarcts. Roberts et al. (164) have compared EEG findings in 48 patients with "nonvascular" dementia and 33 patients with "vascular" dementia. They used four EEG categories: normal (type I), excess beta activity (type II), theta activity predominant (type III), and delta activity predominant (type IV). In vascular dementia, types I and II occurred in 33% of patients, type III in 61%, and type IV in only 6%. In nonvascular dementia, however, type III represented only 46% while type IV represented 19%. Most striking was a prevalence of

focal EEG abnormalities in 74% of patients with vascular dementia as opposed to 19% with nonvascular dementia. Subsequent studies reported by Harrison et al. (74), Soininen et al. (183), and Erkinjuntti et al. (47) have also stressed the occurrence of focal and paroxysmal findings in vascular dementia. Thus, in general, focal slow waves in EEG and focal neurological signs help to distinguish vascular from degenerative dementias.

There is no consensus on the utility of quantitative EEG in differentiating AD patients from those with MID (90). Spectral studies have compared AD and MID. Erkinjuntti et al. (47) found a decline in the percentage of alpha power and a concomitant increase in theta and delta power relative to the degree of dementia for both groups. Furthermore, there were no significant group differences. However, Leuchter et al. (103) reported that 22 of 24 (92%) subjects with either AD or MID were accurately classified using discriminant analysis of both EEG frequency and coherence. Leuchter and Walter (104) subsequently reported topographic mapping findings in 40 subjects: 15 with AD, 13 with MID, and 12 age-matched controls. Functional images using spectral ratios showed that subjects with AD had a characteristic left temporoparietal deficit that distinguished them from subjects with MID and from control subjects. More recently, Leuchter et al. (102), using a ratio of coherence from corticocortical–corticosubcortical networks divided by coherence from long corticocortical tracts, correctly classified 76% of subjects into AD or MID categories. Sloan and Fenton (179) also found some spectral differences, with AD patients having more delta and theta power and less alpha power than MID patients matched for severity of dementia.

A rare form of dementia, *Binswanger's disease*, reflects subcortical arteriosclerotic encephalopathy. Despite preserved cortical architecture, dementia is prominent, presumably as a result of lesions in white matter disrupting corticipetal and corticocortical fibers. Caplan and Schoene (30) have reported on 11 cases, 5 confirmed by autopsy. EEGs of six patients showed "diffuse slowing" (not otherwise described), two showed "focal slowing," and three were normal. Single case reports have described triphasic or sharp waves with a tendency toward periodicity (25,214). The findings differ from the periodic discharges in CJD in that the sharp waves were lateralized and occurred only for brief periods.

Dementia Resulting from Other Causes

Normal-Pressure Hydrocephalus

NPH classically presents with gait difficulty, urinary incontinence, and progressive dementia; it results from known or presumed obliteration of subarachnoid spaces, impairing absorption of spinal fluid. Brown and Goldensohn (21) have reported on 11 patients with NPH. Six had normal EEGs. Four had focal or diffuse theta-delta slowing against a well-preserved alpha rhythm, whereas the remaining patients demonstrated both slowing of the alpha rhythm and focal delta slowing. Subsequent authors have reported a higher incidence of abnormal EEGs among patients with NPH: Wood et al. (216) reported 27 of 32 patients; Hashi et al. (75), 12 of 13 patients; and Greenberg et al. (65), 61 of 67 patients. The reported EEG abnormalities have been focal or diffuse theta-delta slowing superimposed on a normal or slightly slow background. Of particular interest are the "projected" rhythms, which signify, among other processes, raised intraventricular pressure. Paroxysmal monorhythmic theta or delta activity has been reported in a few patients with NPH (75,151). Follow-up EEG studies after a shunting procedure are likely to show significant improvement in the EEG (75).

Neurosyphilis

Once the leading cause of dementia, general paresis resulting from neurosyphilis is now uncommon. Over two-thirds of patients have abnormal EEGs with slowing of the alpha rhythm and generalized slow activity of theta-delta frequency (6). EEGs are more abnormal when neurosyphilis is active, but they may improve with successful therapy (48). In "burnt out" disease, on the other hand, EEGs may be normal or minimally affected even in the face of severe residual neurological deficits.

Alcoholism

Alcoholism is common, and dementia occurs in 3% of chronic alcoholic patients, which accounts for 7% of patients admitted for evaluation of progressive intellectual impairment (36,115). Krauss and Niedermeyer (98) reported on the EEG findings in 213 patients with chronic alcoholism, 152 of whom were referred to the EEG laboratory for epileptic seizure and remaining 61 for delirium or other causes. The majority (almost two-thirds) had normal tracings if one included low-voltage tracing as a normal variant in adults. Approximately 30% had nonlocalized slowing, 2% focal slowing, and 4% focal epileptiform abnormalities. The most common EEG finding was a low-voltage ($< 25\ \mu V$) tracing recorded in one-half of the patients (106 of the 213) compared to a 13.9% incidence of such tracings in the nonalcoholic "control" group. Unlike the low-ampli-

tude EEG encountered at times in anxious patients, the low amplitude in chronic alcoholics persisted during hyperventilation and even during sleep. Presence of cortical atrophy on CT scan was one of the factors that correlated with low-amplitude tracings. Even though the incidence of low-amplitude tracings is significantly higher in chronic alcoholics, this does not constitute an EEG abnormality except in infancy and childhood. Focal or diffuse slowing and epileptiform abnormalities seen in a minority are related to alcohol-related complications such as metabolic encephalopathy, brain injury, and the like.

PSEUDODEMENTIA

Pseudodementia refers to cognitive impairments associated with severe depression. Characteristically, these patients have prominent subjective, as opposed to objective, changes in memory, which distinguishes them from patients with organic dementia. Pseudodementia accounts for 10% of patients presenting with a clinical picture of dementia (180). Because changes in EEG are subtle in early dementia (*vide supra*), the EEG may contribute little to differential diagnosis. By the time abnormalities in EEG become evident, dementia is equally evident. Mildly demented patients may also have reactive depressive episodes, further confounding the problems of diagnosis.

Brenner et al. (17) reported EEG findings in 33 elderly patients with mixed symptoms of depression and dementia who were followed longitudinally to confirm the diagnosis. Two groups of patients, those with dementia with depressive features and those with depressive pseudodementia, were defined. There were significant group differences on waking EEGs between those "mixed" patients who did well after treatment for depression (depressive pseudodementia) and those with dementia with secondary depression. Most patients with dementia with secondary depression had abnormal EEGs, with approximately one-third having moderate or severe abnormalities. In contrast, patients with depressive pseudodementia had EEGs that usually were normal or showed only mild abnormalities.

AMNESIC SYNDROMES

Transient Global Amnesia

Since its first description, transient global amnesia (TGA) has aroused the interest of electroencephalographers, but conflicting reports of normal EEGs, epileptiform activity, and focal slow-wave activity have clouded the picture. In an early study, Jaffe and Bender (87) reported normal EEGs in 26 of 27 patients; the only exception was a patient who showed nonspecific temporal slowing during and after TGA. Subsequently, there have been reports of a small group of patients with TGA in whom interictal EEGs demonstrated spike-and–sharp wave abnormalities (58,66,109,170,189,199). These studies led to the suggestion that TGA may represent an epileptic seizure involving mesial temporal structures involved with recent memory. The evidence for epileptic etiology has been largely based on the presence of interictal EEG abnormality over the temporal region or a good response to antiepileptic medication. Not only is this evidence weak, but also in many studies the illustrations showed a variety of nonspecific benign variants, such as benign epileptiform transients of sleep, that have no correlation with epileptic seizures.

An EEG has rarely been recorded during an actual episode of TGA. In a large series of 117 patients with TGA, Miller et al. (122) had 13 EEG recordings made during episodes of TGA; 8 showed no abnormality, 1 had subclinical rhythmic electrographic discharge of adults, and the remaining 4 had nonspecific theta-delta slowing, either generalized or focal. None contained epileptiform abnormalities during TGA. Only a few patients have been reported who, during a supposed TGA, had an ictal pattern recorded over the temporal region (86,120,196).

Large case–control studies on TGA in recent years have concluded that TGA is commonly related either to cerebral ischemia (thromboembolic or hemodynamic) (70,99) or to migraine (81,118). In only one large series on TGA (81), comprising 114 patients, did a significant minority (7%) develop epilepsy, usually within 1 year of presentation. One can make a valid conclusion that, in most patients with TGA, the EEG both interictally and during the episodes is normal or shows nonspecific slow-wave abnormalities; only on occasion do epileptic seizures masquerade as TGA.

Korsakoff's Syndrome

Korsakoff's syndrome, a chronic amnesic state, usually follows an acute episode of Wernicke's encephalopathy. In the acute phase, EEGs are abnormal in about 50% of patients, with the abnormality consisting of background slowing in the theta-delta range (207). When Korsakoff's syndrome emerges, the EEG usually has become normal.

CONCLUSIONS

In evaluating changes in mental state, EEG has definite advantages counterbalanced by significant limitations. Bearing these in mind, electroencephalographers can offer help to clinicians in certain circumstances. In patients with abrupt onset of confusional or catatonic-like states, EEG can confirm or refute the occurrence of nonconvulsive status epilepticus, which can develop at any time from childhood to old age. In patients in whom mental changes emerge more gradually, EEG may suggest (a) a metabolic basis such as chronic uremia or hepatic encephalopathy or (b) a focal cerebral lesion such as subdural hematoma. With relatively rapidly developing dementia, EEG may provide the first laboratory evidence for CJD, with its characteristic periodic discharges. In the early stage of AD, overlap with healthy elderly persons and depressed patients reduces the specificity of EEG. EEG has value in the differential diagnosis of clinically established dementia. Preserved alpha rhythms characterize Pick's or frontotemporal dementia, as opposed to AD or PSP dementia. "Flat" EEGs with background activity voltages less than 10 μV occur in a majority of demented patients with Huntington's disease. Thus, although most of the EEG abnormalities in dementia are "nonspecific," the available clinical information can enable electroencephalographers to give balanced, useful appraisals.

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Chapter 14

Electrophysiological Evaluation of Coma, Other States of Diminished Responsiveness, and Brain Death

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Electrophysiological Evaluation of Coma: Associated Electroencephalographic Patterns
- Intermittent Rhythmic Delta Activity
- Alternating Pattern
- Continuous High-Voltage Delta Activity
- Pseudoperiodic Patterns
- Interictal Epileptiform Discharges and Seizure Discharges
- Low-Voltage, Slow, Unreactive EEG
- Unilateral, Lateralized, or Focal Alterations
- Triphasic Waves
- Sleep Patterns
- Rhythms of Alpha Frequency

Goals of Electrophysiological Testing in Comatose States
- Providing Objective Measures of Brain Dysfunction
- Establishing the Etiology of Coma: Differentiating between Toxic-Metabolic Causes and Structural Lesions
- Localizing Structural Lesions: Differentiating between Hemispheric and Brainstem Lesions and Determining Rostrocaudal Levels of Brain Dysfunction
- Determining Depth and Predicting Clinical Outcome of Coma
- Following the Evolution of Comatose States
- Distinguishing Coma from Other Conditions of Diminished Responsiveness

Electrophysiological Evaluation of Other States of Diminished Responsiveness
- Selective Failure of Forebrain or Brainstem Function
- Vegetative States

Electrophysiological Evaluation of Brain Death
- Brain Death in Adults
- Brain Death in Neonates, Infants, and Small Children

Conclusions

References

ELECTROPHYSIOLOGICAL EVALUATION OF COMA: ASSOCIATED ELECTROENCEPHALOGRAPHIC PATTERNS

Early work considered bilateral high-voltage slow waves to be the electroencephalographic (EEG) manifestations of coma, which, in turn, was regarded as equivalent to deep sleep (114,178). However, it was soon realized that, as coma deepened, the EEG commonly underwent changes that were different from those of sleep and were associated with increasingly altered and ultimately abolished effects of external stimuli ("EEG reactivity") (159). Distinct EEG patterns were also identified in comatose patients that included "triphasic waves" (TWs) (45), alpha rhythms commonly associated with wakefulness (297), other patterns of alpha frequency (474), and spindles and other waveforms characteristically seen in various stages of normal sleep (86). Special efforts were made and are still in progress to determine the relations between EEG patterns and reactivity and other variables, including etiology and duration of coma and other unresponsive states, underlying pathological lesions, and clinical outcome.

EEG patterns displayed by comatose patients are not unchanging and mutually exclusive features, but instead often transiently express mutable pathological influences. They may also evolve into one another during successive examinations or may occur in the same recording (159). Thus the description of distinct EEG patterns that follows is at least partly artificial and primarily serves descriptive purposes.

Among the EEG patterns variably associated with comatose states, the following deserve special consideration: intermittent rhythmic delta activity (IRDA); alternating pattern; continuous high-voltage delta activity; pseudoperiodic patterns; interictal and ictal epileptic discharges; low-voltage, slow, unreactive EEG; unilateral, lateralized, or focal abnormalities; TWs; sleep patterns; and rhythms of alpha frequency.

Intermittent Rhythmic Delta Activity

IRDA may appear in early stages of coma simultaneously with or after disorganization or loss of alpha rhythm and development of scattered theta and delta waves. IRDA (Fig. 14.1) consists of bursts of high-voltage, regular,

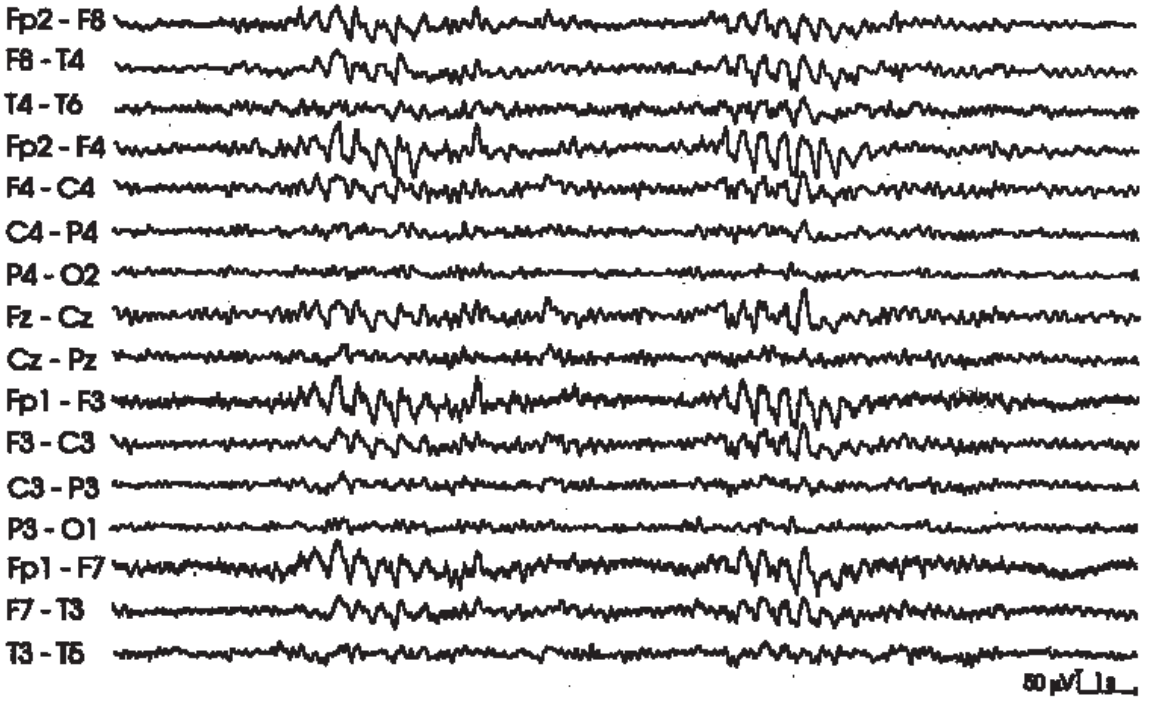


FIG. 14.1. Bursts of high-voltage bilaterally synchronous frontal intermittent rhythmic delta activity in a 41-year-old lethargic patient with uremic encephalopathy. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

quasi-sinusoidal waves, mostly at 2–3 Hz. Bursts may be bilateral or unilateral. When bilateral, they are typically synchronous but may be either symmetrical or asymmetrical (148). IRDA is characteristically most prominent over the frontal regions in adults but over occipital areas in children. Bursts may be blocked by eye opening. Some alteration of consciousness is especially common with bilateral, fairly persistent IRDA. This pattern occurs in a wide variety of conditions, including (a) supratentorial hemispheric or midline lesions (113,148,221), with increased pressure within the third ventricle (113,221); (b) toxic or metabolic encephalopathies (213); and (c) widespread structural brain disease predominantly involving both subcortical and cortical gray matter (183). It is commonly believed that IRDA is an expression of abnormal interactions between cortical and subcortical (thalamic) neuronal systems (181,403). Why IRDA generally prevails over the frontal areas in adults and over the occipital regions in children is unclear.

Alternating Pattern

The alternating pattern consists of alternating periods of high-voltage, widespread delta activity and lower voltage irregular potentials. These two EEG features are accompanied by characteristic autonomic and muscular changes (20,141,159). Noxious and other stimuli delivered during periods of low-voltage activity tend to be followed by high-voltage delta waves, whereas the opposite often occurs with excitations delivered in the presence of high-voltage delta activity (20,159). According to some (141), reactivity of this pattern to noxious and other excitations tends to be associated with favorable clinical outcome.

Continuous High-Voltage Delta Activity

In many comatose states there is continuous or nearly continuous high-voltage, mostly arrhythmic, 1- to 2-Hz activity over all head regions (114,178) (Fig. 14.2). In early stages of coma, this activity may be attenuated by external stimuli, but more commonly it is unaffected. Reactivity to noxious and other stimuli generally is lost in deeper stages of coma (293,414). This pattern tends to be associated with an unfavorable clinical outcome (141). Widespread continuous delta activity is common in patients with encephalopathies caused by structural lesions primarily involving subcortical white matter (183), and localized delta activity appears in the cor-

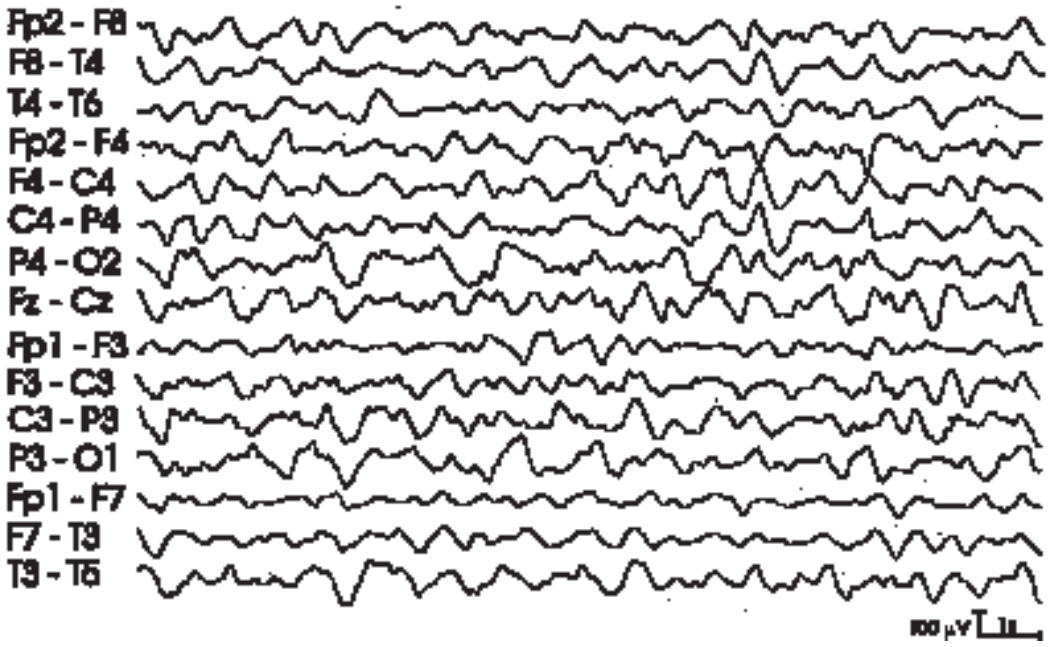


FIG. 14.2. Widespread high-voltage arrhythmic delta activity in a 36-year-old man 13 hours after head injury sustained in a motor vehicle accident. The patient was deeply comatose and artificially ventilated, with midposition fixed pupils, poor oculocephalic and caloric responses, and bilateral extensor posturing with noxious stimulation. He died 5 days later. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.).

tex overlying a circumscribed white matter lesion in animals (182). Thus it has been suggested that cor tical deafferentation may play a major role in generating continuous widespread delta acti vity in comatose indi viduals (182,403).

Pseudoperiodic Patterns

Some comatose patients display bilateral widespread pseudoperiodic patterns in their EEGs. These include burst-suppression and periodic generalized epileptiform discharges.

Burst-suppression (Fig. 14.3) consists of somewhat stereotyped bursts of bilaterally synchronous, widespread high-voltage delta and theta waves with or without intermixed spikes and sharp waves. These bursts are separated by intervals during which the EEG shows no activity discernible at usual instrumental sensitivities or low-voltage potentials of delta and theta frequenc y. Interburst intervals commonly last from 2 to 10 seconds, although durations of several minutes or longer are occasionall y observed. Myoclonic jerks may occur during bursts (257,299,384) or without consistent relationships to them. Clinical conditions most commonly producing coma with EEG burst-suppression include (a) acute intoxication with drugs depressing central nervous system (CNS) function (48,206,252,311,441,489); (b) se vere anoxic encephalopathies (223,281,283,365,377,384,415) (F ig. 14.3); (c) se vere hypothermia (361); and (d) anesthesia produced b y various agents (237,248,317,381,508).

Pseudoperiodic generalized epileptiform discharges (PGEDs) (Fig. 14.4) consist of spik es, multiple spik es, or shar p waves occurring bilaterally synchronously over all head regions, generally at 0.5–1 Hz, with intervening periods of apparent inacti vity or low-voltage slow activity. Bilateral myoclonic jerks are often present and sho w close, variable, or no apparent g ross temporal relations to the EEG dischar ges. PGEDs occur most commonl y in comatose patients following acute, severe cerebral anoxia (235,308,365,449) and in Creutzfeldt-Jak ob disease (1,53,99,291,324), although the y may be absent in the ter minal stages of the latter condition w hen consciousness is most impaired. They have also been reported in metabolic and toxic encepha-

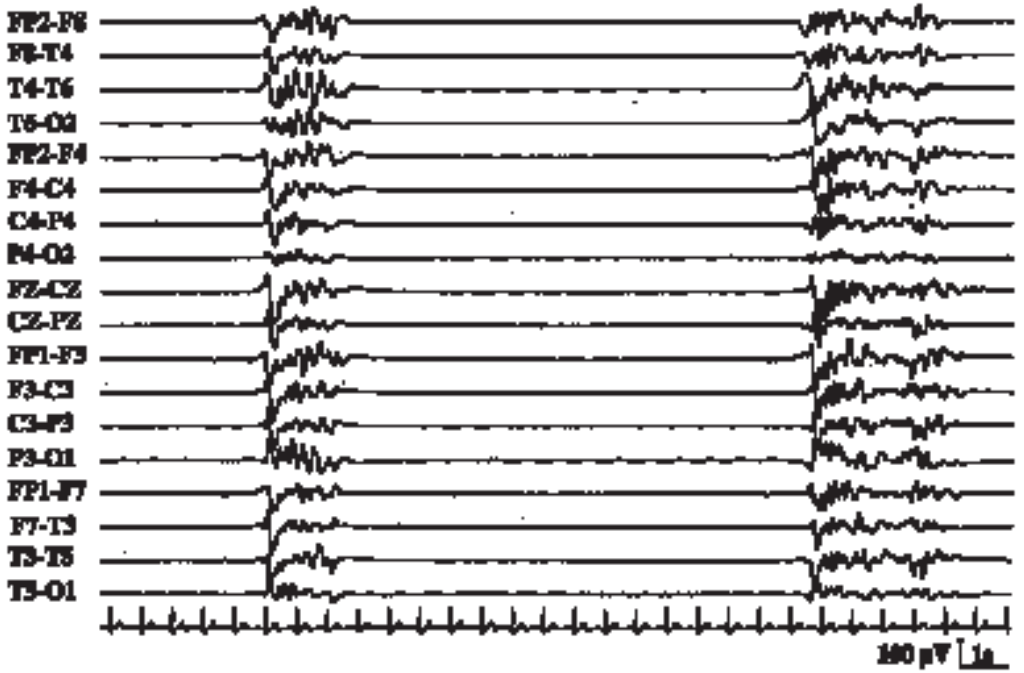


FIG. 14.3. Burst-suppression pattern in a 73-year-old woman 24 hours after a 20-minute cardiac arrest. The patient was comatose, artificially ventilated, and given pancuronium bromide to suppress bilateral myoclonic jerks associated with the bursts. Death occurred 72 hours later. Same patient as in Figure 14.6.

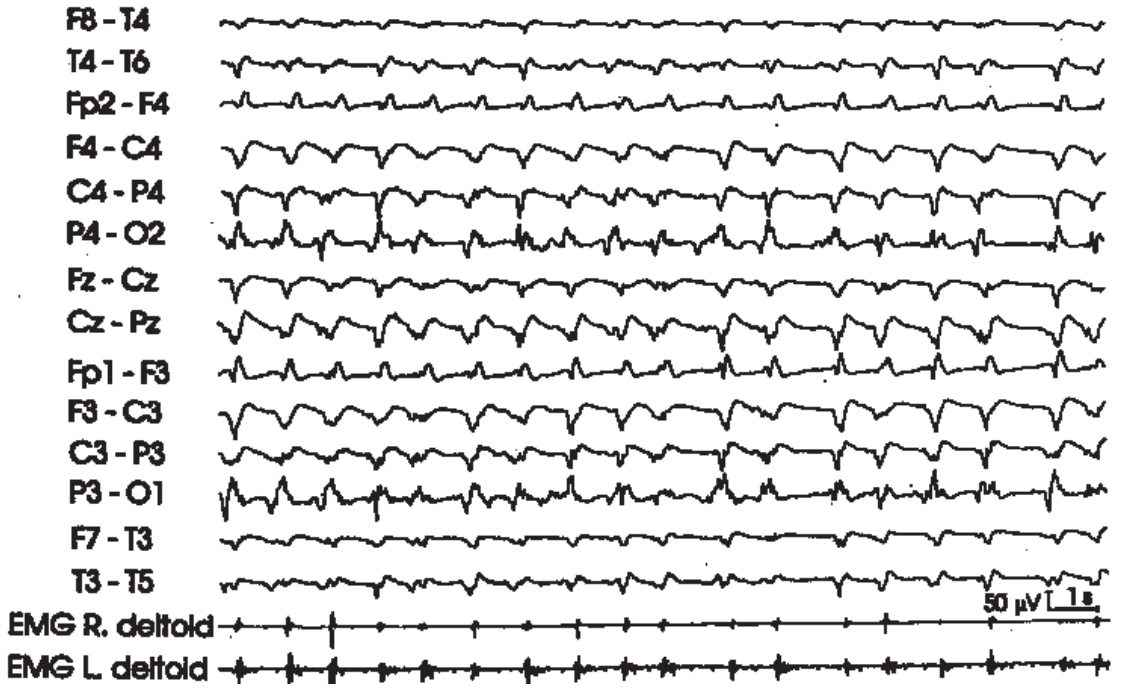


FIG. 14.4. Pseudoperiodic generalized sharp waves and spikes repeating at 1–1.5 Hz. EEG discharges show gross temporal relationships to muscular jerks involving the chin and both shoulders. This 66-year-old man was comatose as a result of alcoholic liver disease with cirrhosis complicated by bowel infarction, recent bowel resection, and respiratory alkalosis. He died 12 days later. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

lopathies such as those induced by lithium (419) and baclofen (147,226). Some authors (235) categorize atypical TWs associated with toxic-metabolic encephalopathies as PGEDs, although this pattern has no clearly established relation to epilepsy. Occasionally, patients comatose from acute anoxia display unremitting bilaterally synchronous spike-and–slow wave complexes occurring rhythmically at 2–3.5 Hz (37,69,299,417) (Fig. 14.5).

Most comatose patients with postanoxic burst-suppression pattern or PGEDs die, but a few survive, generally with major neurological disabilities (223,257,365,377,495,512). In contrast, a substantial number of individuals with burst-suppression caused by drug intoxication recover, often without neurological sequelae (48,311,439). Characteristically, as a patient's condition worsens, bursts become shorter, simpler in form, and lower in voltage, and periods of suppression become longer until electrocerebral inactivity (ECI) supervenes. In contrast, shortened suppression intervals, prolonged bursts, and gradual reappearance of physiological rhythms characterize clinical recovery.

Intracellular recordings during burst-suppression produced by anesthetic agents in cats have demonstrated the occurrence of a characteristic sequence of phasic depolarization of cortical neurons associated with the EEG burst and sustained hyperpolarization of the same elements associated with the interburst interval. Simultaneous recordings from thalamic neurons suggested that thalamic networks might trigger the recurrent EEG bursts (432). However, cortical slabs isolated from all subcortical (as well as cortical) connections characteristically display burst-suppression in both animals and humans (138,217). Evidence has been produced that the mechanisms underlying postanoxic burst-suppression might differ in some respect from those operating in drug-induced burst-suppression (44). Subcortically triggered cortical excitatory events alternating with prolonged inhibitory events have also been postulated by some to account for the PGEDs occurring following cerebral anoxia and in Creutzfeldt-Jakob disease (54,72,183,432). Other investigators have hypothesized that, in Creutzfeldt-Jakob disease, fusion of neuronal processes, particularly dendrites, may lead to abnormal electro-

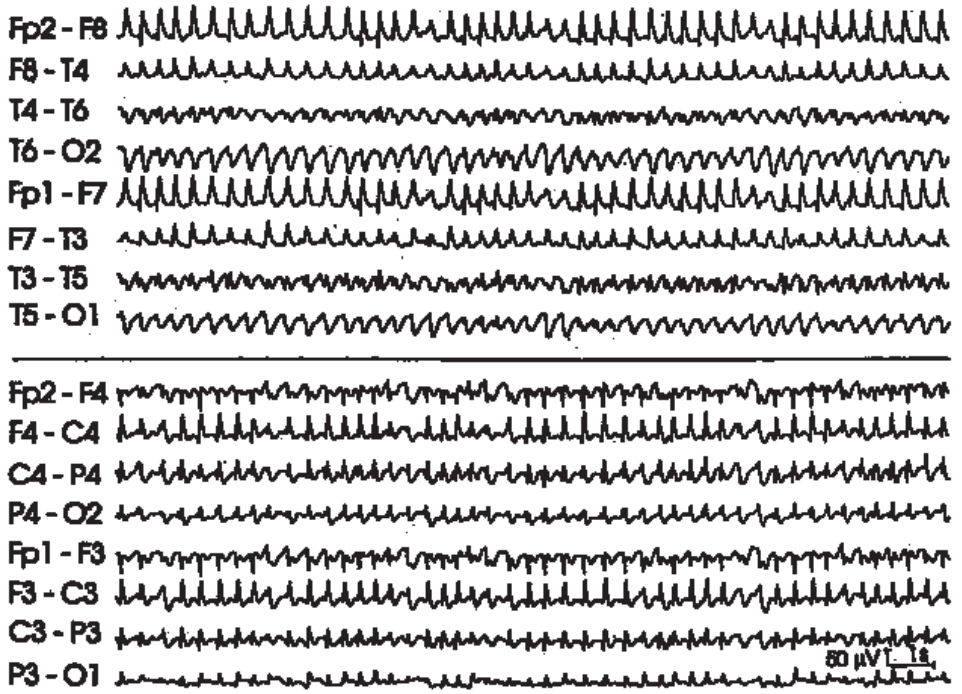


FIG. 14.5. Unremitting generalized 2.5- to 3-Hz spike-and–slow wave complexes in a 78-year-old man. Following a cardiac arrest resulting from myocardial infarction, he was comatose with midposition pupils sluggishly reactive to light, had faint corneal and absent oculocephalic reflexes, and demonstrated intermittent fluttering of the eyelids. Noxious stimuli elicited extensor posturing. He died 4 weeks later. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

tonic coupling between cells, providing the basis for powerful excitatory interactions that cause large neuronal aggregates to burst in near-synchrony (464).

Periodic lateralized epileptiform discharges (PLEDs) (85) sometimes occur over variable extents of one hemisphere (with frequent reflection over the homologous areas of the opposite side) and occasionally appear over both hemispheres independently (117). PLEDs are found in patients with a variety of hemispheric lesions, including acute infarction, hemorrhage, tumors, and infections (85,313), especially when associated with metabolic abnormalities (85,347), infections such as herpes simplex encephalitis (97), long-standing lesions such as old infarcts (85), and chronic seizure disorders (85,371).

Periodic generalized slow-wave complexes that repeat at intervals of 4–14 seconds and are associated with myoclonic jerking characterize patients with subacute sclerosing panencephalitis (102,103), and periodic lateralized slow-wave complexes, also accompanied by focal jerking, occur with various hemispheric lesions (85). These patients' consciousness may be variously impaired.

Interictal Epileptiform Discharges and Seizure Discharges

Interictal epileptiform and seizure discharges, whether focal or generalized, can occur in comatose patients, especially with cortical contusions, intracerebral hematomas (107,436,449), systemic metabolic derangements such as uremic (213) and hepatic (151) encephalopathies, and acute brain anoxia (308,417,449).

Low-Voltage, Slow, Unreactive EEG

A low-voltage, slow, unreactive EEG (Fig. 14.6), consists of arrhythmic potentials in the delta and theta ranges generally not exceeding 20 µV that are unmodified by sensory stimuli. Such a pattern is common among

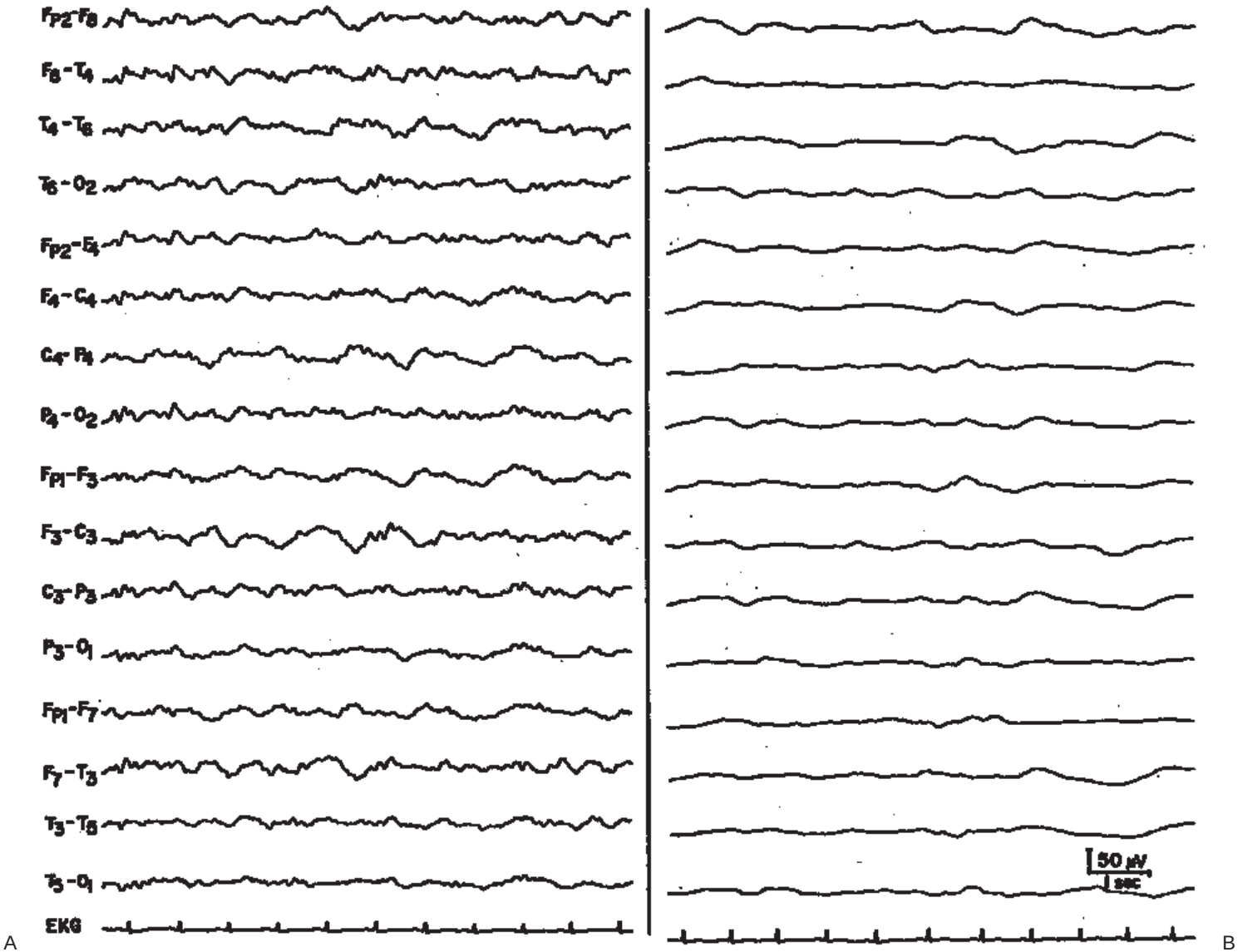


FIG 14.6. Widespread arrhythmic 1- to 2-Hz activity intermixed with 5- to 7-Hz potentials **(A)** evolving into a low-voltage, slow, unreactive pattern **(B)**. This 24-year-old patient was comatose following an episode of ventricular fibrillation that occurred after strenuous exercise. **A:** On admission, he had spontaneous respiration and preserved corneal and oculocephalic reflexes. **B:** Ten days later, he required artificial ventilation and his corneal reflexes could no longer be elicited. He survived 15 days. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

comatose patients with severe, widespread cortical damage, who either die or survive in a vegetative state. One must distinguish this low-voltage, slow, unreactive pattern from the low-voltage EEG found in some healthy subjects. The latter type consists of diffuse activity not exceeding 20 μV, composed of mixed beta, theta, and, to a lesser degree, delta activity, with or without alpha rhythm. Unlike the low-voltage, slow, unreactive EEG of comatose patients, this normal record changes with certain physiological stimuli, hyperventilation, sleep, and pharmacological agents (76).

Unilateral, Lateralized, or Focal Alterations

In some circumstances, large unilateral lesions of the cerebral hemispheres producing coma may cause unilateral, lateralized, or, less frequently, focal EEG changes. These occur ipsilaterally to the lesion and consist of one or more of the following:

Arrhythmic delta activity distinguishable from more widespread slow waves because of slower frequency, higher voltage, or both
Diminished voltage of continuous or intermittent delta activities
Decreased amplitude of intermixed fast activity
Decreased voltage of EEG responses to external stimuli (20)
Diminished amplitude of characteristic EEG patterns such as TWs (154) or sleep patterns (61)
Interictal or ictal epileptic discharges, including PLEDs as noted above (85,107,371,435,449)

Generally, unilateral alterations are especially obvious in lighter stages of altered responsiveness and become less apparent or disappear with deepening coma. They sometimes occur in toxic-metabolic encephalopathies, including nonketotic hyperosmolar diabetic coma, in the absence of hemispheric lesions (213,305). In patients who have undergone surgery, spurious asymmetries may result from apparently augmented voltages over skull defects.

Triphasic Waves

Early studies reported the occurrence of bursts of characteristic complexes in the EEGs of patients with hepatic coma. These waveforms, first described as 2 per second "blunt spike and wave" because of their appearance in referential montages (162), were later renamed "triphasic waves" (45) based on their form in bipolar derivations. TWs consist of a high-voltage "positive" potential preceded and followed by "negative" deflections of lower voltage (45) (Figs. 14.7 and 14.8). They were originally described as bilaterally synchronous, generalized, and maximal over the frontal or, less frequently, the occipital or temporal areas. TWs were said to appear first over anterior regions and later over posterior areas. The fronto-occipital "phase lag" of the major "positive" component varies from 25 to 140 milliseconds (45). In subsequent studies, TWs predominated on anterior regions in 60% of records and posteriorly or diffusely in 40%. They were lateralized in 9% of patients, mostly with structural hemispheric lesions. Phase lags were less apparent in referential (27%) than in bipolar longitudinal (73%) montages (154). The triphasic morphology varies considerably. Some complexes have an especially sharp, spike-like first component, whereas other waves are monophasic, diphasic, or quadriphasic (307,413). Morphological congruence over homologous areas is also mutable. Repetition rate of TWs is mostly about 2 Hz but is occasionally slower (29).

Relation to Diminished Consciousness

Some investigators have reported that, as consciousness declined in patients with hepatic encephalopathy, EEGs successively displayed widespread theta activity, TWs, arrhythmic delta activity, and, finally, generalized "suppression." Patients in the triphasic and delta stages were "semicomatose or completely unresponsive" (45) or were in grades II–III of hepatic coma, characterized by somnolence and stupor (306). However, other researchers observed a wider range of altered consciousness, and some even reported normal responsiveness in patients with TWs from various causes (29,62,154,214,307,374,413,418). EEG reactivity was also variable (154).

Etiological Specificity and Prognostic Significance

The diagnostic specificity of TWs has been the subject of controversy (3,45). Reiher (385) distinguished "typical" TWs having the features described by Bickford and Butt (45) from "atypical" TWs not meeting all criteria. He regarded the former as "pathognomonic" for hepatic coma, whereas the latter could appear in both hepatic and other metabolic encephalopathies, CNS degenerative disorders, cerebrovascular lesions, and supratentorial and infratentorial tumors. This distinction did not win general acceptance. At present, most electroencephalographers agree that TWs, whether typical or atypical, can occur in various toxic-metabolic encepha-

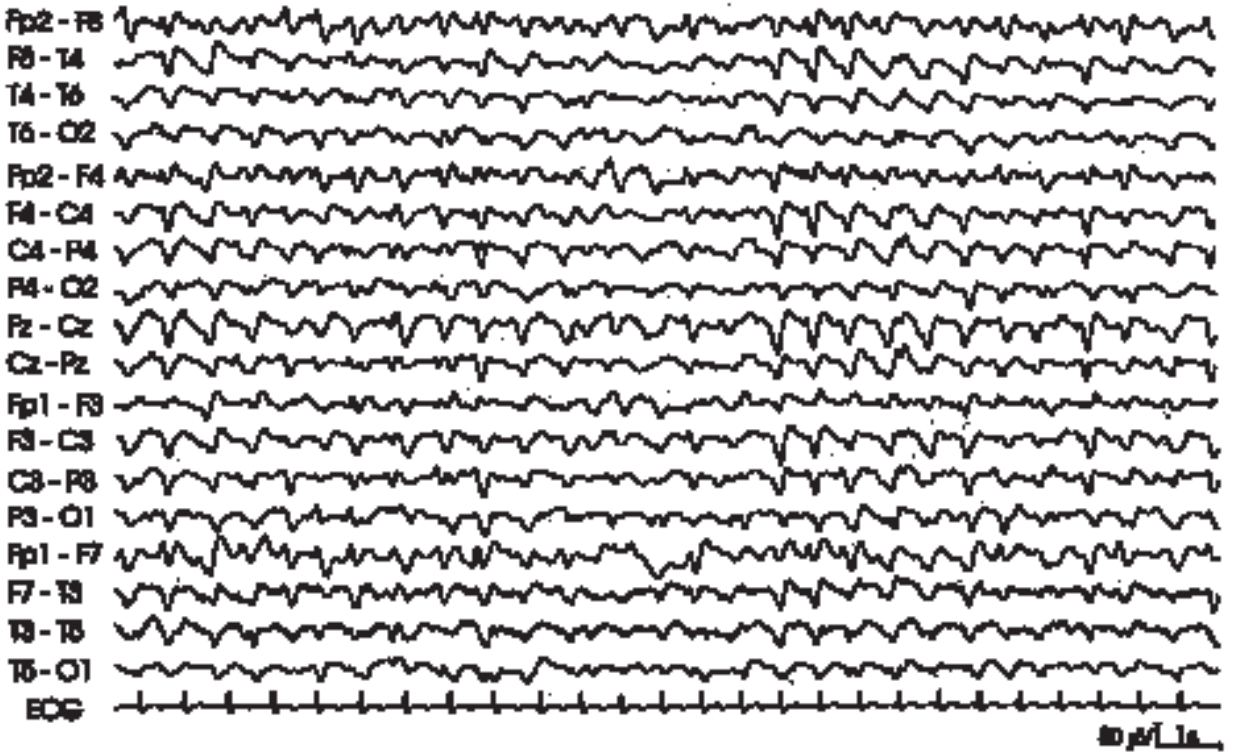


FIG. 14.7. Triphasic waves in a 53-year-old lethargic woman with hepatic encephalopathy. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

lopathies whether the latter are due to hepatic failure (Fig. 14.7) or other causes. These include uremia (29,154,213,214,306,498); valproic acid–induced hyperammonemic encephalopathy (269), severe water and electrolyte imbalance (29,214,266); hypercalcemia (452); anoxia (29,154, 214,452,498) (Fig. 14.8); hypoglycemia (29,214,266); hyperthyroidism (374,376,472); myxedema (391); Hashimoto's encephalopathy (216); accidental hypothermia (390); intoxication with CNS depressant and other drugs (280), including baclofen (226), levodopa (346), and pentobarbital (284); and serotonin syndrome (127). Currently, there is widespread agreement that no single feature or combination of features of TWs distinguishes hepatic from other metabolic encephalopathies or nonmetabolic conditions (29,154,307,418).

Investigators have described TWs in awake, confused patients with Alzheimer's disease and other dementias (50,376,447) and in individuals with vascular, degenerative, neoplastic, infectious, or traumatic brain pathologies (5,154,159,330,385,413,414,446,509) and even in subdural hematomas (307,488). In some publications, it is difficult to determine whether concurrent systemic metabolic derangements existed and whether the EEG patterns were TWs, waveforms superficially resembling TWs, or even triphasically shaped epileptiform discharges. Differentiating TWs from epileptiform patterns is complicated by the finding of TWs in uremic and other encephalopathies frequently associated with seizures (79), and the detection of variously triphasic sharp-and–slow wave complexes in some ictal (353) or postictal (357) stuporous states. To our knowledge, TWs have not been reported in children (306).

Mortality is high among patients with TWs who suffer from metabolic disorders and severe anoxia (29,266,306), whereas it varies in other conditions depending on etiology.

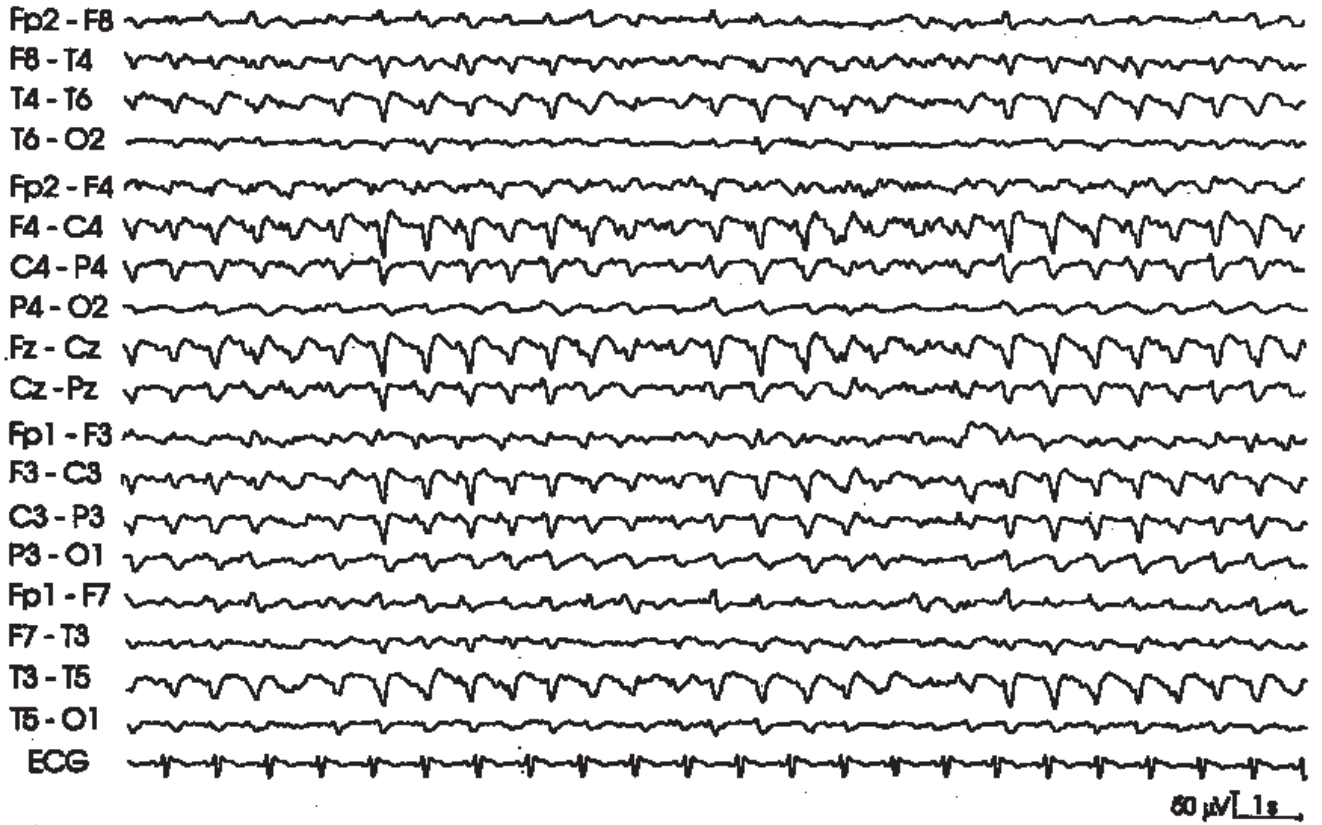


FIG. 14.8. Triphasic waves in a 66-year-old comatose man 2 days after cardiac arrest resulting from myocardial infarction. Following resuscitation, the patient remained comatose and developed episodes of twitching of the face with hiccup and upward deviation of the eyes that subsided with phenytoin and phenobarbital treatment. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

Pathophysiological Interpretations

Factors responsible for TWs are poorly understood. It seems plausible that, in patients with systemic metabolic derangements, this pattern reflects primary biochemical disturbances. The finding that elevated blood ammonia levels cause TWs in patients with hepatic insufficiency (374) remains unconfirmed (413). It seems more likely that TWs in hepatic coma are due to multiple metabolic alterations (306) recently summarized by Young and DeRubeis (511).

In bipolar montages, a fronto-occipital lag of the main "positive" component of TWs suggested a traveling wave sweeping the scalp front to back at about 1.5 m per second (45). However, in referential montages, this phase shift is frequently lacking (45,154,418). To account for this discrepancy, Harner and Simsarian (214) proposed a longitudinal dipole model of TWs, interpreting the apparent anteroposterior delays in bipolar derivations as being due to "differential recording of activity which was synchronous, but 180 degrees out of phase in anterior and posterior loca-

tions." However, Fisch and Klass (154) observed more complex phase relationships.

Some authors (45,162,266) hypothesized that TWs reflected disturbed thalamocortical relays recruiting metabolically impaired cortical neurons. Similar interpretations were offered by other investigators (306). In the absence of animal models of TWs (306), these interpretations remain speculative.

Sleep Patterns

In Diurnal EEGs

Diurnal EEGs of some comatose individuals display patterns of sleep including spindles and vertex sharp waves intermixed with widespread delta and theta activity (Figs. 14.9 and 14.10A). In most patients, loud auditory or noxious stimuli elicit K complexes or bilateral bursts of delta activity, often mixed with rhythmic waves of theta and alpha frequency over posterior areas (Fig. 14.9) (37,40,46,57,61,65,75,86,87,112,141,210,220,229–231,236,245, 298,344,377,398,399,414,434,435,449,454,475). Occasionally, changes occur during an individual EEG that mimic transitions from stages 1 to 4 of non–rapid-eye-movement (NREM) sleep, although consciousness does not appear to vary (87).

In Nocturnal Polygraphic Records

Some individuals who are comatose or vegetative following head injury demonstrate some or all of the nocturnal polygraphic patterns and behav-

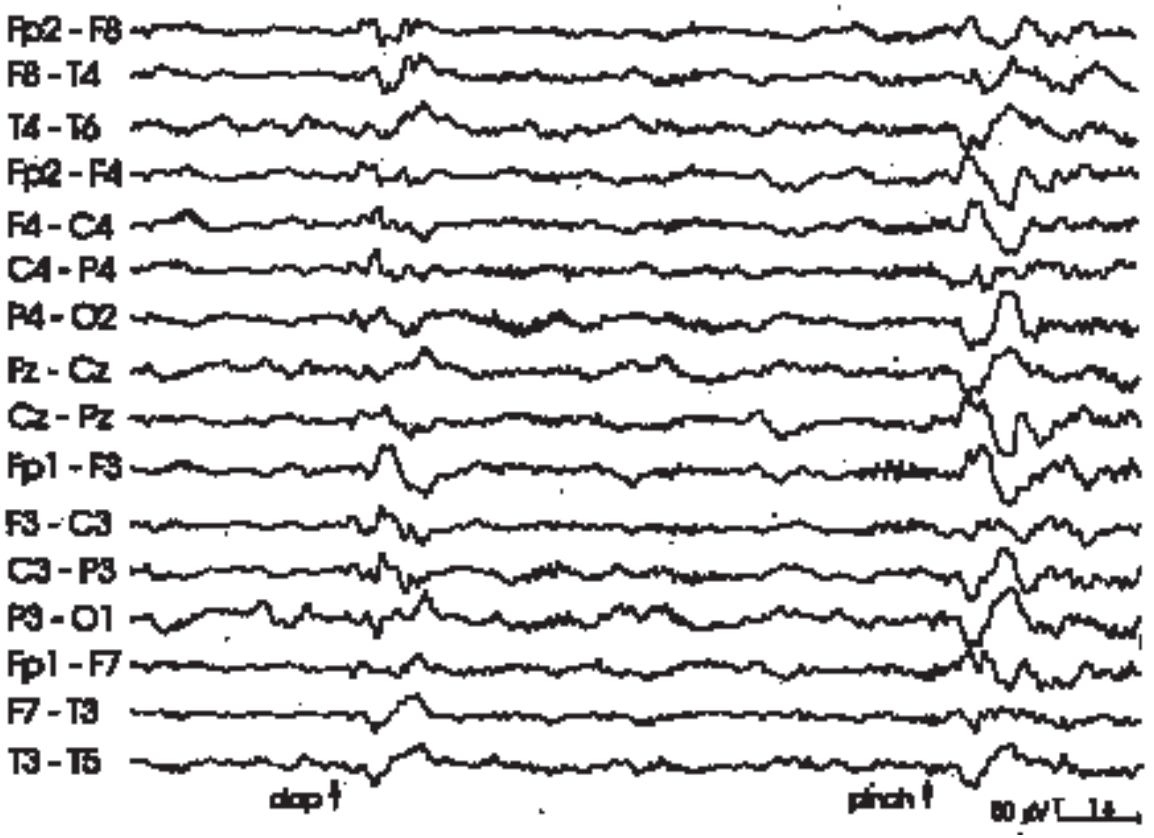


FIG. 14.9. EEG patterns of sleep, including spindles, and K complexes in response to auditory and noxious stimuli. Twelve hours after head injury, this 17-year-old girl was stuporous and demonstrated anisocoria, left pupil larger than right, and left Babinski's sign. Noxious stimulation elicited inconstant withdrawal movements and agitation. The patient recovered with slight left upper extremity paresis. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

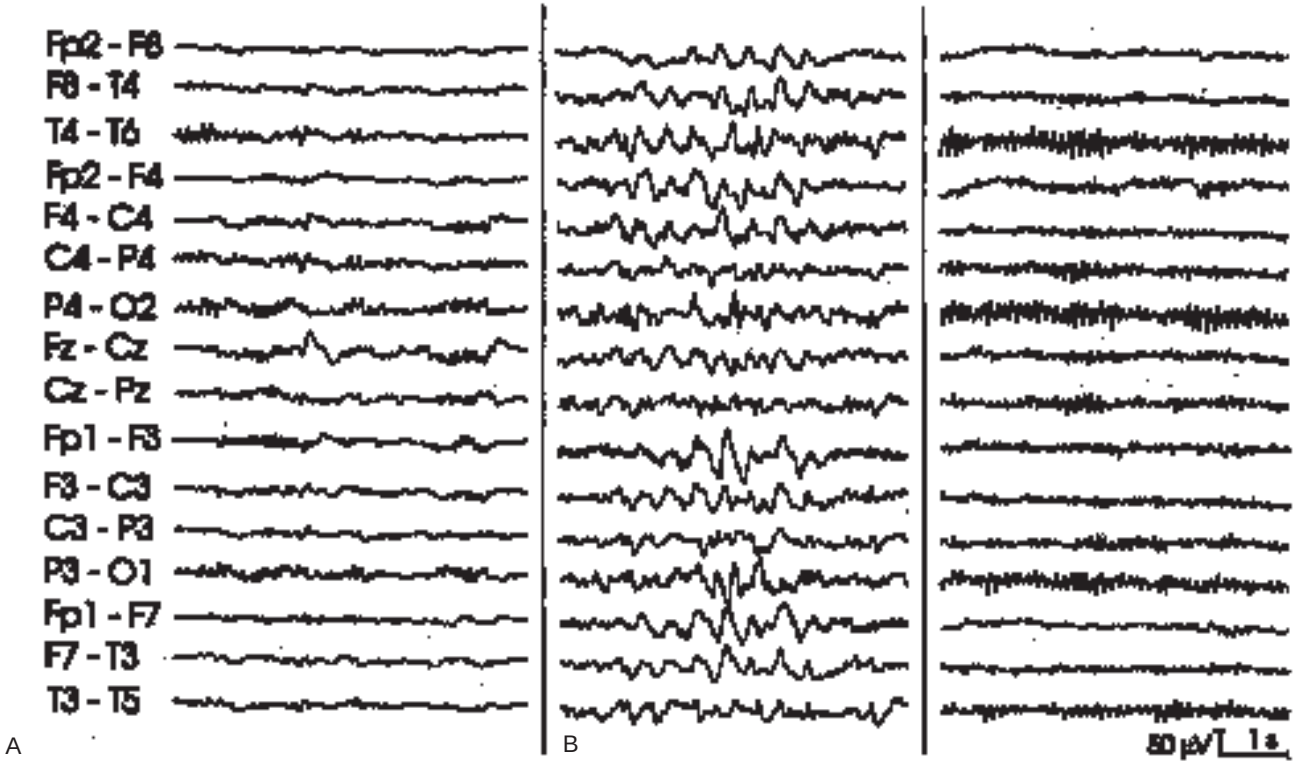


FIG. 14.10. Serial EEGs recorded in the same patient as in Figure 14.9. **A:** Patient stuporous with sleep spindles 12 hours after injury. **B:** Patient alert but agitated 4 days after the accident. **C:** Patient alert and quiet 18 days after trauma. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

ioral signs of sleep (39,40,56,57). In certain subjects, no EEG sleep patterns are detected. Some of these latter patients display "biphasic" nocturnal patterns consisting of alternating periods of high-voltage slow and low-voltage faster activities, whereas a "monophasic" pattern consisting exclusively of slow activity appears in other individuals (39,40,57).

Prevalence and Etiology

Many studies of comatose states associated with spindles and other patterns of sleep in diurnal EEGs were conducted on patients who had suffered head injury (37,39,46,57,59,63,75,86,87,106,136,141,210,220,229,230,236,298,344,377,398,399,414,434,435,449,454,475). However, other etiologies were associated with coma and EEG patterns of sleep. These included tumors principally involving the floor of the third ventricle or midbrain but sparing the thalamus (245); acute cerebral anoxia (61,210,231,377); viral encephalitis (52,112); cerebral, thalamic, brainstem, or cerebellar hemorrhage or infarction (61,210); subarachnoid hemorrhage (61); drug intoxication (61,264); metabolic encephalopathies; postictal state; and other or multiple etiologies.

Pathophysiological Interpretations and Pathological Findings

An early study hypothesized that a transient, reversible functional derangement of the midbrain reticular formation was responsible for the impaired responsiveness and the sleep EEG patterns observed in some patients following head injury (87). Other works suggested that sleep spindles in daytime recordings expressed a functional disturbance or anatomical lesion(s) involving (a) the hypothalamus and midbrain (245); (b) the midbrain (398); (c) deep-

seated structures below the diencephalon (414); (d) rostral parts of the brainstem (220); and (e) the pontomesencephalic reticular formation (301). Regrettably, pathological observations confirming these interpretations are few and scanty. Luecking (301) reported "minimal lesions in the reticular formation of the midbrain" in an unspecified number of patients who had suffered head injury and died from extracerebral causes. Prior (377) described generalized edema, as well as a "rather soft and almost necrotic" brainstem, in an individual following cerebral anoxia. In the patients studied by Hansotia et al. (210), lesions of unspecified nature and extent were found scattered in the cerebral hemispheres, diencephalon, midbrain, and pontomedullary and cerebellar regions. Also, a hemorrhage was demonstrated by computed tomography in the rostral midbrain of a patient in posttraumatic coma with spindles (63). Whatever their nature and location, the structural alterations responsible for the manifestation of sleep patterns in comatose patients appear to be compatible with a considerable degree of functional preservation of the cerebral hemispheres. It is conceivable that preeminent functional alterations of critical brainstem structures may also account for the manifestation of sleep EEG patterns in patients rendered comatose by more widespread disorders such as metabolic, infectious, and anoxic encephalopathies.

Bricolo et al. (57) attempted to explain results of overnight polygraphic records of "prolonged post-traumatic" (presumably vegetative) patients by postulating lesions or combinations of lesions at various brainstem, diencephalic, and cortical levels, but these conjectures were not supported by pathological observations.

Relations to Duration, Depth, and Functional Levels of Coma

Short diurnal (399,475), polygraphic nocturnal (39,57), and spectrally analyzed (58) recordings determined that spindles and other EEG patterns of sleep and organized nocturnal sleep cycles were more common in short-lasting than in long-lasting comatose states resulting from head injury. Spindles progressively decreased as depth of coma increased, becoming distorted and asymmetrical and finally disappearing (398,399,414,475). Also, typical spindles, vertex sharp waves, and K complexes diminished as patients in posttraumatic coma underwent clinically assessed rostrocaudal deterioration (398).

EEG Evolution, Clinical Outcome, and Prognostic Value

Several authors have reported that posttraumatic comas with EEG patterns of sleep in diurnal EEGs had relatively benign outcomes (39,40,56, 57,87,344,475). EEG reactivity, including elicitation of K complexes, was similarly associated with favorable outcome (141,236,399). In many instances, recovery of alertness was first associated with confusion, disorientation, intermittent restlessness, hallucinations, and appearance of widespread high-voltage rhythmic delta waves (see Fig. 14.10B). Subsequently, mental status and EEG gradually cleared, although some neurological deficits often persisted (87) (Fig. 14.10C). Other investigators broadened their observations to include comas with spindles of various etiologies. In the National Institute of Neurological and Communicative Disorders (NINCDS) Collaborative Study, only a few individuals who were comatose and apneic from various causes and demonstrated spindles in their EEGs at one time or another survived (229), an outcome not surprising in such a selection-biased group. Another investigation of patients with comas from traumatic or nontraumatic causes failed to find any relationships among (a) presence and features of spindles and other EEG patterns of sleep, (b) improved sleep organization in successive records, (c) EEG reactivity, (d) duration and depth of coma, and (e) final outcome. Death rates did not significantly differ in comatose individuals with and without spindles (210). In contrast, an individual study reported that deeply comatose patients with impaired brainstem motor functions and spindles in their EEGs had unfavorable evolutions (61). More recently, metaanalysis of the available literature showed an overall mortality of 23% in patients in coma with spindles compared to mortalities exceeding 65% in comas associated with other EEG patterns, including burst-suppression, periodic patterns, and alpha-frequency comas (265). Death or a vegetative state occurred in 73% of patients with structural lesions of the brainstem and cerebrum, 33% of individuals with hypoxia and cardiorespiratory arrest, 15% of subjects with head trauma, and none of the patients with toxic-metabolic encephalopathies or postictal states. (265). We interpret these findings as suggesting that etiology is the prime determinant of outcome in these particular comatose states.

Evoked Potentials

Limited information is available on evoked potentials (EPs) in comatose patients with EEG patterns of sleep. Short-latency somatosensory evoked potentials (SL-SEPs) (321), brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs) (445) were normal in a few infants and children with comas of various etiologies. In contrast, a child with imipramine overdose had prolonged II–V BAEP interpeak intervals (IPIs),

which subsequently returned to normal (378). These patients recovered without neurological sequelae.

Rhythms of Alpha Frequency

The EEGs of some unresponsive patients consist primarily of rhythmic activity of alpha frequency. The term *alpha coma*, coined by Westmoreland et al. (491), has popularized this notion but has done little to clarify the fundamental concept that distinctive alpha patterns characterize clinically and pathologically different entities, including some that superficially resemble, but that must be distinguished from, coma.

Unresponsive states showing EEG rhythms of alpha frequency include (a) coma secondary to acute diffuse brain anoxia or other structural pathology, (b) coma from toxic or metabolic causes, and (c) deefferented states resulting from brainstem lesions.

Widespread Alpha Activity in Coma Resulting from Acute Diffuse Brain Anoxia

The occurrence of a rhythm of alpha frequency in patients with diffuse cerebral anoxia resulting from cardiac or respiratory arrest was briefly alluded to in early reports (47,60,223,286,377). Subsequent detailed accounts described this pattern as typically consisting of a rhythm of 8–13 Hz and 10–50 μV that is detected in patients rendered comatose by acute cerebral anoxia (11,28,33,53,100,161,193,264,423,468,474,491,510). Sometimes this rhythm has a lower frequency (4–7 Hz) or consists of potentials in both the alpha and the theta ranges (264,448,453,455,510) ("theta" or "alpha-theta" coma). Most commonly the alpha activity detected in anoxic coma is sinusoidal, varies little in amplitude, and is distributed widely over the head but dominates frontally (Fig. 14.11). In our experience, this widespread rhythm is rarely modified by manual eye opening or by photic, auditory, tactile, and noxious stimuli. However, in one series, reactivity of the alpha-frequency pattern to noxious excitations was observed more frequently than in earlier studies (264).

The EEG often shows variable amounts of intermixed theta or delta waves, generally widespread but occasionally focal. The prevalence of patients with alpha activity while comatose after cardiorespiratory arrest varies from 13.3% (474) to 25.8% (28). This pattern occurs not only in adults of all ages but also in infants and children (105,225,244,336,515).

EEG Evolution and Clinical Course

The alpha-frequency pattern generally was detected within a few hours to 4 days, but occasionally as long as 6–9 days, after onset of coma (100). In

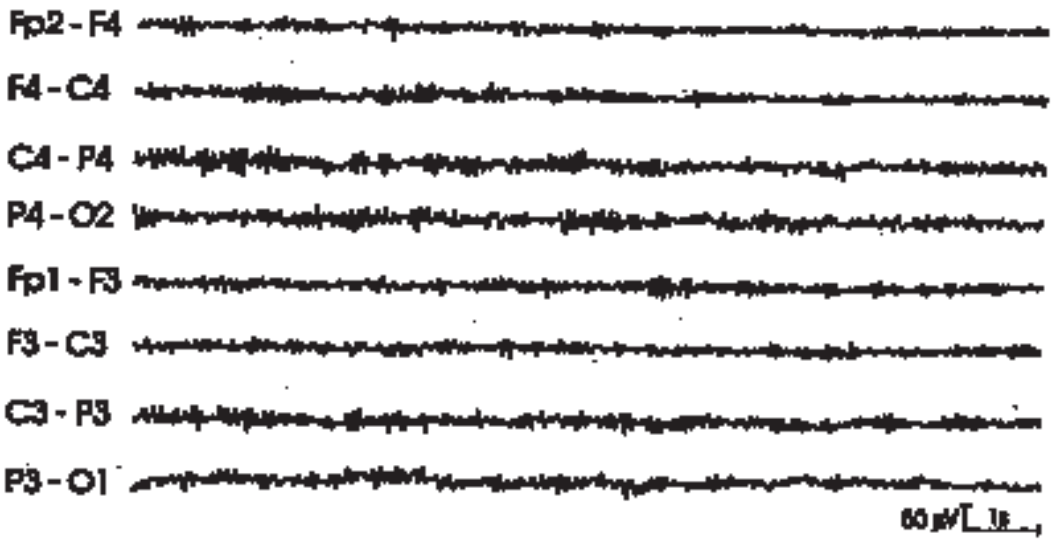


FIG. 14.11. Widespread alpha activity unaltered by sensory stimuli in a 29-year-old man 3 days after cardiopulmonary arrest resulting from accidental strangulation. The patient was comatose and exhibited extensor rigidity, small reactive pupils, and spontaneous hyperventilation. He survived 5 days. (Modified from Vignaendra V, Wilkus RJ, Copass MK, et al. Electroencephalographic rhythms of alpha frequency in comatose patients after cardiopulmonary arrest. *Neurology* 1974;24:582–588.)

serial recordings, sometimes this activity preceded, accompanied, or followed other patterns, including EEGs described as displaying no electrocortical activity (60,100) but probably not fulfilling contemporary criteria for ECI, burst-suppression (193,286,491), low-voltage unreactive activity (166) with discernible potentials in the delta and theta (423) or beta (218) ranges, widespread theta and delta activity of higher voltage (100,218,455), and generalized sharp waves and spike-and–slow wave complexes (193). Sleep (100,244,423,474) and burst-suppression (515) patterns coexisted, although exceptionally, with alpha activity.

Deteriorating clinical state often was associated with the following: diminishing voltage of theta and delta activities (193,218); manifestation of multifocal electrical seizures (225), pseudoperiodic sharp waves (490), and burst-suppression (11,218,510); and ultimately ECI (60,100,355,515). Klem and Henry (273) observed such an evolution in a single recording. In contrast, lightning of coma and gradual neurological recovery generally were first accompanied by widespread theta waves mixed with residual alpha activity unreactive to stimuli (192,335) and were later associated with gradually appearing physiological rhythms. These included alpha rhythms that were frequently low in voltage, posterior in distribution (105,192,193,423, 455), and reactive to eye opening (192,193). Photic driving response and patterns of sleep generally appeared at this time (192). However, widespread or focal abnormalities persisted to varying degrees in some patients (242).

Prognostic Significance

Opinions have varied on the prognostic significance of postanoxic alpha activity. Some authors believe that it has a grave prognostic significance (11,47,335,355,461,474,491). Other investigators challenged this notion (193), and some even found longer survivals and better recoveries in individuals with anoxic coma who displayed widespread alpha-frequency activity, compared to other EEG patterns (423). A review of some published reports disclosed that 73% of patients who demonstrated widespread alpha-frequency activity while in coma following cardiopulmonary arrest died without recovering consciousness, 5% regained consciousness but subsequently died during the hospitalization, 19% survived with neurological sequelae of varying severity, and only 3% had nearly total or total recovery (79). Similar results were obtained in a more recent analysis of the literature (264). Thus the risks of never regaining consciousness and dying in the hospital or surviving with severe neurological deficits are high among patients with this EEG pattern while in postanoxic coma (79). However, it has been shown that there is no significant difference in outcome between patients in postanoxic coma with and without alpha-frequency pattern in their EEGs (28). Thus it seems likely that these patients' outcome is related to the severity of the anoxic insult rather than to the finding of widespread alpha-frequency activity. There is evidence that the outcome tends to be better when this alpha pattern appears and resolves within 24 hours of onset of anoxic coma than when it is detected on or after the second day (242). It has also been suggested that reactivity of the EEG patterns occurring after subsidence of alpha activity may be more prognostically significant than the alpha pattern itself (510).

Pathological Findings

Pathological studies revealed changes typical of brain anoxia (430). Alterations in neocortex ranged from mild and patchy to severe and extensive, especially in deeper cortical layers. The hippocampus and cerebellum were markedly involved, whereas alterations of the thalamus, basal ganglia, midbrain, and pons were inconsistent (100,193,218,474,491). A completely necrotic "respirator brain" occurred in only one patient (100). There is no indication that these anoxic alterations differ in patients with and without an alpha-frequency EEG pattern.

Pathophysiological Mechanisms

A fundamental issue is whether the alpha activity seen in comatose patients with diffuse brain anoxia represents a paradoxically retained "normal" alpha rhythm or a newly generated, abnormal activity of alpha frequency (491). To answer this question, one should consider three lines of evidence:

1. Alpha activity in postanoxic comatose states differs sharply from the alpha rhythm of normal, awake, resting subjects. With some notable exceptions, the former is (a) widely distributed, frequently anteriorly predominant; (b) poorly modulated; (c) unreactive to sensory, including noxious, stimuli; and (d) not associated with a photic driving response. In contrast, as a rule, alpha rhythms of normal, awake, resting subjects are (a) best developed posteriorly, (b) better modulated and slightly faster in frequency, (c) frequently attenuated by eye opening, and (d) often associated with photic driving. These differences appear clearly when comparing EEGs in comatose patients with widespread unreactive alpha activity to EEGs in the same patients before onset (166,242) or after resolution (192,242,455) of coma.

2. The alpha-activity pattern observed in postanoxic infants and children often has a frequency inappropriately fast for age (105,225,244,336, 515). On recovery, an alpha rhythm of slower frequency consistent with the patient's age becomes apparent (105).
3. Computer analyses of the EEG have demonstrated differences between alpha activities detected in comatose patients compared to normal subjects. These include reduced coherence of alpha activity between homologous regions of the two hemispheres (325) and more variable "dimensionality" of alpha activity over different temporal EEG segments in comatose patients compared to normal subjects (270). The evidence strongly suggests that the alpha-frequency pattern of patients in anoxic coma is not a paradoxically retained normal alpha rhythm but newly generated abnormal activity (105,161,242) sharing with the alpha rhythm of normal subjects only the frequency range.

One must assume that preserved neuronal systems within the cerebral hemispheres, diencephalon, or brainstem generate this widely synchronized alpha activity. However, the identity of the generators and the mechanisms producing this rhythm are still unclear. Gurvitch et al. (200) suggested that alpha activity of human postanoxic states may be analogous or identical to spindle bursts recorded in dogs following resuscitation from induced circulatory arrest. Although the amygdaloid nuclei would give raise to these spindles, other subcortical structures, especially the thalamus and caudate nucleus, would play a role in their generalization (200,201). In humans, the relative continuous occurrence and unvarying voltage of alpha activity in postanoxic coma distinguishes it from these intermittent and highly modulated canine amygdaloid spindles. Moreover, the amygdaloid nucleus is relatively smaller in humans than in dogs. Thus the amygdaloid origin of alpha activity in comatose humans remains unproved (79). Multiple mechanisms may be responsible for generating this pattern. It seems likely that subcortical structures, including the thalamus, play a role in producing this rhythmic activity in individuals with acute, widespread cortical anoxic alterations.

Widespread Alpha Activity in Coma Resulting from Toxic-Metabolic Causes

Some patients in coma resulting from acute drug intoxication or high-dose therapeutic sedation show rhythmic activity of 8–12 (and occasionally 12–16) Hz and 20–50 μV mixed with theta and delta waves (Fig. 14.12). Generally, these alpha and slow beta potentials are distributed widely, maximally over the anterior head regions, and are unreactive to manually opening the eyes and to auditory and noxious stimuli (28,43,71,119,120,140,161, 187,193,202,219,244,264,279,280,282,288,327,378,468).

Substances causing these comatose states include sedative-hypnotic drugs such as barbiturates (279,280,327) and the benzodiazepines (71,119,202, 219); imipramine (378); meprobamate (328); and various anesthetic agents such as fentanyl, isoflurane, and nitrous oxide (28), among others. Similar alpha-frequency activity has also been reported in patients with severely disturbed glucose metabolism (27,503).

The prevalence of alpha or low beta frequencies in patients with acute drug intoxication varies from 7% (264) to 29% (279). A few reports have described this pattern in children (288,378).

Clinical Outcome, EEG Evolution, and Prognostic Value

There is general agreement that most patients with drug-induced coma and alpha-frequency pattern in their EEGs recover promptly except when cardiac arrest has occurred, causing severe cerebral anoxia. A published mortality of 8% among these patients included cases complicated by anoxia (264). Clinical recovery is paralleled by evolution of mixed alpha and beta waves into widely distributed theta activity with intermixed beta potentials, in turn succeeded by an alpha rhythm of normal (posterior) distribution and reactivity (71,119,140,282,288). Because both frequently reversible drug intoxication and often-lethal severe cerebral anoxia can be associated with a widespread alpha-frequency pattern, the EEG cannot differentiate between drug intoxication with and without superimposed cerebral anoxia and cannot predict outcome.

Pathophysiological Mechanisms

Most authors emphasize that a widespread, maximally frontal distribution and lack of reactivity to stimuli distinguish alpha activity in coma caused by acute drug intoxication from the alpha rhythm characteristic of normal, awake subjects. These differences strongly suggest that alpha activity of drug-induced coma, like the alpha-frequency pattern of postanoxic patients, is not a persistent normal rhythm but newly generated abnormal activity. Some investigators have postulated pharmacological depression of reticulothalamic pathways with increased, widespread cortical synchronization (71), but no direct evidence supports this conjecture.

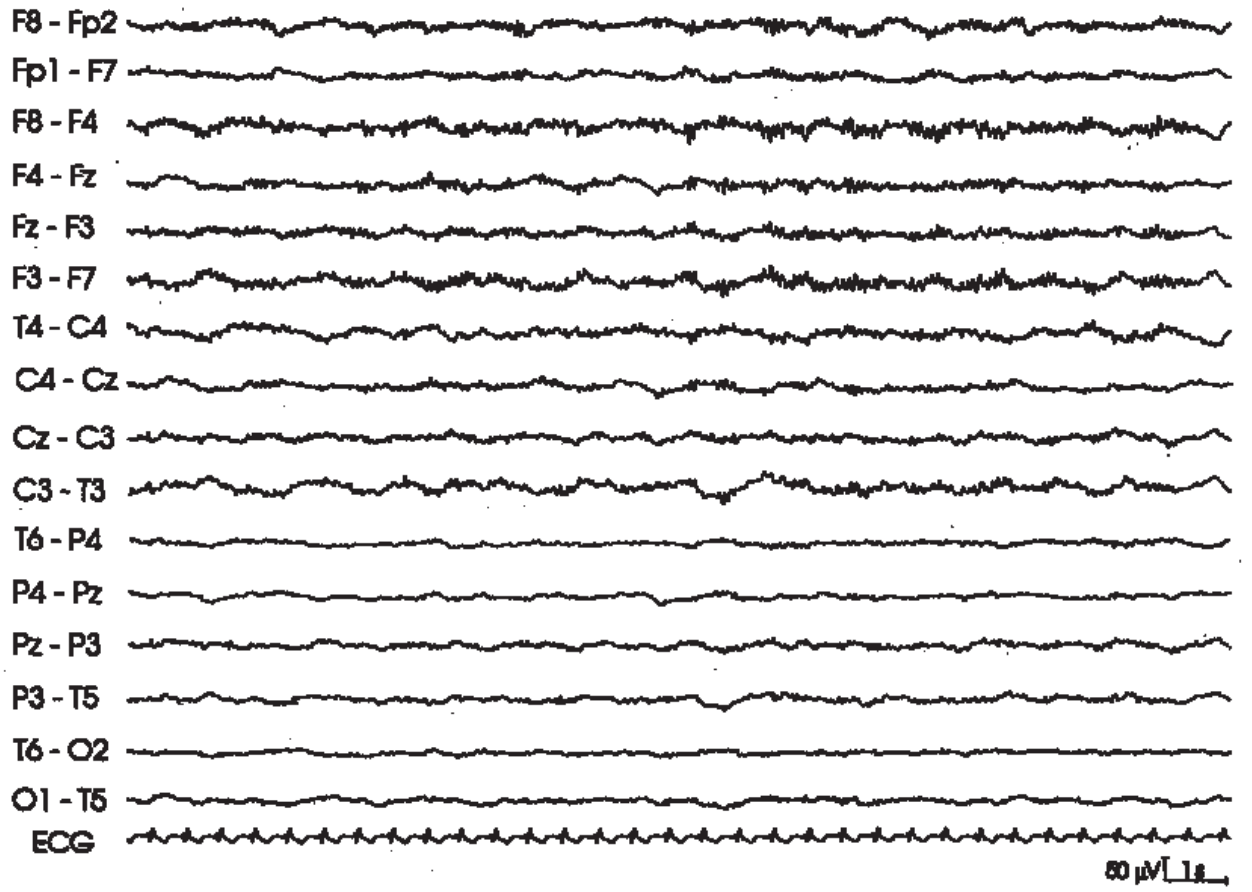


FIG. 14.12. Widespread unreactive 10-Hz rhythm recorded on a 40-year-old man who was comatose 1 day after head trauma. At the time of recording, the patient was receiving high-dose pentobarbital because of elevated intracranial pressure. He survived 9 days. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

Alpha Rhythm in Deefferented ("Locked-In") States

The term *deefferented states* describes individuals who are quadriplegic and mute but demonstrate substantially normal mental functions when properly tested. Usually, these patients have paralysis of lower cranial nerves but have variably preserved vertical eye and eyelid movements that allow them to communicate to some extent. This condition (487) is commonly referred to as the *"locked-in" syndrome* (370). Some "incompletely locked-in" (34) patients have remnants of voluntary movement besides vertical eye and eyelid movements. Still other patients have lost all avenues of communication. In the latter individuals, one cannot determine clinically whether they are comatose or "totally locked in" (34,496), that is, aware of internal and external stimuli but unable to make responses.

Pathological Findings

Patients in deefferented states have various lesions, usually infarcts or hemorrhages (367), destroying the ventral pons bilaterally. There is either substantial sparing of pontine and mesencephalic tegmentum ("ventral pon-

tine syndrome") (409) or variable extension of the lesion to pontine tegmentum without or with only unilateral involvement of the midbrain tegmentum and thalamus (34,74,88,161,205,215,230,297,303,312,316,352,356,491, 497). Limited bilateral midbrain (268,322,373) or internal capsule (93) infarcts have also been described in a few patients. Nonvascular etiologies include tumors (92), trauma (64,160), abscesses (342), multiple sclerosis (163), *Borrelia burgdorferi* meningitis (329), brainstem encephalitis (367), central pontine myelinolysis (367), and heroin abuse (367). Mute paralyzed patients suffering from severe acute polyneuropathy or polyradiculoneuropathy may also appear locked in (71,135).

EEG Findings and Clinical Outcome

The EEGs of deefferented ("locked-in") patients show alpha activity with most or all features of the alpha rhythm of normal individuals (Fig. 14.13). Typically, this rhythm is most prominent over the posterior head regions and is attenuated by eye opening, whether voluntary or passive (Fig. 14.14), and a photic driving response is variably present. However, lower frequencies (6–7 Hz), higher voltage (up to 100 μV), lack of clear posterior preponderance of this rhythm, absence of reactivity to sensory stimuli (205,243), or low-voltage recordings with only intermittent alpha activity can also occur.

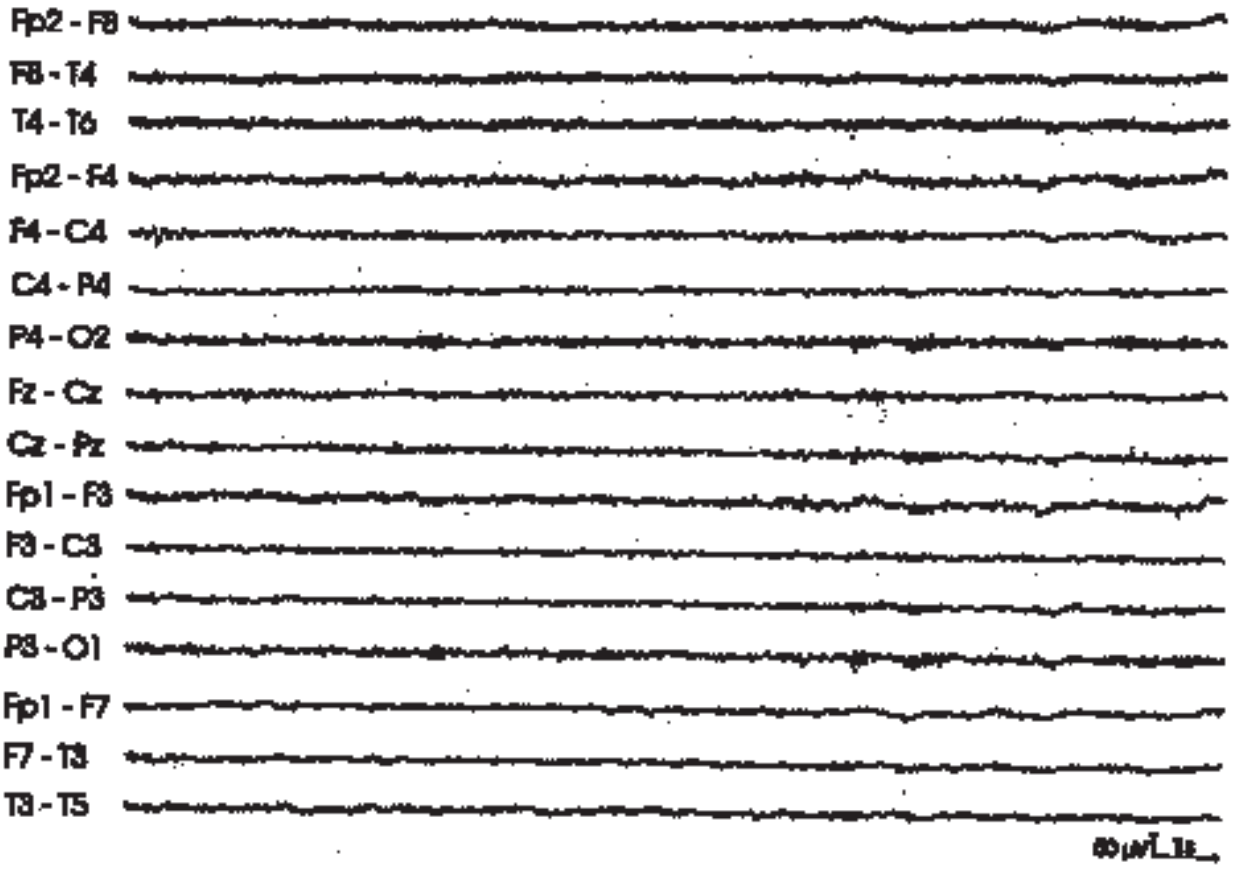


FIG. 14.13. Ten-Hz alpha rhythm in a 65-year-old man who collapsed and became unresponsive after 1 week of dizziness, right hemiparesis, and dysarthria. When the EEG was recorded 2 days later, he was mute and quadriplegic, with bilateral weakness of lower face, tongue, and palate; left gaze paralysis; and right-sided flexor posturing in response to noxious stimulation. He could open his eyes and make slow vertical movements. This patient's "locked-in" state was a result of extensive pontine infarction transecting the pons up to its junction with the midbrain. He survived 2 months. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

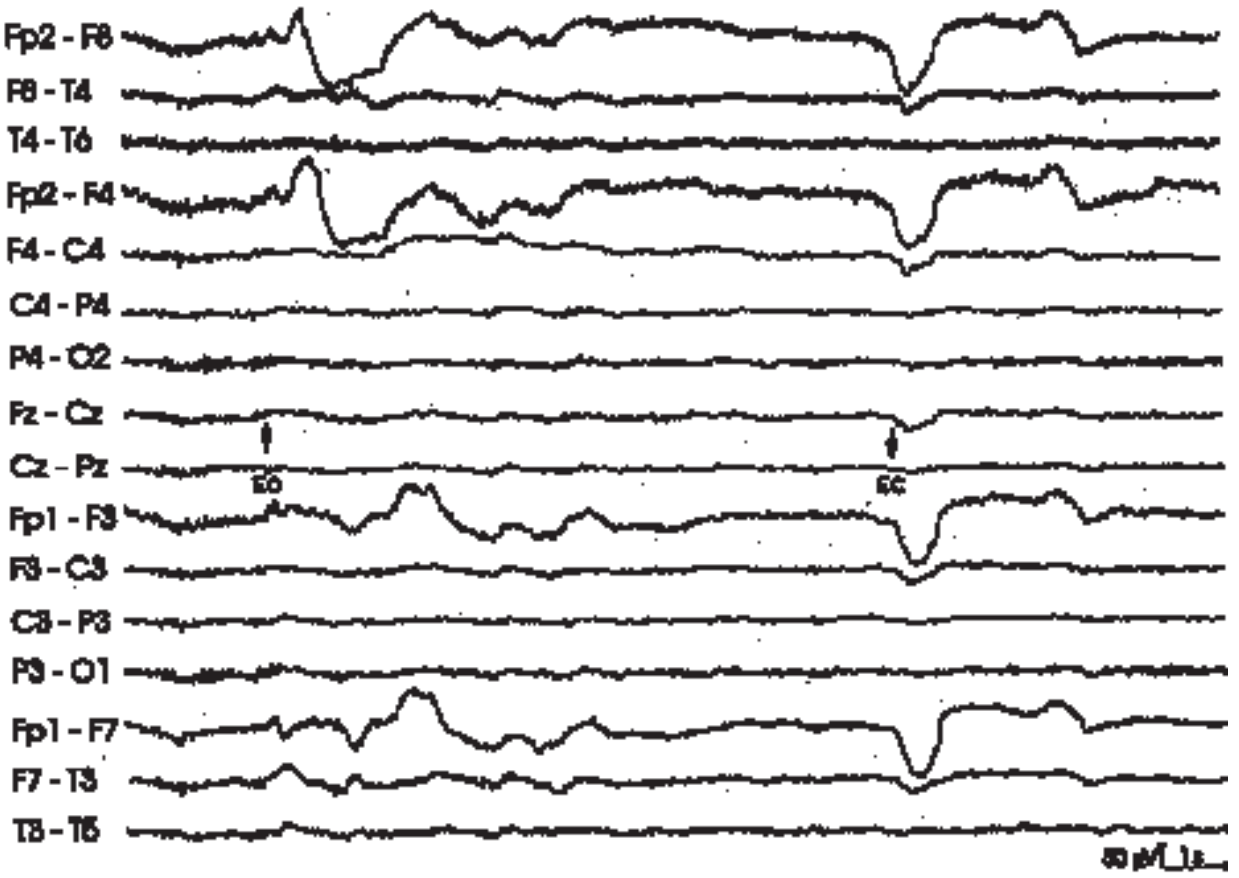


FIG. 14.14. Attenuation of the alpha rhythm by eye opening on command in the same patient and recording as in Figure 14.13. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

Some deefferented patients also demonstrate variable amounts of theta and delta waves, which may be diffuse, lateralized, or focal and are often most prominent over the frontal or temporal areas (34,65,73,74,88,149,150,161, 205,209,212,215,230,243,258,260,276,296,297,303,312,351,352,355,356, 367,407,438,491,497). Prolonged polygraphic studies of some deefferented patients give variable results, including (a) complete loss or marked diminution of rapid-eye-movement (REM) sleep (314,497); (b) moderate to marked decrease in total sleep time, with loss of REM sleep (110,497) and diminished or normal percentage of REM sleep (149,165); and (c) preserved REM and NREM sleep with sleep architecture described as normal or nearly normal (110,276,314,358). The hypothesis that in most deefferented individuals altered sleep may be related to lesions interfering with the functions of the raphe nuclei in the pons and midbrain (165,314) has been called into question (358).

A review of the literature revealed that 60% of deefferented patients died. Among survivors, recovery was faster and more complete in individuals with nonvascular lesions (367).

Pathophysiological Mechanisms

The topography and reactivity of the alpha rhythm of most deefferented patients indicates that this is a preserved normal awake alpha rhythm rather

than newly generated abnormal alpha activity such as characterizes anoxic and drug-intoxicated patients. In addition, the location of the pathology in deefferented individuals confirms the notion that, in humans, not only lesions transecting the brainstem up to the pontomesencephalic junction (337) but also extensive unilateral lesions of the midbrain and thalamus and discrete bilateral lesions of the midbrain (74,322,491) are compatible with a preserved alpha rhythm.

We conclude that the concept that the alpha rhythm that characterizes awake humans can occur in coma is wrong. A true alpha rhythm—usually predominant posteriorly, often reactive to eye opening, and frequently associated with photic driving—can occur in individuals with structural brain lesions that have rendered them mute and quadriplegic. These patients are unable to communicate except by eye movement, if at all, but can demonstrate normal mental function in appropriate circumstances. Thus they are deefferented rather than comatose. In contrast, rhythmic activity of alpha frequency, usually widely distributed but maximal over anterior areas and unreactive to alerting stimuli, appears in some truly comatose patients suffering from acute anoxic or toxic-metabolic encephalopathies. The general term *alpha coma* does not differentiate between these two fundamentally different groups of conditions.

In apparently unresponsive patients, demonstrating a posterior alpha rhythm such as characterizes awake normal subjects is of major importance. Provided psychogenic unresponsiveness is ruled out, such a finding suggests that these individuals may be aware of themselves and of the external environment, that is, that they may be deefferented rather than comatose (215). However, in some instances the alpha rhythm of deefferented patients lacks clear posterior predominance, reactivity to external alerting stimuli, or both. Similarly, in some individuals with anoxic or toxic-metabolic comas, alpha-frequency activity exhibits posterior preponderance, reactivity, or both (205,243,264). In these cases, the EEG gives no indication as to whether the patient's failure to respond is due to deefferentation or coma.

Evoked Potentials

Median nerve SL-SEP findings, known in a limited number of deefferented patients with or without pathologically controlled pontine infarcts, include the following: (a) normal responses to stimulation of either median nerve (144,463); (b) altered responses to the same stimulus (32); (c) abolished N$\overline{20}$ cortical component in response to stimulation of either median nerve (351,463); and (d) N$\overline{20}$ potential preserved in response to stimulation of the median nerve or the fingers of one side but diminished in voltage and prolonged in latency in response to excitation of the same structures contralaterally, and similar findings with posterior tibial nerve stimulation. A report (355) described fully developed responses to stimulation of either median nerve shortly after onset of the locked-in syndrome in a patient also displaying an EEG alpha rhythm. As death neared and high-voltage delta activity developed, all response components disappeared except for a single positive wave. Autopsy demonstrated infarction of the rostral two-thirds of the basis pontis bilaterally with scattered ischemic lesions in the tegmentum.

In deefferented patients, BAEPs have been variously described as (a) normal (32,66,157,209,437,463); (b) abnormal (32,66,73,179,212,260,407,433); (c) initially normal in response to stimulation of either ear but subsequently abnormal (65,260,433); and (d) initially abnormal with later return to normal (438). When present, BAEP abnormalities consisted of prolonged I–V IPIs (73,179,260,438) resulting from lengthened I–III (260) or III–V (65,179,407) intervals; prolonged latencies of all waves (260); and loss of all components, excluding (212,260) or including (65,260,441) wave I. Prolonged latencies and IPIs were frequently associated with diminished amplitudes and altered waveforms (441).

VEPs were elicited in a locked-in individual (79) and in an unresponsive, presumably completely deefferented patient with a pontine infarct and intact cerebrum (497). In one study, motor evoked potentials (MEPs) normally elicited in upper limb muscles by magnetic transcranial stimulation of the motor cortex were either absent or present in deefferented individuals, and these findings were related to motor recovery (32). In another work, MEPs were initially absent and subsequently normal on one side and present although altered in latency and amplitude contralaterally (144).

Highly heterogeneous results of auditory and somatosensory stimulations reflect the variability of the direct and indirect effects of the pathology causing the locked-in syndrome. Normal BAEPs and SL-SEPs suggest a lesion largely confined to the basis pontis and selectively interrupting the corticospinal pathways. In contrast, delayed or abolished BAEPs and SL-SEPs indicate extension into, or indirect effects on, auditory tracts and nuclei of the medial lemniscus. Preserved MEPs in paralyzed limbs may suggest reversible functional changes. Hence, EPs may help in understanding and evaluating deefferented patients, in whom it is difficult to assess the extent of sensory impairment and to forecast the likelihood of motor

recovery. In addition, a P300 (P3) cognitive evoked potential (CEP) has been recorded in some locked-in patients (359). Unlike conventional sensory EPs, which primarily depend on the physical characteristics of the stimulus, long-latency CEPs elicited with particular "oddball" stimulus paradigms mostly reflect cerebral processing of incoming signals related to certain cognitive functions (i.e., higher cerebral activity; see Chapter 30). Demonstrating a P300 was interpreted as evidence of "ongoing cognitive activity" (359). This information is valuable in individuals whose abilities to communicate are dramatically reduced, if not absent, although the P300, like other CEPs, does not indicate to what extent full cognitive capacities are preserved or have been recovered (see "Cognitive Evoked Potentials" later in this chapter).

GOALS OF ELECTROPHYSIOLOGICAL TESTING IN COMATOSE STATES

The goals of EEG and EP studies of comatose patients generally include one or more of the following:

1. Providing objective measures of brain dysfunction
2. Determining the etiology of coma, specifically differentiating between toxic-metabolic causes and structural lesions
3. Localizing structural lesions, specifically differentiating between hemispheric and brainstem lesions and establishing the rostrocaudal level of brain dysfunction
4. Determining depth of coma and predicting clinical outcome
5. Following the course of comatose states
6. Distinguishing coma from diminished responsiveness resulting from seizure activity or psychogenic factors
7. Continuously monitoring brain function in the intensive care unit (ICU)

The availability of multiple potentially useful techniques requires that decisions should be made on the choice of the method, or combination of methods, best suited to each clinical situation. This decision demands a clear understanding of the strengths and weaknesses of each approach. The following generalizations are intended to help in this choice.

Providing Objective Measures of Brain Dysfunction

Because the EEG reflects cerebral cortical activity modulated by diencephalic and brainstem influences, it is potentially useful in providing measures of brain dysfunction in coma and other states of diminished responsiveness. However, these conditions are associated with a wide variety of EEG patterns that are not readily amenable to quantification. In contrast, EP measures can contribute exquisitely quantitative information on neural function at multiple levels within the brain that is well suited for statistical analysis and easily related to other physiological and clinical indices.

Establishing the Etiology of Coma: Differentiating between Toxic-Metabolic Causes and Structural Lesions

In rare instances, a single EEG can suggest the nature of the underlying disorder. For example, finding TWs may raise the suspicion of a metabolic encephalopathy, and the finding of fast intermixed with slow potentials suggests the possibility of drug intoxication. However, most EEG patterns provide no dependable information on the cause of coma. This lack of etiological specificity is perhaps best illustrated by noting that many EEG patterns, including burst-suppression, PGEDs, widespread unreactive activity of alpha or theta frequencies, low-voltage unreactive recordings, and ECI, may occur in patients rendered comatose by brain anoxia as well as in comatose individuals intoxicated by or treated with high doses of CNS depressants. Lack of specificity of individual EEGs is only partly overcome by serial recordings.

Even more than the EEG, EPs lack etiological specificity. However, when used with due caution, SL-SEPs and BAEPs can contribute to broadly differentiating between toxic-metabolic encephalopathies, in which they were traditionally believed to remain unchanged (348,439), and lesions involving the central somatosensory and auditory pathways, which abolish or markedly alter them. However, one should be aware that barbiturate concentrations substantially exceeding those commonly employed in ICUs (134), the intravenous administration of high doses of phenytoin (222,323), and the combined administration of two or more medications (170,320) may variously alter the latencies, amplitudes, and waveforms of both SL-SEPs and BAEPs. In addition, it has long been known that alcohol intoxication (426) and, especially, hypothermia (315,440) can cause prolongations of SL-SEP and BAEP latencies and IPIs that closely resemble those associated with certain structural lesions. Although most marked at esophageal temperatures below 32.5°C, alterations produced by hypothermia may already appear at temperatures as high as 35.5°C. In addition, quantifiable EP alterations occur in certain

systemic metabolic derangements. Patients with chronic renal failure as a group demonstrate delayed pattern reversal and flash VEPs (104,375,394, 484), prolonged latencies of BAEPs with minimal but significant increases of I–V IPIs (375,483,484), and increased latencies of peripheral and central components of SL-SEPs with no central conduction time (CCT) changes (484). These alterations suggested both peripheral and central effects of chronic renal failure. In contrast, progressive prolongation and eventual loss of cortical components of median nerve SEPs of latency with increased IPIs, but normal CCTs, and unaltered BAEPs, characterized hepatic encephalopathy, suggesting dysfunction largely confined to the cerebral cortex (101,198,505).

The notion itself that SL-SEPs and BAEPs are abolished or markedly altered by structural lesions of the brainstem deserves critical consideration. These EP changes generally only occur with brainstem lesions sufficiently extensive to cause coma with loss of cephalic reflexes and spontaneous respiration that are most likely to involve somatosensory and auditory pathways. In contrast, SL-SEPs and BAEPs may persist and may be even normal in individuals with more discrete brainstem lesions causing clinical signs of less global brainstem dysfunction and sparing the somatosensory and auditory pathways (439).

Localizing Structural Lesions: Differentiating between Hemispheric and Brainstem Lesions and Determining Rostrocaudal Levels of Brain Dysfunction

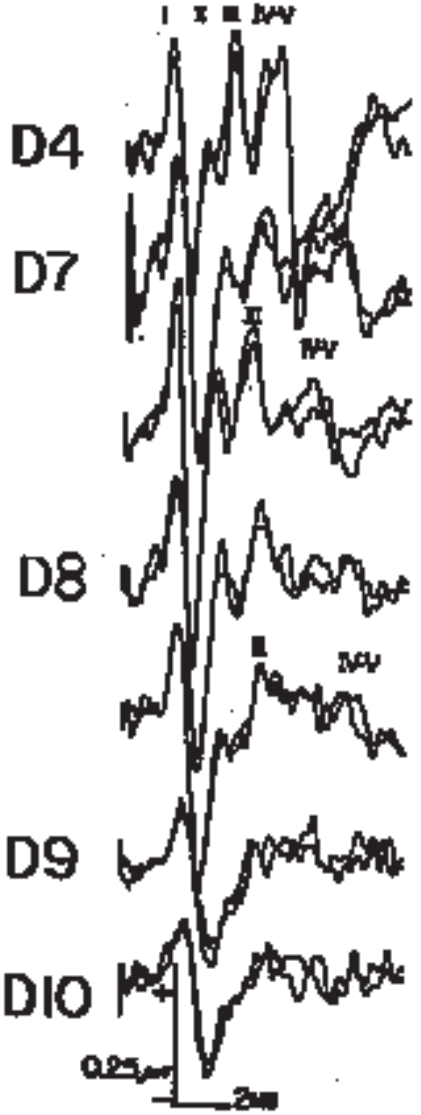
Localization of lesions causing coma is most commonly achieved by neuroimaging techniques that are capable of depicting in detail most structural pathological processes. However, the EEG can provide some information on the location of cerebral hemispheric lesions, and EPs can help differentiate between cerebral hemispheric and brainstem lesions and determine level of dysfunction within the brainstem.

Unilateral loss or marked abnormality of the cortical $N\overline{20}$ component of SL-SEPs is most commonly associated with hemispheric pathology, specifically focal lesions of the parietal cortex or thalamocortical radiations (320). Similarly, unequal ("asymmetrical") CCT prolongation favors primary hemispheric over brainstem pathology, whereas the opposite is true of bilaterally equal ("symmetrical") CCT prolongation (320). Loss of wave V of BAEPs, prolonged I–V and especially III–V IPIs, and diminished V:I amplitude ratio provide evidence of a brainstem lesion. In contrast, a recording showing loss of wave I and of all subsequent waves cannot differentiate between lesion or dysfunction of peripheral auditory structures with substantially intact brainstem, loss of function of both peripheral and brainstem auditory pathways as can be seen with basilar artery occlusion, or global loss of function of peripheral, brainstem, and cerebral auditory structures as in brain death.

Broad relationships have been described between EEG patterns and clinically assessed levels of brain dysfunction in coma. Specifically, it has been reported that, as head-injured patients with central herniation syndrome undergo craniocaudal deterioration (370), the amount of widespread delta activity increases and the range of EEG patterns, the presence of alternating and sleep patterns, and the EEG reactivity to alerting stimuli diminish until slow EEG activity and finally ECI ensue (397,398).

Early studies suggested that, in individuals rendered comatose by severe head injury or acute anoxia, BAEP alterations were closely related to clinically assessed levels of dysfunction within the brainstem (427,469,470). However, less precise relationships were subsequently reported (274,321,466). In particular, Mauguière et al. (321) found that BAEPs persisted in patients with intact brainstem reflexes, whereas they disappeared in individuals in whom these reflexes were abolished. Closer relations between BAEP changes and levels of brainstem dysfunction could not be demonstrated. However, sequential, orderly loss of BAEP components generated at progressively lower levels of the brainstem were repeatedly observed in serial recordings of patients with clinical evidence of rostrocaudal deterioration culminating in brain death (197,406,427, 436,471) (Fig. 14.15).

FIG. 14.15. BAEPs in response to monaural clicks at 65 dB sound level in a patient who had suffered an anoxic episode. *D4* and *D10* refer to day of hospitalization. Two records were taken on days 7 and 8. On day 4, the patient was comatose but withdrew in response to noxious stimuli and had spontaneous respiration and preserved cephalic reflexes. One day earlier his EEG had shown widespread delta activity. On the seventh day, cephalic reflexes were no longer present, there was extensor posturing in response to noxious stimuli, and low-voltage delta activity was present in the EEG. Lack of spontaneous breathing and EEG demonstrating ECI were noted on day 8. On day 10, all responses to noxious stimuli were absent. The patient expired 14 days after admission. Sequential loss of BAEPs of progressively shorter latency paralleled the craniocaudal deterioration of the patient's clinical status. (Modified from Starr A. Auditory brain stem responses in brain death. *Brain* 1976;99:543–554.)



Determining Depth and Predicting Clinical Outcome of Coma

The EEG as a Measure of Depth of Coma and a Predictor of Outcome

Early work established that broad relationships exist between EEG patterns and reactivity to alerting stimuli and clinically assessed depth of coma, but recognized that discrepancies between these features were often observed (20,159). More controversial is the notion, discussed earlier in this chapter, that some particular EEG patterns displayed by unresponsive patients, such as sleep patterns and activities of alpha frequency, can predict clinical outcome.

Some studies reported signifcant statistical associations between graded EEG abnormality and final clinical status of comatose adults (31,59,91,223, 265a,377,380,396,405,453,454,468,504,513,513a,513b) as well as neonates and children (410a). Of special interest is Prior's (377) early study of patients with comas of various, but mostly anoxic, etiologies. She found 85% concordance between the first EEG rating and clinical outcome, and computer-aided discriminant function analysis of large numbers of variables further increased prognostic accuracy. Subsequent work suggested that, in individuals rendered comatose by acute brain anoxia, mild, graded EEG abnormalities were predictive of survival (91,405,454,468,504). There is widespread agreement at present that in anoxic comas the most severe grades of abnormality, such as ECI, burst suppression, and delta activity of very low voltage show strong statistical association with death or a vegetative state. Mortalities of 81–98% have been reported among patients demonstrating these extreme EEG alterations (26,31,91,396,453,468,513a,513b,514). In contrast, the belief that in anoxic comas, mild, graded EEG abnormalities were predictive of favorable outcome (91,405,454,468,504) has met with skepticism (31,396,410a).

Some investigators focused on posttraumatic coma and found strong statistical associations between graded EEG alterations and ultimate clinical state (59,263,379,380,398,454), but a report contended that this relation only applied to recordings of ECI and other severely abnormal EEGs (236). Other studies emphasized the preeminent importance of EEG reactivity to alerting stimuli in forecasting outcome of coma resulting from head injury (9,203,236) or anoxia (264). In a small series, all postanoxic comatose patients with nonreactive alpha-frequency rhythms in their EEGs died (264). We believe that EEG reactivity may deserve more attention in the study of coma than it has received so far. However, determining the presence or absence of reactivity in retrospectively reviewed EEGs carries some imprecision. This phenomenon is influenced to a considerable degree by the tenacity of the technologist seeking to demonstrate it and the type and inten-

sity of stimuli delivered, which are difficult to standardize in routine examinations. The frequent occurrence of noises in busy ICUs and the possible existence of major sensory deficits in the patients may also variously interfere with the assessment of EEG reactivity (198).

The prognostic relevance of computer analyses of the EEGs of comatose patients (9,263,458) warrants further study.

Evoked Potentials as Predictors of Outcome

Somatosensory Evoked Potentials

Abnormalities of median nerve SEPs the prognostic value of which has been investigated in comatose patients, include (a) bilateral loss of the N20 early cortical potential (b) bilateral preservation of the N20 potential (c) unilateral loss of the N20 potential and (d) prolonged somatosensory central conduction time, and (e) alterations of the middle- and long-latency SEPs.

Bilateral loss of the early cortical potential N20 (or N20-P27 complex) with preservation of peripheral N9, spinal N13, brainstem P14 and subcortical N18 (Fig. 14.16) indicates severe cortical dysfunction. Abolition of the N20 potential bilaterally has been reported in patients rendered comatose by severe brain anoxia (6,26,31,67,68,91,184,310,354,395,396,396a,508, 513,514,514a), head trauma (26,35,137,204,227,256,396a) (Fig. 18.3), nontraumatic (116,169), and miscellaneous (95,168,185,505) etiologies. Its prognostic value of this finding varies depending on the etiology of coma.

Meta-analyses of the literature have determined that 100% of adults who demonstrate bilaterally absent N20 potential within 48 hours (31) or 1 week (514a) of onset of coma caused by brain anoxia die or remain vegetative. Their brains disclose widespread ischemic changes of of cerebral (396a) and cerebellar cortices and thalamus (68). In the available literature, only three patients who were comatose following cardiac arrest occurring during anesthesia (197) or heroin overdose (265a) (Kaplan, personal commnuication) and demonstrated bilateral extinction of the N20 potential regained con-

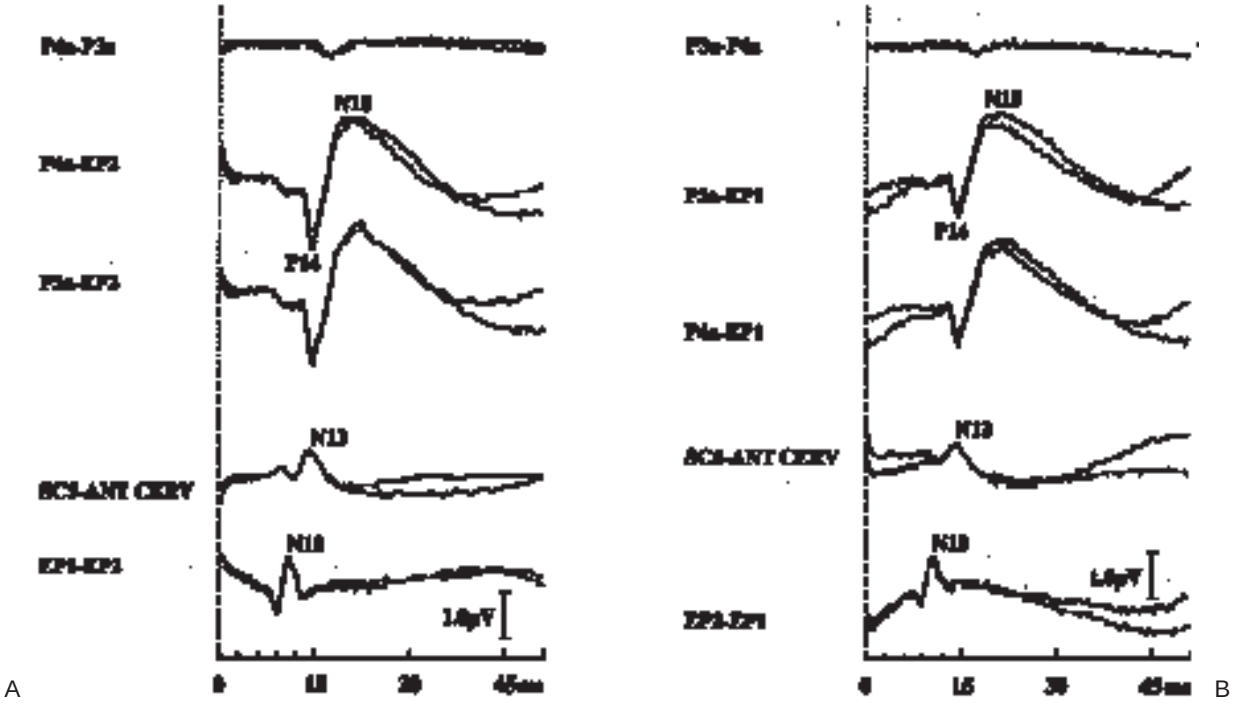
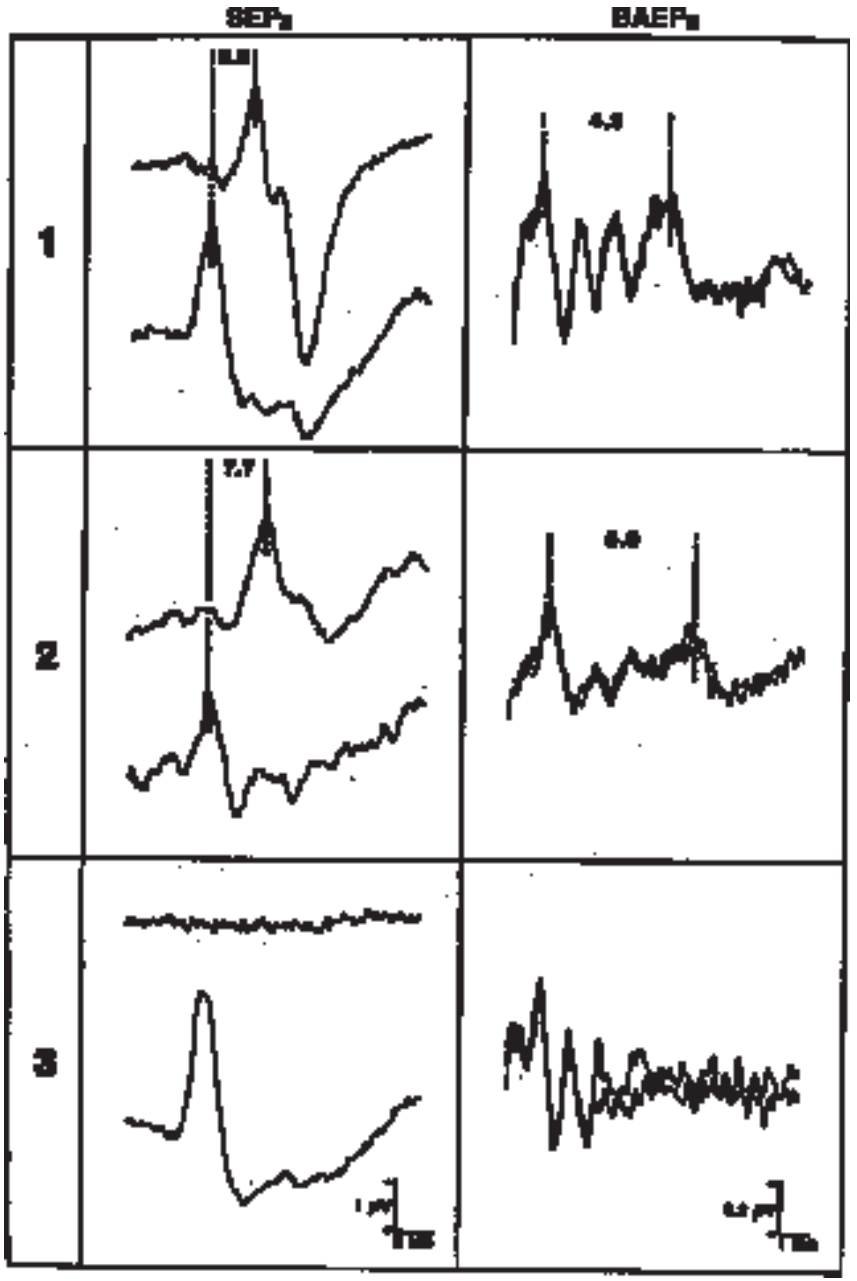


FIG. 14.16. SL-SEPs in response to electrical stimulation of the left **(A)** and right **(B)** median nerves. Electrode P4a (right postcentral) was halfway between standard positions P4 and C4 while electrode P3a (left postcentral) was midway between standard positions P3 and C3. In A and B, recordings demonstrate Erb's point N10, spinal N13, brainstem P14 and bilateral subcortical N18 potentials but no N20 contralateral cortical response. Same patient as in Figure 14.3.



sciousness, two with abnormal neurological function (197). Hence, in adults with coma caused by severe brain anoxia, bilateral obliteration of the N20 potential is virtually 100% specific for death or vegetative survival. However substantial numbers of patients rendered comatose by severe brain anoxia who die or remain vegetative demonstrate variously preserved, rather than bilaterally abolished, N20 potential. Specifically, the sensitivity of bilateral obliteration of the N20 response to these unfavorable outcomes varied from 28% to 73% in different series of individuals in post-anoxic coma (514a). Additional studies are needed to confirm that bilateral loss of the N20 potential also predicts death or vegetative survival in children and infants who suffered severe anoxic insults (163a,410a).

Bilaterally absent N20 potential has lower predictive value in comas related to causes other than brain anoxia. About 90% of patients with coma of traumatic origin (396a) or of predominantly traumatic or cerebrovascular origin (320) who had bilaterally extinguished N20 potential died or became vegetative. Most of the remaining individuals had severe neurologic disabilities, but few recovered fully and showed gradual restoration of the N20 response (197).

According to recent guidelines for the practice of EEG and EPs (198), in patients with alpha coma unrelated to sedative drugs, bilateral loss of the N20 potential would be associated with lack of recovery, whereas preservation of this response would presage a favorable outcome. Evidence substantiating this belief is desirable.

One should be aware that bilateral loss of N20 potential may be caused by a reversible brainstem lesion or a preexisting neurological condition involving the somatosensory pathways (320) and occasionally it may be mimicked by bilateral subdural hematomas (35).

FIG. 14.17. Median nerve SEPs and BAEPs recorded in three patients within 4 days of onset of posttraumatic coma. SEPs 1–3 were recorded over the contralateral central scalp (**top**) and the second cervical vertebra (**bottom**) using a mid-forehead reference. BAEPs 1–3 were detected between the vertex and the ipsilateral earlobe. Grade 1 SEPs demonstrated normal N13-N20 CCT and grade 1 BAEPs showed normal I–V CCT. Grade 2 SEPs and BAEPs were characterized by abnormally prolonged CCTs. Grade 3 responses displayed lack of N20 potentials of SEPs and wave V of BAEPs. In this study, graded SEPs but not graded BAEPs reliably predicted both bad and good outcomes. (Modified from Cant BR, Hume AL, Judson JA, et al. The assessment of severe head injury by short-latency somatosensory and brain-stem auditory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1986;65:188–195.)

Comatose individuals with *bilaterally preserved N20 (and P27) potentials* (whether normal or delayed) have variable outcomes that are strongly influenced by the etiology of their condition (15,31,68,91,189,233,234,295,309,319,396,396a,401,484). Pooling data from various series (396a) indicates that 64% of patients who were comatose after suffering severe anoxia but retained the N20 potential bilaterally died or remained vegetative as opposed to 22% of individuals who demonstrated the same pattern while comatose following head trauma. The remaining patients regained consciousness, most of them with various degrees of neurologic disability. In another review, 35% of individuals with comas of predominantly traumatic or cerebrovascular origin (320) and bilaterally demonstrable N20 potential died, remained vegetative, or had severe neurological neurologic defects.

It appears that the prognosis of coma is more hopeful in patients with bilaterally preserved N20 potential than in individuals in whom this response is bilaterally absent, but carries considerable uncertainty and is strongly influenced by the etiology of coma. Abnormally prolonged latency of bilaterally preserved N20 has been said to decrease substantially the probability of favorable outcome (396a).

Unilateral loss of the N20 (and P27) potential most commonly results from damage to the parietal cortex, the thalamo-parietal radiations, or both (320) whereas it is rare in comas caused by brain anoxia. Pooling published results revealed that 74% of patients with comas of mostly traumatic or cerebrovascular origin who had unilateral obliteration of the N20 potential remained vegetative or severely neurologically disabled whereas 26% had moderate disability or good recovery (320). Similar unfavorable outcomes characterized a substantial portion of patients with comas of various etiologies who demonstrated unilaterally abolished N20 response (94,485).

Determining loss or preservation of cortical SEPs in comatose patients requires sound technique. This should be designed to detect responses generated at several levels from sensory periphery to cerebral cortex, and to differentiate between subcortically generated N18 and early cortical N20 potentials (14a) (Fig. 14.16). In addition, interpretation of test results demands intimate knowledge of temporal and spatial features, and putative sources of each response component.

Initial studies (233) reported that, within 3 ½ days after head injury, the spinal N13–cortical N20 IPI or *somatosensory "central conduction time"* (232) correctly predicted outcome measured by the Glasgow Outcome Scale (GOS) (250) in 78% of patients. In successive examinations performed up to 500 days after onset of coma, CCT predicted final state in 84% of individuals. This measure recovered exponentially over many months, although differences persisted between patients with good recovery and disabled individuals. The association between CCT and outcome was confirmed by subsequent investigations of comas resulting from various causes, including brain anoxia (15,142,146,203,256,262,294,304,310,400,401,485). However, the strength of this relationship varied in different reports. Lumping the results of several studies of coma of predominantly traumatic or cerebrovascular origin determined that a prolonged CCT was associated with death, vegetative state, or severe neurological disability in 58.5% of patients, whereas the remaining 41.5% demonstrated moderate disability or good recovery (320). Some authors concluded that CCT measurement improved only minimally the predictive power of SL-SEPs (294) and was of little clinical value (294,310). In contrast, other investigators pointed out that serial CCT measurements predicted final status more reliably than did single measurements during the acute stage of coma (233,234,349,401).

A few reports (111,197) suggested that additional information of prognostic value could be obtained in coma by including in the SEP analysis one or more cortical components topographically distinct from the parietal N20-P27 complex, specifically the centrofrontal P22, the central P45, and the frontocentral N60 potentials (124,125,204,205). These components are best demonstrated by sequential mapping techniques (see Chapter 24).

Extending the analysis to include *middle-latency and long-latency SEPs (ML-SEPs and LL-SEPs)* in the 30- to 200-millisecond latency range was said to substantially increase the predictive power of median nerve SEPs (118,189,295,309,369,401). Normal potentials with these latencies were associated with good recovery or moderate disability in 86% of patients with coma of predominantly traumatic or cerebrovascular origins. Only 14% of these individuals died, remained vegetative, or demonstrated severe disability (320). In contrast, because ML-SEPs and LL-SEPs were highly variable and were altered by sedative drugs, their absence had little prognostic significance (320).

Auditory Evoked Potentials

BAEP findings most commonly considered in prognosticating the outcome of comatose states include (a) absence of all BAEPs following wave I or waves I and II, (b) absence of wave V or waves III and V, and (c) normal BAEPs.

Bilateral absence of all BAEPs following wave I or waves I and II strongly predicts an unfavorable outcome irrespective of etiology

(15,55,172,185,259,267,304,360,406,466,471). In a review of several studies, 98.2% of patients with coma of traumatic or cerebrovascular origin who displayed this abnormality died or remained vegetative, and the remaining 1.8% survived with severe disability (320). Nevertheless, the possibility of a preexisting neurological condition causing dysfunction of the brainstem auditory pathways should always be considered and investigated.

Bilateral or even unilateral absence (or extreme amplitude reduction) of wave V (or waves III and V) with preserved wave I in a comatose patient presages almost invariably death or a vegetative state, much as does the absence of all BAEP components (15,26,70,267,294,366).

According to some authors, *abnormally prolonged I–V IPIs* (see Fig. 14.17) are associated with variable outcome of coma (185,263,304,360, 471,502), whereas closer associations of this measure to the patient's final state were reported by others (111,458). Other investigators reported empirically determining cutoff values of I–V (145,401,424) and III–V (401) IPIs, which allowed discrimination between individuals who succumbed or remained severely disabled and those with more favorable outcomes. The III–V IPI ("auditory brainstem conduction time") was found to be an especially valuable measure, unaffected by peripheral auditory disorders (401).

Normal BAEPs recorded during the acute phase of coma of traumatic or cerebrovascular origin were associated with good recovery or mild neurological sequelae in about 70% of patients, but death, a vegetative state, or severe disability occurred in the remaining 30% of individuals studied by various authors (320). These unfavorable outcomes also characterize a substantial proportion of patients who display normal BAEPs in the acute period of anoxic coma (90,122,393). In contrast, persistently normal BAEPs following this period would indicate increased likelihood of survival (126,188,406), at least in the absence of hemispheric lesions such as intracerebral hemorrhage or hemorrhagic infarction (171).

Several authors extended their search for prognostically useful indicators to middle-latency and long-latency auditory evoked potential (AEP) components *(ML-AEPs and LL-AEPs)* (156,158,190,208,259,295). These studies indicated that demonstration of a normal Pa component of ML-AEPs strongly predicted return of consciousness (158). However, this potential was detected in only few patients (158) and was very vulnerable to CNS depressants. Similarly, presence of $\overline{N100}$ (158,198) and $\overline{P200}$ (198) LL-AEP components was significantly associated with recovery of consciousness. In contrast, absence of ML-AEPs or LL-AEPs had no prognostic value.

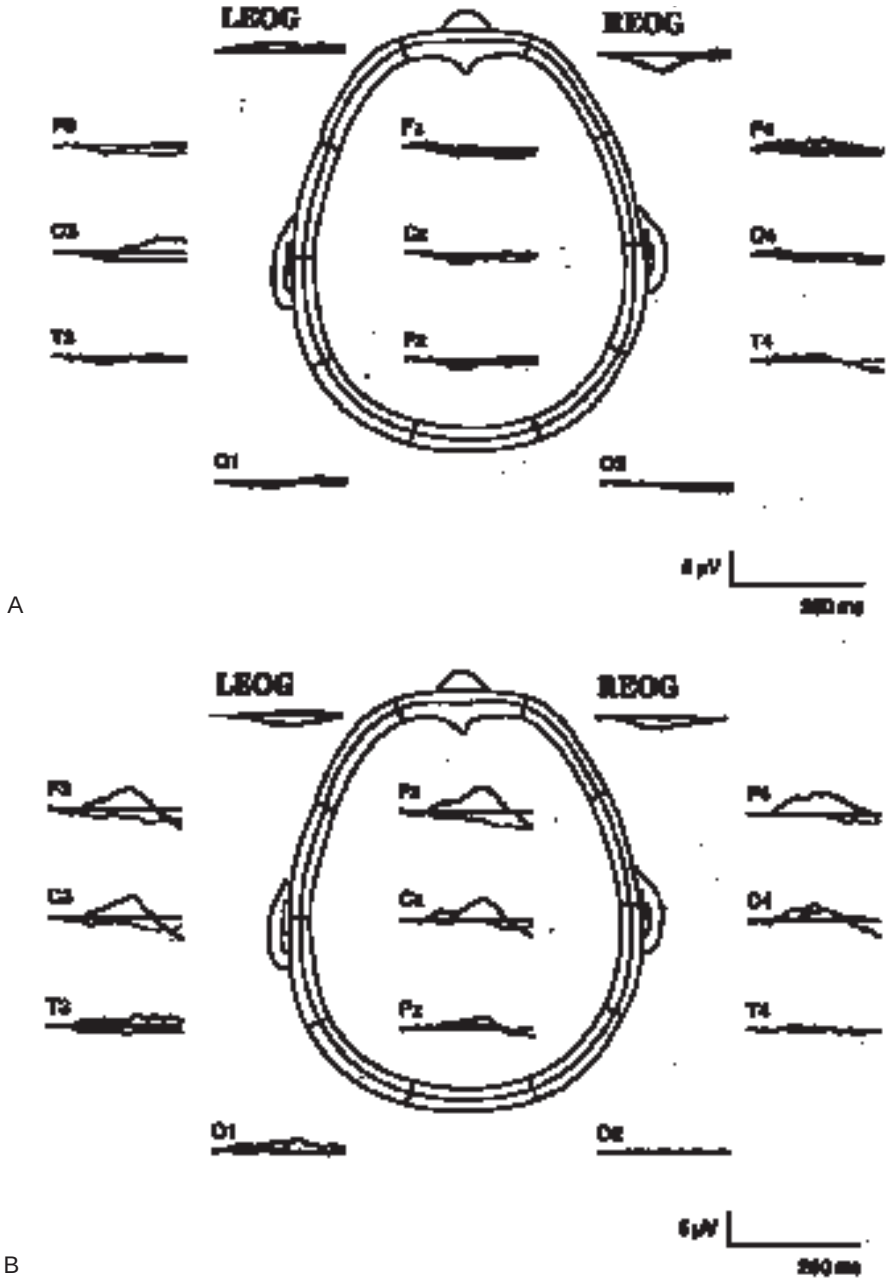
VEPs and MEPs

Except for some early studies (41,486), most investigations of the prognostic value of EPs in coma have used VEPs primarily in conjunction with other EPs. Normal compound MEPs in response to transcranial magnetic stimulation of the motor cortex did not reliably predict good outcome (517), and absent MEPs were even significantly associated with false pessimistic predictions (142).

Multimodality Evoked Potentials

EP testing of two or more sensory modalities (multimodality evoked potentials [MMEPs]) yields greater prognostic power than does the examination of a single modality. In early prospective investigations of severely head-injured patients, Greenberg et al. (188) graded SEPs, AEPs, and VEPs on a 4-point scale according to the number of wave peaks detected, with grades I–IV indicating increasing loss of peaks. One to 7 days after injury, only SEPs were significantly associated ($p < 0.001$) with clinical outcome graded according to the GOS (250). Specifically, patients with grade I–II SEP abnormalities had 90% probability of good recovery or only moderate disability. Eight to 30 days after trauma, BAEPs also showed significant but weaker association with outcome ($p < 0.005$). VEPs correlated least with the patient's final state. Graded MMEPs predicted outcome even 1 year after injury with about 80% accuracy (188). Combining these three-modality EPs yielded 91% correct predictions with no falsely pessimistic errors. These findings indicated that the prognostic power of MMEPs exceeded that of the clinical data, the computed tomography scan, and the intracranial pressure (345). However, other investigations concluded that MMEPs improved only slightly the predictions based on clinical indices (295). Several studies confirmed that SEPs provided earlier and more accurate prognostic information in traumatic coma than did AEPs (15,146,295,382), whereas the value of VEPs remained controversial (90,152,445).

Joint SEP-AEPs with or without VEPs were said to be good predictors of outcome not only in traumatic comas but also in comas caused by brain anoxia (30,196,197,422) and intracerebral hemorrhage (143,146). In an individual study, BAEPs and brainstem trigeminal potentials jointly allowed 84% correct predictions, which increased to 93% when clinical data were included (424). Combined SL-SEPs–MEPs were found by some to improve outcome prediction and to facilitate the assessment of sensorimotor dysfunction (142).



However, others contended that joint SL-SEPs–MEPs as well as SL-SEPs–BAEPs added only minimally to the prognostic value of the neurological examination (294) or were even inferior to it (380,506).

Guérit et al. (197) have developed two graded indices of brain function: an index of global cortical function (IGCF) based on presence or absence and latency of VEP and SEP components, and an index of brainstem conduction based on IPIs of BAEP and SEP. Unfavorable outcome was predicted by both indices in traumatic coma and by the IGCF in anoxic coma, whereas neither measure proved adequate to prognosticate favorable outcome.

Cognitive Evoked Potentials

Several authors have succeeded in eliciting long-latency CEPs in comatose patients. A P300-like wave was recorded in individuals with comas of various etiologies (158,186,262,343,412,507), but the proportion of patients with this response who recovered consciousness varied in these studies from 50% to 100%.

Of special interest is the demonstration of another CEP, the "mismatch negativity" (MMN) (Fig. 14.18*B*), in the initial examination of a proportion (22%–42%) of comatose individuals (158,261,262) most of whom (91%–100%) regained consciousness within 1 or more days (158,261,262), averaging 6.3 days in one study (158). A highly significant association was found between the latency of the MMN and the 90-day outcome (262). In contrast, the absence of MMN in the initial examination of comatose patients was followed by death or lack of recovery of consciousness in a variable proportion of individuals (32%–76%) (158,261,262). When serially studied, most of the remaining patients with no initially demonstrable MMN who subsequently developed this response regained consciousness (261) (Fig. 14.18*A* and *B*). Similar results were reported in the study of a highly variable positive–negative CEP complex detected acutely in a small proportion of comatose patients (199).

It appears that the detection of a MMN predicts awakening from coma with a degree of specificity that substantially exceeds that of other CEPs. However,

FIG. 14.18. A: Absent MMN response in an unconscious patient (Glasgow Coma Scale [GCS] score = 4) following severe head injury. **B:** Subsequent manifestation of this response in the same comatose individual (GCS score = 5) prior to the recovery of consciousness. (Modified from Kane NM, Curry SH, Rowlands CA, et al. Event-related potentials—neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Med* 1996;22:39–46.)

a relatively limited number of comatose patients display this response in their initial examination when prognostication of outcome is most needed, and somewhat elaborate techniques are required to demonstrate it beyond doubt (158). In addition, the detection of a MMN provides no information on the quality of functional recovery as well as the restoration of full cognitive capacities (158,261). Thus, in ordinary clinical circumstances, eliciting a MMN (as other CEPs) may provide intriguing insights into disordered brain functions in comatose states but is of questionable practicality.

Summary and Conclusions

Of all electrophysiological measures investigated, bilateral obliteration of the earliest cortical response to median nerve stimulation, the N20 (or N20-P27 complex) during the first week of coma has emerged as the most reliable predictor of unfavorable outcome in patients rendered comatose by acute, severe brain anoxia: virtually 100% of these individuals who demonstrate bilateral loss of the N20 potential die or remain vegetative (514). However, a meta-analysis of the available literature (514) indicates that, following severe brain anoxia, absence of the pupillary light reflex or motor responses to noxious stimuli predicts death or vegetative survival with the same specificity as the bilateral absence of the N20 potential, although with a slightly lower sensitivity (531). It follows that, when either or both of these clinical signs are demonstrated 72 hours after onset of anoxic coma (514a), bilateral loss of the N20 potential strongly confirms the clinical prediction of unfavorable outcome but is largely redundant (278). In contrast, demonstrating bilateral abolition of the N20 potential provides valuable information on the likelihood of death or vegetative survival when conditions exist that limit or preclude the clinical examination, such as facial or other injuries or the effects of sedative or paralyzing drugs. However, caution should be exercised in using individual neurophysiological prognostic indices in isolation to justify the withdrawal of supportive measures (31,514a). Combinations of clinical, neurophysiologic, and other indices may increase the accuracy of prediction of outcome from anoxic coma in the future (514a).

As opposed to the utility of bilaterally extinguished N20 potential in prognosticating death or vegetative survival in post-anoxic coma, no electrophysiological measure allows at present confident prognostication of unfavorable outcome from comas due to causes other than anoxia, or of favorable outcome from coma of any etiology. Overcoming these limitations is a major challenge for future investigations.

Following the Evolution of Comatose States

Although EEGs, EPs, and CEPs potentials can be useful in following the evolution of comatose states, prompt assessment and management of rapidly evolving comas requires continuously monitoring the EEG, EPs, and systemic functions, often combined with each other. Continuous electrophysiological monitoring in the ICU is reviewed in Chapter 25.

Distinguishing Coma from Other Conditions of Diminished Responsiveness

This chapter has already described EEG features that help distinguish comatose from locked-in states. Other potentially confounding conditions include frequent seizure activity and psychogenic unresponsiveness. In some instances, frequent seizure activity is responsible for or contributes to the patient's diminished responsiveness, and may cause additional brain damage, especially in patients with borderline cerebral perfusion. This ictal activity may be associated with minimal or no detectable clinical manifestations, especially when paralyzing agents are used. Thus its demonstration by EEG, especially continuous monitoring, is crucially important in devising the appropriate treatment and preventing complications. In contrast, EPs are not helpful in detecting epileptic activity (79,198).

Psychogenic unresponsiveness is said to account for 1% of comas "of unknown etiology" (370). A normal EEG with a well-developed alpha rhythm attenuated by sensory stimuli more likely suggests psychogenic, rather than structural or metabolic, causes (370). However, faced with such an EEG, one must take care to exclude a deefferented state mimicking coma. Moreover, the EEGs of psychogenically unresponsive patients may show changes caused by psychotropic and other drugs. EPs may also contribute to differentiation between psychogenic and structural causes of diminished responsiveness.

ELECTROPHYSIOLOGICAL EVALUATION OF OTHER STATES OF DIMINISHED RESPONSIVENESS

Selective Failure of Forebrain or Brainstem Function

The "irreversible loss of function of the brain, including the brain stem" characterizes brain death (389). However, failure may involve the forebrain,

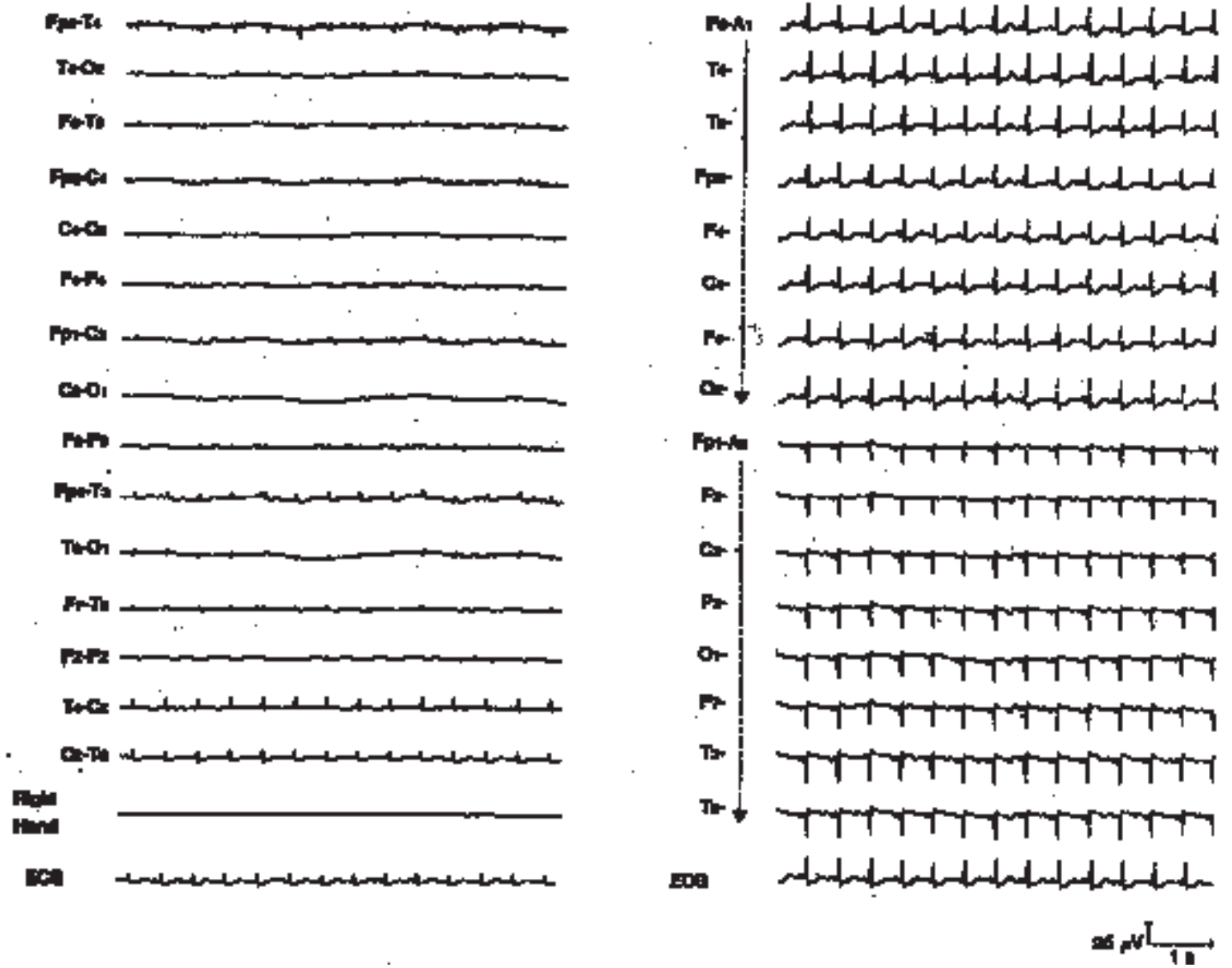


FIG. 14.19. ECI in a 45-year-old woman 3 days after an episode of ventricular fibrillation following coronary artery bypass graft. The patient was comatose with no withdrawal responses to noxious stimuli and was artificially ventilated but exhibited intermittent spontaneous respiration and intact brainstem reflexes. She died 6 days later. Her brain demonstrated pseudolaminar necrosis of the whole cerebral cortex and necrosis of other forebrain structures, with relative preservation of brainstem and spinal cord. (Modified from Wytrzes LM, Chatrian G-E, Shaw C-M, et al. Acute failure of forebrain with sparing of brain stem function: electroencephalographic, multimodality evoked potentials, and pathologic findings. *Arch Neurol* 1989;46:93–97.)

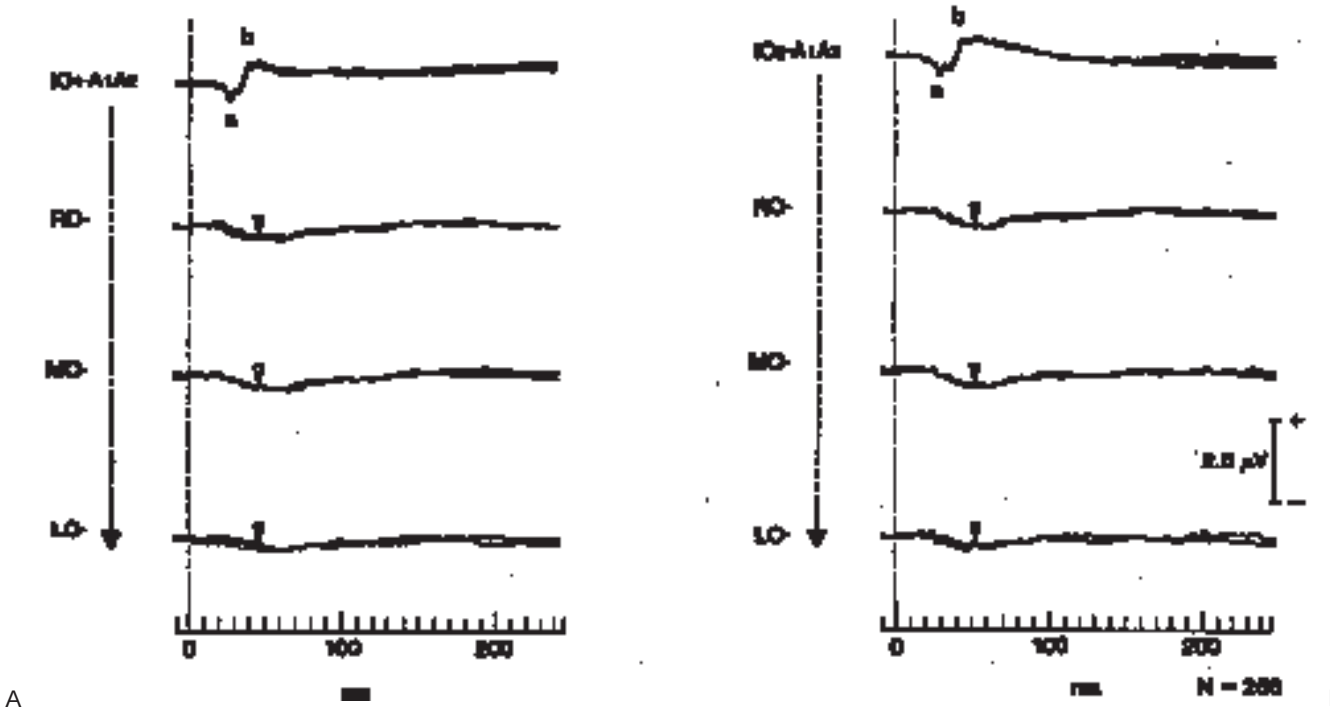


FIG. 14.20. Retinal, but no cerebral, responses to flash stimulation of the left **(A)** and right **(B)** eyes in the same patient as in Figure 14.19. ERGs (waves *a* and *b*) were detected between left (*Io1*) and right (*IO2*) infraorbital electrodes and linked earlobe reference (*A1A2*). Slow downgoing potential (*clear arrows*) in recordings from right (*RO*), midline (*MO*), and left (*LO*) occipital electrodes was interpreted as an ERG detected by the A1-A2 reference. SL-SEPs showed similar abolition of cortical N20 potential with preserved brainstem P14 and spinal N13 components. Same patient as in Figure 14.19. (Modified from Wytrzes LM, Chatrian G-E, Shaw C-M, et al. Acute failure of forebrain with sparing of brain stem function: electroencephalographic, multimodality evoked potentials, and pathologic findings. *Arch Neurol* 1989;46:93–97.)

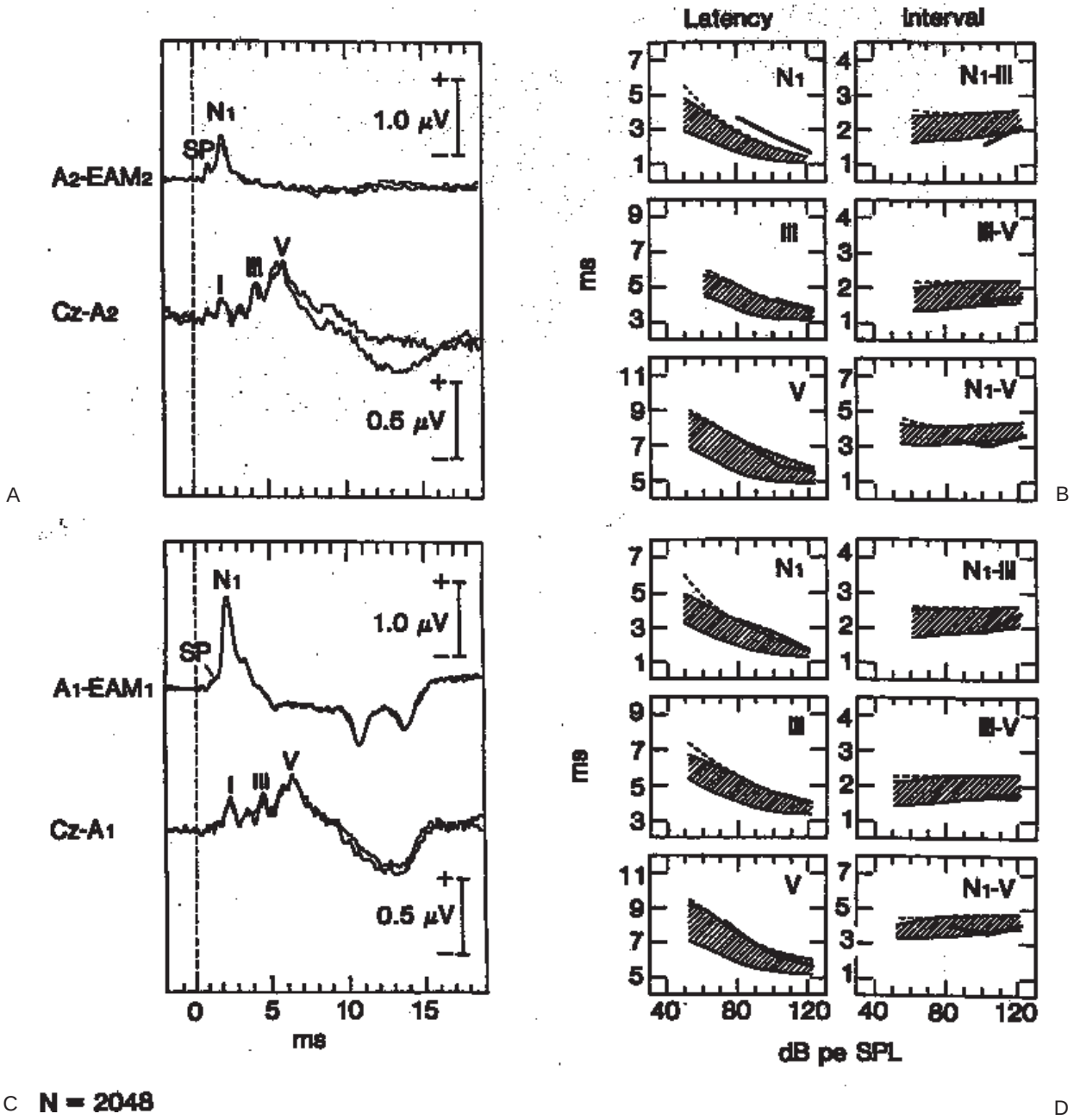


FIG. 14.21. Electrocochleograms (ECochGs) (*top trace*) and BAEPs (*bottom trace*) in response to stimulation of right **(A)** and left **(C)** ears with clicks of alternating polarity at 120 dB sound pressure level and dB peak-equivalent sound pressure level (pe SPL) of 8.3 per second. *EAM2* and *EAM1*, right and left auditory meatuses. **B** and **D:** Plots of latency– and interval–intensity functions for major response components shown in **A** and **C**, respectively. *Shaded areas*, 2 standard deviations; *dashed lines*, 95% tolerance limits for 95% of normal population of the same age; *heavy solid lines*, functions computed in this patient. All IPIs were within normal limits. Same patient as in Figures 14.19 and 14.20. (Modified from Wytrzes LM, Chatrian G-E, Shaw C-M, et al. Acute failure of forebrain with sparing of brain stem function: electroencephalographic, multimodality evoked potentials, and pathologic findings. *Arch Neurol* 1989;46: 93–97.)

with substantially preserved brainstem function, or , conversely, it may involve the brainstem with relative sparing of the forebrain. Clinical states resulting from these failures differ from brain death.

Acute Forebrain Failure (Cortical Death)

Patients studied shortly after resuscitation sometimes have acute failure of the forebrain with variable sparing of brainstem function (501) or "cortical death," described in earlier publications as "neocortical death" (60,333,395), "partial brain death" (372), and "apallic syndrome" (238). This condition, characterized by deep coma with variably preserved brainstem reflexes, differs from vegetative states (251,340) that result from chronic forebrain failure and are manifested by alternating wakefulness and sleep without cognitive awareness. However, acute forebrain failure may evolve into a vegetative state (240).

The EEGs of patients with acute forebrain failure most commonly demonstrate an EEG pattern of ECI (Fig. 14.19) or slow activating of very low voltage. Occasionally they display widespread, frontally dominant alpha activity or burst-suppression later evolving into ECI (60,239,395,501).

EP findings are variable. Median nerve–elicited cortical N$\overline{20}$-P$\overline{27}$ (P$\overline{25}$) potentials are abolished bilaterally in some subjects (68,69,184,395,485, 501). In other individuals, N$\overline{20}$ is present and normal bilaterally but the subsequent P$\overline{27}$ (P$\overline{25}$) component may be normal, altered, or absent (67, 68,137,184,485,501). In the majority of cases, the P$\overline{14}$ brainstem potential is preserved (68). Pathological changes in these patients are variable. In individuals with normal cortical SL-SEPs, histological lesions are commonly restricted to Sommer's sector of the hippocampus (CA1) and Purkinje cells of the cerebellum, which are known to be highly vulnerable to anoxia (67,68). In contrast, the brains of individuals with no recordable cortical SL-SEPs demonstrate anoxic-ischemic alterations involving diffusely cerebral cortex, thalamus, and cerebellum with no or with minor brainstem and spinal cord changes (184,395,501). An exception is the finding of a structurally normal brain in one patient who died few hours after cardiac arrest (184). It thus appears that the variability of cortical SL-SEPs in patients with acute forebrain failure closely reflects the extent and severity of anoxic damage, which, in turn, partly depends on the duration of survival after onset of coma. The predilection of the pathology for the hippocampus is somewhat difficult to reconcile with the appellation "neocortical death" (60). The term *cortical death* describes more accurately this condition.

Generally, no cerebral VEPs can be elicited in patients with acute forebrain failure (Fig. 14.20), whereas BAEPs are most commonly normal (395,501) (Fig. 14.21). The occasional finding in these individuals of absent BAEPs, including wave I, and preserved cortical SL-SEPs suggests hypoxic cochlear damage, precluding the activation and assessment of central auditory pathways (67).

Brainstem Failure (Brainstem Death)

Cases described in the literature as "brainstem" (121,392) or "rhombencephalic" (440) death mostly consisted of individuals who had lesions transecting the brainstem at the pontine level but sparing the midbrain, preserved EEG, and loss of BAEPs. Because these individuals were completely deefferented, it is impossible to determine clinically whether they were comatose or totally locked-in (i.e., aware of stimuli but unable to respond) (34,497).

On occasion, whole-brain death may be mimicked by a lesion destroying the reticular core of the midbrain and causing unresponsiveness and brainstem deficits. Ingvar and co-workers (240,241) described a patient whose acute unresponsiveness evolved into persistent coma culminating in death. In this individual, initial "general depression" of the EEG with unilaterally preserved alpha activity was followed by the development of widespread low-voltage delta waves associated with markedly reduced hemispheric blood flow and cerebral oxygen consumption. Cortical biopsy 18 months after onset of unresponsiveness showed no neuronal loss. Pathological findings 17 months later included a cystic hemorrhagic lesion in the dorsal midbrain destroying most of the periaqueductal gray matter, an infarct in the right posterior thalamus and the adjacent areas of the internal capsule and globus pallidus, and marked cortical atrophy with laminar loss of nerve cells. The authors hypothesized that nearly complete destruction of the midbrain reticular core severely depressed cerebral metabolism and blood flow, causing diffuse low-voltage, slow activity in the EEG.

Vegetative States

Clinical Criteria

As time elapses after onset of coma, some patients neither die nor regain consciousness but rather evolve into a "vegetative state" (251). The Multi-Society Task Force on PVS (340) defined as vegetative states a group of conditions having in common "complete unawareness of the self and the

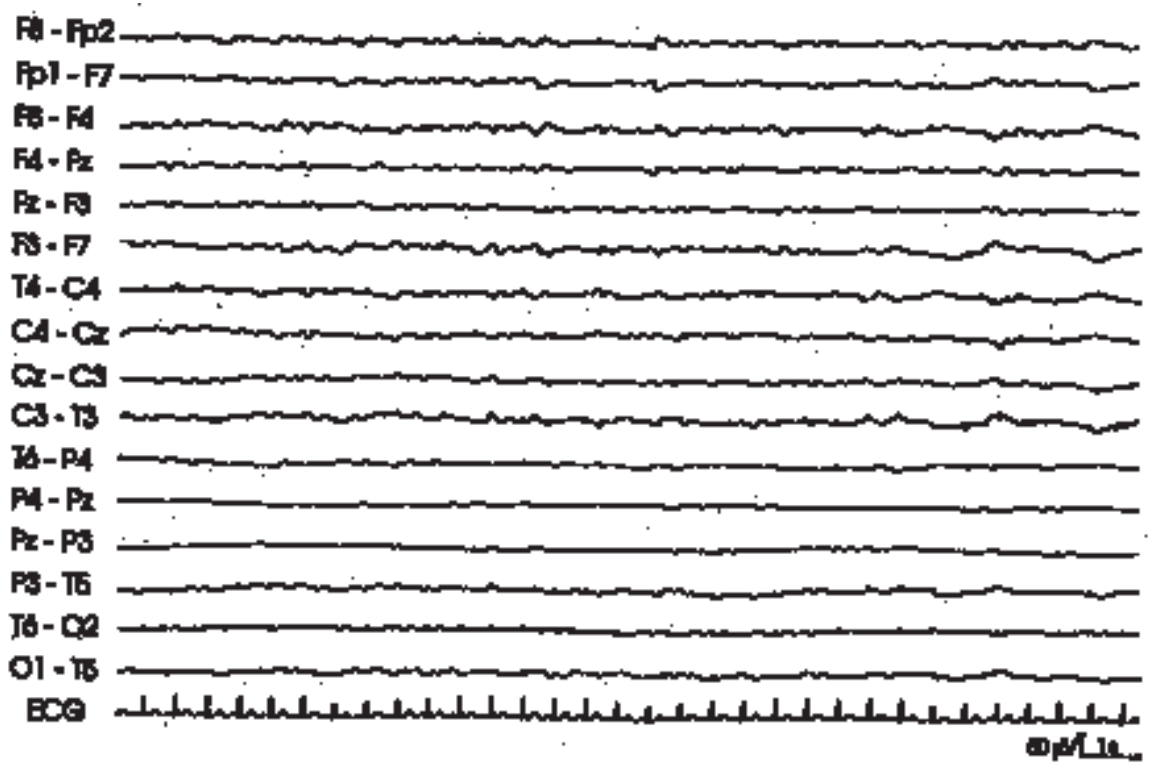


FIG. 14.22. Widespread 1- to 5-Hz activity best developed over the anterior and middle head regions in a 47-year-old woman. The patient had suffered retroperitoneal hemorrhage with circulatory collapse and loss of consciousness following earlier total pelvic exenteration for recurrent adenocarcinoma of the cervix. One month after the onset of coma, she was in a vegetative state. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brain stem autonomic functions." Observation of these individuals indicates that they are incapable of "sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli" and give "no evidence of language comprehension or expression" (340). Terms employed in the past to describe this condition or states resembling it have included "apallic syndrome" (277), "coma vigil" (7), "noncognitive states" (275), and "akinetic mutism," among others.

A vegetative state was observed in 12% of individuals 1 month after onset of nontraumatic coma of various etiologies (290) and in 1%–14% of comatose patients following severe head injury (340). In some patients the vegetative state is transient and reversible (175,176,340), whereas in other individuals it persists for months or years (292,340) ("persistent" and "permanent" vegetative states) (340).

Mortality is high among vegetative patients and is greater in adults than in children and following nontraumatic than traumatic brain injuries (340). A review of earlier reports concluded that average life expectancy for vegetative adults was 2–5 years and that the possibility of survival beyond 15 years after injury was exceedingly small (< 1 in 15,000–75,000) (340), but improved standards of care may modify this outlook (289).

Changing concepts and definitions of vegetative states (12,16,177,340) and studies suggesting a high rate of misdiagnosis of these conditions (98) make it difficult to analyze reported clinical, pathological, and electrophysiological findings.

EEG Findings

In the past, EEGs of some vegetative patients were described as electrocerebrally inactive (37,60,109,175,239). In retrospect, it appears likely that

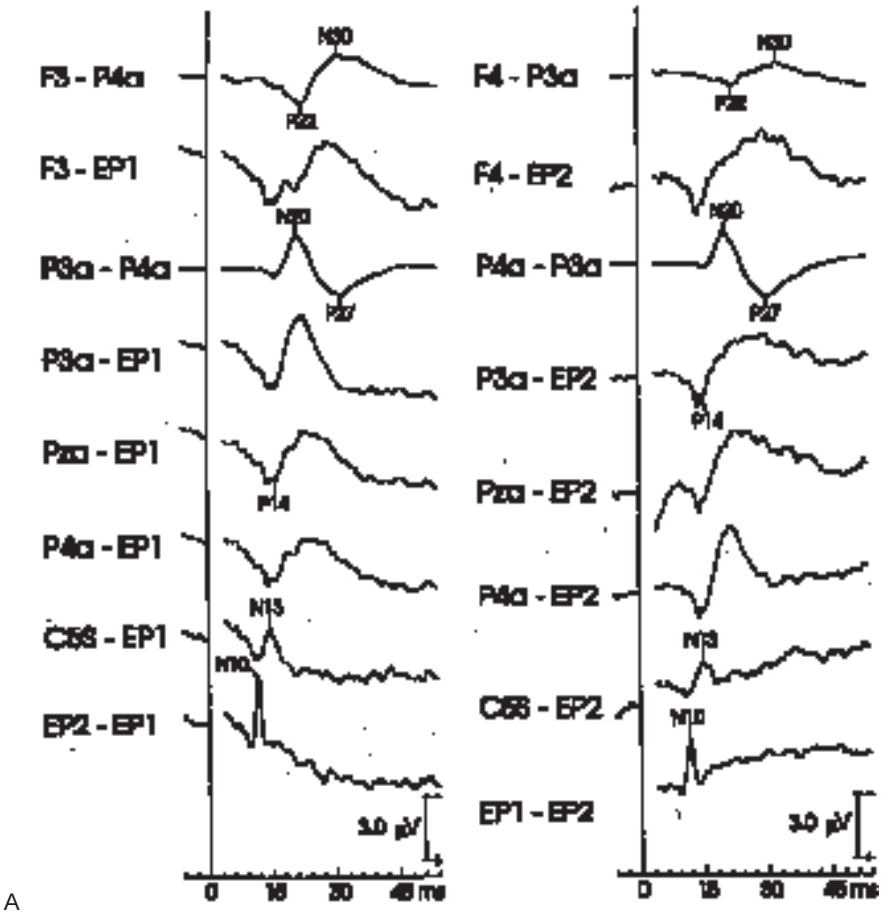


FIG. 14.23. SL-SEPs in response to electrical stimulation of the right **(A)** and left **(B)** median nerves at the wrist. *F3 and F4*, left and right frontal electrodes; *P3a, Pza, and P4a*, electrodes halfway between P3 and C3, Pz and Cz, and P4 and C4 of the 10-20 system; *EP1 and EP2*, left and right Erb's points electrodes; *C5S*, C5 spine electrode. Responses, including early cortical postcentral (N$\overline{20}$-P$\overline{27}$) and frontal (P$\overline{22}$-N$\overline{30}$) potentials, had normal latencies and IPIs. Same patient as in Figure 14.22. Nine days after onset of coma, neurological status remained unchanged. (Modified from Wytrzes LM, Chatrian G-E, Shaw C-M, et al. Acute failure of forebrain with sparing of brain stem function: electroencephalographic, multimodality evoked potentials, and pathologic findings. *Arch Neurol* 1989;46:93–97.)

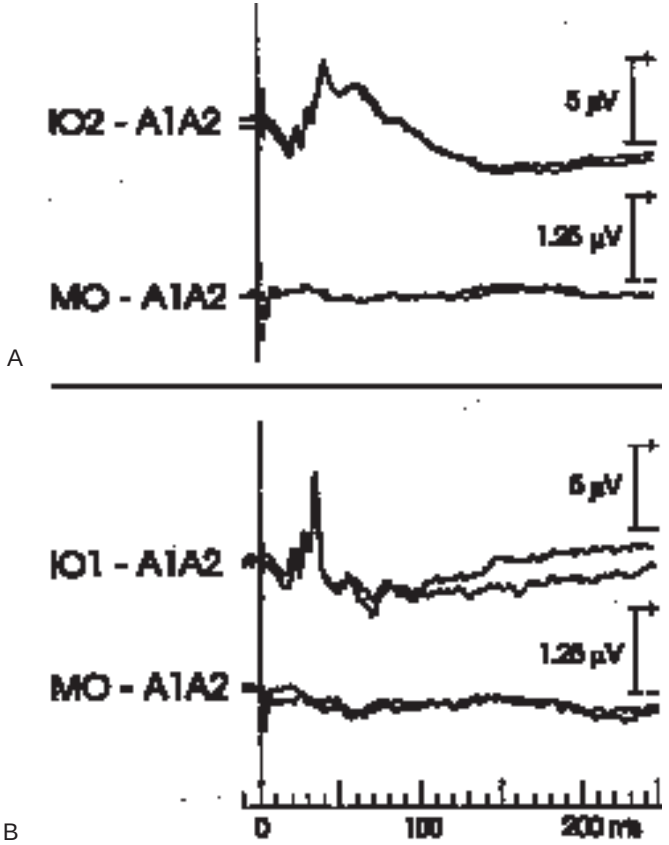
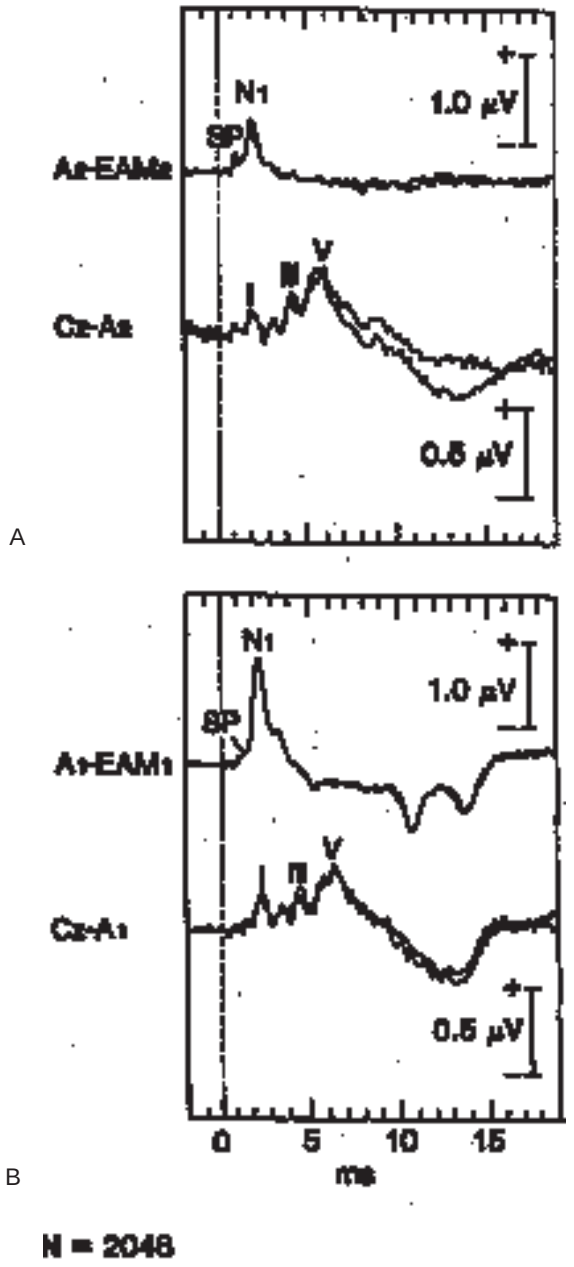


FIG. 14.24. Asymmetrical ERGs (waves *a* and *b*), but no cerebral responses, following flash stimulation of the right **(A)** and left **(B)** eyes. Recording technique and abbreviations are the same as in Figures 14.22 and 14.23. Same patient as in Figure 14.22, 15 days after onset of unresponsiveness. Neurological status remained unchanged.



most of these records demonstrated low-voltage, slow, unreactive activity rather than ECI as currently defined (14). More recent reports have established that vegetative individuals demonstrate a wide variety of EEG patterns, including widespread, slow, unreactive activity often of low voltage (Fig. 14.22); burst-suppression; bilateral pseudoperiodic complexes; epileptiform discharges; diffuse unreactive alpha or theta activity; and even highly organized waking and sleep patterns regarded as only mildly abnormal (4,37, 38,56,57,108,128,174,175,211,239,255,287,300,302,318,372,411,475). Thus individual diurnal EEGs are of little value in diagnosing vegetative states.

Some studies indicated that recovery from the vegetative state was paralleled by diminution of delta and theta activity when present in earlier EEGs, reappearance of a reactive alpha rhythm (247,300), progressive restoration of organized sleep EEG patterns and nocturnal sleep cycles, and recovery of REM sleep (8,174). Extreme variability of findings precludes the use of the EEG to predict the clinical outcome of vegetative states. However, spectral analysis of the EEG was said to indicate that "slow monotonous spectrograms" were mostly associated with death, whereas "changeable spectrograms" had a more favorable prognosis (467).

Evoked Potential Findings

Just as with EEGs, EP findings are extremely variable in vegetative patients. The N20 cortical component of median nerve SL-SEPs may be normal (Fig. 14.23), although CCTs may be increased or may be variously altered or absent with variably preserved brainstem P14 potential (196,211, 372,383). Similarly, cortical VEPs may be variously abnormal (196,383) or absent (196,372) (Fig. 14.24). BAEPs are reportedly normal in many vegetative patients (Fig. 14.25), although brainstem conduction time may be prolonged, but demonstrate various alterations in other individuals (196,211,372,383,470). Heterogeneity of results hinders the use of EPs as predictors of outcome of vegetative states.

Because CEPs are related to certain aspects of cognitive behavior, it seems natural that they should be called on to assess the preservation and to predict the restoration of cognitive capacities in vegetative patients. Thus,

FIG. 14.25. Electrocochleograms and BAEPs in response to click stimulation of the right **(A)** and left **(B)** ears. Recording technique and abbreviations are the same as in Figures 14.23 and 14.24. Latencies and IPIs were normal. Same subject as in Figures 14.22, 14.23, and 14.24.

Guérit et al. (196) suggested that preservation of these faculties could be tested in vegetative individuals by attempting to elicit somatosensory CEPs. Unfortunately, the patient substantiating this belief was capable of following simple orders and producing behavioral responses to various stimuli, at variance with the definition of vegetative state. Another study has claimed that the majority of vegetative patients displaying $\overline{N200}$ and $\overline{P300}$ cognitive potentials eventually regained consciousness, whereas all individuals in whom these responses could not be elicited did not (180). Confirmation of these suggestive findings is desirable.

Neuropathological Findings and Conclusions

Neuropathological changes in vegetative patients are variable. Extensive multifocal or diffuse, laminar cortical necrosis follows acute global hypoxia and ischemia, causing virtual decortication. Scattered small areas of infarction or neuronal loss may be additionally present in the basal ganglia, hypothalamus, or brainstem (129,239). Extensive subcortical axonal injury is caused by shearing of nerve fibers by acute trauma (2,443,444). These last changes cause virtual cortical isolation (249). In patients with head injury complicated by acute circulatory or respiratory failure, axonal injury may be associated with diffuse laminar necrosis (340). Severe brainstem abnormalities are infrequent and primarily follow transtentorial herniation during the early stage of illness (340). Vegetative patients with degenerative disorders and developmental abnormalities display the pathological changes characteristic of their underlying conditions (341). In a highly publicized individual case of "persistent" vegetative state, extensive, bilateral thalamic scarring by far exceeded damage in the cortex, basal ganglia, and cerebellum (272). The fact that in individual patients pathological lesions may primarily involve cerebral cortex, cerebral hemispheric white matter, and thalamic or brainstem structures to a variable degree and in various combinations likely accounts for the remarkable variability of EEG, EP, and CEP findings reported in vegetative states.

ELECTROPHYSIOLOGICAL EVALUATION OF BRAIN DEATH

Brain Death in Adults

Concept, Clinical Criteria, and Confirmatory Tests

The concept of brain death has evolved since it was first formulated and has been the subject of controversy (78). Recent U.S. guidelines define brain death as "the irreversible loss of function of the brain, including the brainstem" (389). The same guidelines specify that the diagnosis of brain death in the adult is established by demonstrating the clinical signs of unresponsiveness, absent brainstem reflexes, and apnea established by a strictly standardized apnea test. Repetition of clinical testing after an interval such as 6 hours is advisable but not required. The application of these clinical criteria is contingent on (a) the demonstration by clinical and neuroimaging studies of an acute CNS catastrophe compatible with brain death and (b) the exclusion of confounding medical conditions that may reversibly cause clinical manifestations mimicking brain death. These complicating conditions include hypothermia with core temperature below 32°C (89.6°F), drug intoxication or poisoning, and severe metabolic derangements and endocrine crises (389,492,493). Brain death as defined excludes other states of diminished responsiveness such as deefferented (locked-in) states (370) and vegetative states (340).

Current U.S. standards emphasize that the diagnosis of brain death in adults can be made in ordinary circumstances by good history and competent clinical examination supplemented by routine laboratory tests and neuroimaging studies. They recommend, but do not mandate, that a confirmatory test should be performed when, after a period of observation exceeding 24 hours, not all prerequisites for clinical testing are satisfied or specific components of clinical testing cannot be reliably performed or evaluated (389,492,494). Such standards vary in other countries; in France (331,332), confirmatory tests are required by law, whereas in the United Kingdom they are regarded as unnecessary (364,429,499). Substantial numbers of small hospitals in developed countries and most hospitals in the developing world lack the instrumentation and skills required to perform and interpret ancillary studies designed to corroborate the clinical diagnosis of irreversible loss of brain viability. In these circumstances, unless the patient can be safely transported to a properly equipped medical center, there are no alternatives but to establish the diagnosis of brain death by clinical observation alone. However, we believe that, whenever the diagnosis of brain death is in doubt and the appropriate resources are available, no effort should be spared to decrease the chances of error, expedite the diagnosis, provide objective proof of irreversible extinction of brain function, and increase the opportunities for removal of viable organs for life-saving transplantation. The following is a critical review of the role currently played by electrophysiological testing in the diagnosis of brain death in the adult.

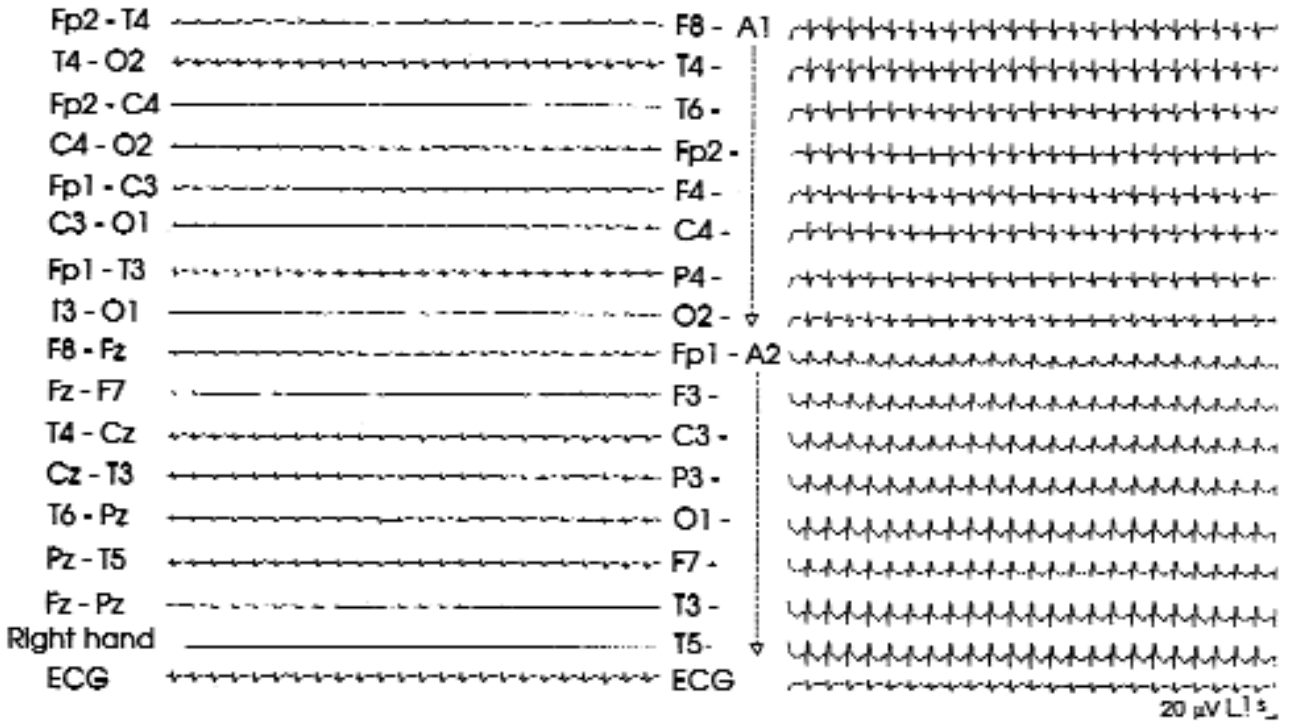


FIG. 14.26. ECI in a 23-year-old hypertensive woman 2 days after intracerebral hemorrhage. The patient was unresponsive to stimuli and had no spontaneous respiration, no cephalic reflexes, and dilated pupils. ECG artifact was especially prominent at high sensitivities and in referential derivations.

The EEG as a Confirmatory Test

ECI: Definition

In a substantial proportion of patients who are clinically brain dead (about 80%) (191), scalp recordings show absence of demonstrable EEG potentials. Such a state of "electrocerebral inactivity" is defined as "absence over all regions of the head of identifiable electrical activity of cerebral origin, whether spontaneous or induced by physiological stimuli and pharmacological agents" (350) (Fig. 14.26). Electrical activity of cerebral origin is identified when it exceeds an assumed instrumental noise of 2 µV. Other terms used in the literature to describe ECI include "electrocerebral silence" and "isoelectric," "flat," and "null" EEG, among others. Our definition of ECI *excludes*

Recordings displaying burst-suppression, which are commonly found in conditions including acute intoxications with CNS depressants, severe anoxic encephalopathies, and deep hypothermia and anesthesia

Low-voltage, slow, generally unreactive EEGs consisting primarily of delta and theta potentials, which usually occur in comatose patients with severe widespread cortical damage

Recordings showing no detectable electrocerebral activity over limited areas of the scalp

TABLE 14.1. *Requirements for demonstrating electrocerebral inactivity in the adult*

1. Sixteen or more EEG channels should be recorded simultaneously (83,389).
2. In addition to all electrodes of the 10-20 system (246) and a ground electrode, two electrodes should be routinely placed on the arms, shoulders, or chest for ECG monitoring, and two should be applied 6–7 cm apart on the dorsum of the right hand to monitor artifacts from the surroundings (14,83).
3. The use of other electrodes may be required, including special transducers for monitoring respiration and related artifacts (14,83).
4. Interelectrode impedance should be below 10,000 but above 1,000 ohms (14,83).
5. The integrity of the entire recording system should be checked (14).
6. Instrumental sensitivities should be no less than 2 μV/mm for at least 30 min of recording time, and calibrations should use appropriate voltages (14,83).
7. Low frequency cutoffs (–3 dB) should be at approximately 0.5 Hz (corresponding to a time constant of 0.3 s). However, in the presence of excessive slow artifacts, the use of low-frequency filters at about 1.5 Hz (corresponding to a time constant of 0.1 s) during part of the recording is justified. High-frequency filter cutoffs should be at approximately 70 Hz. Cutoffs at 50 or even 35 Hz during part of the recording are justified in the presence of irreducible electromyographic activity when pharmacological neuromuscular blockade is contraindicated (83).
8. The recording should include bipolar (anteroposterior and transverse) and referential montages. Bipolar montages should primarily consist of large- (double-) distance electrode linkages (14,83).
9. Requirements 6 through 8 above apply to recordings obtained with analog recorders. When using digital recorders, the same requirements should be fulfilled for on-line data display and off-line data review. Digital instruments offer the advantage that the recording, typically obtained referentially and stored electronically, can be reviewed with different sensitivities, filters, montages, and paper speeds without altering the parameters of the signal stored. This attractive capability does not justify decreasing the overall recording time because of the danger of missing EEG activity that occurs intermittently at long intervals (83).
10. To test EEG reactivity, stimuli, especially noxious excitations, should be delivered with prudence because they can produce marked fluctuations in intracranial pressure or cardiovascular changes that are potentially harmful to individuals with borderline brain perfusion and may cause prolonged electromyographic contamination of the EEG (82,83).
11. The examination should be conducted or closely supervised by a qualified technologist experienced in ICU recordings and working under the direction of an experienced clinical neurophysiologist (14,82,83). The latter should be present during at least part of the recording and should provide prompt interpretation of the test.
12. When doubt exists about whether or not the test demonstrates ECI, the entire procedure should be repeated after an interval such as 6 h (14).
13. Special precautions should be taken against electrical hazard, transmission of infection, and harmful effects of manipulations, especially head lifting and stimulation (83).
14. The minimal duration of actual, interpretable recording should be 30 min or longer (389,492,494).
15. Following resuscitation from circulatory arrest, at least 8 h should elapse between the onset of coma and the EEG examination (253).

Modified from Chatrian G-E. Electrophysiologic evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1999:681–705.

Low-voltage reactive EEGs displaying "activity of amplitude not greater than 20 μV over all head regions" (84), which are found among normal persons

Problems and Pitfalls in Demonstrating ECI

Whenever EEG confirmation of the clinical diagnosis of brain death is requested, the procedure should begin with a brief preliminary recording using all electrodes of the 10-20 system (246) and those instrumental settings and montages that are commonly used in the individual laboratory for the study of comatose patients. If this preliminary sampling suggests absent or questionable electrocerebral activity, the recording technique should be promptly modified to demonstrate ECI. Basic requirements for these recordings are summarized in Table 14.1.

Artifacts often contaminate EEG records designed to demonstrate ECI. These spurious electrical events include potentials generated by instruments near or connected to the patient, such as electrocardiographic (ECG) monitors, pacemakers, warming blankets, and dialysis units, as well as biopotentials of cardiovascular, muscular, and respiratory origin (37).

The most frequent and disturbing of all biological artifacts is the ECG, especially prominent in ear reference montages. ECG potentials occasionally resemble sharp-and–slow wave complexes or TWs. Premature ventricular contractions or ventricular tachycardia may produce potentials appearing as sharp transients or theta or delta rhythms, respectively. In addition, rhythms of mostly alpha frequency occasionally result from head vibrations caused by the systolic pulse wave (ballistocardiogram) (37). Disconnecting ECG monitors, repositioning the patient's head, and selecting montages less prone to EEG pickup may reduce, but frequently do not eliminate, ECG arti-

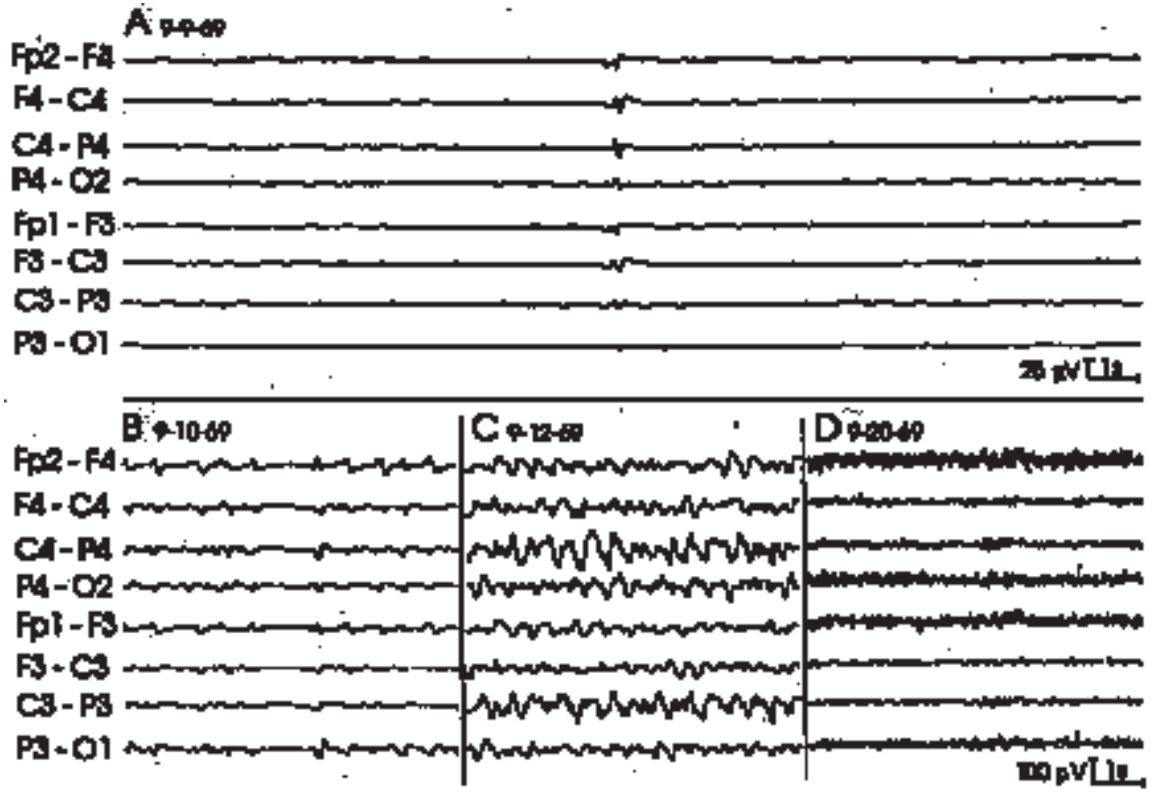


FIG. 14.27. Serial EEGs of a 30-year-old woman with secobarbital overdose. **A:** Second day of hospitalization. The patient was comatose and artificially ventilated, with a blood barbiturate level of 35 mg per 100 milliliters. The EEG showed isolated sharp-and–slow wave complexes separated by periods of suppression lasting up to 22 seconds. **B:** One day later, her clinical condition was unchanged. The EEG showed bilateral asymmetrical pseudoperiodic sharp waves at 1–2 Hz. **C:** Four days after admission, the patient was withdrawing in response to noxious stimuli, with pupils reacting to light. The EEG showed high-voltage bilateral 2- to 3-Hz activity. **D:** Eight days later, the patient was alert and responsive to verbal commands. The EEG showed 9- to 10-Hz posterior reactive rhythm. (From Chatrian G-E. Electrophysiological evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1980:525–588, with permission.)

fact. Thus, having attempted these and other maneuvers, the technologist generally can do little but accept this artifact and try to prove its origin by monitoring the ECG simultaneously with the EEG. Methods proposed to remove the ECG artifact from the EEGs of patients suspected of being brain dead (42) are of questionable practicality (78).

Electromyographic potentials may obscure possible electrocerebral activity unless neuromuscular blocking agents, such as pancuronium bromide (425) or succinylcholine (449,450), are given. However, caution is suggested by a report of cardiac arrest and death following administration of succinylcholine to reduce myogenic artifact (473).

It is sometimes more difficult to identify the origin of respiration-related artifacts. Respirators delivering a bolus of air to the patient through flexible tubes may cause the tubes to vibrate and to produce rhythmic activity of alpha or other frequencies, and head movements associated with respiration may generate large transients resembling periodic paroxysmal discharges (37). Monitoring with appropriate transducers can distinguish these artifacts from EEG potentials. On occasion, it may even be necessary to briefly stop the respirator to assess questionable activity (37). However, whenever this test is carried out over minutes, adequate oxygenation must be provided to avoid additional anoxic damage (83).

Technical Requirements for Demonstrating ECI

Obtaining in the ICU recordings that satisfy stringent technical requirements for demonstrating brain death often seriously challenges the competence, experience, ingenuity, and determination of the EEG technologist. In the NINCDS Collaborative Study, 22.3% of recordings required special efforts to identify and eliminate artifacts, although only 5.2% were considered technically unsatisfactory (37). Additional delays are caused by the prudent preparation of patients hovering between life and death and by interruptions of the EEG examination to allow performance of essential therapeutic maneuvers (83). Thus the production of at least 30 minutes of interpretable recording that fulfills present technical requirements may take as long as 2 hours and sometimes longer (368).

Recordings made by means of electrodes directly applied on the cerebral cortex or implanted within the brain have been advocated (479) but are of questionable utility and carry substantial risks (78).

Prerequisites for the EEG Confirmation of Brain Death: Significance of ECI. The demonstration of ECI in adult patients with clinical diagnosis of brain death indicates absence of cerebral cortical function, but does not imply that this functional loss is permanent unless confounding pathological conditions that may cause reversible extinction of electrocerebral activity have been ruled out. These conditions include drug intoxication, hypothermia, profound hypotension, and severe metabolic and endocrine derangements—that is, those same disorders that may reversibly cause the clinical manifestations of brain death.

Patients rendered comatose by overdoses of CNS depressants most frequently display a burst-suppression pattern in their EEGs. In some instances, electrocerebral activity is reduced to brief bursts or isolated waves of low voltage separated by intervals lasting several minutes (Fig. 14.27A). Most early reports of ECI persisting 24 hours or longer in patients who were drug intoxicated described EEGs that probably were not electrocerebrally inactive by present standards. However, other evidence of the occurrence of ECI in short-term EEGs of patients with overdoses of CNS depressants is more credible (37,479). Only sparse information is available on the blood levels of CNS depressants causing ECI in adults, who often are under the influence of multiple drugs and suffer from local or systemic conditions that alter the blood–brain barrier. Thus, caution should be exercised in interpreting the significance of ECI in adults with evidence of even small amounts of CNS depressants in their blood. Hypothermia with core temperature below 32.3°C (90°F) can cause reversible extinction of electrocerebral activity (388). The EEG may also be abolished by cardiovascular shock with low cerebral perfusion pressure and may be restored when blood pressure is raised above 80 mm Hg (479). Severe metabolic and endocrine disorders that can cause or contribute to the generation of ECI (388) include profound abnormalities of blood serum electrolytes, acid–base balance, blood gases, and the alterations resulting from severe dysfunction of the liver, kidneys, and pancreas.

Meticulous serial studies by Jørgensen and Malchow-Møller determined that ECI developed immediately in patients who suffered circulatory arrest of primary cardiovascular etiology. EEG activity, first intermittent and then continuous, recovered from 10 minutes to 8 hours after resuscitation in those individuals who subsequently regained consciousness (253) and from 11 to 128 hours after resuscitation in those patients who remained unconscious 1 year later (254). It follows that, at variance with current guidelines (14), no less than 8 hours should elapse after circulatory arrest before an EEG seeking confirmation of brain death is recorded.

Whenever the confounding conditions just alluded to are ruled out in an adult patient at least 8 hours (253,254) after an acute, catastrophic insult to the brain, the combination of the EEG pattern of ECI with the clinical signs of

coma, absent brainstem reflexes, and apnea attests to a global failure of brain function that is highly likely to be permanent (14,37,79–82,388,416,479).

Persistence of EEG Activity in Adults Who Satisfy All Preconditions and Clinical Criteria of Brain Death

As many as 20% of patients who satisfy all preconditions and clinical criteria for brain death do not demonstrate ECI but display some electrocerebral activity in their EEGs several hours to several days after death of their brains has been diagnosed clinically (191). This activity often consists of multifocal bursts of potentials of variable amplitude and duration. It has been conjectured that islands of relatively preserved brain tissue may still be capable of generating this aberrant electrical activity in brain-dead adults (78,191). This contention is partly supported by pathological findings indicating that remnants of EEG activity most commonly characterize patients whose brains show only patchy swelling, edema, infarction, and necrosis (285,338,481), whereas patients with ECI have a significantly higher incidence of swollen brains, cerebral herniations, and "respirator brains" (271,481). Individuals with EEGs classified as equivocal display pathological changes intermediate between these two groups.

Preservation of minimal EEG activity in clinically brain-dead patients is most likely incompatible with both lasting survival and any form of residual sentience, and does not justify the continuation of life-supporting measures (78,81,82). However, how much EEG activity is compatible with brain death and justifies cessation of life-supporting measures has not been established. In these circumstances, justifiably hesitant EEG interpretations are often greeted with understandable impatience by transplant teams.

Neuropathological Alterations and EEG Changes

The neuropathological changes in brain death are remarkably diverse (49,271,285,338,481). No statistically significant association was demonstrated between ECI and any specific pathology, although there was a tendency for this pattern to be more common in cases with hemorrhage, edema, and necrosis than with other types of lesions (481,482). Some patients with ECI who died less than 24 hours after onset of coma had minimal or no pathological alterations. Changes of "respirator brain" developed 12–36 (usually about 24) hours after onset of coma and apnea (229,285,478,480). Contrariwise, patients with some preserved EEG activity in their last recording sometimes revealed a respirator brain. However, in general, severity of EEG changes as measured by preserved electrocerebral activity in all, some, or none of the EEGs was said to be related to the degree of pathological changes in the brain. Additionally, progression to ECI, loss of brainstem reflexes, and evidence of herniation showed significant association with the presence of a "respirator brain" (285). In contrast, no significant association was demonstrated between ECI and site of primary pathology: 63% of patients with brainstem lesions exhibited ECI, as did 60% of individuals with diffuse cerebral lesions and 60% of patients with focal cortical lesions (479,481).

Suitability of EEG as a Confirmatory Test

In some countries, including the United States, the EEG has long enjoyed the status of test of choice for confirming the clinical diagnosis of brain death in adults. In other countries such as France, the performance of an EEG for the determination of brain death is even mandated by law (332). Yet growing recognition of limitations and pitfalls of the EEG indicates that primary reliance on this test is no longer justified (81,82,155,198). EEGs recorded according to current rigorous standards on adults suspected of being brain dead are difficult, cumbersome, time-consuming procedures that require a high degree of specialized technical and professional expertise, are subject to failures and misinterpretations, and have low specificity and sensitivity (78,81,82,362,363). In particular, ECI can be reversibly caused by those same conditions that may also transiently cause clinical manifestations of global loss of brain function (i.e., drug intoxication, hypothermia, profound hypotension, and severe metabolic or endocrine disorders). This is a major limitation because laboratory confirmation of irreversible failure of brain function is especially needed when the existence of these conditions hinders the clinical diagnosis (80–82). In addition, the consideration that, in the absence of these confounding conditions, ECI shows a high degree of statistical association with brain death (14) should not obscure the finding that a substantial number (about 20%) of clinically brain-dead patients do not demonstrate ECI but rather various amounts of residual EEG activity the relations of which to brain death are less clearly established (191). The tendency to identify the specificity of the particular EEG pattern of ECI in the absence of complicating conditions with the specificity of the EEG method in general in the context of brain death is a major source of confusion in official recommendations (389) and individual publications (494). We believe that medically sound and cost-effective management requires that, when available, tests other than the EEG should be

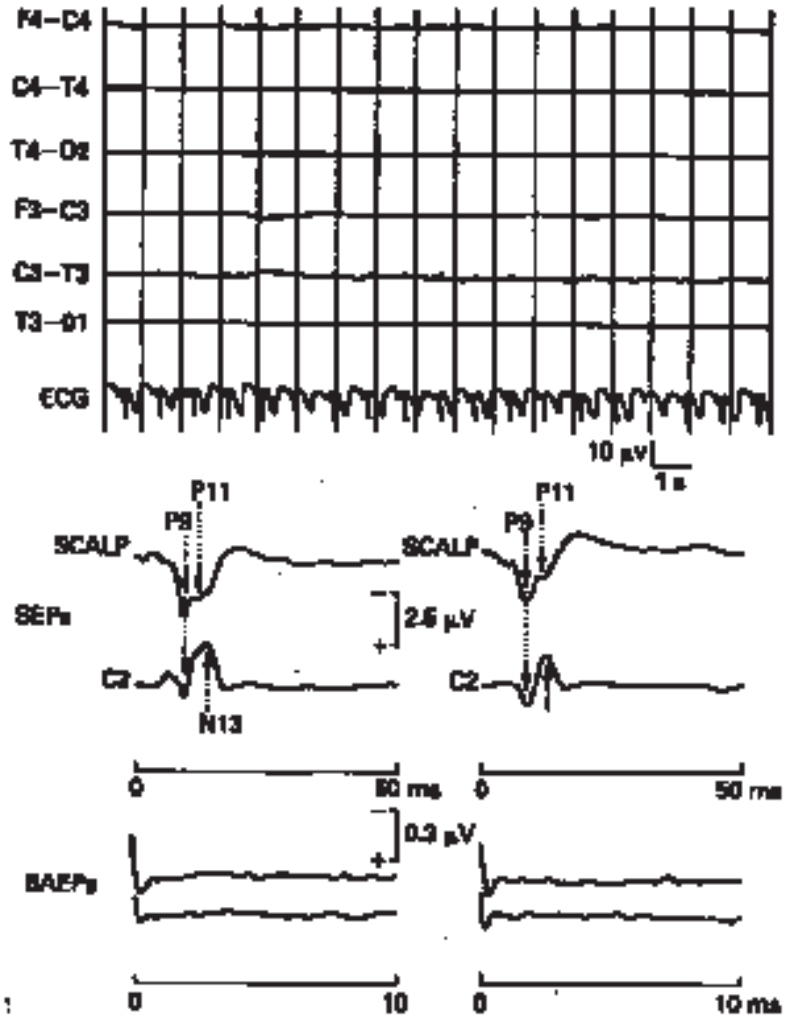


FIG. 14.28. Electrophysiological studies in a 20-year-old clinically brain-dead woman with absent cephalic reflexes. **Top:** The EEG demonstrated ECI. **Middle:** SL-SEPs showed peripheral P9 and spinal P11 and N13 components, while brainstem P14 and cortical N20-P27 potentials are bilaterally absent. **Bottom:** BAEPs showed absence of all response components, including wave I. (Modified from Mauguière F, García-Larrea L, Murray NMF, et al. Evoked potential diagnostic strategies: EPs in coma. In: Osselton JW, ed. *Clinical neurophysiology. Vol. 1. EMG, nerve conduction, and evoked potentials*. Oxford, England: Butterworth-Heinemann, 1995:482–522.)

used as first choices to corroborate the clinical diagnosis of brain death. These procedures continue to evolve rapidly as new technologies become available. At present, methods designed to demonstrate absence or critical deficit of brain perfusion, although not entirely free of shortcomings, deserve special consideration (81,82,198).

Evoked Potentials as Confirmatory Tests

Short-Latency SEPs

In clinically brain-dead individuals, SL-SEPs in response to electrical stimulation of the median nerve show (a) bilateral obliteration of cortical N20 and subsequent components of SL-SEPs (17,36,184,194,321,400,401, 465); (b) loss of medullary P14 potential; (c) inconstant preservation of spinal N13 potential; and (d) frequent persistence of N9 brachial plexus potential (17,184,194) (Fig. 14.28, middle section). Reports of variable preservation of the P14 potential in some brain-dead individuals (36,321) are of uncertain significance. It has been suggested that, in patients who gradually evolve from deep coma to brain death, the medial lemniscus that presumably generates the P14 potential undergoes gradual rostrocaudal destruction. Occasional transient functional preservation of caudal portions of this structure at a time when brain death is already clinically apparent would result in a P14 potential of reduced amplitude in scalp-noncephalic reference derivations (477). In these circumstances, a simultaneous mid-frontal scalp-nasopharyngeal recording would demonstrate loss of the P14 potential from rostral portions of the medial lemniscus. This last finding has been said to differentiate brain-dead from deeply comatose patients in whom the rostral component of the P14 potential would be preserved (477).

SL-SEPs (as well as BAEPs) are extremely resistant to barbiturates and other CNS depressants causing coma or used in the treatment of coma (134,173,233,420,428,441,451). However, they are profoundly altered by hypothermia (207,315,441). Cortical SL-SEPs may also be abolished or altered by peripheral nerve, brachial plexus, cervical root, and spinal cord injury; dysfunction of somatosensory pathways as a result of preexisting conditions such as multiple sclerosis, degenerative diseases, and Arnold-Chiari malformation (320); and extensive brainstem lesions. On occasion, myogenic contamination may complicate them (194). In addition, recordings of median nerve SL-SEPs taken between the Fz (scalp) and C2 (spine) electrodes (184) pose special interpretive problems. These are overcome by derivations utilizing a noncephalic or ipsilateral ear reference (123,139,198,462).

Brainstem Auditory Evoked Potentials

Brain death is associated with obliteration of all BAEP components with or without preservation of waves I or I and II (184,259,274,321,334,406, 431,439,456,469–471,491) (see Fig. 14.28, lower section). A review of the available literature (79) found that loss of all BAEPs including wave I occurred in 57% of brain-dead patients, loss of all waves except I in 37%, and absence of all waves except I and II in 6%.

A major limitation of BAEPs in the study of patients with suspected brain death is that obliteration of wave I (the auditory nerve compound action potential) and all subsequent BAEP components attests to loss or severe impairment of peripheral (cochlear and auditory nerve) function. This deficit precludes the activation of central auditory pathways. Thus loss of wave I and of all subsequent BAEPs is compatible with, but cannot be taken as evidence of, loss of function of the auditory pathways in the brainstem such as occurs in brain death. In patients with suspected irreversible extinction of brain function, obliteration of wave I and all subsequent BAEPs can result from a variety of causes, including cochlear ischemia secondary to arrest of the intracranial circulation (67,184,319) and deafness or profound hearing loss, whether preexisting or caused by trauma or meningitis. In head-injured patients, in particular, cochlear or auditory nerve damage secondary to fracture of the temporal bone, injury to the middle ear or the tympanic membrane, and blood in the external auditory canal may result in complete absence of BAEPs. The detection of BAEPs may be further hindered by protracted nasotracheal intubation and positive-pressure ventilation, which can cause obstruction of the eustachian tubes and middle ear effusions resulting in conductive deficits. Because absence of wave I limits the utility of BAEPs in corroborating the clinical diagnosis of brain death, this finding should be scrutinized with special care. To this end, the possibility that failure of the stimulus or the recording circuit may be responsible for failure to demonstrate this wave (and all subsequent BAEPs) must be tested and excluded. The use of sufficiently high stimulus intensities and of recording electrodes in the external auditory meatus is also suggested to maximize the chances of detecting wave I (89,96).

Visual Evoked Potentials

Cerebral VEPs (in response to flash stimulation) are abolished in individuals fulfilling clinical criteria of brain death (19,194,427,465,486). In contrast, VEPs (and the EEG) are preserved in patients with large brainstem lesions who are deefferented and have lost both SL-SEPs and BAEPs. These findings help to differentiate between brain death and deefferented states.

A major limitation of VEPs in the corroboration of brain death is that they are highly vulnerable to the effects of CNS depressants and hypothermia (386,402). Moreover, because the retina is more resistant than the brain to anoxia, flash stimulation may elicit electroretinograms (ERGs) over the anterior head regions in the absence of cerebral responses. Preservation of the ERG is irrelevant to the outcome of clinically brain dead patients (77). Thus, when attempting to average cerebral VEPs in patients suspected of being brain dead, the possibility that the ERG may simulate them should be carefully assessed (18,77,79,82,465).

Motor Evoked Potentials

In patients with irreversibly extinguished brain function, MEPs are absent in response to magnetic (or electrical) transcranial stimulation of the motor cortex but are preserved in response to cervical excitation (153). However,

TABLE 14.2. *Types of studies and observation periods for determining brain death in children*[a,b]

Patient's age	Types of studies and observation periods
2 mo to 1 yr	Two physical examinations and two EEGs demonstrating ECI at least 24 hr apart ; or a physical examination, an EEG demonstrating ECI, and a cerebral radionuclide angiogram demonstrating nonvisualization of cerebral arteries.
Over 1 yr	Assuming demonstration of irreversible cause of coma, two physical examinations 24 hr apart should fulfill the criteria of brain death when laboratory testing is not to be performed. The period of observation should be prolonged by at least 24 hr if the extent and irreversibility of brain damage are uncertain (especially in hypoxic-ischemic encephalopathy), or it may be reduced if the EEG demonstrates ECI or if cerebral radionuclide angiography does not visualize cerebral arteries.

EEG, electroencephalogram; ECI, electrocerebral inactivity.

[a]Summary of the Report of Special Task Force on Brain Death in Children (387). (From Chatrian G-E. Electrophysiologic evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1999:681–705, with permission.)

[b]*Note:* The above guidelines have been seriously questioned, as indicated in the text.

TABLE 14.3. *Physical examination and laboratory criteria for determining brain death in children*[a,b]

Physical examination	EEG	Cerebral angiography
1. Coma and apnea. 2. Absence of brainstem function. 3. Lack of significant hypothermia or hypotension for age. 4. "Flaccid tone and absence of spontaneous or reflex movements excluding spinal myoclonus." The above findings should remain constant throughout the observation period.	Electrocerebral inactivity over a 30-minute period according to American Electroencephalographic Society guidelines. In small children, "inter-electrode distances should be decreased proportional to the patient's head size." "Drug concentrations should be insufficient to suppress EEG activity.	Lack of visualization of intracranial arterial circulation in cerebral radionuclide angiography or lack of blood flow to brain in contrast angiography. Value of cerebral radionuclide angiography in infants under 2 months is under investigation.

[a]Summary of the Report of Special Task Force on Brain Death in Children (387). (From Chatrian G-E. Electrophysiologic evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1999:681–705, with permission.)

[b]*Note:* The above guidelines have been seriously questioned, as indicated in the text.

experience with the routine clinical use of this method to confirm brain death is limited so far.

Summary and Conclusions

When all confounding conditions have been excluded, abolished EPs—including median nerve SL-SEPs after N$\overline{12}$, BAEPs with or without preserved waves I or I and II, VEPs with or without preserved ERGs, and transcranially elicited MEPs—indicates widespread failure of brain function, and adds substance to the clinical diagnosis of brain death. Because of limitations and pitfalls inherent in the study of a single neural pathway, exploring multiple sensory modalities is highly desirable in patients suspected of being brain dead (195). However, special emphasis should be placed on the study of SL-SEPs. BAEPs are of more uncertain assistance in confirming brain death, and VEPs are indicated primarily to differentiate between brain death and deefferented states caused by brainstem lesions that obliterate SL-SEPs and BAEPs. Although multimodality EPs can confirm that brain functions are irreversibly extinguished, their performance in the ICU is a time-consuming task that requires technical expertise and interpretive skills not available in all medical centers.

Methods chosen to confirm irreversible extinction of brain functions in the adult may vary according to the instrumentation and the technical and professional skills available in each medical center, and are dictated in some countries by governmental regulations. The nature of these tests is in constant evolution as new technologies become available. At present, techniques designed to demonstrate absence or critical deficit of brain perfusion, including radioisotope scintigraphy and Doppler ultrasonography, although not entirely free of shortcomings, are most commonly used in the United States to routinely confirm brain death in adults.

Brain Death in Neonates, Infants, and Small Children

Doubts have long been expressed that standards established for adults may be applicable to young patients. Guidelines issued in the United States by a Special Task Force for the Determination of Brain Death in Children (387) warned that establishing cessation of cerebral and brainstem functions and determining its irreversibility following severe brain insults was not possible in newborns earlier than 7 days after term. Clinical criteria of brain death applicable after this age did not differ from those recommended for adults. However, between the ages of 7 days and 1 year, the validity of these clinical standards depended on their persistence over specified periods of time and on their confirmation by EEG, cerebral radionuclide or contrast angiography, or both. No such constraints were advocated after the age of 1 year (Tables 14.2 and 14.3). These recommendations drew sharp criticism from Freeman and Ferry (164) and from Shewmon (410), who thought that the proposed standards were premature and based on combined clinical criteria and laboratory tests none of which had been validated. Perhaps in keeping with these objections, a survey of diverse pediatric ICUs in the United

TABLE 14.4. *Suggested requirements for demonstrating electrocerebral inactivity in children*

Patient age	Requirements
7 d–2 mo	Multiple physiological measures (typically eye movements, mental, electromyographic, respiration, and ECG) should be monitored in addition to the EEG (13). Numbers and locations of electrodes, and montages should meet guidelines for recordings in neonates and young infants (13). Effective recording time should be no less than 1 hr (13). The technologist obtaining the recording and the physician interpreting it should have special expertise in the EEG of neonates and young infants. Recordings demonstrating ECI should be repeated after a suitable interval to ensure persistent lack of electrocerebral activity (387).
> 2 mo–1 yr	Recording technique does not differ substantially from that recommended for adults. However, EEGs demonstrating ECI should be repeated after a suitable interval to ensure persistent lack of electrocerebral activity (387).
> 1 yr	Recording technique does not differ substantially from that recommended for adults.

Modified from Chatrian G-E. Electrophysiologic evaluation of brain death: a critical appraisal. In: Aminoff MJ, ed. *Electrodiagnosis in clinical neurology*. New York: Churchill Livingstone, 1999:681–705.

States (326) revealed only scant adherence to the guidelines of the Special Task Force. In the United Kingdom, a Working Party of the British Paediatric Association (500) thought that the concept of brain ("brainstem") death was itself "inappropriate" before 37 weeks' gestation and that confident diagnosis of this condition was "rarely possible" between the ages of 37 weeks' gestation and 2 months of age. For children older than 2 months, the assessment of brain death should be "approached in an unhurried manner" to ensure that all preconditions and clinical criteria are satisfied. The Working Party also denied the need to perform EEG, EP, angiographic, radioisotope, and Doppler studies to confirm the diagnosis of brain death in the developing child.

Clinical Criteria

There is general agreement that unique problems are met in attempting to determine by clinical observation and ancillary methods that brain functions have ceased in newborns and young infants and in establishing that this functional failure is irreversible. The clinical criteria of deep coma, absent brainstem reflexes, and apnea have limitations as indicators of loss of brain function in neonates and young infants, and periods of observation longer than in older patients are essential to establish their irreversibility (22,476).

The EEG as a Confirmatory Test

Technical and Interpretive Requirements

The EEGs of children have peculiar features (see Chapters 5 and 6) that evolve particularly rapidly from prematurity to 2 months after term. Neonatal EEGs are characteristically discontinuous; that is, they display bursts of activity separated by periods of apparent inactivity or generalized voltage attenuation that decrease in duration with increasing age. Widespread voltage depression, burst-suppression, and ultimately ECI readily develop in these recordings under the influence of a variety of factors, including hypoxia, hypotension, hypothermia, drug intoxication, and metabolic disorders (131–133,228,442). These particular features and the small head size of these young patients require substantial modifications of the recording technique used to demonstrate ECI in the adult (Table 14.4) as well as special interpretive skills that are uncommon even among pediatric neurologists. These requirements received little consideration in the report of the Special Task Force (387).

Reliability

Newborns up to 7 days after term with clinically diagnosed brain death may display in their EEGs either a pattern of ECI or variously preserved

electrocerebral activity irrespective of whether cerebral blood flow is abolished, critically diminished, or preserved (21,23,25). Early reports of restoration of EEG activity following ECI in young patients were not documented beyond doubt in the absence of hypothermia, hypotension, CNS-depressant drugs (339,421), cerebral malformations, and the postictal state. It is now apparent that, however infrequently, recovery of EEG activity did occur in neonates with ECI who had none of these complicating conditions (23,228). In most instances, ECI was followed by other abnormal EEG patterns and the patients demonstrated neurological sequelae. However, a few neonates were said to survive over 2 years while continuing to display ECI (228).

ECI was reported in newborns in the presence of cerebral blood flow (23,25,460), and at least some electrocerebral activity was observed in the absence of demonstrable flow (21,23–25,130,224,459), although repeated EEG recordings ultimately demonstrated ECI in some of these patients (21,23–25,130). Conflicting results of these ancillary methods, and discrepancies between either of them and the clinical diagnosis, suggest that the EEG (and probably also cerebral perfusion tests) are of questionable assistance in confirming brain death in the immediate postnatal period (81,82). However, a review by Ashwal and Schneider (23) affirmed the notion that ECI persisting over 24 hours in the absence of complicating conditions in a neonate who remains clinically brain dead confirms that brain function has been irreversibly lost.

Evidence has been adduced by Alvarez et al. (10) that EEG recordings demonstrating ECI are more helpful in confirming the clinical diagnosis of brain death in patients older than 2–3 months. Their retrospective study showed that even a single EEG demonstrating ECI in the absence of hypothermia, hypotension, and toxic or metabolic disorders was sufficient to confirm permanent loss of brain viability above the age of 3 months. However, an appreciable proportion of patients of the same age suspected of being brain dead display some electrocerebral activity in their recordings. Incongruent results of EEG and brain perfusion tests also occur, although less commonly than in neonates, in small infants between the ages of 7 days and 2 months (21,23–25,130,459,460), and even in older infants and children up to the age of 5 years (21,23–25,51,167,224,459). Hence, special caution should be exercised in assessing the results of EEGs even after the age of 2–3 months. In particular, the detection of some electrocerebral activity in the face of persistent clinical manifestations of extinguished brain function, especially if associated with absent cerebral blood flow, should not be viewed as inconsistent with brain death and as encouraging the continuation of life-supporting measures in neonates, infants, and young children (21,22,130,224,404,476), as in adults (80,191,285,338,478). However, the amount of EEG activity that is compatible with brain death in these young patients is even less clear than in adults.

Evoked Potentials as Confirmatory Tests

Limited and primarily anecdotal data have been reported on EPs in neonates, infants, and children with suspected loss of brain function. Obliteration of cortical SL-SEPs and BAEPs was described in a limited number of patients of these ages in whom brain death had been diagnosed (115,130,408,431,457). However, loss of BAEPs occurred transiently following hypoxic episodes in a few newborns, infants, and small children who did not fulfill criteria of brain death and survived, although mostly with neurological sequelae (115,130,431,457).

CONCLUSIONS

Assessing the literature on the EEG in the developmental period poses major problems. These include extreme paucity of published data and their mostly anecdotal and retrospective nature; the use of EEG techniques often not or incompletely described or inadequate by present standards to demonstrate ECI, especially in neonates and small infants; and the heterogeneity of constantly evolving cerebral perfusion tests performed in conjunction with the EEG (81). In our opinion, these limitations justify some of the reservations expressed by concerned physicians regarding the guidelines issued by the Special Task Force for the Determination of Brain Death in Children (387) as well as the caution inspiring the report of the Working Party of the British Paediatric Association (500). We also believe that, until much additional information becomes available, EPs should not be routinely relied on to confirm irreversible loss of brain viability in young patients (79–82).

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Chapter 15

Drug Effects and Toxic Encephalopathies

Anne C. Van Cott and Richard P. Brenner

Antiepileptic Drugs
Neuropsychiatric Drugs
Anesthetics and Analgesics
Drugs of Abuse
Miscellaneous Drugs and Toxins
Conclusion
References

The literature addressing the effects of drugs and toxins on electroencephalographic (EEG) activity is abundant and rapidly expanding. Because it is not possible to summarize all the available information, the goal of this chapter is to review the commonly encountered and clinically relevant EEG patterns associated with some drugs and toxins. Reports of the effect of drugs on EEG activity are contradictory; this may result in part from the variety of methods used in analysis of EEG data. Although quantitative EEG analysis has provided a wealth of information, the authors choose to emphasize the changes seen on visual inspection, because this most closely approximates clinical EEG interpretation. A large percentage of patients undergoing EEG are taking one or more medications. Both the EEG technician and interpreter must be aware of changes that may be induced by medications.

A drug or toxin's effect on the EEG is dependent on numerous factors not limited only to its chemical composition. The dose administered and the duration of exposure are critical. Alterations of EEG activity may also reflect systemic effects of a medication: for example, generalized slowing may be secondary to central nervous system hypoperfusion caused by hypotension. Individual patient characteristics, including preexisting brain disease and EEG abnormalities, can influence the impact of drugs and toxins on background EEG activity. The EEG changes vary considerably from patient to patient, and thus a drug effect cannot be predicted in an individual. The withdrawal of a drug may also greatly influence central nervous system function as reflected by the EEG.

Although changes in EEG activity may indicate central nervous system dysfunction, they are not specific. Diffuse slowing of background EEG activity is the most commonly encountered drug effect, but it does not implicate a particular agent. The presence of superimposed generalized fast activity on an EEG should arouse suspicion of drug toxicity, particularly of medications that are recognized to increase beta activity, such as barbiturates or benzodiazepines. In general, focal slowing or asymmetry of EEG activity is not encountered in toxic encephalopathies; it suggests instead an underlying localized abnormality. Drugs may influence epileptiform discharges. Certain medications, such as clozapine (*Clozaril*) and metronizamide, can activate ictal and interictal epileptiform discharges, which indicates that they reduce seizure threshold. Other medications, including antiepileptic drugs (AEDs), can suppress epileptiform activity, which reflects their anticonvulsant effect. As discussed later, more unique patterns have been associated with certain agents. Generalized, bisynchronous sharp complexes, at times

periodic and often with a triphasic configuration, have been associated with a variety of medications, including baclofen, lithium, levodopa, and metrizamide (69,106,110,119,141,145,167,171). Drug intoxications and anesthetic agents can result in seemingly ominous EEG patterns, including alpha-pattern coma, spindle-pattern coma, burst-suppression pattern, and electrocerebral silence.

ANTIEPILEPTIC DRUGS

EEG is an invaluable tool in the management of patients with epilepsy. EEG findings can play a critical role in a variety of decisions, including initiation and withdrawal of antiepileptic drug therapy. In certain situations, the EEG may be used to determine whether AEDs are therapeutic. AEDs have been found to affect both background EEG activity and interictal epileptiform activity. All of the older AEDs may result in increases in slow activity and slowing of the dominant posterior rhythm (28). Each of these issues is addressed for the established AEDs.

Rhythmic fast activity increases with therapeutic doses of both benzodiazepines and barbiturates. With benzodiazepines, rhythmic beta activity increases and is most prominent during drowsiness (17) (Fig. 15.1). A decrease in the voltage of the alpha frequency may also be present (156). These changes depend on the patient's age; they are more marked in younger individuals. In addition, the presence of fast activity is also dependent on duration of treatment; it is more pronounced after the acute administration of benzodiazepines. As the level of the benzodiazepine rises and intoxication occurs, faster frequencies become higher in voltage and are more sustained (5). Eventually, with increasing levels, there is more prominent generalized slowing, which is correlated with the depressed level of consciousness (28).

Rhythmic fast activity associated with barbiturates is usually 18 to 25 Hz and is more prominent in the frontal head regions (121). As the patient becomes increasingly intoxicated with a marked decrease in level of consciousness, background EEG activity can reveal prominent delta activity with superimposed spindle-like activity (12). In deep coma caused by barbiturates, the EEG may show a burst-suppression pattern or even electrocerebral silence (143). A burst-suppression pattern is the therapeutic goal in patients treated for status epilepticus or increased intracranial pressure with intravenous pentobarbital.

At therapeutic levels, phenytoin has no visually discernible effect on background EEG activity. In quantitative EEG analysis, phenytoin, alone or in combination with other drugs, has been reported to decrease background frequency, in comparison with other AEDs (64). With increasing levels (greater than 20 μg per milliliter), there can be slowing of the mean alpha frequency. With clinical neurotoxicity, increased generalized theta activity and intermittent delta activity are present (Fig. 15.2). With severe toxicity, high-voltage delta slowing may be present (128). EEG changes reported with carbamazepine therapy are not consistent and are of no recognized clinical significance. Both mild slowing of the mean alpha frequency and intermittent random generalized theta activity have been reported with therapeutic carbamazepine levels (48,123,126). These changes can be more pronounced with toxic drug levels. Carbamazepine discontinuation has been associated with an increase in the frequency of the dominant rhythm and reduction of slow activity (29). At therapeutic levels, valproic acid has not been found to have an effect on background EEG activity (64), whereas valproate intoxication has been associated with diffuse slowing (1).

Less information about the effect of the newer AEDs on EEG activity is available. Lamotrigine has not been found to slow background activity in normal volunteers or epileptic patients (45,101). In one study (78), patients with partial epilepsy receiving tiagabine had no new EEG abnormalities. Several studies have reported no change in background EEG activity with vigabatrin treatment (58,102).

In general, the reported effects of AEDs on interictal epileptiform activity are variable and inconsistent (5). Most important clinically, for seizures other than absence, the amount of interictal epileptiform activity is often not related to seizure frequency (8,28). Abrupt withdrawal of AEDs has been reported to increase interictal epileptiform discharges (94,100), although later reports found no increase of interictal epileptiform abnormalities after withdrawal of AEDs (54). With regard to seizure activity, reduction of AED dosage can increase seizure frequency and the likelihood that seizures will secondarily generalize. However, So and Gotman (146) found no difference in the electrographic ictal morphological appearance of seizures with dose reduction. With high or low drug levels, there were no changes in the onset of the electrographic seizure, time to contralateral spread, or coherence between discharges in patients.

Ictal and interictal epileptiform activity can be suppressed acutely by benzodiazepine therapy administered intravenously or rectally, but the effects of long-term oral therapy with these agents is less defined (28). Huang and Shen (71) reported that an abnormal EEG pattern that responded positively to intravenous diazepam is a good prognostic indicator of future seizure control with AEDs. Phenobarbital and primidone have been shown to decrease interictal epileptiform abnormalities in patients with controlled seizures (18,80).

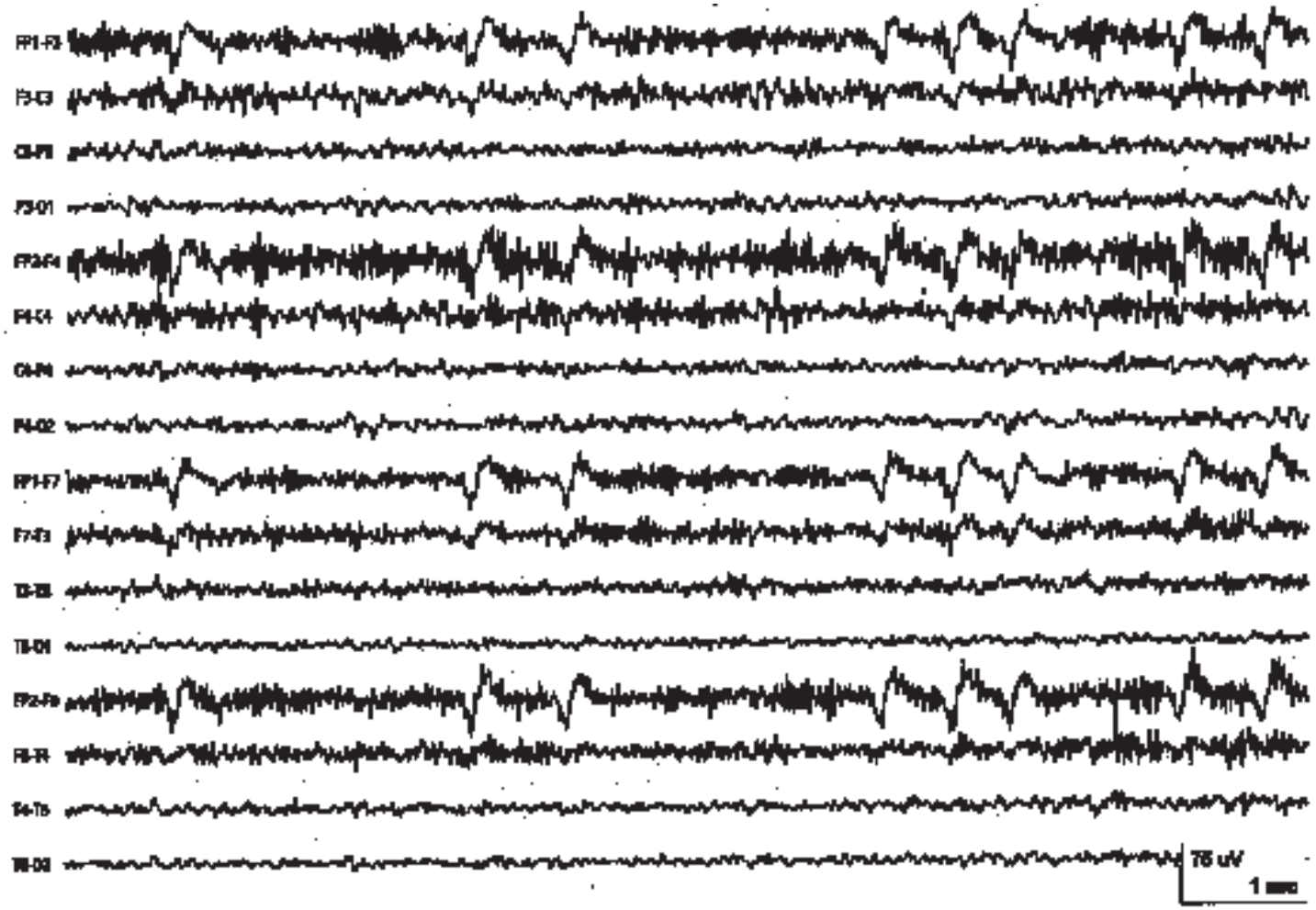

FIG. 15.1. Faster frequencies are prominent in the EEG of an 18-year-old man with a psychotic disorder who was medicated with lorazepam.

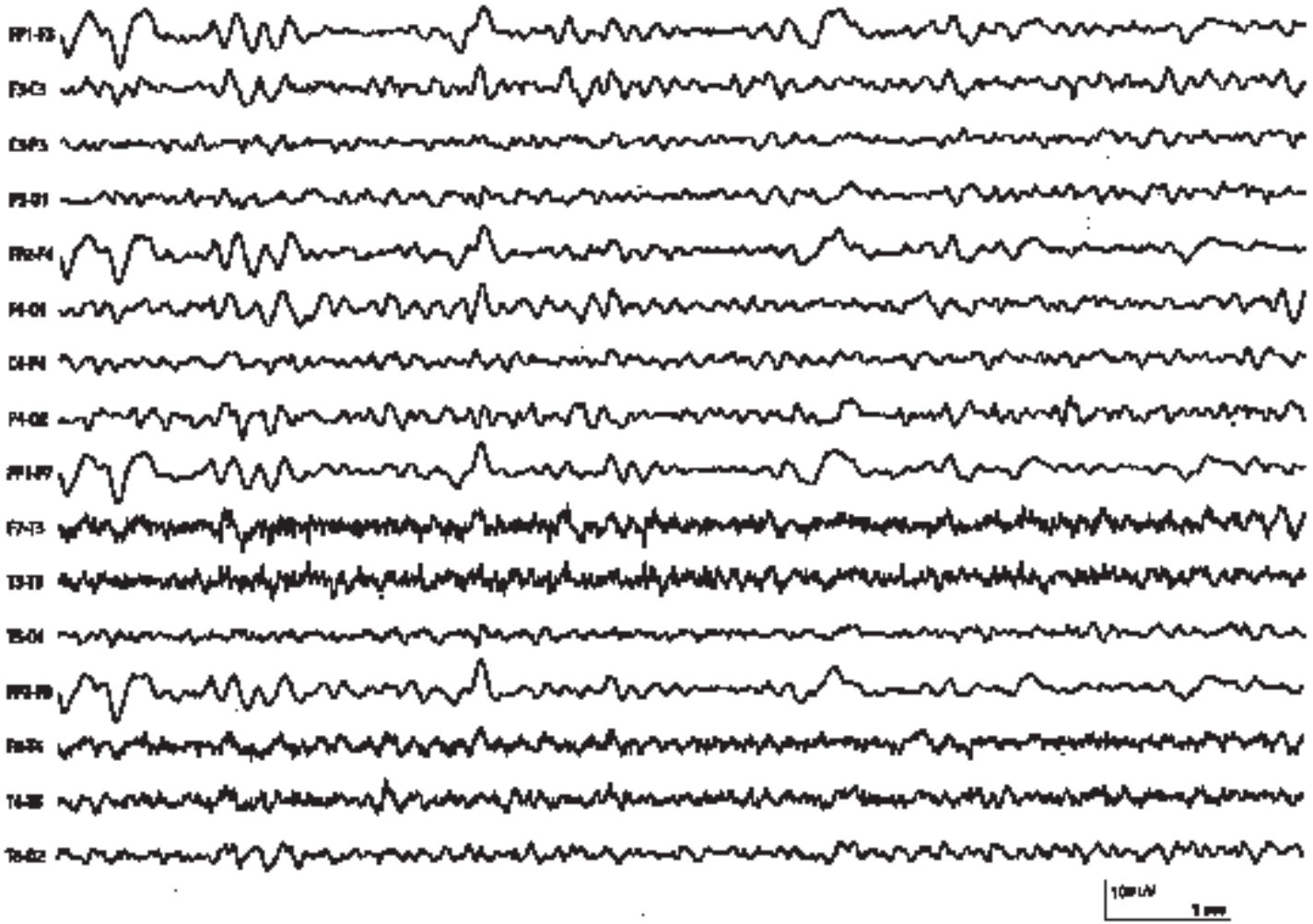

FIG. 15.2. Generalized slowing of the background EEG activity is present in this tracing from a 20-year-old woman with a phenytoin level of 34 μg per milliliter.

Both benzodiazepines and barbiturates can play a useful role in localization of epileptogenic foci. Intravenous diazepam and clonazepam have been shown to suppress spread of electrographic seizures to the contralateral hemisphere (16,89). This may be useful in resolving issues of secondary bilateral synchrony. In a similar manner, barbiturates (intravenous thiopental) have been administered to patients with generalized seizures and bilateral spike-and-wave discharges to allow identification of a focal EEG abnormality (93). Conversely, in patients with partial epilepsy, withdrawal of barbiturates can precipitate generalized epileptiform activity or, less commonly, new or additional foci of seizure onset (148). Barbiturate withdrawal in drug-addicted patients may produce epileptiform discharges consisting of high-voltage bisynchronous spike-and-wave abnormalities superimposed on generalized slowing of background EEG activity (37).

There are contradictory data regarding the effect of phenytoin on interictal epileptiform discharges. Most reports found no effect on interictal epileptiform discharges with phenytoin treatment (5). Phenytoin withdrawal has been reported to falsely localize ictal onset (35). The data about the effect of carbamazepine on interictal discharges is also conflicting. Increased interictal epileptiform activity reported with carbamazepine treatment was not correlated with worse seizure control (75,132,169). Carbamazepine has also been reported to have no effect on interictal abnormalities (123). The frequency of interictal abnormalities was found to be related to seizure activity and not to AED withdrawal (54). Marciani et al. (97) proposed that changes in interictal epileptiform abnormalities may be related to seizure occurrence and not to the direct action of carbamazepine on spike activity.

The effect on valproate therapy on epileptiform activity depends on the epilepsy type. Valproic acid can reduce or abolish generalized spike-and-wave discharges but has little or no effect on focal interictal epileptiform activity (5). The ability of valproic acid to abort or suppress 3-Hz spike-and-wave discharges in patients with absence epilepsy can help gauge therapeutic efficacy (162). Valproate also suppresses photoparoxysmal responses (59). The suppression of generalized epileptiform discharges by valproate may continue for up to 3 months after discontinuation of the medication (59,129). Ethosuximide, like valproate, can reduce generalized spike-and-wave discharges (136).

The effect of the newer AEDs on epileptiform abnormalities in humans is not completely understood. Binnie et al. (9) found that lamotrigine has been reported to decrease spontaneous and light-induced generalized spike-and-wave discharges. Vigabatrin has not been shown to have any consistent effect on interictal spikes (7,99). AEDs may activate epileptiform discharges. Generalized spikes, at times accompanied by myoclonic jerks or absence seizures, have been reported in patients receiving vigabatrin (98,103). In addition, two epileptic patients receiving tiagabine developed nonconvulsive status epilepticus with electroclinical features consistent with atypical absence seizures (32).

EEG can assist in making decisions about the discontinuation of AED therapy in patients who are seizure free. In adult patients who have been seizure free for 2 years or more, EEG abnormalities increase the risk of seizure recurrence after AED withdrawal (20). Some reports refute this finding, stating that only an increase in interictal epileptiform abnormalities during withdrawal of AEDs is associated with a higher seizure relapse rate (49). In children, EEG abnormalities that are present before withdrawal of medications portend a very poor prognosis and are considered a major risk factor for seizure recurrence after discontinuation of medications (140).

Treatment of epileptic patients with AEDs may result in a paradoxical reaction and induction of seizures. Identified clinical risk factors that may predispose a patient to such a reaction include youth, mental retardation, polytherapy, high seizure frequency, and prominent epileptiform abnormalities in EEG before treatment (4). Syndromes in which seizure exacerbation has been attributed to AED therapy include Lennox-Gastaut syndrome and West's syndrome (4). Carbamazepine has been reported to exacerbate a variety of seizures, including absence, atonic, and myoclonic seizures (133, 152). EEGs may reveal bursts of diffuse and bilaterally synchronous spike-and-wave discharges (116).

Increased seizure frequency and an encephalopathy can occur with valproate therapy. This most frequently occurs in patients early (first week to nine months) during a first-time exposure. Valproate levels are frequently within normal limits, and the EEG reveals generalized slowing with an increased number of generalized spike discharges. This has raised the issue about whether the encephalopathy truly represents nonconvulsive status epilepticus. However, no change in the background EEG activity or clinical state after treatment with intravenous benzodiazepines has been reported. Valproate therapy withdrawal is recommended in patients with suspected encephalopathy (4).

NEUROPSYCHIATRIC DRUGS

As a group, the conventional neuroleptic agents, including phenothiazines, butyrophenones, and thioxanthenes, produce similar changes in background EEG activity. Visual analysis of the EEG shows little or no

change at therapeutic drug levels, although there are some reports of slowing of the alpha rhythm, reduction of beta activity, and increased amplitude of theta transients (3). Slowing, both focal and generalized, that is present on pretreatment EEGs may be accentuated by phenothiazine administration (92). With acute intoxication, generalized slowing of background EEG activity may be accompanied by generalized paroxysmal activity (72). The neuroleptic agents have been reported to lower seizure threshold in patients with chronic epilepsy (113). Seizure occurrence is usually, but not always, dose dependent, and nonconvulsive status epilepticus has been described (159). Of the newer antipsychotic agents, risperidone has not been associated with seizures and does not produce EEG changes in the awake record (23). However, another novel antipsychotic agent, clozapine, has marked effects on background EEG activity and seizure threshold, both of great clinical significance.

Clozapine selectively blocks cortical and limbic dopamine receptors and is used in the treatment of refractory schizophrenia and schizoaffective disorders. It produces minimal extrapyramidal side effects and has proved beneficial in the treatment of psychosis induced by dopaminomimetic agents in patients with Parkinson's disease. In addition to agranulocytosis and autonomic instability, a serious potential adverse effect of clozapine is seizures.

Clozapine can produce generalized tonic-clonic seizures and myoclonus (135). Myoclonus may manifest as jerking movements of the face, head, fingers, toes, or trunk and can proceed to generalized convulsive seizures (57) (Fig. 15.3). Large-scale studies have previously reported generalized seizure rates of 1.9% to 10% (26,114,170). The risk of seizures is higher during the initial treatment phase than in the maintenance treatment period. Rapid titration of clozapine may be a risk factor in the development of seizures during the initiation of treatment (114). Seizures have been reported with a wide range of dosages, but they seem more likely to occur at higher doses (56,135). Clozapine-associated seizures have been treated with dosage reduction and/or the addition of an antiepileptic agent, most commonly valproic acid or phenytoin.

A wide spectrum of EEG changes can occur in patients treated with clozapine. A high percentage–estimates of 16% to 74%–of patients receiving clozapine have abnormal EEGs; the most prevalent finding is generalized slowing (56,60,96,147). Interictal epileptiform activity indicating a seizure tendency may be present but is less prevalent than slowing of the background EEG activity (Fig. 15.4). Malow et al. (96) described the spectrum of EEG abnormalities in ten patients being treated with clozapine. Interictal epileptiform abnormalities were described as bilateral spike-and-wave discharges predominating in the anterior parasagittal head region and becoming more frequent during drowsiness. Activation by hyperventilation and photic stimulation was present in a few patients. Decreasing the clozapine dosage and/or adding valproic acid therapy diminished epileptiform discharges but did not change background slowing.

Abnormal EEGs have been found to be more common in patients receiving high dosages (56) and with high serum levels of clozapine (47). Even at low dosages in the treatment of delusions and psychotic behavior in parkinsonian patients, clozapine may cause EEG changes, including increased generalized or focal slowing (107). Interestingly, there may be a positive association between clozapine-induced EEG abnormalities and clinical improvement in certain patient populations (118,124,157).

In a retrospective study of 680 EEGs in 593 patients receiving psychopharmaceutical agents, the proportion of abnormal EEGs was found to be highest in patients receiving clozapine (59%), and next highest in those receiving lithium (50%) (147). Lithium is a mood-stabilizing agent with antimanic properties that is used in the treatment of bipolar mood disorders. After a single dose of lithium in an adult, little or no EEG change is observed visually. With ongoing treatment, EEG changes may include slowing of background EEG activity. Frontal intermittent rhythmic delta activity (FIRDA) may be present and accentuated by hyperventilation. EEG abnormalities present before treatment may become more pronounced (144). EEG abnormalities increase with higher serum plasma levels but can occur at therapeutic levels (63). With lithium intoxication, the EEG may show diffuse slowing, paroxysmal abnormalities, and triphasic waves (10) (Fig. 15.5). The electrical abnormalities lessen in parallel with improvement in the patient's clinical state but can persist despite normalization of serum levels (3).

Lithium can enhance preexisting sharp waves and spikes in patients with epilepsy (52,144). However, lithium's actual epileptogenicity remains unclear. According to some reports, lithium treatment has increased seizure frequency in patients with epilepsy and induced seizures in patients without a seizure disorder; according to other reports (36,51), seizure frequency has decreased in epileptic patients receiving lithium. Julius and Brenner (76) reported on two patients who, soon after starting lithium therapy, developed generalized tonic-clonic seizures followed by myoclonic seizures associated with repetitive sharp waves on EEG, which resolved after lithium discontinuation. Smith and Kocen (145) described two cases of a Creutzfeldt-Jakob–like picture accompanied by typical EEG changes (generalized slowing with synchronous periodic complexes) with lithium toxicity that

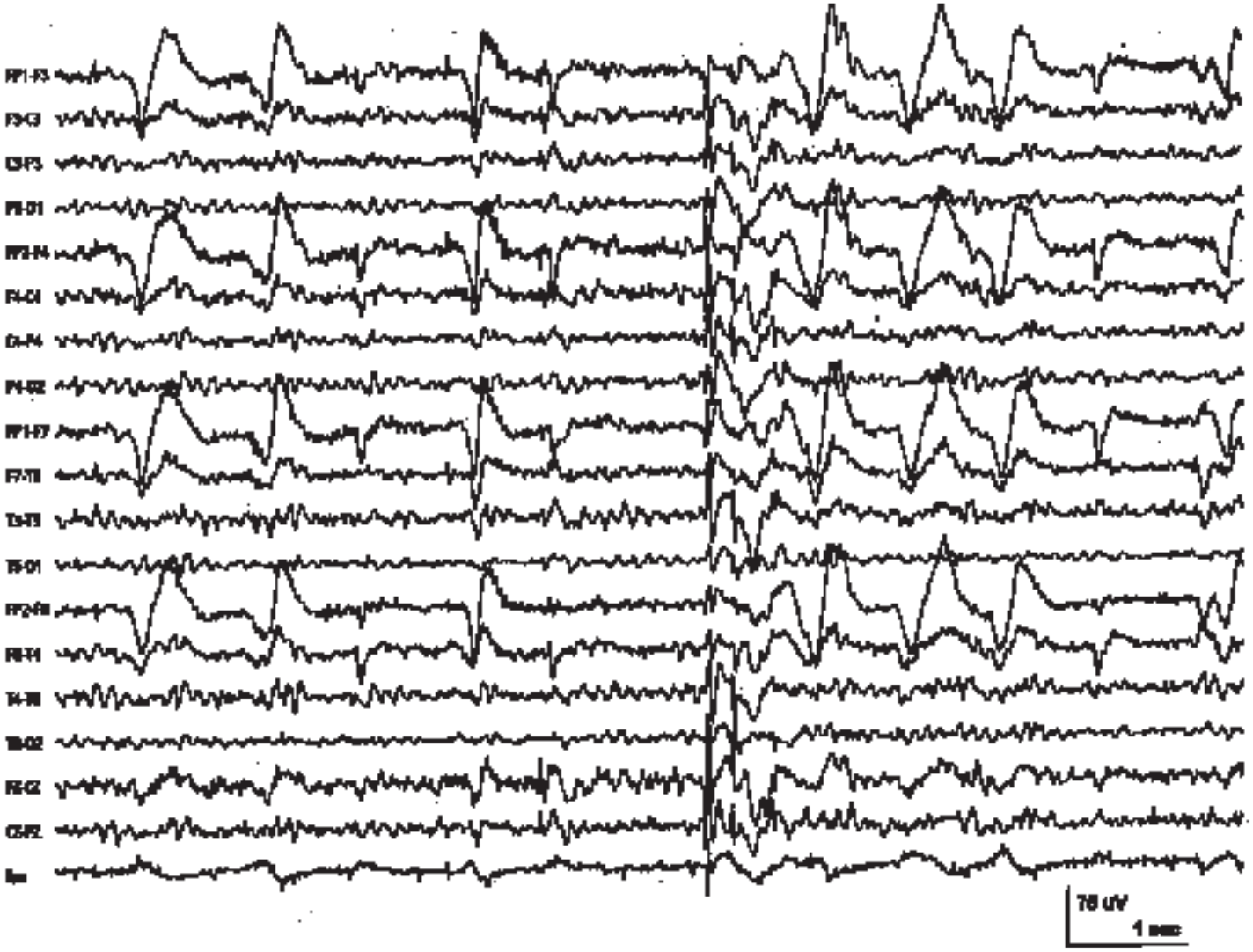

FIG. 15.3. Polyspike discharge in a 32-year-old man taking clozapine (*Clozaril*) therapy for schizophrenia associated with myoclonic movements, including those of the face (lip channel).

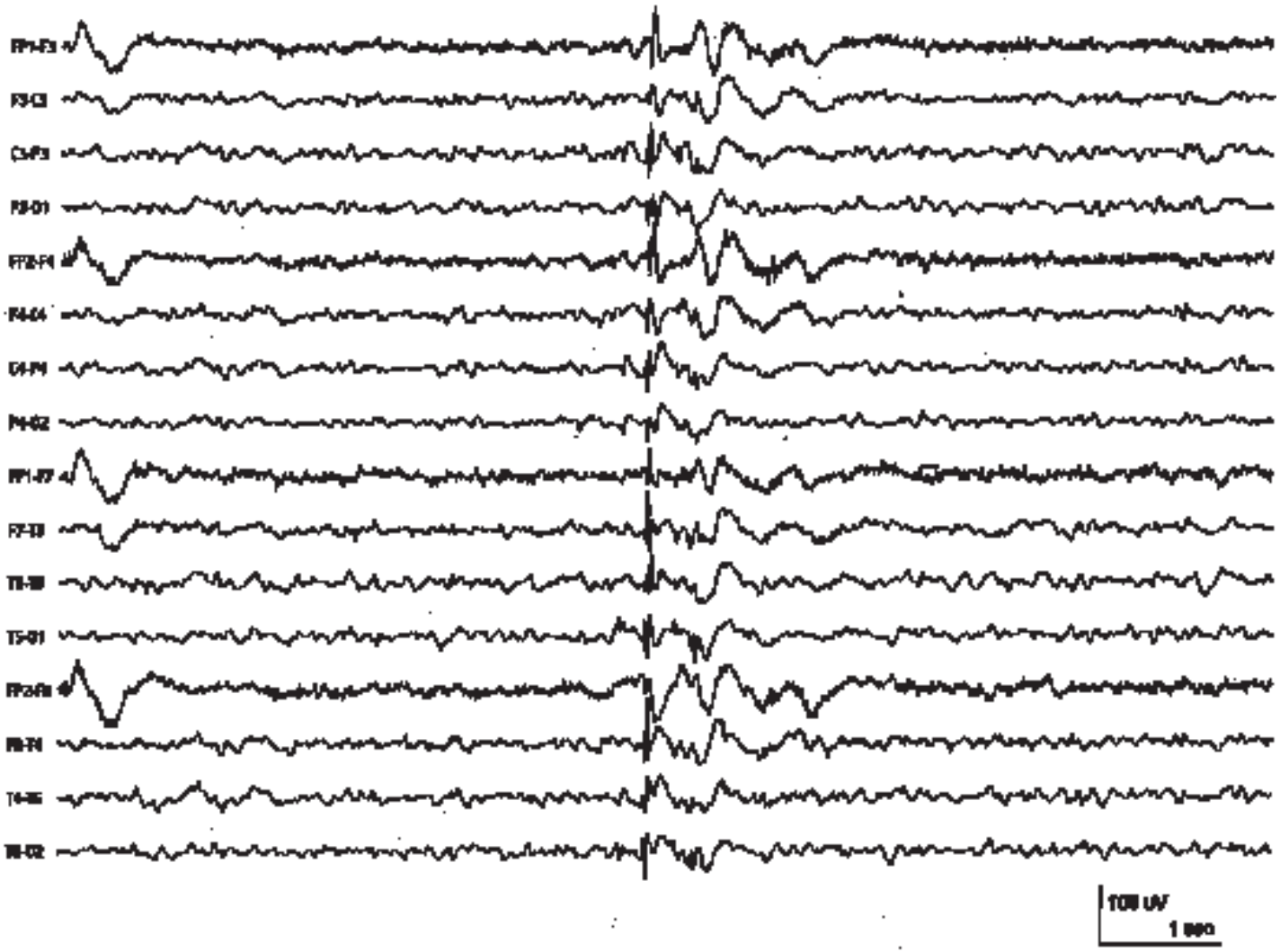

FIG. 15.4. Generalized polyspike discharge accompanied by myoclonic jerks in a 34-year-old woman with bipolar disorder and psychotic symptoms who was taking clozapine (*Clozaril*).

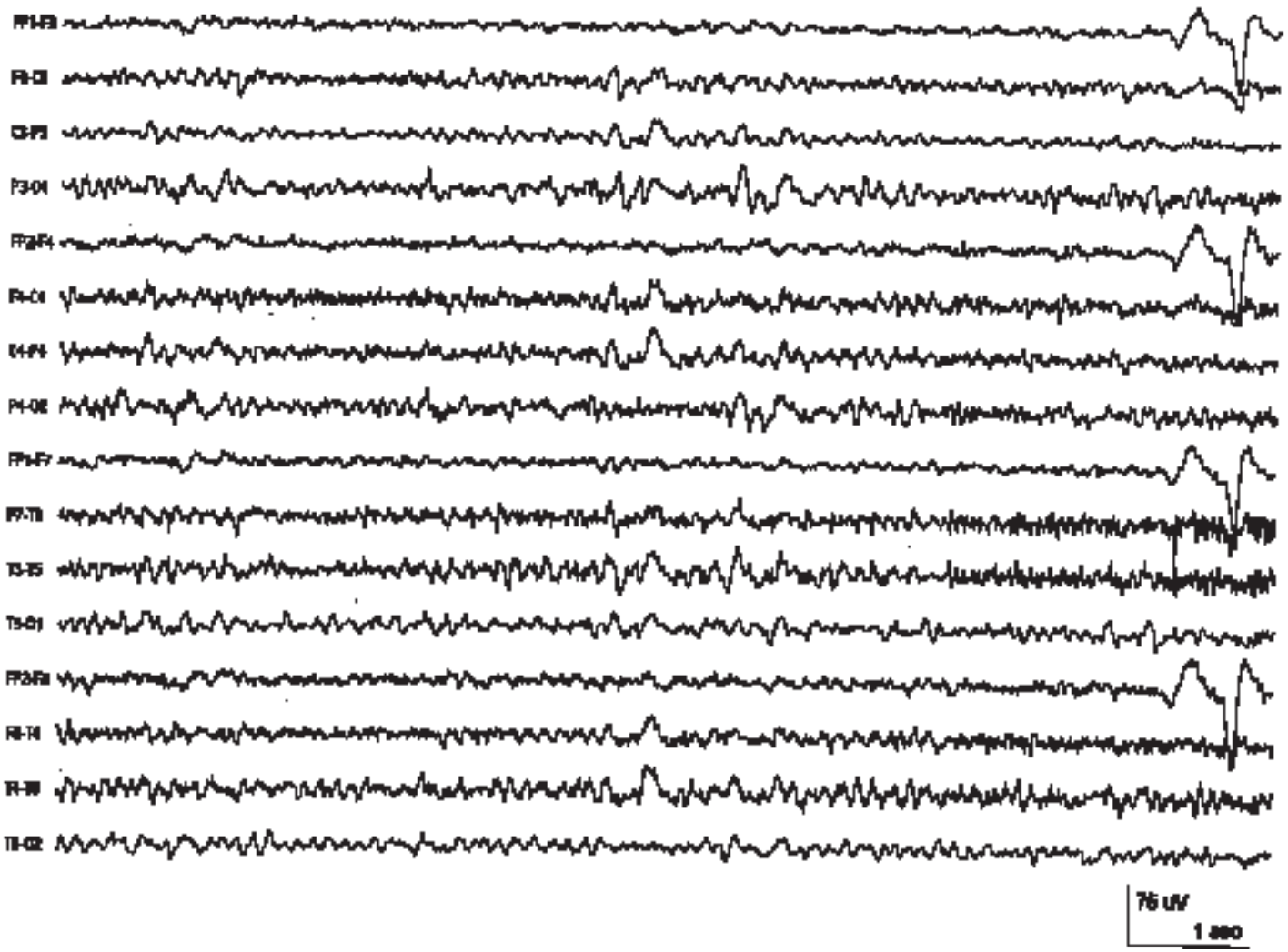

FIG. 15.5. EEG shows generalized slowing in a 50-year-old woman receiving lithium for psychotic depression.

resolved with discontinuation of the medication. Additional cases of Creutzfeldt-Jakob—like syndrome during lithium use, alone or in combination with other medications (including levodopa and tricyclic agents), were reported later (39).

The pharmacological agents available for the treating depression have become more numerous and less toxic since the early 1970s. The first generation of antidepressants included the monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs). Amoxapine and maprotiline, two TCAs, are pharmacologically similar but differ in chemical structure. Although highly effective, these agents had serious and potentially fatal side effects, particularly if taken in overdose. The first serotonin selective reuptake inhibitor (SSRI), fluoxetine, was introduced in the mid-1980s and provided a much higher therapeutic index. The SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) and a heterogeneous group of atypical antidepressants (mirtazapine, nefazodone, and venlafaxine) have largely replaced the TCAs and MAOIs as first-line treatments for depression (46).

Tricyclic drugs, at therapeutic levels, produce only subtle changes on background EEG activity (68). Tricyclic drugs may increase the amount of both fast and slow activities (in the beta and theta frequencies), along with a slowing of the alpha rhythm (40,41). Acute intoxication from overdosage may result in cardiac arrhythmias and is life-threatening. Along with seizures, the clinical picture can include hyperpyrexia, hypertension, and coma (22). During acute intoxication, background EEG activity reveals generalized slowing and paroxysmal activity, including interictal spikes (87) (Fig. 15.6).

Tricyclic agents can lower seizure threshold to a variable degree (142). Seizure frequency may increase in patients with epilepsy after initiation of tricyclic drug therapy. Intravenous administration of imipramine (81) and amitriptyline (24) increased the number of epileptiform discharges in epileptic patients. Although these drugs are rarely a *de novo* cause of seizures, single and multiple seizures have been reported in nonepileptic patients, especially those receiving high doses (32). Itil and Soldatos (73) classified imipramine, along with the MAOIs, as having a slight or no tendency to potentiate epileptiform discharges.

The newer antidepressants offer safer treatment options. Serious adverse events occur rarely; few deaths have resulted from overdose. According to visual analysis, EEG activity exhibits subtle changes in background frequency (3). Maprotiline and bupropion have been reported to have a higher propensity to cause seizures than do the SSRIs trazodone, nefazodone, and mirtazapine (46).

Sleep disturbances, including hypersomnia and insomnia, are an integral feature of the depressive disorders. Polysomnography may document abnormal sleep patterns, including decreased amounts of slow-wave sleep, early onset of first episode of rapid-eye-movement (REM) sleep, and increased amounts of phasic REM sleep (154). Both the tricyclics and MAOIs tend to suppress REM sleep. Paroxetine and fluvoxamine, both SSRIs, showed effects on polysomnographic testing in depressed patients similar to those of amitriptyline; all decreased the amount of REM sleep. However, the SSRIs exhibited an alerting effect on sleep (86,149).

Benzodiazepines, a large class of medications that include diazepam, midazolam, clonazepam, and flurazepam, bind at the γ-aminobutyric acid A (GABA-A) receptor chloride ionophore (50). As already discussed, these drugs can be used as anticonvulsant agents. In addition to being potent anxiolytic agents, benzodiazepines can produce muscle relaxation. As anesthetic agents, they produce hypnotic and amnestic states. As previously indicated, these agents increase beta activity and may cause mild generalized slowing of background EEG activity. Fast activity may persist for up to 2 weeks after drug ingestion. Benzodiazepine-induced fast activity can be reduced at the site of a focal cerebral lesion (53). In addition to producing seizures, psychosis, and delirium, benzodiazepine withdrawal can produce a delirium with catatonic features accompanied by generalized slowing of the background activity without epileptiform discharges (61). Acute withdrawal contributes to *de novo* absence status epilepticus of late onset (155).

Midazolam, frequently used as a sedative or treatment for status epilepticus in the critical care setting, has EEG effects similar to those of other benzodiazepines (65). Side effects, including respiratory depression, hypnosis, and incoordination, may be reversed by a specific benzodiazepine antagonist, flumazenil. In normal controls, flumazenil has no significant effect on EEG activity (13). Although benzodiazepine antagonists have been shown to improve background EEG activity and symptoms of encephalopathy in patients with hepatic failure, several studies have not supported a major therapeutic benefit of flumazenil in most patients with hepatic encephalopathy (2,19,55,158).

Buspirone offers an alternative to diazepam in treatment for patients with generalized anxiety disorders but may lack efficacy in patients with previous exposure to benzodiazepine (88,112). Unlike diazepam, buspirone has little or no effect on background EEG activity (11).

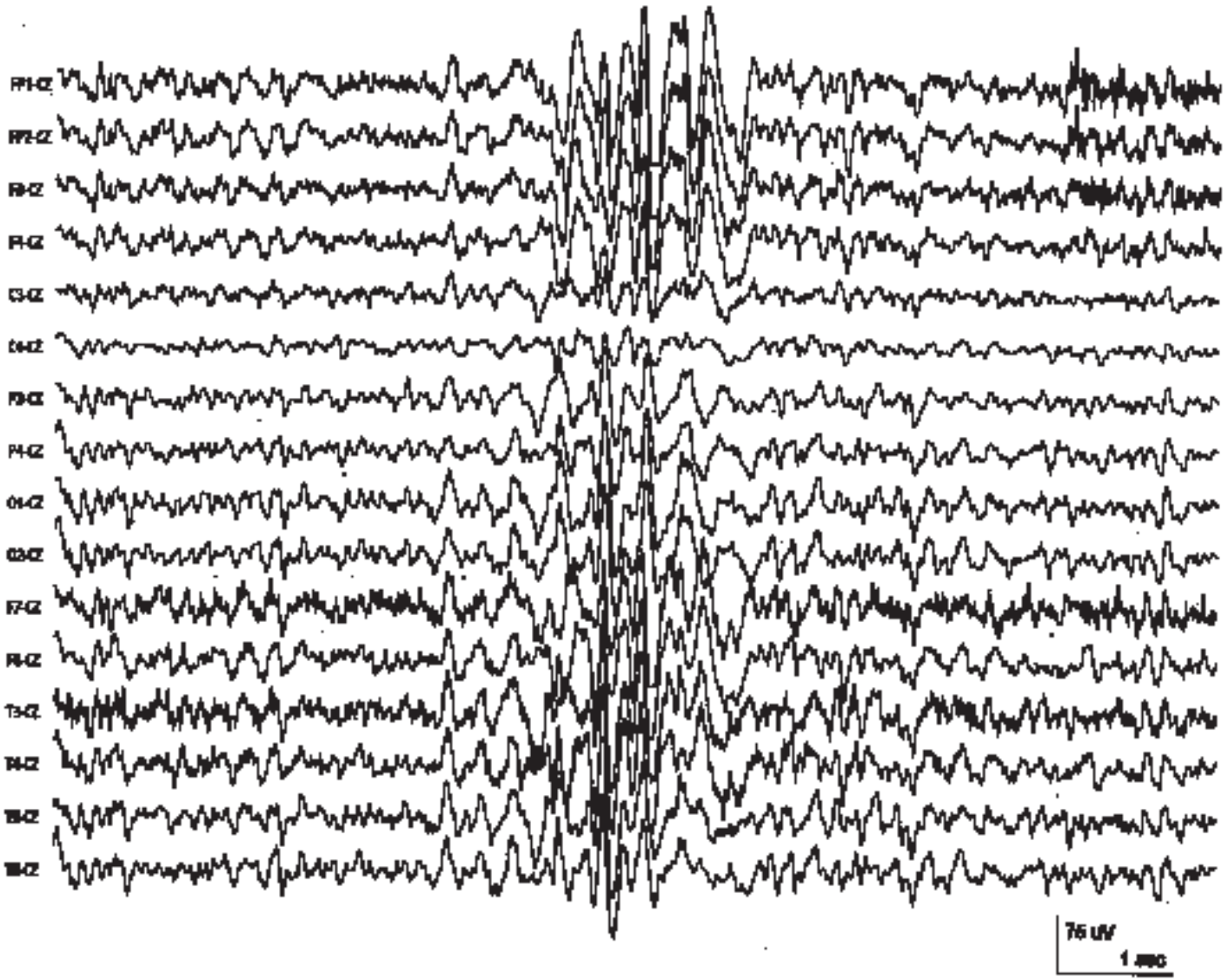

FIG. 15.6. Generalized burst of high-amplitude sharp activity in a 48-year-old woman with toxic levels of amitriptyline and nortriptyline.

ANESTHETICS AND ANALGESICS

The effect of anesthetic agents on the EEG is reviewed elsewhere in this textbook (Chapters 21, especially, but also 25, and 31). The associated EEG patterns depend on several factors, including the type and quantity of the drug used. To complicate the issue, it is common for multiple anesthetic agents to be used in the operative setting. A combination of anesthetics produces an EEG pattern that reflects the impact of the blend of these medications (95).

In selecting anesthetic drugs, in conjunction with EEG recording, the clinician must consider the goal of monitoring. For example, the most common monitoring application is for the detection of focal ischemia intraoperatively. The halogenated inhalation anesthetics, which induce background EEG activity of moderate amplitude and frequency, allow for rapid detection of decreased amplitude and frequency that are associated with reduced blood flow (139). On the other hand, etomidate, which increases epileptiform activity in patients with seizure disorders (30), may be used to enhance spike activity during electrocorticography. In contrast, agents such as barbiturates, which are cortical depressants and can produce electrocerebral silence, have been used to lower cerebral metabolism and oxygen demand.

Most anesthetic agents produce similar changes in the EEG. Barbiturates and most of the nonbarbiturate anesthesia-induction agents (etomidate, propofol) initially cause an increase in faster frequencies (beta) with a loss of the alpha rhythm. As the anesthetic dose is titrated, the frequency of EEG activity decreases and the amplitude increases, accompanied clinically by a loss of consciousness. At high doses, a burst-suppression pattern occurs (Fig. 15.7), and if the dose is titrated further, electrocerebral silence may be present. Surgical stimulation may alter this pattern, opposing the frequency slowing caused by higher doses (95).

Propofol is an ultra–short-acting intravenous agent that is used for both induction and maintenance of anesthesia. Used at doses appropriate for maintenance, propofol induces a regular, frontally dominant delta rhythm with superimposed faster frequencies (Fig. 15.8). Propofol has been reported to have different effects on epileptiform activity (27,31). At lower doses (0.5 mg per kilogram), epileptiform discharges were present in epileptic (40%) and nonepileptic patients (33%). At higher doses (1.5 mg per kilogram), this activating effect was increased to 67% and 73%, respectively. When additional doses were administered, the spike discharges disappeared (166). Propofol at high doses (maintenance infusions of 2 to 4 mg per kilogram per hour) controls refractory status epilepticus more rapidly than high doses of barbiturates (150). Recurrent seizures were common when propofol infusions were abruptly discontinued and may be related to the proconvulsant effects of this medication at lower doses.

Ketamine, which is structurally related to phencyclidine (also known as PCP and angel dust), is useful for anesthesia induction. Initially, a loss of the alpha rhythm and a decrease in background amplitude is present. Increasing the dose further produces frontally dominant rhythmic theta activity. Higher doses produce high-amplitude theta activity accompanied by an increase in beta activity (95).

In general, the halogenated inhalation anesthetics (desflurane, enflurane, halothane, isoflurane, and sevoflurane) produce EEG changes similar to those produced by the barbiturates. With the exception of desflurane, induction with these agents produces alpha frequencies in the anterior head region that may resemble sleep spindles. At higher concentrations, sufficient to produce anesthesia, there is a reduction in the amplitude and frequency of background EEG activity. Unlike isoflurane and desflurane, halothane does not produce a burst-suppression pattern or electrocerebral silence at clinically relevant doses (143). Enflurane may produce interictal epileptiform abnormalities in patients with or without a history of a seizure disorder (44,105). Isoflurane, in comparison with enflurane, has been found to decrease the frequency of spikes on the electrocorticogram of patients with intractable epilepsy who undergo temporal lobectomy (74). Fiol et al. (42) refuted this, reporting that isoflurane in combination with nitrous oxide had no significant effect on spike activity on the electrocorticogram during epilepsy surgery. Enhancement of the EEG activity by enflurane has been considered a disadvantage during neurosurgical procedures, in which increased cerebral metabolic activity is undesirable (143).

A nonhalogenated inhalation anesthetic, nitrous oxide, possesses analgesic and amnestic properties and is used in combination with other agents to achieve surgical anesthesia. In concentrations sufficient to produce analgesia and depressed consciousness, fast (>30 Hz) oscillatory activity is often present (95). The effect of nitrous oxide on the EEG depends on what agents it is combined with, and it has been reported to have both proconvulsant and anticonvulsant properties (143). Hosain et al. (70) found no difference in spike rate during electrocorticography in patients undergoing epilepsy surgery with or without nitrous oxide; this suggests that it may be used without concerns about suppression of epileptiform activity.

The effect of the short-acting synthetic opiates including fentanyl, sufentanil, and alfentanil, on EEG activity can be described on the basis of dosage. At low concentrations, loss of beta activity and slowing of alpha activity occur. With moderate doses, the amplitude increases, whereas the

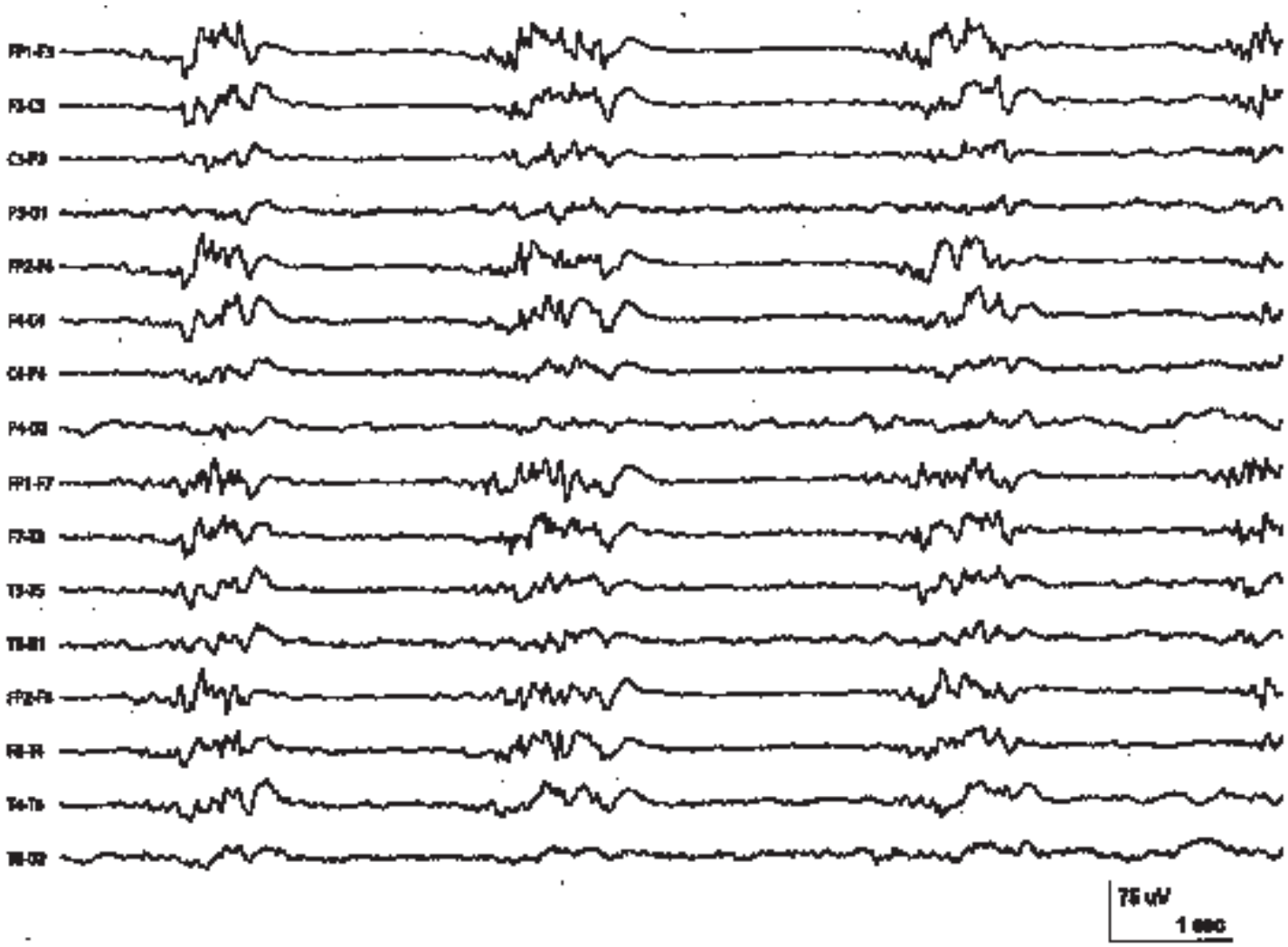

FIG. 15.7. A burst-suppression pattern in a 65-year-old man after an intravenous thiopental sodium (*Pentothal*) bolus during a carotid endarterectomy.

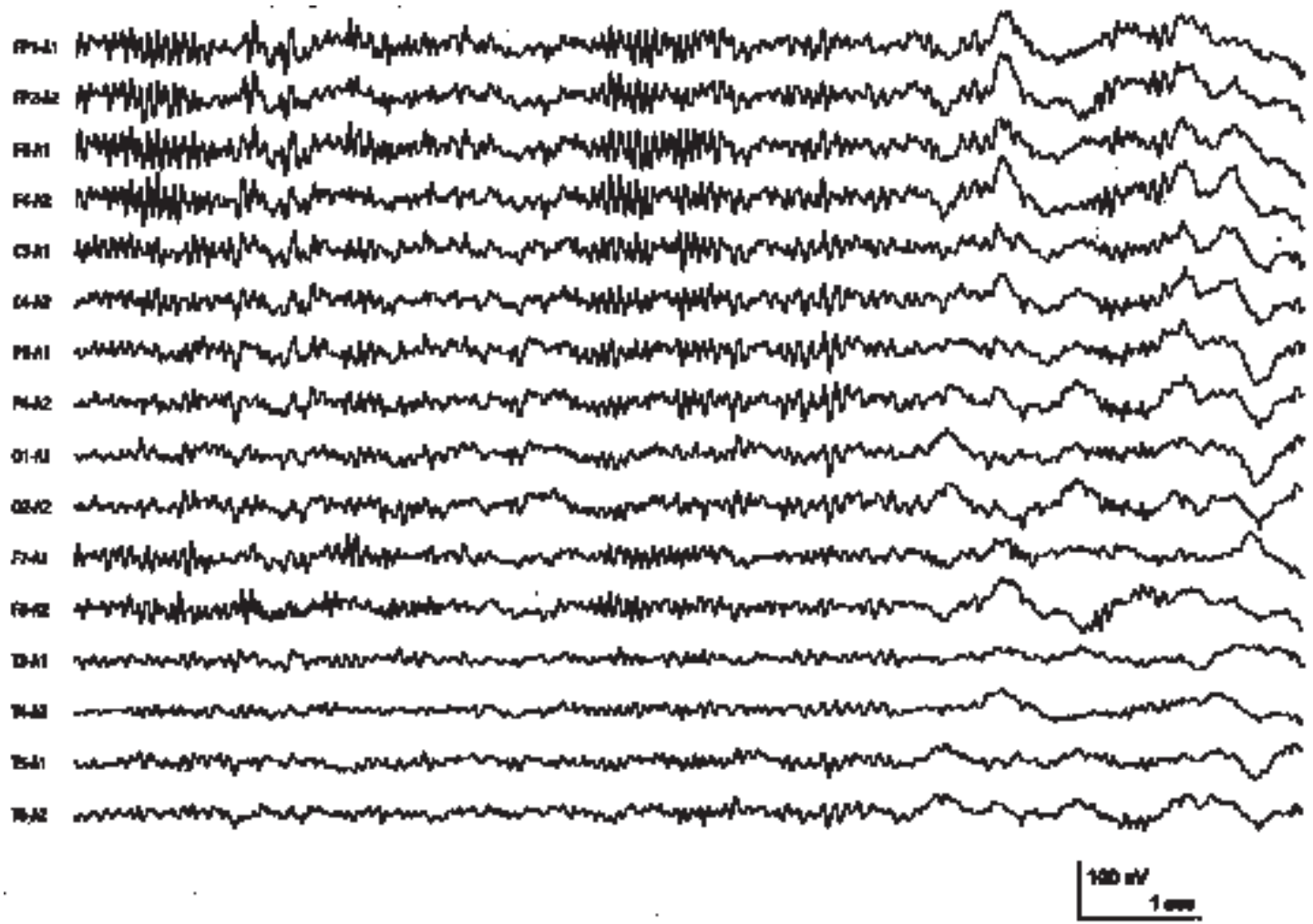

FIG. 15.8. Spindle coma in a 33-year-old woman sedated with propofol after arteriography.

frequency (diffuse theta with some delta activity) decreases. At high concentrations, delta activity, often synchronized and of high amplitude, predominates. Burst-suppression or electrocerebral silence is not present at higher doses (95). Opioid agents are frequently cited as being epileptogenic. Kearse et al. (79) reported that 19 of 20 patients undergoing coronary artery revascularization developed epileptiform activity characterized as low- to moderate-voltage, generalized single-phasic and multiphasic spike discharges "similar in appearance to benign epileptiform transients of sleep." Because of the predominance of slower frequencies at higher doses, opioid agents may reduce the ability to detect changes indicative of ischemia (143).

Benzodiazepines may be used to premedicate or supplement general anesthesia. As reviewed in the AED section, these drugs may produce frontal beta activity with slowing of the alpha rhythm at lower doses. At higher anesthetic doses, benzodiazepines cause generalized slowing (theta and delta activity) without producing a burst-suppression pattern. Because of their potent anticonvulsant properties, they are not used during electrocorticography.

DRUGS OF ABUSE

EEGs are frequently requested for patients who abuse alcohol. In certain patient populations, as many as 15% of EEG referrals are obtained for patients who have a history of chronic alcoholism (85). As with many of the medications already reviewed, alcohol may produce certain characteristic EEG changes, but none are pathognomonic of use or abuse. Patients with a history of alcohol abuse may have EEG abnormalities related to intoxication (both acute and chronic) or withdrawal. Alcohol abusers are prone to a variety of central nervous system diseases and systemic illnesses that may produce additional EEG changes, including focal and interictal epileptiform changes.

During acute alcohol intoxication, mild slowing of the alpha rhythm occurs. Quantitative EEG reveals spectral density shifts to lower frequency ranges (33). The effect of rising concentrations of alcohol is generalized reduction in frequency of EEG activity. With severe intoxication, marked generalized slowing may be present. EEG slowing during intoxication diminishes as tolerance develops (168). EEGs in alcohol abusers are normal or demonstrate only minor degrees of diffuse slowing (85). Patients with a history of chronic alcohol abuse have been reported to have higher incidence (56%) of low-voltage (defined as less than 25-μV) records. Caution is necessary during interpretation because low-voltage background EEG activity in isolation is not considered abnormal, being present in 14% of nonalcoholic adults (84).

Signs of alcohol withdrawal in chronic abusers usually begin within 24 hours after diminished consumption. Mild background EEG slowing may be associated with physiologic artifact (muscle, movement, and sweat) (134). Abstinence may result in alcohol-related seizures, the majority being generalized tonic-clonic, 8 to 72 hours after discontinuation of alcohol (161). Generalized epileptiform discharges during alcohol-related seizures have been described (168). Interictally, patients with seizures associated with withdrawal rarely (2% to 12%) have epileptiform discharges (85).

Withdrawal seizures typically precede delirium tremens, during which time background EEG activity is low voltage with a poorly developed dominant posterior rhythm (138). Most patients with delirium caused by a toxic metabolic encephalopathy have diffuse slowing of background rhythms with theta and delta activity. Thus, an EEG in a delirious patient, which shows generalized low-voltage activity with minimal slowing, should make the interpreter consider that the patient is in a withdrawal state (not limited to alcohol, inasmuch as barbiturate withdrawal may produce similar findings). Niedermyer et al. (109) described periodic lateralized epileptiform discharges (PLEDs) in the rare withdrawal syndrome termed *subacute alcoholic encephalopathy.*

An interesting EEG occurrence described in patients during alcohol withdrawal is photosensitivity, manifested by photomyogenic and photoconvulsive responses during stimulation. Early reports of these phenomena in unmedicated patients led to a hypothesis that they represented a hyperexcitable state of the neuromuscular system and possibly of the central nervous system. Later studies have refuted these findings (62,165), raising the issue that treatment of alcohol withdrawal with benzodiazepines and aggressive medical management of electrolyte abnormalities reduces photosensitivity (43).

Patients with a history of alcohol use are at risk for a variety of medical conditions that may produce abnormalities of the EEG. Focal EEG abnormalities and seizures may result from head injury. The Wernicke-Korsakoff syndrome is caused by thiamine deficiency in chronic alcoholism. It may precipitate an acute psychosis associated with moderate to severe diffuse slowing of EEG activity. In the chronic phase of this illness, EEG slowing is less prominent. Hepatic encephalopathy resulting from alcoholic cirrhosis produces an EEG typical of a metabolic encephalopathy, with generalized slowing and triphasic waves.

Central nervous system stimulants (amphetamines, cocaine, and methylphenidate) potentiate dopamine activity in the brain. These drugs increase faster activity in the beta and alpha ranges and reduce voltage and the amount of slower frequencies (3). Herning et al. (67) examined the effect

of various doses of cocaine administered intravenously and orally. Using quantitative EEG techniques, they found an increase in the beta power at all doses and that it occurred earlier in subjects receiving intravenous cocaine. At toxic levels, cocaine produces a nonspecific pattern of generalized slowing with theta and delta activity (68). Quantitative EEG analysis of cocaine-dependent men abstaining from drug use suggests that beta activity may be a neurophysiological sign of withdrawal (66). Cocaine can provoke seizures in nonepileptic patients and can exacerbate seizures in patients with a history of seizures (115). Other cocaine-induced neurological conditions also include vascular insults, including subarachnoid and intracerebral hemorrhages, which can produce focal abnormalities on the EEG, alerting the clinician to other problems besides intoxication.

Information regarding the effects of cannabis on EEG activity is conflicting. Inhalation of both hashish and marijuana produces little or no effect on EEG activity according to visual analysis (25,125). However, the active component of cannabis, delta-9 tetrahydrocannabinol, produces an increase in alpha activity with a decrease in beta and theta frequencies (163). Lysergic acid diethylamide (LSD) and mescaline, both potent hallucinogenic agents, can produce nonspecific changes with reduction in EEG voltage and slower frequencies during the psychotic state (15,41). Phencyclidine, which was introduced as an intravenous veterinarian anesthetic, is structurally related to ketamine. Acute phencyclidine intoxication produces an unusual pattern of rhythmic, nonreactive theta activity interrupted by periodic bursts of delta activity that is highly suggestive of the diagnosis (38,151).

MISCELLANEOUS DRUGS AND TOXINS

It is not possible to review all EEG changes caused by exposure to drugs and toxins. This section summarizes some additional medications and inorganic compounds that can produce distinctive EEG patterns.

Baclofen is a GABA-B receptor agonist used in the treatment of spasticity. Despite its mechanism of action and proepileptic effect in animal models (104), therapeutic levels of this medication do not increase seizure frequency in epileptic patients (153). An encephalopathy associated with periodic sharp waves (similar to the EEG pattern with lithium toxicity) has been reported in a patient receiving low-dose therapy. However, Zak et al. (171) believed that this pattern was ictal, representing nonconvulsive status epilepticus. The encephalopathy and EEG pattern cleared after discontinuation of baclofen (69). Intrathecal baclofen administration by means of an implanted drug delivery system has been used to maximize therapy in the treatment of spinal and supraspinal spasticity. Kofler et al. (82) reported that of 39 of patients, without a prior history of convulsions, who underwent this treatment for "supraspinal" spasticity, four (10.3%) experienced epileptic seizures. All four patients had traumatic brain injuries, and seizure activity was associated with sudden alterations in baclofen levels.

Metrizamide, the first water-soluble contrast medium with mild subarachnoid neurotoxic effects, was used during myelography and cisternography. EEG changes associated with these procedures included slow activity and epileptogenic discharges in 16% to 35% of patients. In the prospective study of Ropper et al. (127), 34% of patients (21 of 62) developed EEG abnormalities, including paroxysmal slow-wave bursts, triphasic waves, spike discharges, and spike-wave discharges. Non-convulsive status epilepticus after metrizamide myelography has been described as either generalized (111,122, 164) or complex partial (34,131). This discrepancy in seizure type may reflect the difficulty in distinguishing these EEG patterns. Iohexol, a second-generation nonionic monomeric contrast media, greatly reduces the risk of neurotoxic side effects (including seizures and mental status changes), but it has been associated with acute encephalopathy, accompanied by diffuse slowing of the background EEG activity, in three patients (21).

Chemotherapeutic and immunosuppressive agents have been associated with slowing of background EEG activity. In pediatric patients, both methotrexate and ifosfamide have been associated with unusual EEG changes. Methotrexate can cause focal polymorphic delta activity, in addition to generalized slowing of background activity (83). Ifosfamide can lead to generalized slowing and high-voltage rhythmic delta activity (120). Ifosfamide can also produce a generalized periodic pattern with bisynchronous sharp complexes, possibly representing nonconvulsive status epilepticus (141,167). L-asparaginase can increase theta and delta activity (90). An encephalopathy related to infusion rate of hepsulfam in patients with hematological malignancies was accompanied by slowing of the alpha rhythm (91). Cyclosporine is associated with diffuse and focal slowing in addition to epileptiform discharges (130).

Antimicrobial agents may lower seizure threshold. An overdose of isoniazid can produce seizures. The interictal EEG shows bilateral sharp waves and generalized paroxysmal and diffuse slowing. Topical application of penicillin is used in experimental models of epilepsy. In humans, intrathecal administration and very high (40 to 80 million units per day) parenteral doses may produce ictal phenomena (3,52).

In animal models, atropine produces slowing of EEG activity, which suggesting a disturbance in cholinergic input to the cortex (137). Atropine is

used in military medicine as an antidote after exposure to cholinesterase-inhibiting nerve agents. Quantitative EEG analyses show an increase in delta and theta power with a decrease alpha and beta activity in healthy male volunteers (117). Cholinergic deficits in patients with senile dementia of the Alzheimer type may play a role in memory impairment. In an age-matched normal control population, intravenous scopolamine produced statistically significant changes in quantitative EEG delta activity that was not present in patients with Alzheimer's disease (108).

Bromide salts were the first anticonvulsant agents and were widely used as sedatives. Dose-related toxicity has been related to chloride ion replacement. Advanced forms of bromide encephalopathy are associated with diffuse slowing of background EEG activity (160). Mercury neurotoxicity is most commonly associated with industrial exposure. The EEG changes may include generalized slowing and epileptiform discharges. The severity of the EEG abnormalities and the patient's clinical condition may be correlated with age (14). Lead toxicity may result from ingestion or inhalation of lead-containing compounds (such as paint) and can produce seizures. The EEG shows diffuse slowing in subacute and severe forms of lead poisoning. Diffuse and focal paroxysmal discharges may be present. In chronic lead encephalopathy, the EEG is low voltage with a poorly developed alpha rhythm (6,77).

CONCLUSION

Although the EEG is sensitive to the effects of drugs and toxins on the central nervous system, changes in background activity are not specific. AEDs may reduce ictal phenomena and affect background EEG activity, but most do not suppress interictal abnormalities. Medications used in the treatment of psychiatric disorders may reduce seizure threshold and produce interictal epileptiform activity. Anesthetics and analgesics produce dose-related effects. Drugs may induce EEG changes that include electrocerebral silence and status epilepticus. Drug toxicity should be considered in any comatose patient, especially if background EEG activity includes increased fast activity. As with any neurodiagnostic test, the EEG is a tool that is an adjunct to the clinical evaluation of the patient's history and physical examination.

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Chapter 16

Progressive Pediatric Neurological Syndromes

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- Pyridoxine Dependency
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The Role of the EEG in a Child with a Suspected Progressive Encephalopathy

References

Electroencephalography (EEG) is one of the most readily available and well-studied tools for measuring cerebral cortical activity. It is a highly reliable measure of physiological activity, capable of detecting even minor degrees of diffuse cortical dysfunction. It may be useful in the evaluation of the patient with a suspected encephalopathy to confirm the presence of diffuse cerebral dysfunction, suggest a specific etiology, or both. In contrast to the findings in patients with static encephalopathies, for which the EEG is often a sensitive but etiologically nonspecific indicator of dysfunction, the findings in patients with progressive encephalopathies may be very informative. There are more than 11,000 well-recognized and well-characterized inherited disorders in humans, many of which can affect the central nervous system function either directly or indirectly. Published information on the EEG findings in the majority of these disorders is scant, and the EEG results are unlikely to contribute significantly to the clinical decision making. In a subset of nearly 200 disorders, there are associated seizures and epilepsy. The EEG findings in these conditions, whose pathophysiological processes must have some impact on cortical grey function, have been studied in greater detail; in some, very specific EEG findings have been noted. This chapter consequently focuses on the progressive disorders that are associated with seizures or that are characterized by distinctive EEG findings. In addition to progressive encephalopathies, brief mention is made of disorders that manifest with static encephalopathies and prominent seizures, particularly disorders that manifest in childhood or early adolescence.

It is a challenge to organize this wealth of material. In practice, the authors have found it clinically useful to separate diseases by the typical age at manifestation. Accordingly, the conditions are categorized into those commonly manifesting in the neonatal period, those appearing in early and late infancy, and those appearing during childhood. The age of the patient is one piece of clinical information that should always be available to electroencephalographers. This approach has value, but also limitations. Diseases manifest in a biological spectrum, often as a continuum across several age brackets and seldom exclusively at any given age. Diseases categorized within a certain age group may certainly manifest outside that age group. With this caveat in mind, the clinician has at least a starting point for consideration of a differential diagnosis, which may be refined by specific EEG, clinical, or laboratory features.

For each condition, there is a brief description of the clinical manifestation, a concise review of the most recent genetic information available at the time of this writing, and a description of the relevant neuropathological processes. These data will assist the electroencephalographer to be aware of the appropriate clinical context and to integrate EEG and clinical findings. After a discussion of the various entities, we consider an approach to obtaining an EEG in a child with a suspected progressive disorder.

METABOLIC DISORDERS IN THE NEWBORN

In a number of metabolic disorders manifesting in the first month of life, seizures may be a clinical feature. Although the following section cannot be a comprehensive list of all the disorders that should be considered in this age group, it contains those in which seizures are a prominent feature.

Nonketotic Hyperglycinemia

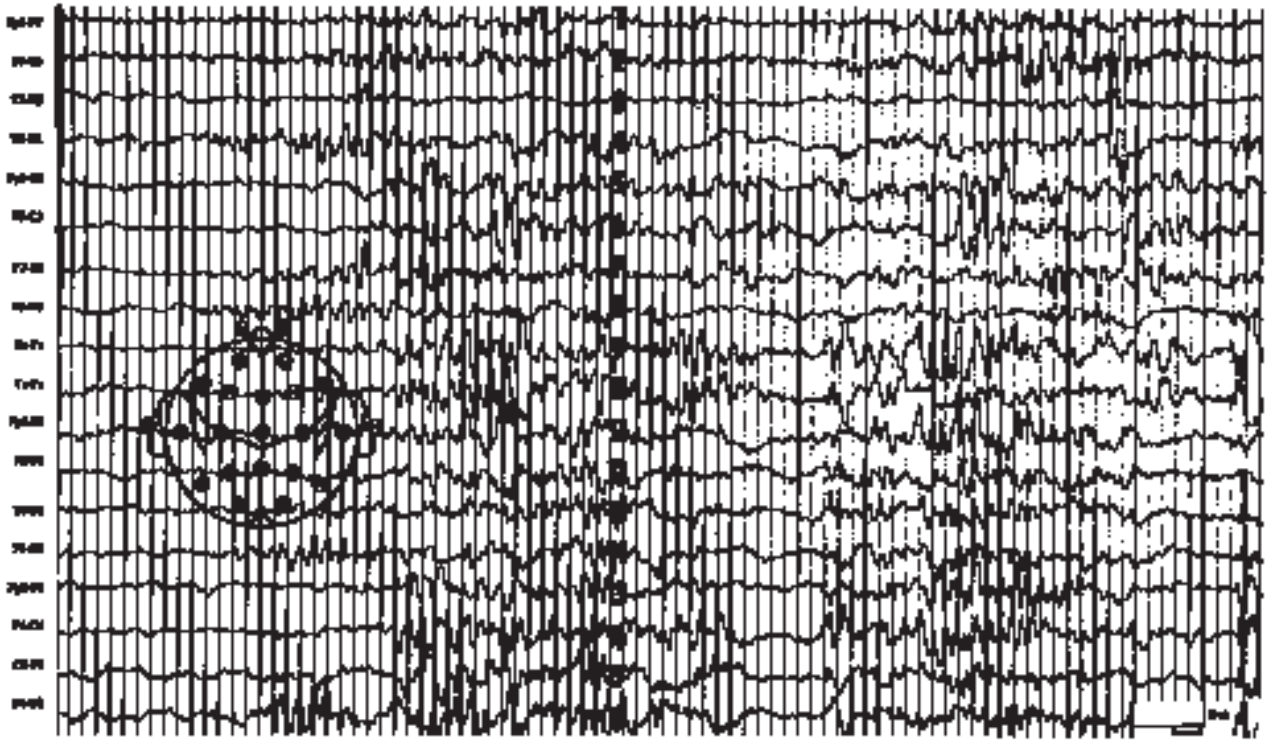
In this inborn error of amino acid metabolism, large amounts of glycine accumulate in the body fluids because of a defect in the multienzyme complex for glycine cleavage. The enzyme system is confined to the mitochondria and is composed of four protein components. A gene localized to 9p24-p23 encodes one component: glycine decarboxylase. The pathophysiological processes have not been fully elucidated, but the elevated glycine level is believed to affect the central nervous system through its roles as an inhibitory transmitter in the brainstem and spinal cord and as an excitatory transmitter in the cortex (62). Cortical malformations or corpus callosum defects may be present. The majority of cases manifest within the first 48 hours after birth, with lethargy, respiratory difficulties, and seizures that are often myoclonic or characterized as infantile spasms. EEG findings may reveal a characteristic burst-suppression pattern or hypsarrhythmia (18). This disorder has been identified as one of the most important metabolic derangements responsible for Ohtahara's syndrome, in which patients present with tonic spasms and a burst-suppression pattern. Similar clinical and electrographic patterns can also be seen with early myoclonic epilepsy, as described by Jean Aicardi. This can lead to diagnostic uncertainty in the differentiation of these two early infantile epilepsy syndromes (48). As patients with these disorders mature, infantile spasms may persist, and the EEG often reveals hypsarrhythmia.

Of note, a transient form of nonketotic hyperglycinemia exists with similar early clinical and biochemical findings. In this condition, however, glycine concentrations normalize between 2 and 8 weeks after birth, and the prognosis is favorable.

Pyridoxine Dependency

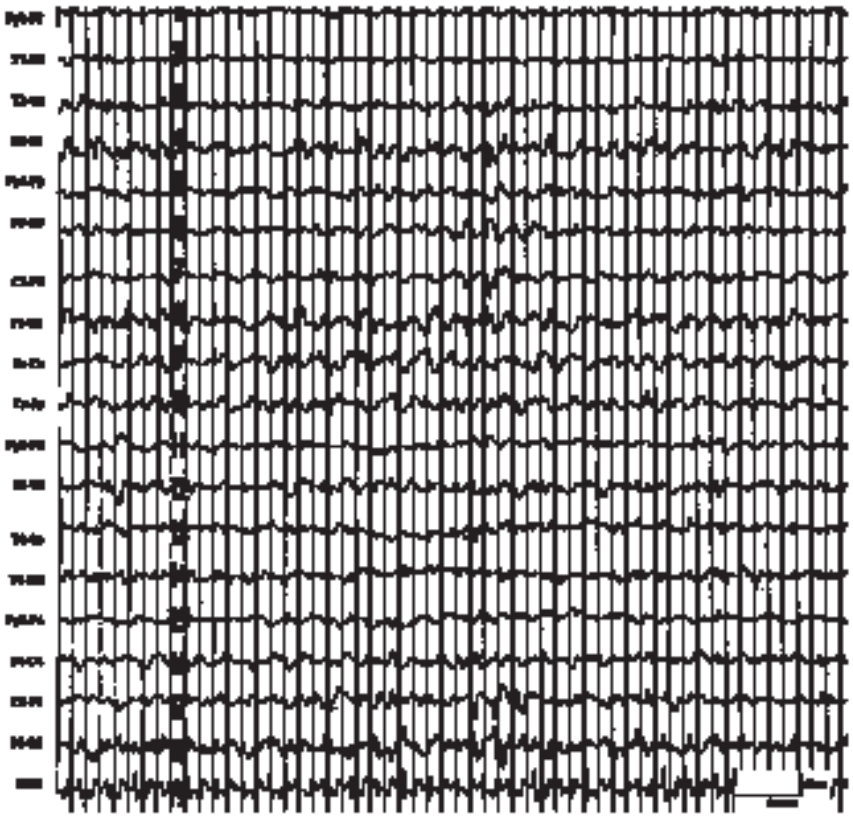
In this condition, refractory seizures typically develop within the first several days after birth; they are characterized by infantile spasms or a variety of partial, myoclonic, and atonic seizures. The disorder results from a defect on the binding site of glutamic acid decarboxylase (GAD). Pyridoxine is a key cofactor for this enzyme, and the insufficient γ-aminobutyric acid formation seen in this disorder can be corrected by high doses of pyridoxine. Two different genes code for GAD in mammalian brains: GAD1 (gene locus, 2q31) and GAD2 (gene locus, 10p11.23) (10,11).

The EEG is characterized by generalized bursts of high-voltage delta with intermixed spike-and-sharp waves and periods of asynchronous attenuation (Fig. 16.1*A*). Treatment with high doses (100 to 200 mg intravenously) of pyridoxine can result in cessation of seizures, conversion of the EEG to a burst-suppression pattern, and later normalization of the EEG with subsequent doses (128) (see Fig. 16.1*B*). The onset of this disease may occur after



A

FIG. 16.1. Pyridoxine dependency. **A:** EEG of a 4-week-old child with intractable neonatal seizures. There are bursts of high voltage delta with intermixed spikes and sharp waves and asynchronous epochs of attenuation.
(Figure continues.)



B

FIG. 16.1. *Continued.* **B:** EEG of the same child after pyridoxine treatment. The tracing is now continuous, and only occasional epileptiform discharges persist. (Courtesy of C. Stack, M.D., and L. Laux, M.D., Children's Memorial Hospital, Chicago, Illinois.)

the newborn period, which makes this disorder a consideration in older infants with refractory seizures as well (14,38).

Molybdenum Cofactor Deficiency and Sulfite Oxidase Deficiency

These rare conditions manifest shortly after birth. Affected neonates develop a progressive encephalopathy, feeding difficulties, hypotonia, and refractory partial, myoclonic, or apparently generalized seizures. Dysmorphic features, lens dislocation, and hepatomegaly are characteristic (46). Neuroimaging may show poor differentiation between the gray and white matter, severe cerebral and cerebellar atrophy, and multiple cystic cavities in the white matter. The relatively more common molybdenum cofactor deficiency results from an absence of the hepatic cofactor, which leads to a combined enzyme deficiency of the three molybdenum-dependent enzymes: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase (99). This may be caused by mutations in the gene (MOCS1; gene locus, 6p21.3) that encodes the two enzymes for synthesis of a precursor. Mutations in molybdopterin synthase (MOCS2; gene locus, 5q11), which converts the precursor into the organic moiety, are responsible for the other form of the disorder (88).

Multifocal paroxysms and a burst-suppression pattern on the EEG have been described (56).

Peroxisomal Disorders

Disorders of the peroxisome have been divided into three categories: disorders of peroxisomal biogenesis (Zellweger's syndrome, neonatal adrenoleukodystrophy [NALD], infantile Refsum's disease], disorders of a single peroxisomal enzyme (X-linked adrenoleukodystrophy, acyl–coenzyme A [CoA] oxidase deficiency AOXD]), and disorders with deficiencies of multiple peroxisomal enzymes (rhizomelic chondrodysplasia punctata. This discussion will be limited to Zellweger's syndrome, AOXD, and NALD.

Zellweger's Syndrome

Zellweger syndrome is the most frequent peroxisomal disorder in early infancy; its incidence is estimated to be 1 in 50,000 to 1 in 100,000. The phenotype in Zellweger's syndrome is caused by mutations in any of several genes involved in peroxisome biogenesis, including peroxin-5 (chromosome 12), peroxin-2 (chromosome 8), peroxin-6 (chromosome 6), and peroxin-12. In addition to these, a locus for Zellweger's syndrome on 7q11 is suspected on the basis of chromosomal aberrations. Mutations in the PEX1 gene, which maps to 7q21-q22, were identified in cases of Zellweger's syndrome, complementation group 1 (70).

Dysmorphic features may be noted shortly after birth. Within the first week, the affected child develops a severe encephalopathy, hypotonia, and hyporeflexia. Eighty percent of patients experience partial, generalized tonic-clonic (rare), and myoclonic seizures and atypical flexor spasms. Multisystem abnormalities of the brain, kidneys, liver, skeletal system, and eyes may be present. Eye abnormalities include cataracts, glaucoma, corneal

clouding, optic nerve hypoplasia, pigmentary retinal degeneration, and Brushfield spots. The presence of the latter, along with hypotonia and a mongoloid appearance, may cause the clinician to confuse Zellweger's syndrome with Down's syndrome. Findings on neuroimaging and pathological examination are distinctive, with pachygyria or polymicrogyria localized to the opercular region and with cerebellar heterotopias.

Patients with Zellweger's syndrome have partial motor seizures originating in the arms or legs or corners of the mouth. Their seizures do not culminate in generalized seizures and are easily controlled by antiepileptic drugs (AEDs). Interictal EEGs of the patients with Zellweger's syndrome showed infrequent bilateral independent multifocal spikes, predominantly in the frontal motor cortex and its surrounding regions (113). Less frequently, hypsarrhythmia is observed.

Neonatal Adrenoleukodystrophy

NALD, an autosomal recessive disorder with pathological and biochemical findings resembling those of X-linked adrenoleukodystrophy, bears some similarity to Zellweger's syndrome. Distinguishing features include absent or minimal facial dysmorphisms, later onset of seizures, absent or minimal cerebral malformations, and longer life span. There is evidence that this disorder may be caused by a number of different gene defects, including a mutation in the C-terminal peroxisomal targeting signal (PTS1) receptor gene, PXR1 (25). Frequent, often intractable seizures that may be tonic, clonic, myoclonic, or epileptic spasms occur (122). No characteristic EEG pattern has been defined, but descriptions have included high-voltage slowing, polymorphic delta activity, multifocal paroxysmal discharges, burst-suppression, and hypsarrhythmia.

Acyl-Coenzyme A Oxidase Deficiency

AOXD was initially described in two siblings by Poll-The et al. (86). Clinical features include hypotonia, pigmentary retinopathy, hearing loss, developmental delay, adrenocortical insufficiency, absence of dysmorphic features, and onset of seizures shortly after birth. A deficiency in acyl-CoA oxidase, resulting from a deletion in its coding gene, was identified. Serum levels of very long chain fatty acids are elevated, with normal levels of pipecolic acid. Cortical malformations are generally absent, and the interictal EEG may show continuous, diffuse, high-voltage theta activity.

Urea Cycle Disorders

There are six enzymes in the urea cycle that convert ammonia to urea; five of these may have defects that cause neonatal seizures. The associated diseases and their incidences are as follows: carbamoylphosphate synthetase deficiency, 1 in 800,000; ornithine transcarbamylase deficiency, 1 in 80,000; argininosuccinate synthetase deficiency, 1 in 250,000; argininosuccinate lyase deficiency, 1 in 70,000; and *N*-acetylglutamate synthetase deficiency, with only a few cases reported. The clinical disorder resulting from a deficiency in the sixth enzyme, arginase, manifests later in infancy. All of these disorders are autosomal recessive except for ornithine transcarbamylase deficiency, which is X-linked dominant.

The clinical manifestations are similar and result, at least in part, from ammonia elevations. Typically, affected newborns exhibit poor feeding, emesis, hyperventilation, lethargy, or convulsions 1 to 5 days after birth. These signs give way to deepening coma with decorticate and decerebrate posturing and progressive loss of brainstem function. Brain imaging and pathological studies reveal cerebral edema with pronounced astrocytic swelling. Ammonium is taken up by the astrocytes and rapidly converted to glutamine in an energy-dependent process. The edema is associated with glutamine accumulation and energy depletion. In experimental models, blocking glutamine synthesis has prevented cerebral edema associated with hyperammonemia (131).

The EEG shows a low-voltage pattern with diffuse slowing and multifocal epileptiform discharges (33) (Fig. 16.2*A*). Two patients studied by Verma et al. in 1984 (121) demonstrated episodes of sustained monorhythmic theta activity (see Fig. 16.2*B*). In acute neonatal citrullinemia, a burst-suppression pattern has been described (74).

Maple Syrup Urine Disease

This disease, resulting from a defect in the branched chain α-keto acid dehydrogenase complex, was first reported by Menkes et al. in 1954 (67). The enzyme defect leads to accumulation of the branched-chain amino acids—valine, leucine, isoleucine—and their keto acids in the body tissues and fluids. The gene locus is 19q13.1-13.2 (29). Pathological studies have revealed diffuse myelin loss and increased total brain lipid content. Cystic degeneration of the white matter associated with gliosis is seen. Disordered neuronal migration may occur with heterotopias and disrupted cortical lamination.

Feeding difficulties and lethargy are observed during the first to second weeks after birth. If left untreated, symptoms may progress to stupor, apnea,

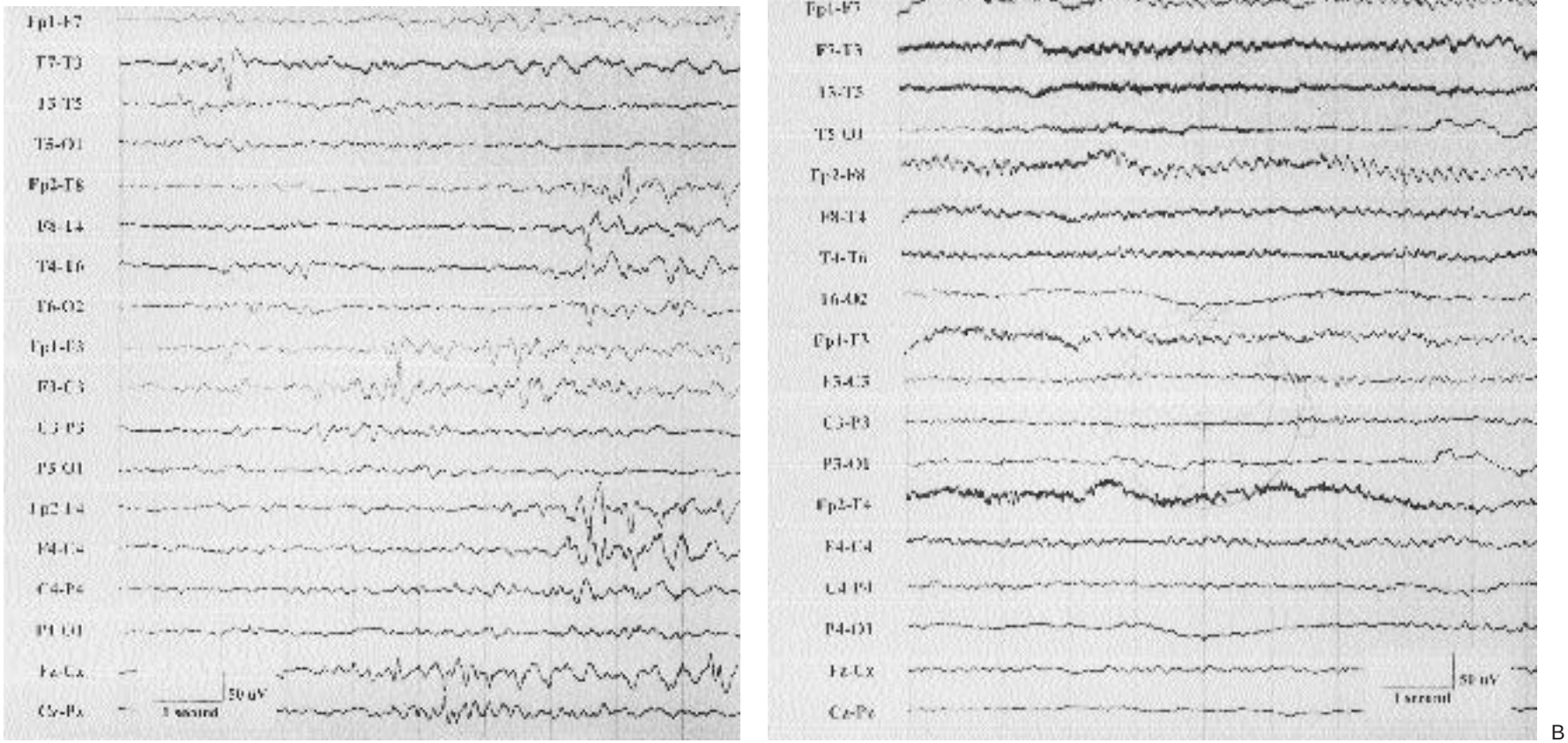


FIG. 16.2. EEGs of a 2-week-old child with ornithine transcarbamylase deficiency. **A:** There is marked attenuation and disorganization of the background with multifocal spikes. **B:** Sustained monorhythmic theta activity is present in the frontal regions. (Courtesy of C. Stack, M.D., and L. Laux, M.D., Children's Memorial Hospital, Chicago, Illinois.)

opisthotonus, myoclonic jerks, and partial and generalized seizures. A characteristic odor can be detected in urine and cerumen, but this may not be detectable until several weeks after birth.

The EEG shows diffuse slowing and a loss of reactivity to auditory stimuli. The comb-like rhythm characteristic of this disease was initially described by Trottier et al. in 1975 when bursts of a central mu-like rhythm were observed in four affected patients (116). Tharp also described this pattern in an infant who developed bursts of primarily monophasic negative 5- to 7-Hz activity in the central and parasagittal regions, which resolved with dietary therapy (115).

Organic Acidurias

The disorders of organic acid metabolism comprise a large number of inborn errors, including isovaleric aciduria and several ketotic hyperglycinemic syndromes (propionic acidemia, methylmalonic acidemia and β-ketothiolase deficiency).

Symptoms of isovaleric aciduria (gene locus, 15q14-q15), which develop during the neonatal period in half of affected children (54), include poor feeding, vomiting, dehydration, and a progressive encephalopathy manifested by lethargy, tremors, seizures, and coma. Platelet and leukocyte counts may be depressed, and the odor of the urine has been described as similar to that of sweaty feet (100). Cerebral edema is present, and seizures are most often partial motor or generalized tonic. The EEG shows dysmature features during sleep.

The symptoms of propionic acidemia also appear during the neonatal period, and in 20% of affected newborns, seizures are the first symptom. Characteristic features include vomiting, lethargy, ketosis, neutropenia, periodic thrombocytopenia, hypogammaglobulinemia, developmental retardation, and intolerance to protein. Patients may have very puffy cheeks and an exaggerated Cupid's bow–shaped upper lip. The gene locus is 13q32 (49). Convulsions are the rule, although more limited partial seizures have also been reported. The EEG shows background disorganization with marked frontotemporal and occipital slow wave activity (109). In 40% of affected children, myoclonic seizures develop in later infancy, and older children may have atypical absence seizures.

Methylmalonic acidemia is the metabolic signature of seven biochemically distinct entities, all of which show decreased activity of methylmalonyl-CoA mutase. Stomatitis, glossitis, developmental delay, failure to thrive, and seizures are the major features. Lesions of the globus pallidus, visible on computed tomography or magnetic resonance images, are characteristic. Diffuse tonic seizures and partial seizures with secondary generalization are the most frequent seizure types. Seizures may also be characterized by eyelid clonus with simultaneous upward deviation of the eyes. In a review of 22 affected patients, Stigsby et al. described abnormalities in seven. These consist of multifocal spike discharges and depressed background activity in two, excessive generalized slowing in two, and mild background slowing with lack of sleep spindles in three (29,109).

Pyruvate Dehydrogenase Deficiency, Pyruvate Carboxylase Deficiency, and Leigh's Syndrome

The pyruvate dehydrogenase complex is composed of multiple copies of three enzymes: pyruvate decarboxylase (E_1), dihydrolipoyl transacetylase (E_2), and dihydrolipoyl dehydrogenase (E_3). The core of the complex is formed by sixty E_2 subunits, and the other enzymes are attached to the surface. The E_1 enzyme is itself a complex structure, a heterotetramer of two α and two β subunits. The E_1-α subunit is particularly important inasmuch as it contains the E_1 active site; its gene locus is Xp22.2-p22.1.

There are various clinical manifestations of pyruvate dehydrogenase deficiency, ranging from acute lactic acidosis in infancy with severe neurological impairment to a slowly progressive neurodegenerative disorder (9). It is one of the most common defined genetic defects of mitochondrial energy metabolism. Structural abnormalities, such as agenesis of the corpus callosum, can be visible on neuroimaging. Seizures frequently occur and may take the form of infantile spasms and myoclonic seizures (80). Electrographic findings include multifocal slow spike-and-wave discharges.

Pyruvate carboxylase deficiency has two predominant clinical forms. The neonatal type manifests with severe lactic acidemia and death in the first few months of life. The juvenile type begins in the first 6 months of life with episodes of lactic acidemia precipitated by an infection. Seizures are related to the hypoglycemia that occurs secondary to dysfunction of the Kreb's cycle. Developmental delay, failure to thrive, hypotonia, and seizures, including infantile spasms with hypsarrhythmia, may be seen. In milder forms, diffuse 1.5- to 3-Hz slowing has been observed (29,109).

Leigh's syndrome (subacute necrotizing encephalomyelopathy) may be related to various metabolic defects, including cytochrome c oxidase deficiency, and defects in other enzymes involved in energy metabolism. Mutations in the mitochondrial deoxyribonucleic acid (DNA)–encoded ATP6 subunit of adenosine triphosphate (ATP) synthase (complex V) and any of

the three catalytic subunits (E_1, E_2, or E_3) of the pyruvate dehydrogenase complex may result in the same phenotype described by Leigh in 1951 (23,60). The syndrome may also be caused by isolated deficiency of mitochondrial complex I (reduced nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase) and complex II. In addition, rare causes of Leigh's syndrome include myoclonus epilepsy with ragged red fibers (MERRF), mitochondrial encephalomyopathy with lactic acidosis and stroke-like symptoms (MELAS), and mitochondrial DNA depletion (22). Within the first year of life, classic features include failure to thrive, lactic acidosis, and developmental delay. As the disease progresses, infants develop spasticity, abnormalities of eye movements, and central respiratory failure. Various seizures, including focal and generalized seizures, have been described (24). Cases of infantile spasms and hypsarrhythmia are reported with Leigh's syndrome (47,117). In addition, there have been several cases of epilepsia partialis continua (27). EEG abnormalities, although present, do not appear to be distinctive enough to contribute to the clinical diagnosis of Leigh's syndrome (119).

Disorders of Biotin Metabolism

Early-Onset Multiple Carboxylase Deficiency (Holocarboxylase Synthetase Deficiency)

This rare disorder manifests in the first week after birth with lethargy, respiratory abnormalities, irritability, poor feeding, and emesis. A rash is present in more than 50% of patients. Generalized tonic convulsions, partial motor seizures, and multifocal myoclonic jerks develop in 25% to 50% of cases. A deficiency in the enzyme holocarboxylase synthetase leads to a decrease in holocarboxylase (110). Because this enzyme links biotin to four carboxylases in the mitochondrial and one in the cytosol, an inactivity of all carboxylases results. Electrographically, either multifocal spikes or a burst-suppression pattern is seen.

METABOLIC DISORDERS OF EARLY INFANCY

Lysosomal Disorders

Tay-Sachs Disease

GM_2 gangliosidosis is a lysosomal disorder that invariably includes seizures as a prominent feature. The infantile form of GM_2 gangliosidosis includes Tay-Sachs disease, caused by deficiency of hexosaminidase A, and Sandhoff's disease, caused by deficiency of hexosaminidases A and B.

Tay-Sachs disease, an autosomal recessive disorder localized to chromosome 15 (15q23-q24) (75), is found in the Ashkenazi Jewish population of Eastern or Central European descent. The enzymatic defect leads to intraneuronal accumulation of GM_2 ganglioside. Development is normal until the age of 4 to 6 months, when hypotonia and a loss of motor skills occur. Within the next 1 to 2 years, spasticity, blindness, and macrocephaly develop. The classic cherry-red spot is present in the ocular fundi of more than 90% of patients. At this stage, seizures become prominent with frequent partial motor, complex partial, and atypical absence seizures that respond poorly to medications. Myoclonic jerks are frequent and are often triggered by the exaggerated startle response to noise. The EEG is normal early in the course of the disease. Gradually, background activity slows with bursts of high-voltage delta waves and very fast central spikes (15). Diffuse spike-and-sharp-wave activity can be abundant, and acoustically induced myoclonic seizures appear. As the disease progresses, EEG voltage declines, and background activity becomes undifferentiated.

Krabbe's Disease (Globoid Cell Leukodystrophy)

Another lysosomal disorder occurring at this age is globoid-cell leukodystrophy (Krabbe's disease). This disorder, linked to chromosome 14q31, is caused by a deficient activity of galactosylceramidase. There are four forms of galactosylceramidase: infantile, with onset before the age of 6 months; late infantile, with onset between the ages of 6 months and 3 years; juvenile, with onset between the ages of 3 and 7 years; and adult, with onset after the age of 7 years (132). The majority of cases begin within 3 to 6 months of life with irritability, poor feeding, emesis, and rigidity. Muscular spasms induced by stimulation are prominent. Blindness and optic atrophy ensue. Initially, tendon reflexes are increased; then they gradual diminish as breakdown of peripheral myelin occurs. Partial or generalized clonic or tonic seizures and infantile spasms are seen; they may be difficult to distinguish from muscular spasms (6,40). In contrast to what is observed in many classic white-matter diseases, seizures occur early in the course of 50% to 75% of infants with Krabbe's disease. EEG characteristics include a hypsarrhythmia-like pattern with irregular slow activity and multifocal discharges of lower amplitude than that typically seen with West's syndrome (51). In a study of seven infants by Kliemann et al. in 1969, six children had prominent beta activity independently occurring in the posterior temporal regions

and vertex that was superimposed over slower, high amplitude waves. This activity was observed to be state dependent and to occur in long runs without any observed clinical manifestations (51). In the terminal stages of the disease, little electrical activity is detected.

GM_1 Gangliosidosis, Type I and Type II

The infantile form of this disorder, type I, has been localized to chromosome 3 (3p21.33). A deficiency of β-galactosidase leads to the accumulation of GM_1 ganglioside and degradation products in nerve cells and other tissues. Regression of development begins at 3 to 6 months of age with rapid neurological deterioration. Seizures develop by the age of 2 years. Clinical features may include coarse facial features, hepatomegaly, bone deformities (dysostosis multiplex), visual abnormalities, hypotonia, progressive microcephaly, and hematological abnormalities. Examination of the ocular fundi reveals a macular cherry-red spot.

Neurological deterioration in the juvenile form (GM_1 gangliosidosis, type II) is generally slower than in type I. Cerebral manifestations with regression of developmental milestones and visual symptoms typically manifest by the ages of 2 to 4 years. EEG features of both forms include background slowing with increasing, irregular slow activity as the disease progresses (42). In type II, a fluctuating 4- to 5-Hz temporal rhythmic discharge has been observed.

Disorders of Vitamin Metabolism

Biotinidase Deficiency

Disorders of vitamin metabolism with symptoms that appear in early infancy include biotinidase deficiency and disorders of folic acid. As described previously, biotinidase deficiency produces multiple carboxylase deficiency. Seizures occur in 50% to 75% of patients and are the presenting clinical symptoms in one-third of cases. Generalized clonic or tonic-clonic convulsions, infantile spasms, and myoclonic seizures are seen. EEG findings may include a burst-suppression pattern, absence of physiological sleep patterns, poorly organized and slow waking background activity, and frequent spike and spike-and-slow-wave discharges.

Methylene Tetrahydrofolate Reductase Deficiency

Methylene tetrahydrofolate reductase deficiency (gene locus, 1p36.3) (39) is the most common inborn error of folate metabolism. The metabolic defect results from insufficient production of 5-methyltetrahydrofolate, which is needed for the remethylation of homocysteine to methionine, because of a deficiency of methylenetetrahydrofolate reductase. In affected patients, a progressive neurological syndrome develops in infancy. Children with this disorder have acquired microcephaly and seizures, characterized by intractable infantile spasms, generalized atonic and myoclonic seizures, and partial motor features. EEG findings vary from diffuse slowing of background activity to continuous spike-and-wave complexes or multifocal spikes.

Defects in methionine biosynthesis are also associated with seizures. Convulsions are frequent and are predominantly generalized, although myoclonic seizures with hypsarrhythmia have been reported.

Late-Onset Multiple Carboxylase Deficiency (Biotinidase Deficiency)

Seizures are a prominent feature of late-onset multiple carboxylase deficiency, occurring in approximately 75% of affected children. The gene locus is 3p25 (16). Onset of the disease process begins at the age of 3 to 6 months with hypotonia and psychomotor delay. Seborrheic or atopic dermatitis and alopecia are common. As the disease progresses, intermittent ataxia, optic atrophy, and sensorineural hearing loss develop. Seizure types, including generalized tonic-clonic, partial, myoclonic, or infantile spasms, are the presenting symptom in 38% of patients. The EEG may be normal, contain epileptiform discharges, or show diffuse slowing (92).

Glucose Transporter 1 Deficiency Syndrome

The glucose transporter 1 (GLUT-1) deficiency syndrome, previously referred to as the glucose transporter protein deficiency syndrome, was first described in 1991 (20). Affected infants become encephalopathic with seizures and delays of motor and mental development (19). Seizures typically begin after the second month of life and are initially characterized by subtle behavioral alterations consistent with infantile partial seizures. GLUT-1 mutations have been described in several patients (96). The initial EEG may be normal or may show interictal epileptiform discharges in the posterior quadrants. As the child matures, more generalized seizures occur, manifested by nonconvulsive events, myoclonic jerks, or atypical absence seizures. Some patients exhibit 3-Hz spike-and-wave discharges indistinguishable from those seen in childhood absence epilepsy (pyknolepsy). Bursts of generalized spike-and-wave discharges are seen in one-third of older children.

Organic Acidurias

Seizures in early infancy may be the presenting symptom of branched-chain organic acidurias. These include isovaleric aciduria, 3-methylcrotonyl CoA carboxylase deficiency, 3-methylglutaconic aciduria with normal 3-methylglutaconyl-CoA hydratase, and 3-hydroxy-3-methylglutaric aciduria. Seizures, including convulsions and infantile spasms, tend to be prominent in 3-methylcrotonyl CoA carboxylase deficiency.

Severe developmental delay, progressive encephalopathy, and seizures are the most common features of 3-methylglutaconic aciduria with normal 3-methylglutaconyl-CoA hydratase (35). Seizures occur in one-third of cases, and infantile spasms have been reported early on. In another study, eight patients with this disorder were studied, and the most typical finding was mild to moderate slowing of the EEG background. One patient had multifocal sharp-wave discharges as well (109).

Seizures are the presenting symptom in 10% of patients with 3-hydroxy-3-methylglutaric aciduria, a disorder caused by a deficiency of the lyase enzyme that mediates the final step of leucine degradation and plays a pivotal role in hepatic ketone body production. This disorder is one of an increasing list of inborn errors of metabolism that clinically present as Reye's syndrome or nonketotic hypoglycemia. The odor of the urine may resemble that of a cat. The chromosome location for this disorder is 1pter-p33 (129). In many affected patients, EEGs are normal between crises. EEGs in one girl with progressive encephalopathy showed multifocal spikes and intermittent episodes of background attenuation between crises, and focal epileptiform activity during an episode of clinical deterioration (109).

Infantile spasms have been reported in patients with 3-hydroxybutyric aciduria. Facial dysmorphism and brain dysgenesis are prominent manifestations. The enzyme deficiency causing this condition is unknown.

Type I glutaric acidemia is a more common autosomal recessive disorder of lysine metabolism that is caused by a deficiency of glutaryl-CoA dehydrogenase (gene locus, 19p13.2). Seizures are often the first clinical signs of metabolic decompensation after a febrile illness. EEGs are initially normal, but slight background slowing may develop during times of seizure exacerbation (109).

Aminoacidurias

Phenylketonuria and Hyperphenylalaninemias

One of the most frequent inborn errors of metabolism, occurring in 1 in 10,000 to 15,000 live births, phenylketonuria is caused by a deficiency of hepatic phenylalanine hydroxylase (gene locus, 21q24.1) (78). As a consequence of the metabolic defect, toxic levels of the essential amino acid phenylalanine accumulate. If these toxic levels are left untreated, severe mental retardation, behavioral disturbances, psychosis, and acquired microcephaly can result. Seizures are present in 25% of affected children. The majority of children with phenylketonuria (80% to 95%) are found to have abnormalities on EEG. An age-related distribution of EEG findings and seizure types has been observed. Low et al. (61) described characteristic features in 1957. Infantile spasms and hypsarrhythmia predominate in the young affected infant. As the children mature, tonic-clonic and myoclonic seizures become more frequent, and the EEG pattern evolves to mild diffuse background slowing, focal sharp waves, and irregular generalized spike-and-slow waves (84,111). An increase in delta activity has been seen as levels increased during phenylalanine loading (26).

Tyrosinemia, Type III

An inborn error of tyrosine metabolism, type III tyrosinemia (4-hydroxyphenylpyruvate dioxygenase deficiency), has been reported in a newborn with intractable seizures and in children who later developed infantile spasms (98). The EEG pattern has been described as low voltage with spike and polyspike discharges in the parietal-occipital regions.

Menkes' Disease (Kinky Hair Disease)

This X-linked (gene locus, Xq12-q13) disorder of copper absorption was first described by Menkes et al. in 1962 (66). A feature of this disorder is the "kinky hair" of the head and eyebrows. A characteristic twisting of the hair shaft is noted on microscopic examination of these poorly pigmented hairs. Affected boys may be premature, may have neonatal hyperbilirubinemia, or may have hypothermia. Progressive neurological deterioration with spasticity manifests by the age of 3 months, and affected children may have associated bone and urinary tract abnormalities as well. The disease has a rapidly fatal course.

Godwin-Austen et al. (37) described a disorder clinically reminiscent of Wilson's disease but without Kayser-Fleischer rings. Symptoms began at the age of 12 years, and defective copper absorption from the distal intestine, with high copper levels in rectal mucosa, was demonstrated. There is also phenotypic overlap between Menkes' disease and occipital horn syndrome. The topic has been thoroughly reviewed (118).

Seizures, in the form of intractable generalized or focal convulsions, are a prominent feature in Menkes' disease. Stimulation-induced myoclonic

jerks are also present. Multifocal spike-and-slow-wave activity can be seen on EEG, sometimes resembling hypsarrhythmia (112).

Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy (PEHO Syndrome)

PEHO syndrome, described by R. Salonen and colleagues in 1991, is characterized by infantile spasms, arrest of psychomotor development, hypotonia, hypsarrhythmia, edema, and visual failure with optic atrophy (105). Characteristic features include epicanthal folds, midfacial hypoplasia, protruding ears, gingival hypertrophy, micrognathia, and tapering fingers. Edema develops over the limbs and face. The progressive decline seen with this disease is suggestive of a metabolic defect, although no biochemical marker has been identified. It is presumed to be an autosomal recessive disorder by its pattern of inheritance. Neuroimaging shows progressive brain atrophy and abnormal myelination. Hypoplasia of the corpus callosum has been reported. Seizures generally begin as infantile spasms with associated hypsarrhythmia on the EEG. Later, other seizure types may be seen, including tonic, tonic-clonic, and absence seizures. The EEG pattern may evolve to a slow spike-and-wave pattern.

METABOLIC DISORDERS OF LATE INFANCY

Metachromatic Leukodystrophy

Metachromatic leukodystrophy is the result of a deficiency of arylsulfatase A (gene locus, 22q13.31-qter) (94). Hypotonia, weakness, and unsteady gait suggestive of a neuropathy or myopathy are the most common presenting symptoms. These are followed by a progressive decline in mental and motor skills. It has become apparent that in some genetic situations, there may be remarkable phenotypic heterogeneity (2). Partial seizures develop late in the clinical course in 25% of patients with the late-infantile form of metachromatic leukodystrophy and in 50% to 60% of patients with the juvenile-onset form (1,32). EEG findings include diffuse high-voltage slowing, which may be asymmetrical, and occasional bursts of spikes.

Schindler's Disease

Schindler's disease results from a deficiency of (α-*N*-acetylgalactosaminidase (gene locus, 22q11) (50,94,127). Affected patients appear normal at birth, but progressive neurological decline becomes evident in the second year. Manifestations include spasticity, cerebellar signs, and extrapyramidal dysfunction. Generalized tonic-clonic seizures and myoclonic jerks are common. EEG abnormalities include multifocal spikes and spike-and-wave complexes. In older children, Schindler's disease can have the clinical and pathological findings of neuroatonal dystrophy (p. 496).

Mucopolysaccharidoses

The mucopolysaccharidoses are a family of lysosomal storage disorders caused by the deficiency of several enzymes involved in the degradation of glycosaminoglycans. The various mucopolysaccharidoses share many clinical features, including a progressive course, multisystem involvement, organ enlargement, dysostosis multiplex, and abnormal facial features. The most common mucopolysaccharidosis is Sanfilippo's syndrome (mucopolysaccharidosis, type III), in which only heparitin sulfate is excreted in the urine; four different subtypes have been described, each associated with a different enzymatic defect (64). The gene locus is 17q25.3 (95). Generalized seizures develop in about 40% of patients with Sanfilippo's syndrome, but these are often easily controlled by antiepileptic drugs. Progressive dementia and severe behavioral disorders are other features. In a careful study of one patient, the EEG showed lack of normal sleep staging, absence of vertex waves and sleep spindles, and an unusual alteration of low-amplitude fast activity (12 to 15 Hz) with generalized slowing (55).

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses (NCLs) are a group of diseases that result in storage of lipopigments in the brain and other tissues. At least five clinical subtypes and rare, atypical forms have been reported, and most are transmitted as autosomal recessive traits.

The infantile form of NCL (type I) is predominantly found in Finland, where the incidence is 1 per 20,000. The majority of affected patients are homozygous for a missense mutation at 1p32 (69). This disorder typically manifests at the age of 12 to 18 months with developmental regression, myoclonus, ataxia, and visual failure. Other features include incoordination of limb movements, acquired microcephaly, and optic atrophy. Seizures, in the forms of myoclonic jerks and astatic, atonic, or generalized seizures, are prominent. EEG features, which include an early, progressive loss of electrocortical activity and attenuation of the background (93), aid in the diagnosis.

Type II NCL shares many clinical features with the infantile form. In contrast to type I NCL, no ethnic predilection for type II NCL exists. The gene

responsible for most cases has been mapped to the locus 11p15 (103). Early development is normal or may be mildly delayed. By the age of 2 to 4 years, insomnia, an early clinical sign, and intractable seizures develop. Multiple seizure types develop with staring spells and generalized tonic-clonic, myoclonic, and atonic components. As the disease progresses, irregular myoclonic jerks evoked by proprioceptive stimuli, voluntary movement, or emotional fluctuations become prominent. Cognitive decline, ataxia, and visual failure with optic atrophy and abnormal electroretinographic findings are all common (43). A characteristic EEG pattern of occipital spikes on low-frequency photic stimulation is observed (81). Giant visual evoked responses and somatosensory evoked potentials are also seen.

Alpers' Syndrome (Progressive Infantile Poliodystrophy)

This syndrome of unknown cause probably represents a number of familial disorders that are manifested by a rapidly progressive encephalopathy with intractable seizures and diffuse neuronal degeneration. In the Alpers-Huttenlocher subgroup, liver involvement is present and an autosomal recessive pattern of transmission is suggested. A diagnosis of Alpers' syndrome should be made only in the absence of known metabolic disease or an antecedent event. Along with clinical features suggestive of Alpers' syndrome, neuroimaging should exclude other diagnostic possibilities and should show progressive brain atrophy on successive studies with relative sparing of the white matter. Seizure types include myoclonic, focal, and generalized tonic-clonic convulsions. Brick et al. (8) described continuous anterior high-voltage 1- to 3-per-second spike-and-wave–like activity that persisted despite intermittent focal seizures (Fig. 16.3*A*). Brick et al. also noted progressive slowing of background activity as the disease progressed. Epilepsia partialis continua and convulsive status epilepticus have been observed in these patients (126). Diffuse slowing with admixed polyspikes has also been described in this disease (see Fig. 16.3*B*) (7).

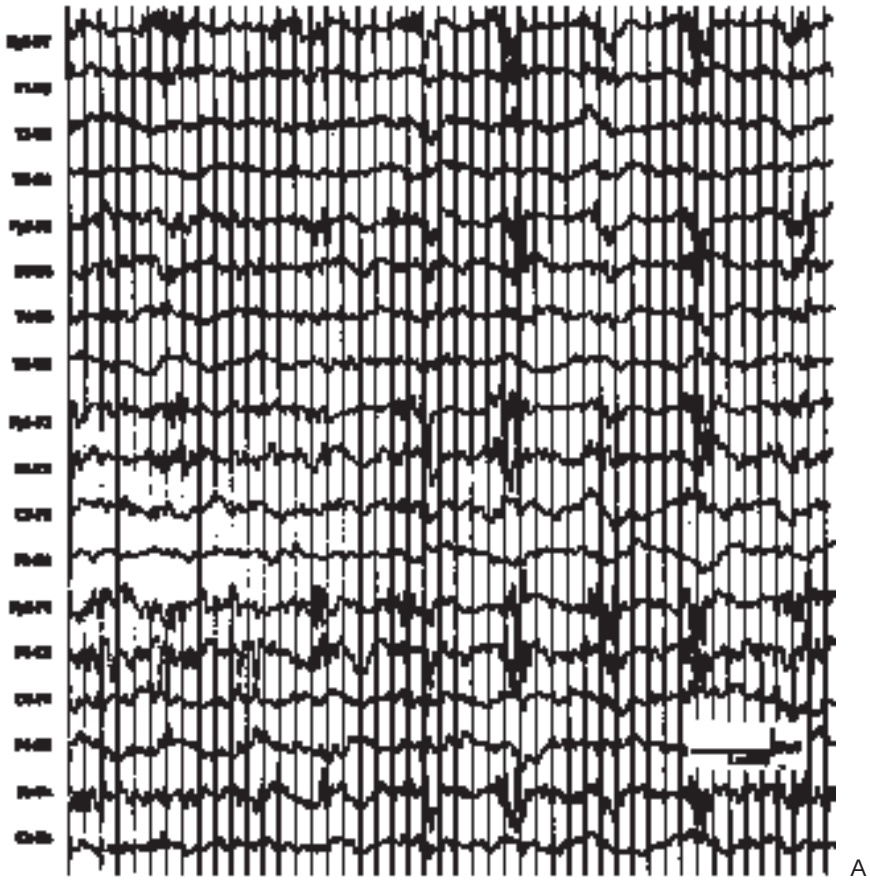
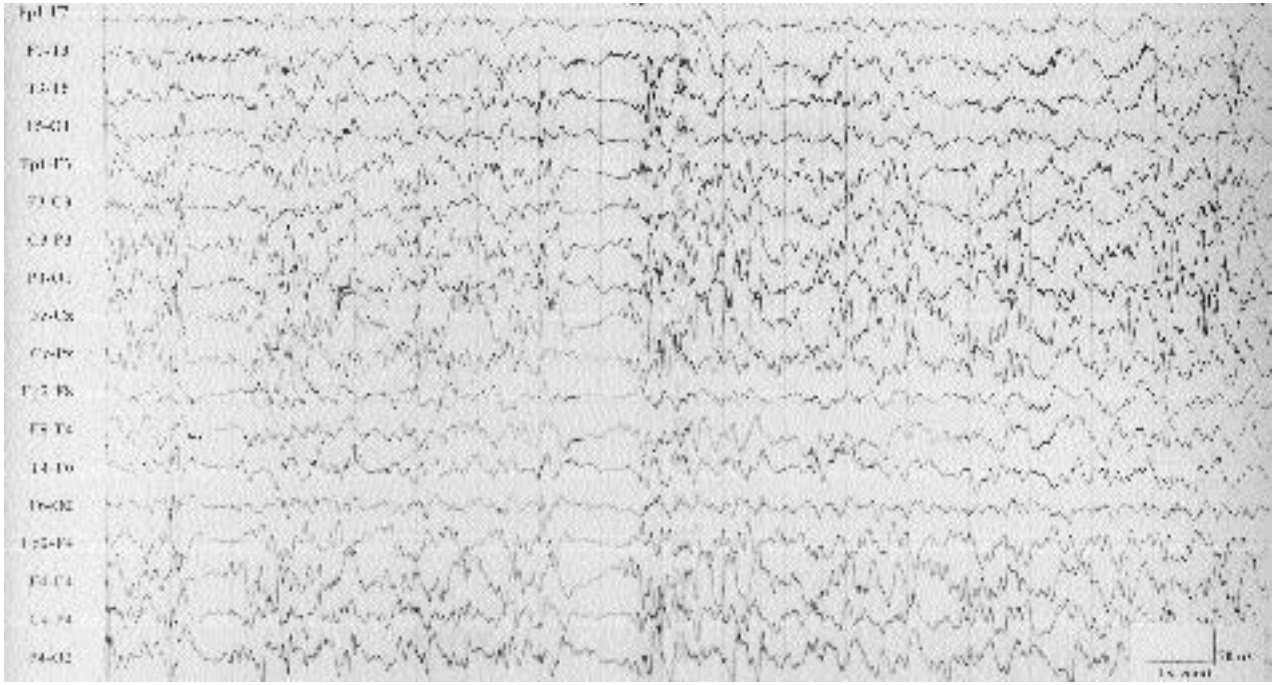


FIG. 16.3. Alpers' syndrome. **A:** EEG of a 10-year-old boy with Alpers' syndrome. Nearly periodic bursts of frontally dominant epileptiform discharges are recorded. (*Figure continues.*)

Carbohydrate-Deficient Glycoprotein Syndrome

Carbohydrate-deficient glycoprotein syndrome (CDGS) is a multisystemic disease that is characterized by a carbohydrate defect in glycoproteins. Orlean (79) reviewed the congenital disorders of glycosylation caused by defects in the addition of mannose during oligosaccharide assembly. CDGS can be divided into two types, depending on whether they impair lipid-linked oligosaccharide assembly and transfer (CDGS I) or alter trimming of the protein-bound oligosaccharide or the addition of sugars to it (CDGS II). Participants at the First International Workshop on CDGS in Leuven, Belgium, in November 1999 proposed new nomenclature for CDGS (79). Type Ia CDGS, phosphomannomutase-2 deficiency, is the best characterized and most common of these syndromes (gene locus, 16p13.3-p13.2) (45,65). During infancy, internal organ symptoms are the predominant feature and



B

FIG. 16.3. *Continued.* **B:** EEG of a 3-year-old girl with Alpers' syndrome. Bursts of high-voltage slowing with intermixed epileptiform activity punctuated by brief epochs of attenuation were seen. (Courtesy of C. Stack, M.D., and L. Laux, M.D., Children's Memorial Hospital, Chicago, Illinois.)

may be life-threatening. In later childhood, mental deficiency, ataxia, progressive neuropathy involving the legs, retinal degeneration, and skeletal deformities are most common. Subcutaneous tissue changes with an odd distribution of fat, retracted nipples, and odd facies, including almond-shaped eyes, have been described. Imaging studies reveal cerebellar hypoplasia (83). There is a unique pattern of coagulation changes associated with the syndrome, including depression of factor XI, antithrombin III, protein C, and, to a lesser extent, protein S and heparin cofactor II. These changes may account for the stroke-like episodes observed in affected children (120). Clinical neurophysiological studies have demonstrated interictal epileptiform discharges and giant somatosensory evoked potentials (114).

Each of the other subtypes has been found in several patients (41). Type III CDGS was first described by Stibler et al. in 1993 (108). Two patients had severe visual, motor, and mental problems and developed infantile spasms with hypsarrhythmia. Interestingly, these patients had patchy skin changes, similar to those of incontinentia pigmenti (108). The absence of polyneuropathy, pigmentary retinopathy, and cerebellar hypoplasia were thought to differentiate this disorder from the previously described CDGSs. Neuroimaging showed dysmyelination and brain atrophy. A defect in glycosylation of transferrin was identified in both patients. A third child was reported in 1999 by Stibler et al. (107) with similar clinical and biochemical features. EEG findings in this child also showed hypsarrhythmia.

METABOLIC DISORDERS OF CHILDHOOD AND ADOLESCENCE

Homocystinuria

Disorders of transsulfuration include cystathionine β-synthase deficiency, the most frequent cause of homocystinuria. The gene locus is 21q22.3 (72). Some patients respond to pyridoxine administration. Mental retardation, behavioral disturbances, and seizures are manifestations of nervous system involvement; ectopia lentis, osteoporosis, and scoliosis are other common clinical findings (34,71). Generalized seizures occur in about 20% of patients with pyridoxine-nonresponsive homocystinuria and in 16% of patients with the pyridoxine-responsive form. EEG features are relatively nonspecific, with slowing and focal interictal epileptiform discharges that may be ameliorated with treatment (21).

Adrenoleukodystrophy

Symptoms of the X-linked form of adrenoleukodystrophy (gene locus, Xq28) classically appear in early childhood. Parietal motor seizures, often with secondary generalization and generalized tonic-clonic seizures, are common in the peroxisomal disorder. Status epilepticus has been the initial presenting symptom, and epilepsia partialis continua has also been reported. The EEG is characteristic, with high-voltage polymorphic delta activity and loss of faster frequencies over the posterior regions (63).

Lysosomal Disorders

Sialidosis, Type I: Cherry-Red Spot–Myoclonus Syndrome

This autosomal recessive disorder, which appears in late childhood to adolescence, is characterized by progressive visual loss, polymyoclonus, and seizures. The myoclonus can be debilitating and is provoked by voluntary movement, sensory stimulation, or excitement. Reports of increased myoclonus with cigarette smoking and menstruation have been noted. As the disease progresses, cognitive decline, cerebellar ataxia, and blindness with optic atrophy occur. Dysmorphic features, bone abnormalities, and hepatosplenomegaly are absent in contrast to type II and mucopolysaccharidosis. Neuroimaging shows diffuse cerebral and cerebellar atrophy. The EEG contains rhythmical spiking over the vertex with a positive polarity overlying a low-voltage background (28).

Sialidosis, Type II/Galactosialidosis

The juvenile form of this group of disorders has features similar to those of type I sialidosis. Distinguishing characteristics are the less prominent myoclonic activity and the presence of coarse facies, corneal clouding, dysostosis multiplex, and hearing loss. Inheritance is autosomal recessive, and this form has a higher incidence in Japan. In the majority of cases, a partial deficiency of β-galactosidase can be seen in addition to neuraminidase deficiency (galactosialidosis), and this may be caused by a defect in protective protein; the gene locus coding for this protein is 20q13.1 (130).The EEG contains moderate-voltage, generalized four- to six-spike/second paroxysms.

Gaucher's Disease, Type III

Three types of Gaucher's disease are known: type I, a chronic form with adulthood onset; type II, a rare form associated with infantile death; and type III, a chronic form with neurological involvement. These disorders result from a deficiency of glucocerebrosidase, which leads to the accumulation of glucosylceramide in the lysosomes of cells in the reticuloendothelial system. In the type III form, hepatosplenomegaly may be present from birth or early infancy, which may cause it to be confused with the more common type I fom of Gaucher's disease. When neurological symptoms develop in childhood to early adulthood, it can be clearly distinguished from type I because cerebral features are absent. Frequent myoclonic jerks and tonic-clonic seizures ultimately develop. A supranuclear palsy of horizontal gaze is present in the majority of cases and is an important diagnostic sign. Generalized rigidity, progressive cognitive decline, and facial grimacing may be present. Paroxysmal EEG abnormalities may be seen before the onset of convulsions with worsening as the disease progresses, and diffuse polyspikes and spike-wave discharges are present. The most characteristic EEG findings are rhythmical trains of spikes or sharp waves at a rate of six to ten per second (77).

Neuroaxonal Dystrophies

Neuroaxonal dystrophies include infantile and juvenile forms of neuroaxonal dystrophy, Hallervorden-Spatz syndrome, and one type of Schindler's disease.

Infantile neuroaxonal dystrophy is an autosomal recessive disorder affecting both the central and peripheral nervous systems. It was first described by Seitelberger in 1952 (97). Characteristic pathological features of axonal

spheroids within the peripheral and central nervous system are seen. Clinical manifestations begin between the ages of 1 and 2 years with psychomotor regression, hypotonia, and development of a progressive sensorimotor neuropathy. Seizures occur in one-third of patients with this disease, onset after the age of 3 years. The electrographic finding of high-voltage fast activity (16 to 24 Hz) that is unaltered by eye opening or closure is characteristic of all children with this disorder, regardless of the occurrence of seizures. During sleep, the fast activity may persist, and K complexes are typically absent (30). Seizure types described with infantile neuroaxonal dystrophy include myoclonic and tonic (13,125). In a video EEG case report, Wakai et al. (124) described tonic spasms and an electrographic correlate of a diffuse, 1-second, high-voltage slow complex followed by desynchronization suggestive of infantile spasms. A juvenile form of the disorder presenting with clinical and EEG features of progressive myoclonic epilepsy has been described (26A). The pathological features are identical to those of one infantile type.

Schindler's disease in older children can present as a neuroaxonal dystrophy. It is due to a deficiency of the lysosomal enzyme, α-*N*-acetylgalactosaminidase, coded on chromosome 22 (50). Tonic seizures and myoclonus are also seen in patients with this disorder. The EEG pattern has been described as diffuse and multifocal paroxysmal discharges with slowing that is maximal over the centroparietal-occipital regions.

Neuronal Ceroid Lipofuscinosis, Type III (Spielmeyer-Vogt Disease or Late-Onset Batten's Disease)

This syndrome with onset in early childhood begins between the ages of 5 and 10 years with visual failure, slow intellectual deterioration, and seizures. A diffuse rigidity later ensues. An autosomal recessive inheritance pattern with localization to 16q12.1 is seen with a worldwide distribution of the disorder. EEG changes are nonspecific. In contrast to the Bielschowsky form of NCL, low-frequency photic does not evoke occipital spikes.

Progressive Myoclonus Epilepsies

Progressive myoclonus epilepsies are a collection of rare disorders characterized by the triad of myoclonic seizures, tonic-clonic seizures, and progressive neurological dysfunction, which often manifests as dementia and ataxia. Onset generally occurs in late childhood to adolescence. If myoclonic features are not prominent, children with this syndrome may be erroneously diagnosed with Lennox-Gastaut syndrome (4). For this reason, a careful history for myoclonic features is important in children with intellectual deterioration and frequent seizures.

Lafora's Disease

Although the biochemical error remains unknown, the autosomal recessively inherited defect that causes this disease has been localized to 6p23-25. The mean age at onset is 14 years, but symptoms may begin in adulthood. Seizures may precede other clinical signs by months to years; multiple seizure types may occur in a previously normal person. Cognitive decline and personality changes are prominent features. Seizure types include tonic-clonic, myoclonic, and polymyoclonus. Occipital seizures with visual phenomena have been reported in 30% to 50% of cases. Cerebellar ataxia, hypertonia, dyskinesias, and exaggerated tendon reflexes may develop later. Generalized bursts of spikes and polyspikes superimposed on a normal background may be seen initially on EEG. The presence of spikes over the posterior regions is a distinguishing feature that may alert the electroencephalographer to the diagnosis in the appropriate clinical setting (87). Spike-and-wave discharges are uncommon. As the disease progresses, the EEG pattern becomes increasingly disorganized. A photoconvulsive response can be seen with photic stimulation (74). On neuroimaging, cerebellar atrophy is occasionally observed.

Unverricht-Lundborg Progressive Familial Myoclonic Epilepsy (Baltic Myoclonus)

This familial form of progressive encephalopathy is characterized by relentless myoclonus and generalized seizures. The gene locus is 21q22.3 (59). Onset occurs in childhood or adolescence with seizures that are predominantly myoclonic and frequently occur after awakening. Absence and atonic seizures are also observed. Although the familial pattern can initially suggest an idiopathic form of epilepsy, the severity of the myoclonus soon suggests a form of progressive myoclonic epilepsy. Myoclonus can become quite disabling, interfering with speech and swallowing, and is often provoked by voluntary movement and excitement. Cognition is generally retained, although a mild decline may be observed later in the course of the disease. Cerebellar ataxia, hyporeflexia, wasting of the distal musculature, and signs of chronic denervation on electromyograms may be seen. The EEG reveals progressive slowing with generalized spike-and-wave–like bursts at a rate of three to five per second that are frontally predominant. Paroxysmal flicker responses and generalized spikes and polyspikes with photic stimulation are also seen (5,53).

Myoclonic Epilepsy with Ragged Red Fibers (MERFF) and Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes (MELAS)

In MERRF, disease onset occurs before the age of 20 years with ataxia and seizures that are predominantly myoclonic. The inheritance pattern is compatible with maternal transmission. In the majority of cases, a point mutation at position 8344 of the mitochondrial gene for transfer ribonucleic acid (tRNA)–lysine has been identified. Affected patients may have short stature, neurosensory hearing loss, optic atrophy, myopathy, or encephalopathy. EEG findings include background slowing, focal epileptiform discharges, and atypical spike- or sharp-and-slow-wave discharges that have a variable association with the myoclonic jerks (104). Suppression of these discharges during sleep is characteristic. As with many of the progressive myoclonic epilepsies, giant somatosensory evoked potentials are observed.

Classically, MELAS manifests during childhood with the sudden onset of stroke-like episodes (Fig. 16.4). Migraine-like headaches, progressive deafness, seizures, cognitive decline, and myopathic features may accompany these symptoms. In an evaluation of 12 patients with MELAS by Berkovic et al. (3), epilepsia partialis continua was frequently seen, and seizures often evolved into partial or generalized status epilepticus. Fujimoto et al. (31) reviewed 79 EEGs in six patients with MELAS and two of their relatives with mitochondrial myopathy, encephalopathy, and lactic acidosis, without stroke-like episodes. In the acute stage after a stroke-like episode, 10 of 11 EEGs showed focal high-voltage delta waves with polyspikes. These discharges were interpreted as ictal phenomena. Later, focal spikes or sharp waves and 14- and 6-Hz positive bursts were frequently recorded (31). The observed seizures were characterized by focal clonic and myoclonic movements with migrainous headache. Four point mutations are predominantly seen with MELAS. Three of these (3243, 3250, 3271) affect the mitochondrial DNA gene of tRNA-leucine. The other mutation involves a coding region of complex I of the respiratory chain. An overlap between clinical characteristics of MERRF and MELAS can be seen with myoclonic features in both syndromes.

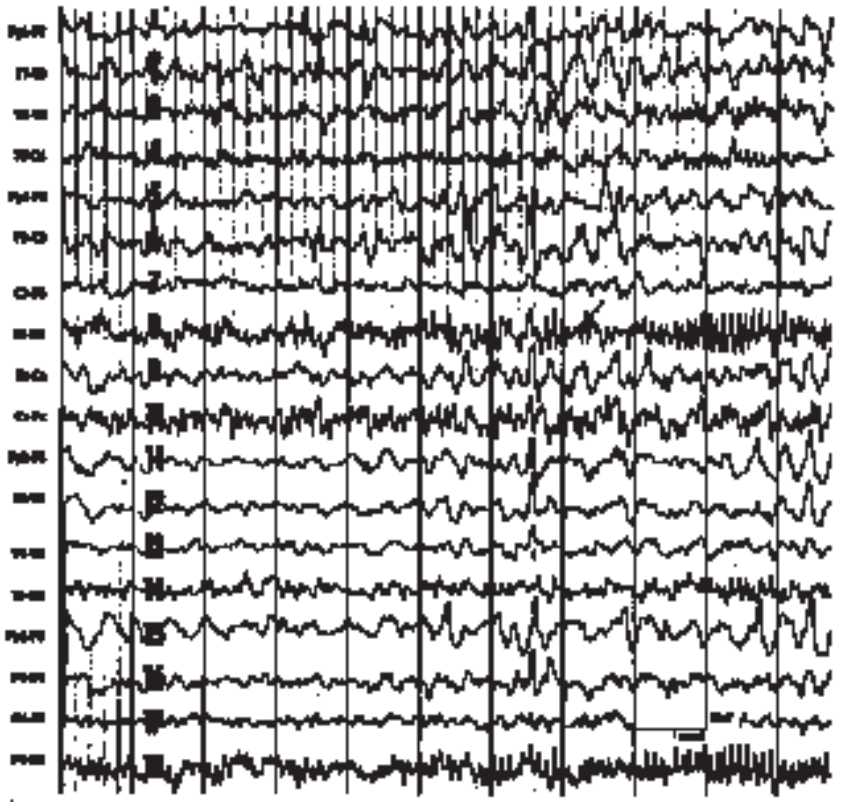


FIG. 16.4. EEG of a 10-year-old boy with mitochondrial encephalomyopathy with lactic acidosis and stroke-like symptoms (MELAS). This tracing was obtained shortly after an acute stroke-like episode. A focal seizure arising from the left posterior quadrant is seen. (Courtesy of C. Stack, M.D., and L. Laux, M.D., Children's Memorial Hospital, Chicago, Illinois.)

Dentatorubral-Pallidoluysian Atrophy

This rare autosomal dominant disease is seen predominantly in the Japanese population. The disorder is related to a trinucleotide (CAG) expansion at 12p13.31 (57). Clinical manifestations are dependent on the length of the unstable trinucleotide repeats and vary from a juvenile-onset progressive myoclonic epilepsy to an adult-onset syndrome with ataxia, dementia, and choreoathetosis (44). The juvenile form can also be variable in its manifestation. In general, symptoms begin in infancy to early childhood with myoclonus, ataxia, dementia, opsoclonus, or seizures that can be generalized tonic-clonic, atypical absence, or atonic (91). Pathological features are striking, with neuronal loss and gliosis in the dentatorubral and pallidoluysian

structures. EEG characteristically shows bursts of slowing, irregular spike-and-wave discharges, and multifocal paroxysmal discharges. A photoparoxysmal response is seen, and myoclonic seizures can often be triggered by photic stimulation.

OTHER ENCEPHALOPATHIES MANIFESTING IN INFANCY, CHILDHOOD, AND ADOLESCENCE

Fragile X Syndrome

The clinical features of this condition are often characterized by moderate mental retardation; large ears; macroorchidism; large chin; hyperkinesias; jocular, high pitched speech; and associated speech and language disorders. The inheritance pattern of this X-linked condition has been explained by maternal imprinting, with loss of gene deactivation after transmission to offspring of the opposite sex. EEGs in affected boys may show a characteristic pattern of centrotemporal spikes indistinguishable from or very similar to those seen in children with benign epilepsy with centrotemporal spikes. The features of these centrotemporal interictal epileptiform discharges include a stereotyped, diphasic morphological appearance with an apparent horizontal dipole, enhanced by drowsiness and sleep. Musumeci et al. (73) studied 192 boys with fragile X syndrome and found that 18.2% had seizures. The onset occurred exclusively between the ages of 2 and 9 years. The majority of affected boys demonstrated interictal centrotemporal spikes. Interestingly, Singh et al. (102) reported focal spikes similar to those in benign rolandic epilepsy in three related female patients with fragile X syndrome. Two sisters of a boy with fragile X syndrome showed mild developmental delay, but their grandmother was of normal intelligence, and all were carriers of the fragile X chromosome. In a smaller study, Kluger et al. (52) found that the interictal epileptiform discharges were detected in boys between 4 and 8 years of age and were not seen in children younger than 4 years or older than 8 years.

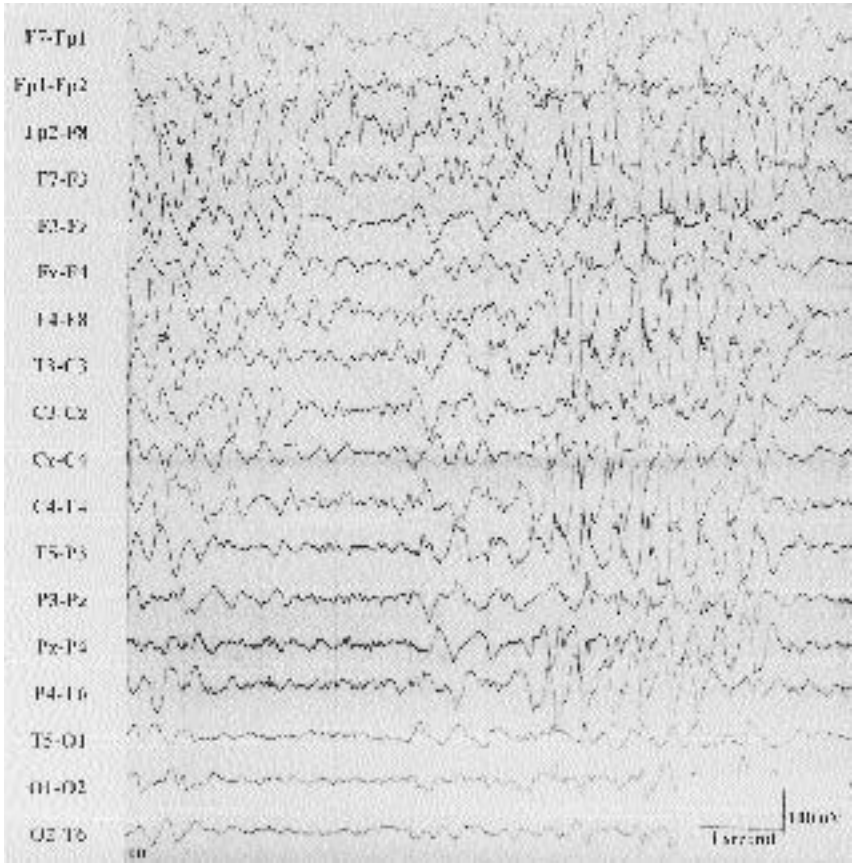


FIG. 16.5. EEG of a 5-year-old with Angelman syndrome. Characteristic high-amplitude 1- to 3-Hz notched slow-sharp-wave complexes are present. (Courtesy of C. Stack, M.D., and L. Laux, M.D., Children's Memorial Hospital, Chicago, Illinois.)

Angelman Syndrome

Children with this disorder exhibit developmental delay, craniofacial abnormalities, ataxia, paroxysmal laughter, and seizures. Children may have atypical absence seizures, partial seizures, and myoclonus. Characteristic EEG findings are diffuse, bilaterally frontal dominant, high-amplitude (1- to 3-Hz) notched or triphasic slow waves (68) (Fig. 16.5). These appear as slow-sharp-wave complexes with a notch of epileptiform activity appearing on the descending portion of the slow wave. Similar discharges have been reported in the occipital region and were facilitated by eye closure (90). In a report on 20 patients with Angelman syndrome, Minassian et al. (68) noted more severe epilepsy in those with maternally inherited 15q11-13 deletions than in patients with loss-of-function UBE3A mutations, uniparental disomy, or methylation imprint abnormalities (68). Angelman syndrome is the probable diagnosis

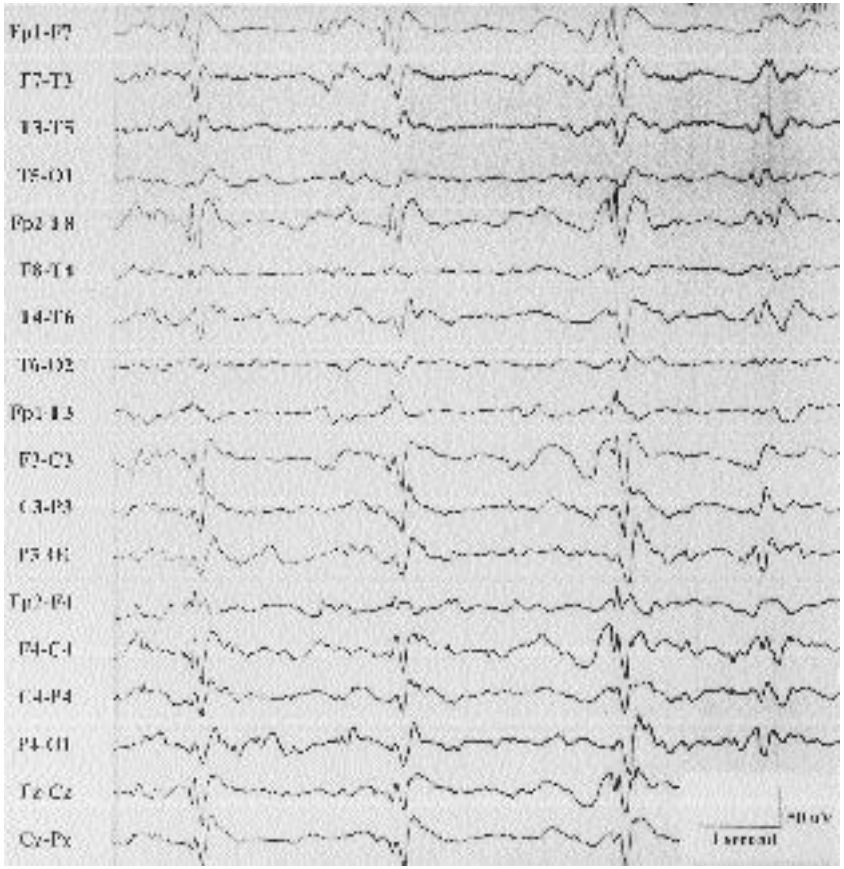


FIG. 16.6. EEG of a 15-year-old girl with Rett syndrome. Characteristic fronto-central needle-like spikes are present. (Courtesy of C. Stack, M.D., and L. Laux, M.D., Children's Memorial Hospital, Chicago, Illinois.)

when the characteristic clinical and electrographic features are present, but it must also be considered in children with severe epilepsy and mental retardation, even when typical EEG features are not present (12).

Rett Syndrome

Rett syndrome is observed only in girls. It is characterized by early psychomotor regression with autistic features, loss of purposeful hand function, ataxia, and acquired microcephaly. The onset of the disease occurs between the ages of 6 months and 3 years, most often before 18 months. Affected girls next experience a rapid decline in function with irritability and loss of purposeful hand use. In the third stage, between the ages of 2 and 10 years, seizures and neurological signs develop. At this stage, the EEG shows interictal epileptiform discharges and a progressive slowing and deterioration of the background in 75% of patients (17,36,89). Characteristic EEG findings include needle-like central spikes, activated by contralateral passive finger pulp palpation (Fig. 16.6). In addition, an unusual and prominent rhythmic theta rhythm (four to five waves per second or five to six waves per second) in the waking state has been noted at the central vertex region and vicinity. This activity blocks with active or passive movements and suggests a slowed equivalent of the mu rhythm (76). These findings can be reliably distinguished from those noted in Angelman syndrome (58).

Down's Syndrome

Children with Down's syndrome are at increased risk for infantile spasms, accompanied by hypsarrhythmia, which is symmetrical and rapidly clears after intravenous administration of diazepam (85,101). Older children may exhibit a variety of seizure types and EEG findings. Overall, epilepsy occurs in 5% to 6% of patients (106). In adulthood, deterioration of the alpha rhythm and changes in its reactivity appears at the onset of dementia in patients with Down's syndrome (82,123).

THE ROLE OF THE EEG IN A CHILD WITH A SUSPECTED PROGRESSIVE ENCEPHALOPATHY

When confronted with a child who is not meeting expected developmental milestones or who exhibits cognitive difficulties, one of the first questions that may arise is whether the patient has a diffuse encephalopathy. The

most important parts of the evaluation are the complete medical history and the results of a comprehensive neurological examination. The EEG may help to confirm an encephalopathy by demonstrating diffuse background slowing. The degree of tolerable slowing varies as a function of age and state of the child. In very young children, unrecognized drowsiness can produce abundant intermixed slowing and prolonged bursts of diffuse or posteriorly dominant rhythmic slowing during transition states. In these circumstances, other characteristics of the EEG can be helpful in evaluation, including the frequency of the posterior dominant rhythm, voltage and frequency organization of the background, and sleep architecture.

If an encephalopathy is confirmed, than it should be determined whether it is progressive or static. Progressive encephalopathies are suggestive of a neurodegenerative process, an inborn error of metabolism, or some other type of progressive etiology. Progressive encephalopathy, a family history of relatives with similar unexplained neurological illnesses, and unexplained paroxysmal bouts of obtundation, ataxia, or other neurological phenomena are all indicators of inborn errors of metabolism and merit further investigation. The EEG may help to confirm the presence of a progressive encephalopathy, particularly if serial studies are performed. Deterioration of the background organization, progressive slowing of the dominant rhythm, attenuation of the background, or loss of the usual signposts of maturation are reliable indicators of progressive disease.

The EEG can help to localize the pathological process, thereby limiting the differential diagnosis. Epileptiform discharges indicate the presence of a potentially epileptogenic encephalopathy and implicate at least some degree of gray matter involvement (as in Tay-Sachs disease, NCL, and Alper's syndrome). Conversely, slowing without epileptiform activity indicates dysfunction in the thalamocortical projections and is consistent with white matter involvement (as in NALD, metachromatic leukodystrophy, and Krabbe's disease).

In rare circumstances, the EEG findings are so distinctive that they limit the differential diagnosis. Examples (Table 16.1) include a burst-suppression pattern in nonketotic hyperglycinemia, phenylketonuria, maple syrup urine disease, molybdenum cofactor deficiency, and sulfite oxidase deficiency, in addition to other disorders. A comb-like rhythm with 7- to 9-Hz central activity is present in maple syrup urine disease and propionic academia; vertex positive polyspikes are present in type I sialidosis; bioccipital polymorphic delta activity is present in X-linked adrenoleukodystrophy; and 16- to 24-Hz invariant activity is present with infantile neuroaxonal dystrophy. Some static encephalopathies have unusual and distinctive EEG patterns: for example, centrotemporal spikes in fragile X syndrome; needle-like central spikes in Rett's syndrome; and frontally dominant, rhythmic slow-sharp complexes in Angelman syndrome.

Finally, patients with inborn errors of metabolism resulting in epileptogenic encephalopathies may initially appear to have cryptogenic epilepsy. The patterns of clinical presentation and the EEG findings can be organized by epilepsy syndromes in order to facilitate recognition of the more common diagnoses (Table 16.2).

TABLE 16.1. *EEG patterns and their associated disorders*

EEG pattern	Disorder
Comb-like rhythm	Maple syrup urine disease
	Propionic acidemia
Fast central spikes	Tay-Sachs disease
Rhythmic vertex positive spikes	Sialidosis type I
Vanishing EEG	Infantile NCL (type I)
High-voltage 16- to 24-Hz activity	Infantile neuroaxonal dystrophy
Diminished spikes during sleep	PME
Giant somatosensory evoked potentials	
Marked photosensitivity	PME and NCL, particularly type II
Burst-suppression pattern	Neonatal citrullinemia
	Nonketotic hyperglycinemia
	Propionic acidemia
	Leigh's syndrome
	D-glycine acidemia
	Molybdenum cofactor deficiency
	Menkes' disease
	Holocarboxylase synthetase deficiency
	Neonatal adrenoleukodystrophy
Hypsarrhythmia	Zellweger's syndrome
	Neonatal adrenoleukodystrophy
	Neuroaxonal dystrophy
	Nonketotic hyperglycinemia
	Phenylketonuria
	Carbohydrate-deficient glycoprotein syndrome type III

NCL, neuronal ceroid lipofuscinosis; PME, progressive myoclonus epilepsy.

TABLE 16.2. *Metabolic diseases masquerading as epilepsy syndromes*

Neonatal seizures (ILAE 3.1)
1. Urea cycle defects: argininosuccinic acidemia, ornithine transcarbamylase, carbamylphosphate synthetase
2. Organic acidurias: maple syrup urine disease
3. Disorders of biotin metabolism: early-onset multiple carboxylase deficiency (holocarboxylase synthetase deficiency)
4. Peroxisomal disorders: Zellweger's syndrome, acyl-coenzyme A oxidase deficiency
5. Other: molybdenum cofactor deficiency, sulfite oxidase deficiency, disorders of fructose metabolism, pyridoxine dependency
Early myoclonic encephalopathy and early infantile epiletogenic encephalopathy (ILAE 2.3.1)
1. Nonketotic hyperglycinemia
2. Propionic aciduria
3. *D*-glycine acidemia
4. Leigh's disease
Cryptogenic myoclonic epilepsies (ILAE 2.2), other than infantile spasms or Lennox-Gastaut syndrome
1. GM_2 gangliosidoses
2. GM_1 gangliosidosis
3. Infantile neuroaxonal dystrophy
4. Neuronal ceroid lipofuscinosis
5. Glucose transporter 1 deficiency
6. Late-onset multiple carboxylase deficiency
7. Disorders of folate metabolism, methylenetetrahydrofolate reductase deficiency
8. Arginase deficiency (urea cycle defect)
9. Tetrahydrobiopterin deficiency (aminoaciduria)
10. Tyrosinemia type III (case report)
West's syndrome, generalized (ILAE 2.2)
1. Phenylketonuria, hyperphenylalaninemias
2. Pyruvate dehydrogenase
3. Pyruvate carboxylase
4. Carbohydrate-deficient glycoprotein syndrome, type III
5. Organic acidurias
6. Aminoacidurias
Lennox-Gastaut syndrome (ILAE 2.2)
1. Neuronal ceroid lipofuscinosis
2. Sialidoses
Progressive myoclonic epilepsy (ILAE 2.2)
1. Lafora's disease
2. Unverricht-Lundborg disease
3. Myoclonic epilepsy with ragged red fibers and mitochondrial encephalomyopathy with lactic acidosis and stroke-like symptoms
4. Dentatorubral-pallidoluysian atrophy
5. Neuronal ceroid lipofuscinosis
6. Sialidoses
7. Gaucher's disease

ILAE, International League Against Epilepsy.

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Chapter 17

Seizures and Epilepsy

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Electroencephalography in the Diagnosis of Epilepsy
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- Specificity of Interictal Epileptiform Discharges
- Positive Predictive Value of Interictal Epileptiform Discharges
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In spite of the many remarkable advances in the variety and sensitivity of diagnostic techniques since the mid-1970s, electroencephalography (EEG) continues to play a central role in the diagnosis and management of patients with epilepsy. Epilepsy is a disorder of cortical excitability, and the interictal EEG remains the most convenient and least expensive way to demonstrate the physiological manifestations of this. Although the electrocerebral potentials indicating epileptogenic excitability have not changed, clinicians' ability to interpret these patterns has grown in tandem with the expanding understanding of the manifestations and natural history of different types of epilepsy. In the past, there was considerable controversy about the relationship between interictal epileptiform discharges and the clinical diagnosis of epilepsy. This was often viewed primarily as a problem of sensitivity and specificity, and this issue remains problematic for some authors (112,221). As it became clear that some forms of epilepsy could be identified as rela-

TABLE 17.1. *Uses of electroencephalography in diagnosis and management of epilepsy*

Diagnosis
1. Is a paroxysmal event an epileptic seizure?
2. Is seizure onset focal or generalized?
3. Are seizures a manifestation of an epilepsy syndrome?
Management
1. What is the probability of recurrence after a single, unprovoked seizure?
2. What types of antiseizure drugs are likely to be most effective in this patient?
3. Is the patient a candidate for epilepsy surgery? Can the area of seizure onset be identified?
4. Why has the patient's cognitive function deteriorated?
5. Is the patient's change in behavior caused by non-convulsive status epilepticus?
6. What is the likelihood of recurrent seizures after discontinuation of antiseizure drugs?

tively unique epilepsy syndromes, EEG findings in patients and close family members became one of the key components of syndromic diagnosis. It has also become clear that EEG is more than a diagnostic tool; it can be very helpful in management decisions that commonly face clinicians treating patients with epilepsy. Thus, even in the era of high-resolution anatomical and functional brain imaging, the information provided by routine EEG is as important as ever, if not more so.

This chapter reviews the use of EEG in addressing several basic questions regularly encountered in clinical practice: (a) Does the patient have epilepsy? (b) Are seizures focal or generalized at their onset? (c) Does the patient have a particular epilepsy syndrome (Table 17.1)? This chapter also reviews how EEG can be used to aid in management of patients with epilepsy by using a few common situations as examples.

ELECTROENCEPHALOGRAPHY IN THE DIAGNOSIS OF EPILEPSY

Epilepsy can have protean clinical manifestations, and some of these can be easily confused with those of other medical conditions. Thus, the first question the physician must address is whether the patient's symptoms represent epileptic seizures or some other disorder. Although the diagnosis of epilepsy remains a clinical judgment, EEG findings, interpreted in the context of other clinical data, are often pivotal in reaching an answer. However, it is important to recognize that different EEG findings have different degrees of association with epilepsy. This basic observation explains, in part, much of the confusion regarding the sensitivity and specificity of interictal EEG. Clinicians may encounter any of the following abnormalities when evaluating a patient with possible seizures: interictal epileptiform discharges (IEDs), focal slowing, periodic lateralized epileptiform discharges (PLEDs), generalized periodic epileptiform discharges (GPEDs), diffuse slowing, and several nonspecific paroxysmal abnormalities (e.g., frontal intermittent rhythmic delta activity) (Fig. 17.1). Among all of these, *only* IEDs and perhaps PLEDs are associated with epilepsy at rates sufficiently high to be clinically useful. The remaining patterns are much less useful in supporting the diagnosis of epilepsy, although they may provide very important information regarding the underlying conditions associated with seizures or epilepsy.

Sensitivity of Interictal Epileptiform Discharges

The sensitivity of IEDs in identifying patients with epilepsy is an important measure of their clinical utility. Sensitivity is determined by asking how often IEDs are seen in people with epilepsy. Many factors influence the appearance of IEDs, and available studies have not usually standardized or controlled for these. Duration and number of EEG studies are probably the most important variables, because IEDs are intermittent phenomena and thus more likely to be detected with more samples and longer sampling times. Other methodological difficulties further limit most studies. In some, diagnostic criteria for epilepsy are not specified or are unclear. Epilepsy is most often a history-based diagnosis, and this diagnosis may be inaccurate, even when made by experienced clinicians. The possibility that the interictal EEG findings themselves influenced the diagnosis of epilepsy is difficult to exclude in many studies, and this could obviously introduce substantial bias. Furthermore, much of the existing data come from epilepsy centers, which tend to see patients with more refractory and complex cases. Finally, different interpreters have used different criteria for visual detection of IEDs. In view of these difficulties, it is reassuring that the results among different studies are reasonably consistent.

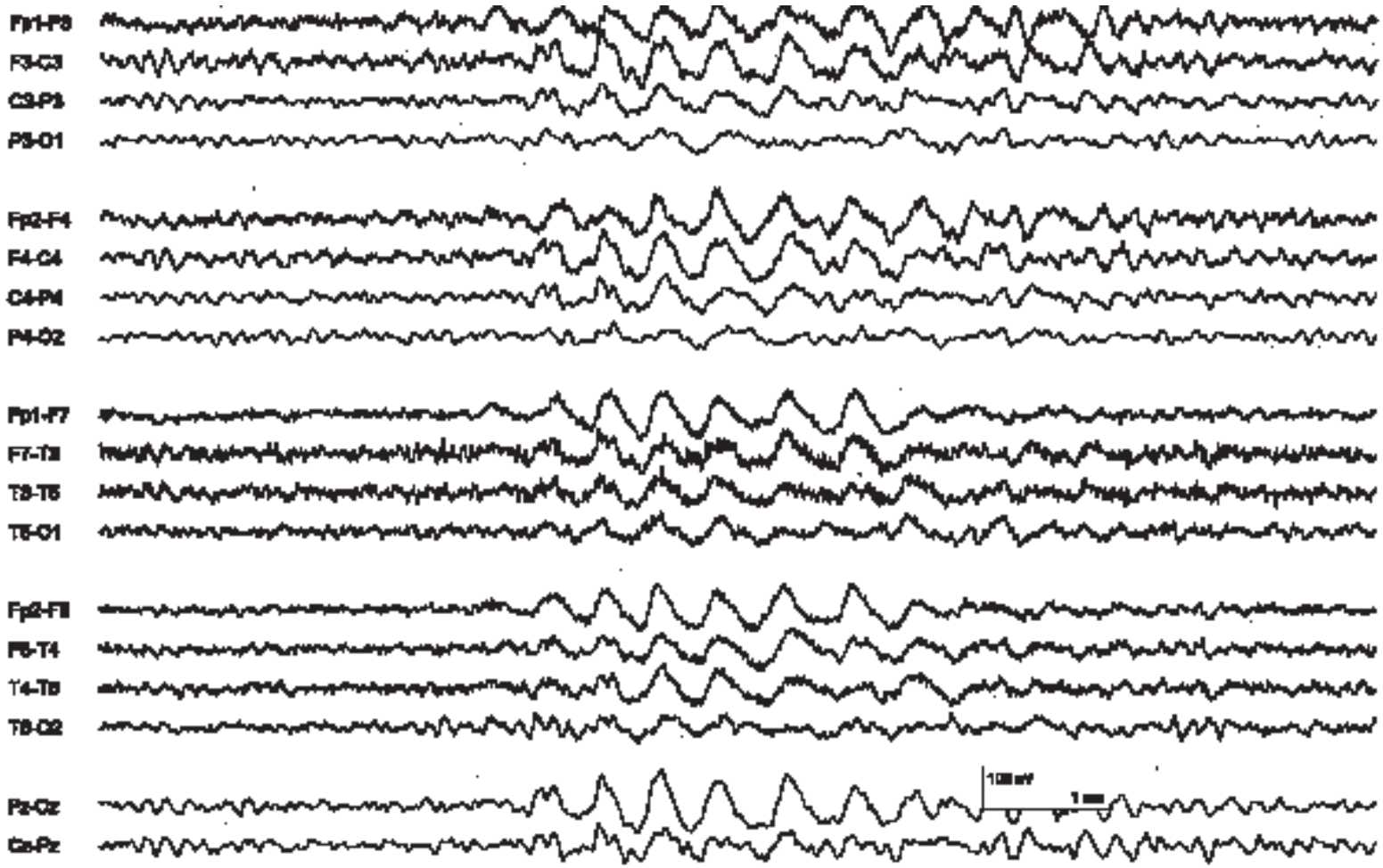


FIG. 17.1. EEG of a 46-year-old man with uremic encephalopathy. The EEG shows 2-Hz frontal intermittent rhythmic delta activity (FIRDA). TC, 0.1 second; HFF, 70 Hz.

In three large studies, mainly of adult patients evaluated at epilepsy centers, initial EEGs detected IEDs in 29% to 55% of patients (117,188,248). Repeated EEGs over varying intervals ultimately demonstrated IEDs in 80% to 90% (188,248). IEDs, if present, were detected by the fourth EEG in 90% of patients (188,248). If the first EEG contained only nonspecific abnormalities (no IEDs), subsequent EEGs were more likely to demonstrate IEDs (248). In another approach (292), adult patients undergoing video-EEG monitoring were screened continuously for IEDs with standard IED detection software. Because the analysis was confined to patients with recorded seizures, the diagnosis was not influenced by the presence of IEDs. Of patients with seizures (average recording duration, 6.9 days), 19% did not have IEDs.

Studies of patients who have experienced only one seizure or of patients for whom antiepileptic drugs were being withdrawn provide information about the prevalence of IEDs in patients with infrequent seizures. Although such studies have less selection bias, the diagnosis of epilepsy was often less secure. In addition, those studies were not designed to evaluate EEGs, and so fewer details are available. What is known is that 12% to 50% of such patients had IEDs recorded during the initial EEG (Table 17.2). Nonepileptiform abnormalities occurred in 6% to 45%, and EEGs were normal in 32% to 74% (see Table 17.2). In two studies (161,285), mainly of adult patients with single seizures, researchers examined the yield of repeated EEGs. EEGs were repeated if no IEDs were found on the first recording, and these subsequent EEGs captured IEDs in an additional 14% to 18% of such cases. This increased the total yield after two EEGs to 26% in the first study (285) and 61% in the second (161). The wide variability reported in detecting IEDs in patients with infrequent seizures may result from differences in study populations, from different criteria used for classifying or detecting IEDs, and from the many intrinsic and extrinsic factors that affect the occurrence of IEDs.

Several factors influence the likelihood of recording IEDs in patients with epilepsy. These factors were not controlled for in studies in which the sensitivity of IED was evaluated; as a result, they probably account for much of the variability in the findings. IEDs are recorded more frequently in children than in adults, and IEDs are more frequent when epilepsy begins earlier in life (188). Epilepsy syndrome diagnosis also plays a role. For example, IEDs are almost invariably present in children with untreated infantile spasms, Landau-Kleffner syndrome, and benign rolandic epilepsy. Sleep, sleep deprivation, and use of additional recording electrodes also improve detection of IEDs (see Chapter 8), and these were not used consistently in the different studies. In one study, researchers found that greater seizure frequency was associated with an increased likelihood of recording IEDs (188), but in another, researchers obtained opposite results (292). This discrepancy probably arose because the first series included many children, whereas the sec-

TABLE 17.2. *Yield of initial EEG in patients with infrequent seizures*

	Number of patients	Age	Percentage with IED	Percentage with non-IED (abnormal)	Percentage normal
Patients with first unprovoked seizure					
Hopkins et al. (136)	408	Adult	26.8%	26.8%	46.4%
FIRST Group (232)	397	Mixed	50%	6%	44%
Van Donselaar et al. (285)	157	Adult	12%	45%	43%
King et al. (161)	300	Mixed	43%	25%	32%
Shinnar et al. (258)	283	Pediatric	28%	10%	63%
Patients being withdrawn from antiseizure drugs					
Callaghan et al. (44)	92	Mixed	—	—	74%
Shinnar et al. (260)	88	Pediatric	18%	—	49%
Emerson et al. (85)	68	Pediatric	—	—	50%

IED, interictal epileptiform discharge.

ond was performed only in adults. Proximity of the EEG recording to clinical seizure activity seems also to be important, as results of other studies of patients with intractable epilepsy report that IEDs occur more frequently immediately after a seizure (118). In patients who had experienced only one seizure, IEDs were also found more often when the EEG was obtained within 24 hours of the seizure (51%) than when the EEG was obtained later (34%) (161).

In some situations, antiepileptic drugs can affect the likelihood of recording IEDs. The studies just cited did not distinguish among effects caused by the patient's state or by the antiepileptic drug regimen. Furthermore, these studies emphasized findings in patients with frequent IEDs, because effects are easier to demonstrate with a higher baseline IED rate. The effects of antiepileptic drugs on IED are briefly summarized as follows (further details are available in Chapter 15 and in other reviews [12,254]). Benzodiazepines and barbiturates consistently decrease the occurrence of IEDs after acute administration, but this effect wanes with chronic therapy. Acute barbiturate withdrawal may provoke generalized epileptiform discharges or trigger focal discharges in areas from which the habitual epileptogenic abnormality does not originate. Neither chronic phenytoin nor carbamazepine treatment seems to affect either the occurrence or distribution of IEDs in any consistent way. Valproate suppresses generalized spike-wave discharges. In one study (40,286), generalized IEDs were decreased in frequency in 76% of patients ten weeks after valproate treatment began. One year later, discharges remained less frequent in 57% of the patients. Similarly, photoparoxysmal responses were eliminated in 25% of patients ten weeks after they started taking valproate; after 1 year of treatment, photosensitivity was absent in 75% of the patients. Valproate-induced suppression of the photoparoxysmal response persists even after the drug is no longer detectable in the plasma. Although treatment with benzodiazepines, barbiturates, and valproate clearly decreases the amount of recordable IEDs, it is not usually necessary to discontinue these drugs for routine EEGs obtained for diagnostic purposes. In contrast, medication withdrawal is often necessary to facilitate recording of seizures during continuous video-EEG monitoring.

Even after all these factors are considered, EEGs of some patients with epilepsy still lack IEDs. The persistent lack of IED in a minority of patients with an unambiguous diagnosis of epilepsy continues to trouble many physicians. Several explanations can be offered. IEDs may be very infrequent and therefore are not detected even with lengthy recordings. IEDs may be present but not detectable by conventional scalp recordings and montages (1). The relatively small area of cortex involved in generating the epileptiform activity and the resistive properties of the overlying dura and scalp are partly responsible for this inability to detect IEDs. Furthermore, some areas of cortex, such as the opercular, subfrontal, interhemispheric, and medial temporal areas, are not directly accessible to scalp recording techniques. Therefore, IEDs originating in these areas may not be detected with standard scalp electrodes. Finally, some people with epilepsy apparently lack IEDs, inasmuch as IEDs are not detectable even when intracranial electrodes are used, although such patients are rare. Further study of the pathogenesis of IEDs and of epileptic patients without IEDs should help define characteristics of such patients and explain why this unusual circumstance occurs.

Specificity of Interictal Epileptiform Discharges

How specific IEDs are for epilepsy is another measure of their clinical utility. Specificity is determined by asking how often IEDs occur in normal subjects in comparison with patients with epilepsy. Studies of this issue have all reported that IEDs are rare in EEGs of persons without a history of seizures. Persons with IEDs but without epilepsy at the time of EEG recording seem to have a greater likelihood of developing epilepsy in the future. Occurrence of IEDs in nonepileptic subjects is influenced by the subject's age, the subject's general medical condition, and the circumstances of EEG recording. Only one study was community based (49); some degree of patient selection bias was present in the remainder.

Table 17.3 summarizes available data, and several trends are evident. Among healthy subjects without epilepsy, IEDs are more common in children (1.9 to 3.5%) than in adults (0.5%). Seizures are more likely to develop if IEDs are encountered in a healthy child than if they are encountered in a healthy adult (see also Thorn [277]). In hospitalized adults without neurological or psychiatric disease, the prevalence of IEDs is similar to that found in healthy people (20). As might be expected, the prevalence of IEDs is higher in hospitalized patients with neurological illness but without epilepsy than in adults hospitalized with other conditions (313), probably because the neurologically ill patients included those with cerebral neoplasms, stroke, and craniotomies. Similarly, IED prevalence among psychiatric outpatients is higher than among other hospitalized adults (38), perhaps because anorexia and barbiturate withdrawal are more common in this population.

The types of IEDs seen in nonepileptic subjects differ from those seen in large series of patients with epilepsy. Central-midtemporal discharges, gen-

TABLE 17.3. *Prevalence of interictal epileptiform discharge in subjects without epilepsy*

	Number	Age	General condition	Number with IEDs	Number with IEDs developing seizures
Eeg-Olofson et al. (80)	743	1–15	Highly screened	14 (1.9%)	Not reported
Cavazzuti et al. (49)	3,716	6–13	Screened community-based	131 (3.5%)	7/131 (5.3%)
Bennet (20)	424	Adult	Healthy flight personnel	2 (0.5%)	0/1 (0%)
Gregory et al. (122)	13,658	17–25	Healthy flight personnel	69 (0.51%)	1/38 (2.6%)
Bennet (20)	908	Adult	Hospitalized patients, no neurological illness	6 (0.6%)	0/1 (0%)
Zivin et al. (313)	6,497	1–74	Hospitalized patients, including neurological illness	142 (2.2%)	20/142 (14.1%)
Bridgers (38)	3,143	11–85	Psychiatric inpatients	81 (2.6%)	Not reported

IED, interictal epileptiform discharge.

eralized spike-wave discharges, and photoparoxysmal responses account for the great majority of IEDs, especially in children (20,49,80,122). In contrast, focal (especially temporal) or multifocal IEDs predominate in series of patients with epilepsy (142,158,188). The three types of IEDs observed most often in nonepileptic subjects probably have a lower association with epilepsy than do other types of IEDs. Both central-midtemporal IEDs (132) and generalized IEDs (194) can be seen as asymptomatic manifestations of genetic traits, and so their presence may merely be indicative of epilepsy in siblings or other family members. In an EEG laboratory population, only 40% of children whose EEGs contained central-midtemporal spikes had epileptic seizures (158). Patients who have only photoparoxysmal responses develop seizures infrequently (122,257,266).

Sharp transients are frequent in normal newborns. They occur during all states in the preterm neonate, are present mainly during quiet sleep at term, and gradually disappear over the first 6 to 8 weeks of life. Sharp waves are abnormal in full-term newborns if they are numerous, repetitive, persistently focal, or of positive polarity. Only one study has compared features of sharp waves in normal newborns with those occurring in neonates with epilepsy (57). Epileptiform transients were more abundant, more often spikes, more repetitive, and more persistently focal in newborns with epilepsy (57). It is unlikely, however, that these features alone are sufficient to distinguish between neonates with seizures and those with cerebral abnormalities but no seizures. (For more complete discussion, see Chapter 6).

In infants and older children, the association of IEDs with epilepsy seems to vary with location, distribution, and morphological appearance of the IEDs. Multifocal IEDs and IEDs occurring over the midline, frontal, and anterior temporal regions are highly correlated with clinical seizures: 75% to 95% of patients with these IEDs have epilepsy (82,158). In contrast, only about 40% of patients with central-midtemporal spikes and 50% with occipital spikes had seizures in one study (158). Blindness occurring in infancy may be associated with occipital spikes and, in the study of Smith and Kellaway (263), accounted for 15% of occipital IEDs. Finally, IEDs that occur in both normal (49) and ill (158,176) children tend to disappear over time, but this is less common in adults (142).

Such observations lead to the conclusion that interictal sharp transients, even those of frankly epileptiform configuration, largely reflect unique responses of the immature brain. They can occur as normal findings, especially in preterm infants, or as an indication of cerebral dysfunction that may or may not be associated with seizures. The occurrence and epileptogenic significance of such discharges change with brain maturation. As a result, sharp transients and IEDs are associated with epilepsy less frequently in children. The age at which the degree of association between IEDs and epilepsy reaches that found in adults is unclear. In infants and children, even more so than in adults, it is essential to consider critically the clinical context for which the EEG recording was obtained before concluding that the presence of IEDs supports a diagnosis of epilepsy.

The association between IEDs and epilepsy is much stronger in adults. However, IEDs without a history of clinical seizures may also be found under certain circumstances. EEGs recorded during periods of metabolic disarray may occasionally reveal IEDs. Triphasic waves, seen in various metabolic encephalopathies, can sometimes be difficult to distinguish from generalized epileptiform activity. Focal spikes, multifocal spikes, and diffuse spikes or sharp waves can occur with the dialysis dementia syndrome, uremic encephalopathy, and hypocalcemia (55,205,284). How-

ever, seizures are not regularly observed in the majority of patients with these conditions. IEDs can be recorded in nonepileptic patients treated with chlorpromazine, lithium, or clozapine, especially at high doses (133,144). Some, but by no means all, of such patients develop seizures. IEDs disappear when drug dosages are decreased. EEGs obtained in nonepileptic patients during withdrawal of short-acting barbiturates sometimes demonstrate generalized IEDs or prolonged photoparoxysmal responses (300,309). This is less common with longer acting barbiturates (309). Meperidine, especially when used for a long time, can unmask epileptiform discharges, probably because of an excitatory metabolite interacting with a receptive brain substrate (157; personal observation). Finally, IEDs without a history of clinical seizures are occasionally seen in patients with cerebral mass lesions who do not have a history of seizures. These IEDs are most likely to be seen with cerebral abscesses and slow-growing neoplasms such as astrocytomas and oligodendrogliomas. IEDs in these situations presumably indicate a higher risk of seizures, but studies demonstrating this are not available.

Positive Predictive Value of Interictal Epileptiform Discharges

Although general considerations of sensitivity and specificity are important and useful, clinicians are usually most often interested in knowing the likelihood that an individual patient with IEDs has epilepsy. This probability is termed the *positive predictive value* (PPV) of IEDs. The PPV of IEDs for epilepsy is the ratio of the number of subjects with epilepsy who have IEDs to the number of all subjects (those with epilepsy and those without epilepsy) with IEDs. The PPV is dependent on the sensitivity and specificity of the EEG. However, the prevalence of epilepsy in the population under study may be an even more important determinant of the PPV (116). The following examples illustrate how the PPV varies in accordance with the likelihood of encountering epilepsy in the population being studied. Assume that the prevalence of IEDs in the first EEG of a subject with epilepsy is 55%, and that the prevalence of IEDs in the first EEG of a subject without epilepsy is 4% under similar conditions. When studying a random sample of unselected patients drawn from a defined geographic area, assume an epilepsy prevalence rate of 0.5%. Such a sample of 1,000 patients would therefore be expected to include five persons with epilepsy, three of whom would have IED, and 40 people without epilepsy but whose EEGs show IEDs. In this particular situation, the PPV of IEDs for epilepsy would be only 3/43, or 7%. As a second example, consider a group commonly used for EEG studies: the referral population of a clinical EEG laboratory. In this setting, the likelihood of encountering epilepsy is much higher because of selection. Assume that 50% of patients referred to a hospital's EEG laboratory have epilepsy. Among 1,000 patients with EEGs recorded in this laboratory, 500 would have epilepsy, and 275 of these would have IEDs. Of the 500 patients who would not have epilepsy, 20 would have IEDs. In this setting, the PPV for IED would be very high: 275/295, or 93%.

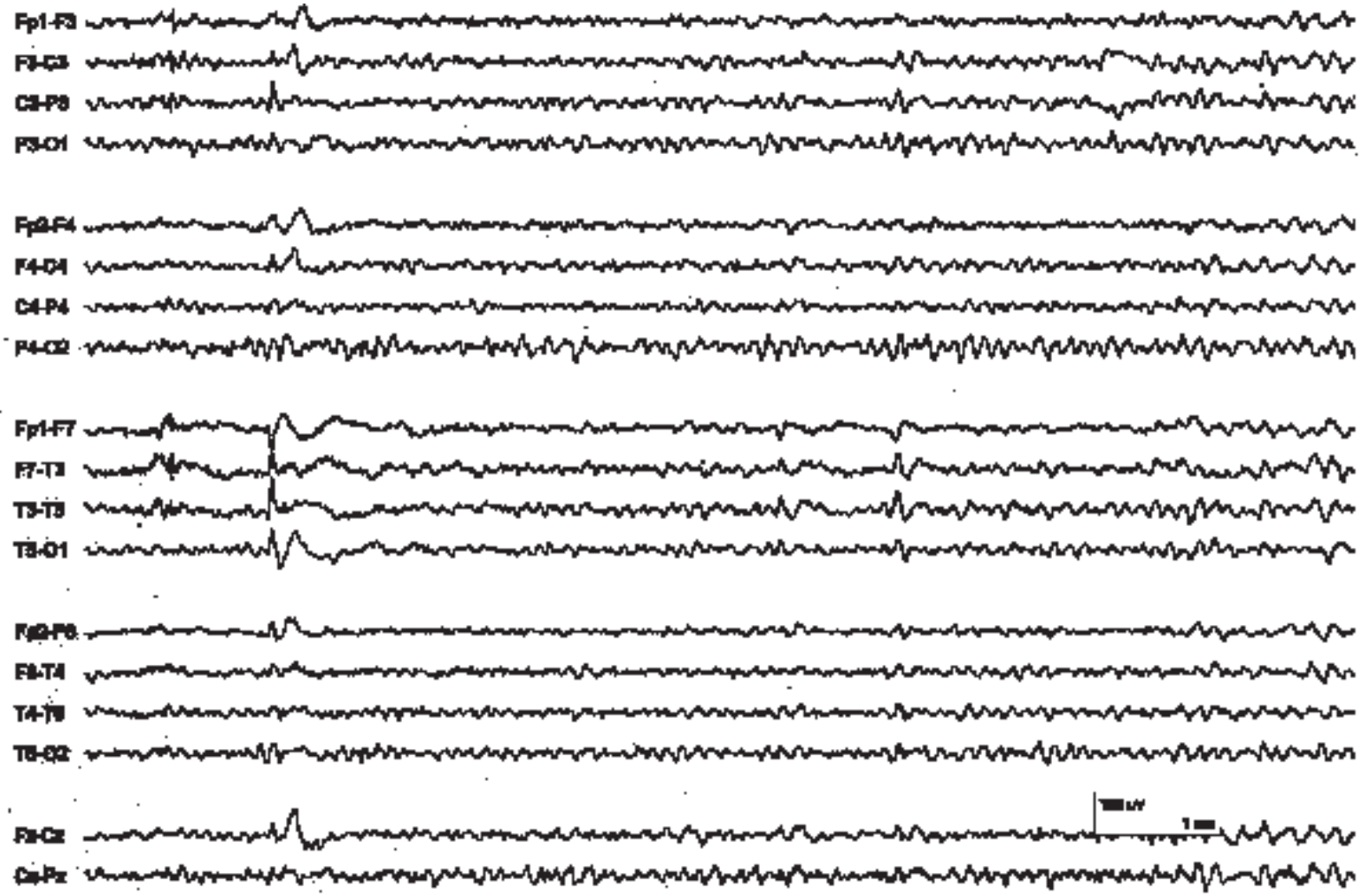
The PPV can be calculated more generally in terms of the prevalence of epilepsy in a population, the prevalence of IEDs in the epilepsy patients, and the prevalence of IED in the nonepileptic population, as follows:

$$PPV = \frac{(E)\ (IED_E)}{(E)\ (IED_E) + (1-E)\ (IED_{NE})}$$

where E is the prevalence of epilepsy in a population, IED_E is the prevalence of IEDs in epilepsy patients, and IED_{NE} is the prevalence of IEDs in the nonepileptic subjects (116). This equation allows determination of the PPV of the IEDs for epilepsy on the basis of conditions encountered in different populations.

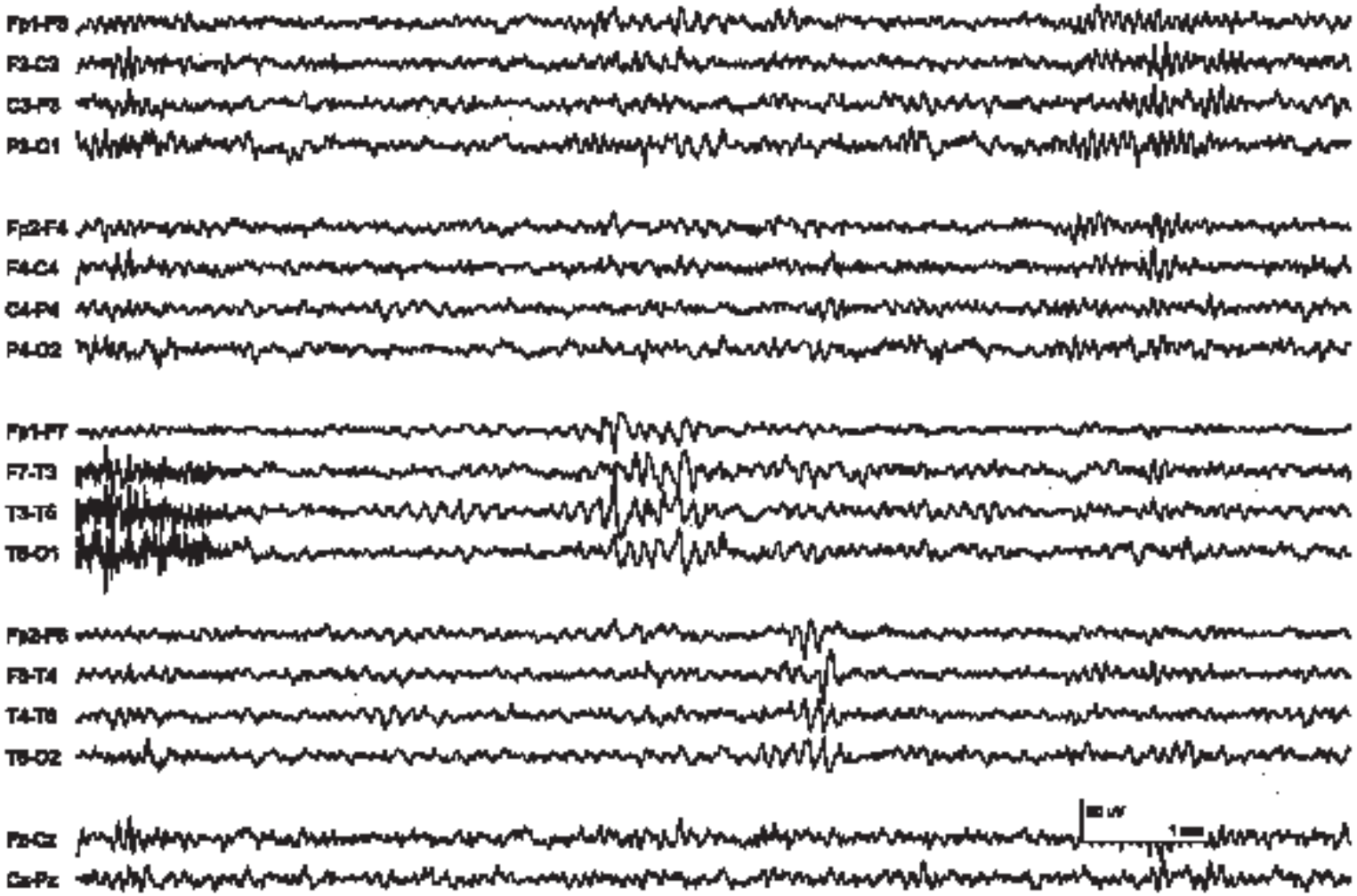
Interictal Epileptiform Discharges

IEDs (Fig. 17.2) are difficult to describe with meaningful accuracy. To be designated IEDs, discharges should meet at least the following criteria (50,224): (a) They must be paroxysmal; that is, they must be clearly set apart from ongoing background activity and not simply a sharply contoured component of a sequence of waves. (b) They must include an abrupt change in polarity occurring over several milliseconds; this results in the sharp contour or "spikiness" of IED. (c) The duration of each transient should be less than 200 milliseconds. The Committee on Terminology distinguishes between "spikes," which have a duration of less than 70 milliseconds, and "sharp waves," whose duration is between 70 and 200 milliseconds. However, the clinical utility of this distinction has not been demonstrated. Whether an epileptiform discharge has the morphological appearance of a "spike" or "sharp wave" depends on many factors, including the synchrony of the epileptic neuronal aggregate, the proximity of the epileptogenic cortical area to the recording electrodes, and extent of spread of the IED within complex polysynaptic pathways before it is detected at the scalp. (d) The discharge must have a physiological field. This generally means that the discharges are recorded from more than one



A

FIG. 17.2. A: EEG of a 22-year-old man with complex partial seizures. The EEG shows mild intermittent left temporal theta activity and anterior temporal epileptiform discharges, which phase reversal at F7. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.2. *Continued.* **B:** EEG of a 27-year-old man with no neurological abnormalities. The EEG shows "wicket spikes," a normal variant. Although the waveform is sharply configured, this is not an epileptogenic pattern. (See Chapter 7.) TC, 0.1 second; HFF, 70 Hz.

electrode and typically have a voltage gradient across a region of the scalp. This criterion is particularly useful in distinguishing IEDs from electrode or other artifacts. On occasion, IEDs have very restricted fields, as, for example, in neonates or in children with benign rolandic epilepsy. Additional electrodes can help distinguish IEDs from noncerebral potentials in these situations. In addition to these necessary criteria, the great majority of IEDs are of negative polarity at the scalp, and the majority of IEDs are followed by a slow wave in the range of 2 to 4 Hz. These two features, although not inevitable, are present with sufficient frequency that they are extremely helpful in distinguishing IEDs from other types of paroxysmal activity. Furthermore, they relate closely to the underlying physiological epileptogenic phenomena occurring at the cellular level (see Chapter 1). Within the limitations noted further on, IEDs defined in this manner are highly correlated with epilepsy and are rare in samples of the normal population.

Periodic Lateralized Epileptiform Discharges and Other Periodic Epileptiform Discharges

PLEDs occur most often with acute, usually relatively large, destructive lesions caused by hemorrhagic cerebral infarction or a rapidly growing cerebral malignancy (52,187). The EEG abnormality consists of persistent sharp waves that occur with a nearly regular repetition rate of 0.5 to 2 Hz (Fig. 17.3). PLEDS typically involve a large area of one hemisphere and frequently reflect to homologous regions of the opposite side. They are not sharply focal; hence, the adjective *lateralized.* PLEDs are a transient phenomenon, rarely persisting for more than a few weeks (256), but they are strongly correlated with acute drug-resistant focal seizures during this time. In patients with PLEDs, acute symptomatic seizures occur in about 70% of cases (265). About 20% of patients with PLEDs have preexisting epilepsy (265). Of those without a history of epilepsy, 3% to 66% develop epilepsy after recovering from the acute cerebral injury (255,293,312). In children, PLEDs are more often seen in the setting of seizures and various chronic diffuse encephalopathies (223). De La Paz and Brenner (65) described bilateral independent PLEDs (BiPLEDs). These occur most often with acute infections of the nervous system (especially herpes simplex encephalitis), anoxic encephalopathy, and severe chronic epilepsy. Seizures occur in 55% of affected patients, but 22% have preexisting epilepsy (65). Because the mortality rate is high among patients with BiPLEDs, there is no information on how often epilepsy develops in survivors. Generalized rather than focal seizures predominate in this group. GPEDs are sometimes recorded in patients with severe bilateral brain damage, especially when caused by anoxia, Creutzfeldt-Jakob disease, and refractory status epilepticus. To what extent GPEDs are correlated with the seizures that are common to these conditions is not known. Additional information about periodic epileptiform discharges can be found in Chapters 11 and 14.

Nonepileptiform Electroencephalographic Findings in Epilepsy

Focal slow-wave activity and generalized slowing of background rhythms are common findings in patients with partial seizures and symptomatic epilepsies. However, such findings are also frequent in patients with other neurological disorders, especially focal structural lesions, regardless of whether there are associated seizures. Thus, their specificity and positive predictive value for epilepsy are relatively low. For example, a structural lesion is present in two-thirds of adults with continuous focal polymorphic delta activity, but seizures occur in only about 20% (110). Of patients with continuous focal polymorphic delta activity and no evidence of a structural lesion, seizures occur in more than 50% (110,189). Focal structural lesions are found in only half of children with focal polymorphic delta activity, and only 23% of those without structural abnormalities have epilepsy (192). Transient focal slowing is common after partial and secondarily generalized seizures (156,291), but it is also a frequent interictal finding that localizes to the epileptogenic brain area. Focal interictal slow activity can reflect inhibition evoked by undetected epileptiform discharges occurring deep in the brain (1,63,99) or pathological changes—such as neuronal loss and gliosis, abnormalities of dendrites, axonal sprouting, and changes in neurotransmitters—that are common in chronic epileptogenic foci (for review, see Farrell and Vinters [90]).

A particular form of focal slowing that is more specific and predictive of temporal lobe epilepsy is temporal intermittent *rhythmic* delta activity (TIRDA) (Fig. 17.4). TIRDA is distinct from the more common *polymorphic* delta activity, in which frequencies and amplitudes are more variable. TIRDA is found in only 0.3% of all recordings obtained in a general EEG laboratory (206) but in as many as 28% of patients being evaluated for temporal lobe resection (107). TIRDA is often associated with temporal IEDs, and it has a high PPV for temporal lobe epilepsy (107,206,241).

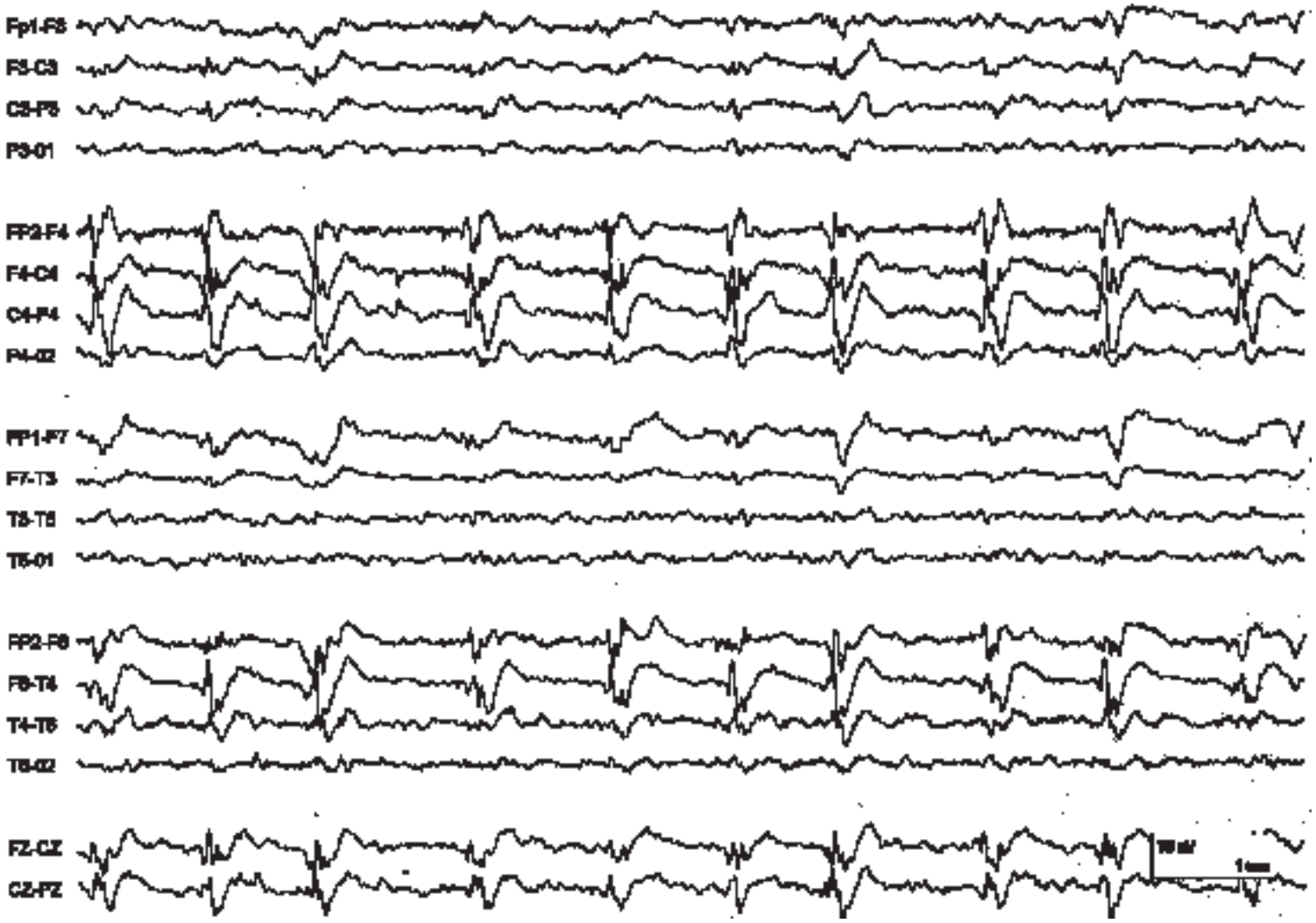


FIG. 17.3. Periodic lateralized epileptiform discharges (PLEDs). EEG of a 78-year-old woman with generalized convulsive seizures after acute infarction of the right middle cerebral artery territory. There are broadly distributed right hemisphere spikes and sharp waves, occurring repetitively at about 1 Hz (PLEDs). TC, 0.1 second; HFF, 70 Hz.

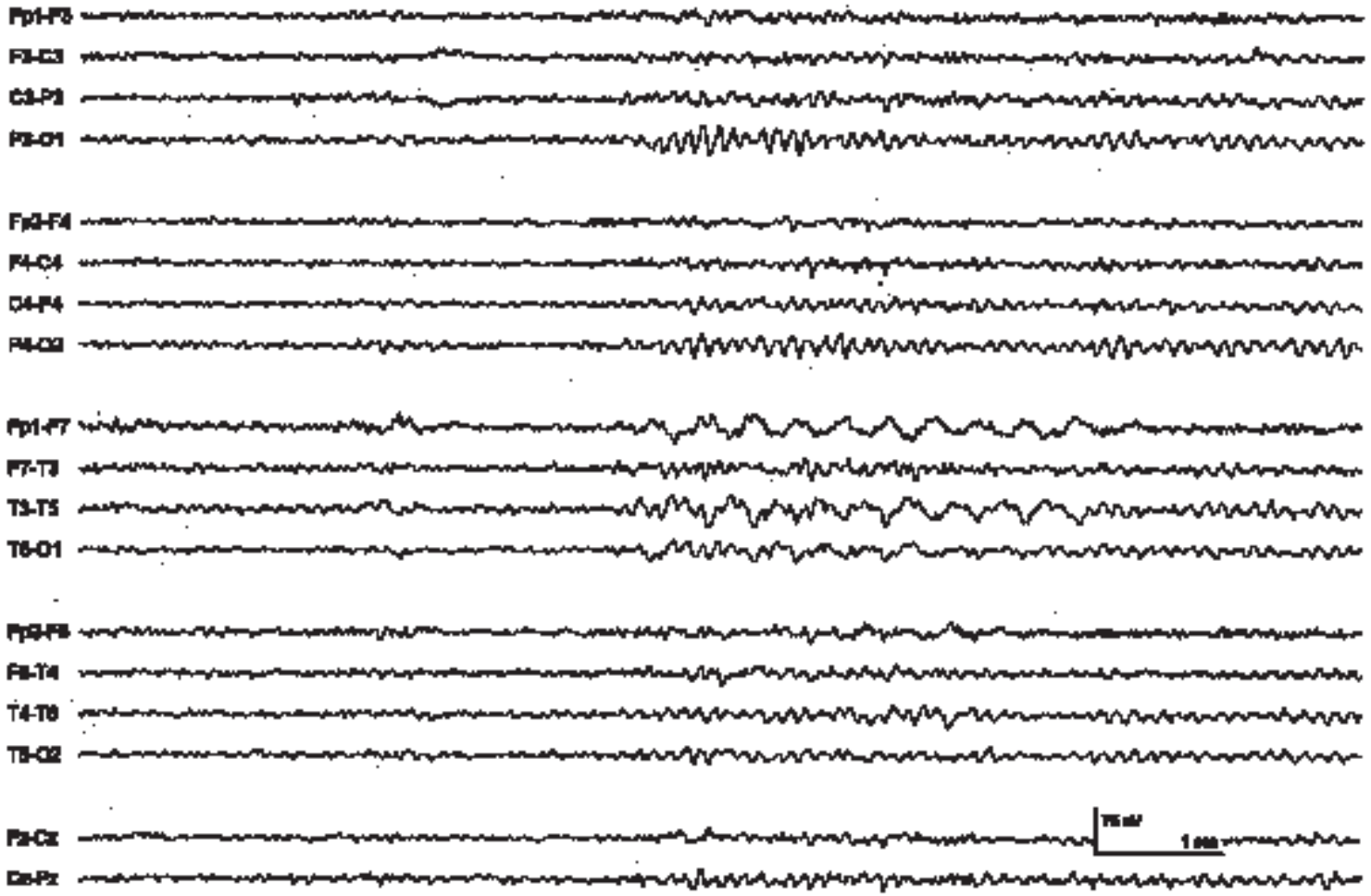


FIG. 17.4. EEG of a 75-year-old man with complex partial seizures. Previous EEGs had shown left temporal spikes. This EEG demonstrates 2.5-Hz left temporal intermittent rhythmic delta activity (TIRDA). TC, 0.1 second; HFF, 70 Hz.

EPILEPSY SYNDROMES

Identifying the type of epilepsy or "epilepsy syndrome" is important for optimal management and for advising patients and families about prognosis. After the medical history, EEG findings provide the most important information necessary for syndromic diagnosis. The Classification of Epilepsy Syndromes (228) includes more than 24 entities, some of which have engendered controversy. More detailed descriptions (245) have entailed the use of specific features of EEG abnormalities to define syndromes. Because EEG findings are an integral part of syndrome classification, critical analysis of sensitivity, specificity, and predictive value of different EEG features is not possible. Nonetheless, EEG remains very useful in prompting consideration of a particular type of epilepsy and in distinguishing among several possible syndromes in complicated or confusing clinical situations.

Characteristics of the Major Categories of Epilepsy Syndromes

The Classification of Epilepsy Syndromes is based on two distinctions: first, between localization-related and generalized epilepsies and, second, between idiopathic and symptomatic epilepsies. EEG findings assist in making these distinctions. Focal IEDs are seen in localization-related epilepsies, whereas generalized IEDs indicate one of the generalized epilepsies. In the localization-related epilepsies, the location of IEDs usually corresponds approximately to the area of seizure onset, but there are exceptions (described later). Normal or near-normal background activity is most characteristic of idiopathic epilepsy syndromes; focal, multifocal, or diffuse abnormalities of background activity are most suggestive of the symptomatic epilepsies. Persistent focal voltage attenuation, especially of faster frequencies, or polymorphic delta activity is correlated strongly with a structural lesion as the cause of symptomatic epilepsy. These general guidelines help focus initial clinical impressions and prompt a search for the more specific EEG findings associated with the particular epilepsy syndromes.

Specific Epilepsy Syndromes

Childhood and Juvenile Absence Epilepsy

Clinical Features

The International Classification of Epilepsy Syndromes distinguishes between childhood and juvenile onset forms of absence epilepsy. Childhood absence epilepsy (CAE) manifests between the ages of 3 and 12 years. Absence seizures are frequent, often occurring in clusters, a phenomenon known as *pyknolepsy*. In contrast, generalized tonic-clonic seizures are infrequent, and remission by late adolescence is the rule (179). Juvenile absence epilepsy (JAE) manifests at the ages of 10 to 12 years (or later). Absence seizures are less frequent, and generalized tonic-clonic seizures more frequent, than in CAE. Remission is less likely to occur, and seizures often persist into adulthood (307). Such distinctions, although generally applicable to large numbers of patients, are not always clear in individual patients. In addition, the clinical features of JAE overlap with those of two other syndromes: tonic clonic seizures upon awakening and juvenile myoclonic epilepsy. EEG features of CAE and JAE are also broadly similar. Minor differences, however, can sometimes be diagnostically useful.

Electroencephalographic Findings

The classic EEG finding in CAE is the 3-Hz spike-and-slow-wave discharge (Fig. 17.5). Historically, this pattern has been described as consisting of a bisynchronous and symmetrical surface-negative spike that is of maximal voltage in the frontal-central regions. The spike is followed by a surface-negative slow wave. However, careful visual and computerized analyses demonstrate a more complex situation. Depending on electrode location, the duration of the spike-wave paroxysm, and whether a bipolar or referential montage is used, up to three spikes of varying polarity are recorded before the negative slow wave (243,297). The less obvious spike components are of lower voltage and best visualized laterally with the use of referential montages. Consequently, a longitudinal bipolar montage that emphasizes parasagittal regions leaves the impression of a single negative spike and wave. Inspection of the complex through oscillographic or other high-resolution displays reveal that the 3-Hz spike-wave discharge is not truly bisynchronous; rather, spike onset in one hemisphere randomly precedes that of the other by a few milliseconds (243). (Distinguishing primary generalized epileptiform activity from secondary bilateral synchrony is discussed further on p. 570.) Finally, a prolonged surface-negative change in the direct current (DC) potential begins at the onset of each burst and reaches maximal voltage in about 1.5 seconds (53). These observations suggest multiple discrete, albeit linked, sites of cortical onset. Such findings must be accounted for by any theory seeking to explain the origin of the 3-Hz spike-wave discharge. Studies in which magnetoencephalographic imaging and functional magnetic resonance imaging were used have

confirmed that several cortical areas are activated during 3-Hz spike-wave bursts (244,294).

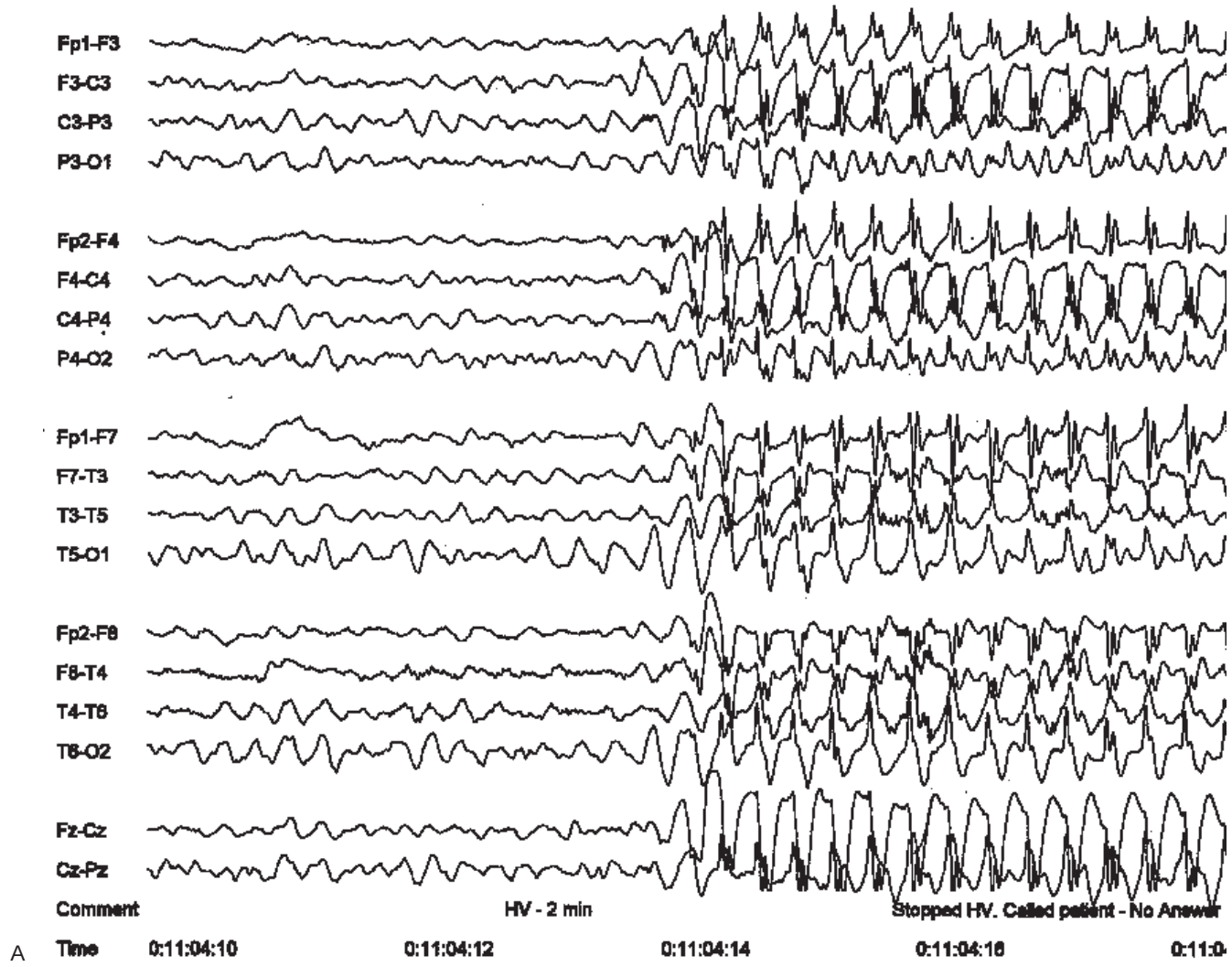
Spike-wave frequency varies during the discharge, averaging 3.4 to 4.5 Hz at onset and gradually slowing to an average of 2.5 to 2.8 Hz by the end of the paroxysm (64,218). Eye opening and alerting may terminate the bursts (127). Non–rapid-eye-movement (NREM) sleep increases the number of spike-wave bursts but typically changes their morphological appearance, often dramatically (Fig. 17.6). During sleep, spike-wave discharges are of briefer duration and become fragmented and irregular (250). The repetition rate is usually slower than in the waking state, and polyspike components are common (250). During rapid-eye-movement (REM) sleep, the frequency and morphological appearance of the spike-wave complexes are similar to those of wakefulness, but the duration and number of bursts are somewhat less (246,250). Hyperventilation increases 3-Hz spike-wave bursts in 50% to 80% of patients with CAE, especially if occipital intermittent rhythmic delta activity (OIRDA) is present (64,251). Photic stimulation increases spike-wave bursts in about 18% of cases (307). Valproic acid and ethosuximide typically decrease the number of spike-wave bursts; these bursts cease completely in one-third to one-half of patients treated with either drug (40,252). Both medications also eliminate or greatly attenuate activation by photic stimulation (129).

The distinction between an interictal burst of generalized spike-wave activity and an absence seizure has important clinical implications, but it remains confusing to many. Several studies reported that clinically overt absence seizures averaged 12 seconds in duration (64,179,218) and rarely exceeded 40 seconds and that the spike-wave frequency slowed as the ictal discharge progressed. However, the practical questions are (a) how often cognitive impairment occurs during spike-wave bursts not associated with an obvious absence seizure and (b) whether impairment is related to the duration of the burst of spike-wave activity. Several investigators have carefully analyzed auditory reaction times and demonstrated that about 50% of responses were delayed at the onset of a generalized spike-wave burst. In 80% of responses, the delay occurred within 2 seconds of onset. The degree of responsiveness improved during the remainder of the spike-wave burst, but no more than half of response times were normal at any point. Responsiveness returned abruptly to normal when the burst ended (39,227). A particularly important finding was that responsiveness was equally likely to be impaired in shorter (<3-second) and longer (>3-second) spike-wave paroxysms (39). These data indicate that spike-wave bursts can impair responsiveness regardless of their duration, depending on the sensitivity of the test used. The therapeutic implication of such findings is that treatment should aim at controlling all spike-wave bursts as much as possible. Duration of bursts also remains important, because longer bursts imply longer periods of altered responsiveness, and duration of impairment is often clinically important. Because valproic acid and ethosuximide decrease the number and duration of generalized spike-wave activity, longer EEG recordings can be used to gauge the efficacy of treatment.

Interictal background activity is usually normal in both CAE and JAE, although minor degrees of slowing have been reported in heterogeneous groups of children (135,251). High-voltage OIRDA is a frequent interictal finding, occurring in 15% to 38% of all patients with absence epilepsy (64,135) (Fig. 17.7). However, the occurrence of OIRDA is strongly age-related: it is found in more than 70% of children between 6 and 10 years of age, and it is rare in persons older than 15 years (64). It is also rare in children with atypical absence seizures (135). Thus, OIRDA is more strongly associated with CAE than with JAE. OIRDA is predictive of activation of generalized spike-wave activity by hyperventilation. OIRDA is distinguished from posterior slow waves of youth by its high-voltage, prominent rhythmicity, persistence, and disruption of the alpha rhythm. However, both OIRDA and posterior slow waves of youth attenuate with eye opening and increase with hyperventilation (59,64).

Ictal EEG recordings during generalized tonic-clonic seizures have shown that the first visually detectable change is usually the appearance of generalized low-voltage beta activity that decreases in frequency (often to 10 Hz or so) as it assumes an increasingly "spiky" configuration and increases in voltage. This electrographic pattern is typically associated with the tonic portion of the seizure. Slower frequencies then appear, developing into repetitive complexes of polyspike and wave activity, which are associated with the clonic portion of the seizure. Immediately after the seizure, EEG voltage is markedly and symmetrically attenuated, but low-voltage polymorphic slow frequencies gradually appear, followed by higher voltage faster and more rhythmic activity as the patient recovers. Normal background activity may not be observed for 30 minutes to 24 hours.

As already noted, EEG findings in CAE and JAE are similar. Background activity is usually normal in both types. OIRDA is uncommon in JAE. The repetition rate of generalized spike-wave bursts is faster at onset in JAE than in CAE, and polyspikes are seen more often in JAE (218). Hyperventilation activates spike-wave activity with equal frequency in CAE and JAE, but photic stimulation is less activating in JAE than in CAE (308).


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
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A

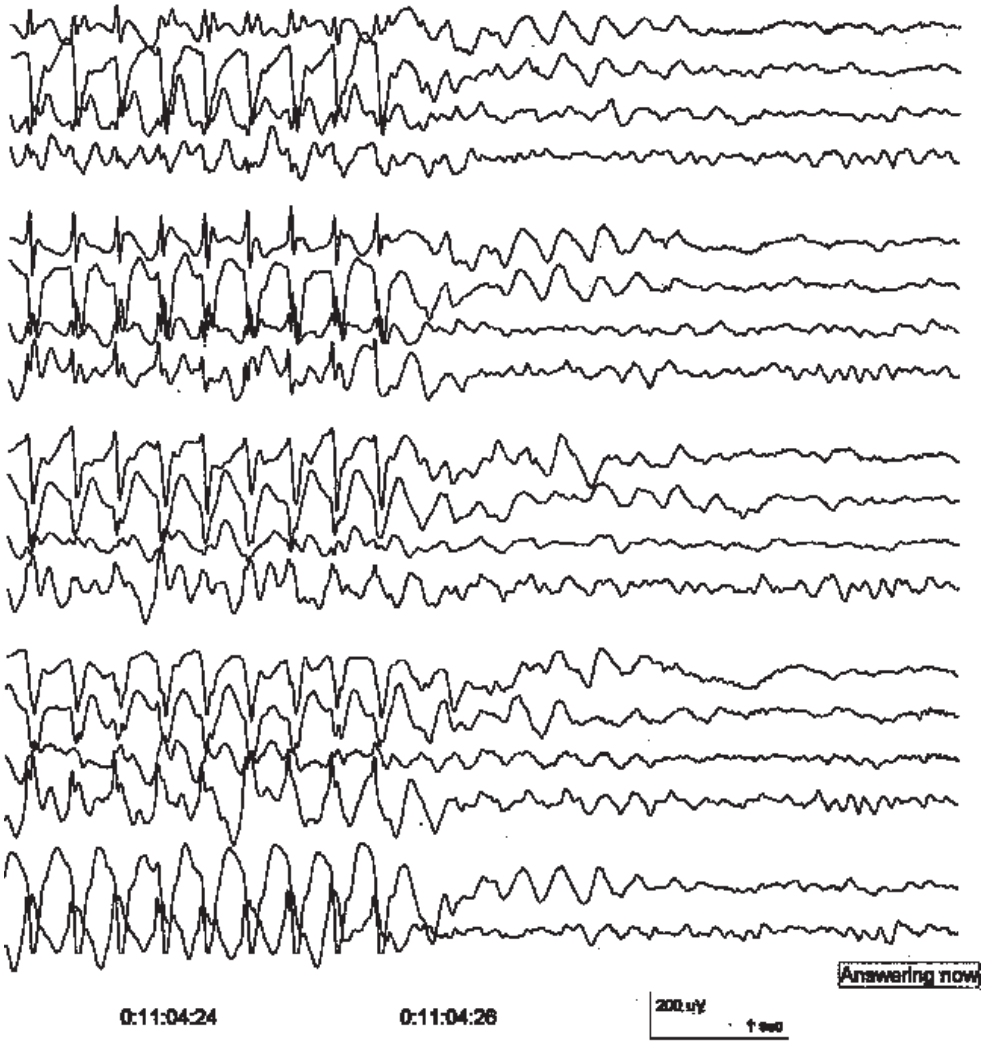
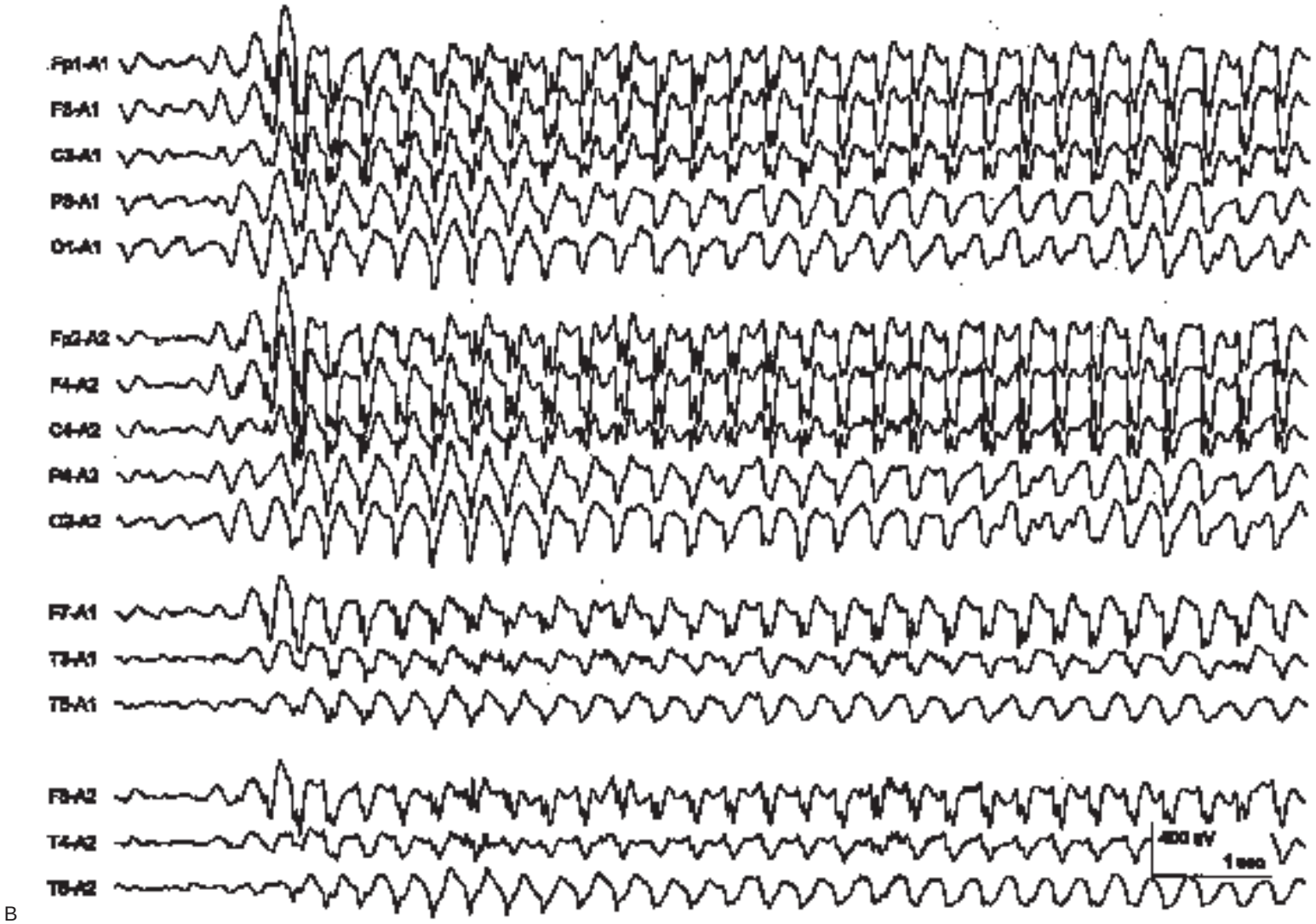


FIG. 17.5. EEG of a 6-year-old girl with absence seizures. After 2 minutes of hyperventilation, she had a typical absence seizure. The EEG shows the abrupt onset of bilateral synchronous 3-Hz spike-wave discharges lasting 12 seconds (note 5-second break in EEG recording). She began responding normally as soon as the discharge ended. **A:** Longitudinal bipolar montage. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.5. *Continued.* **B:** Ipsilateral ear referential montage. See text for further details. TC, 0.1 second. HFF, 70 Hz.

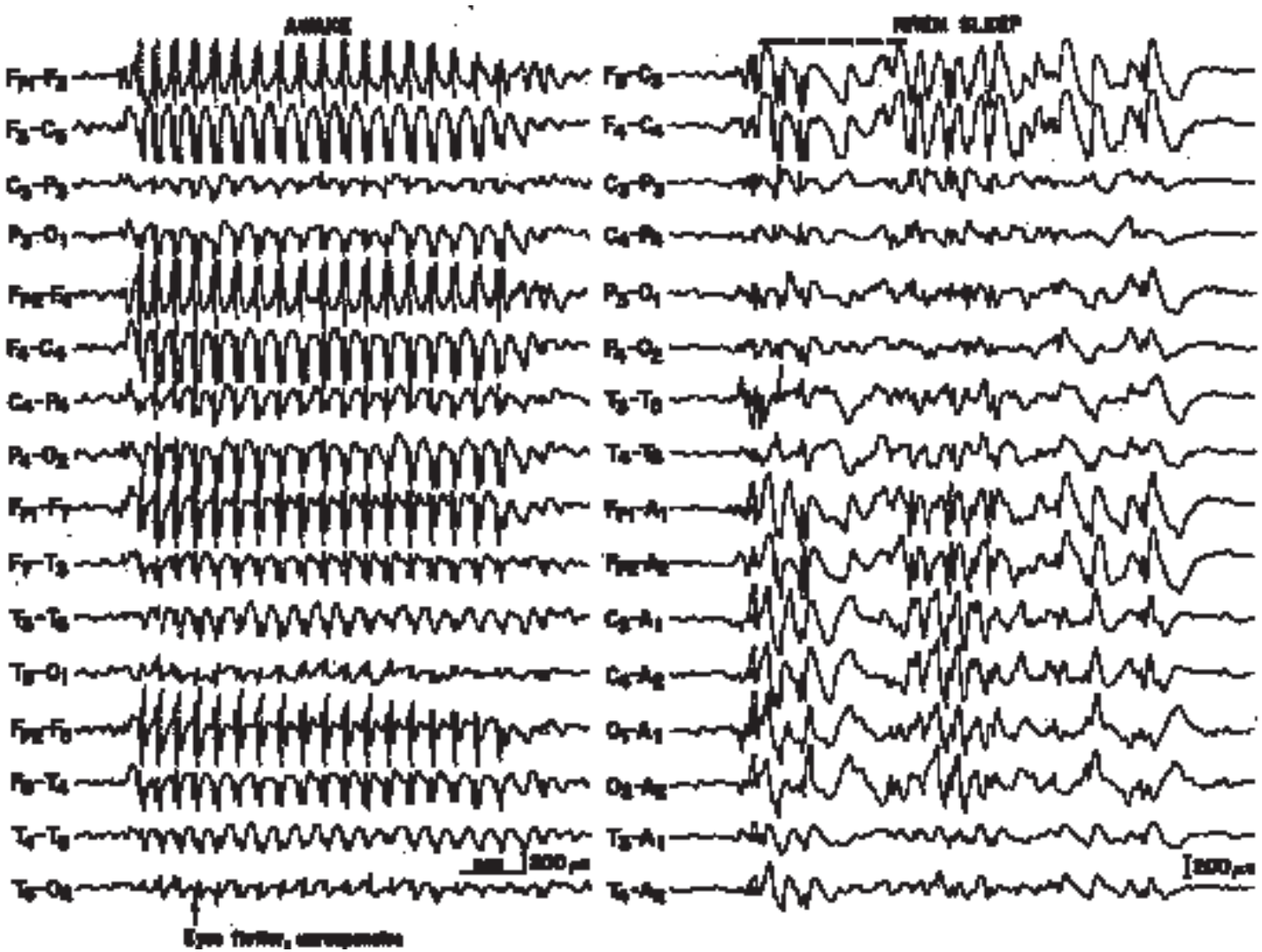
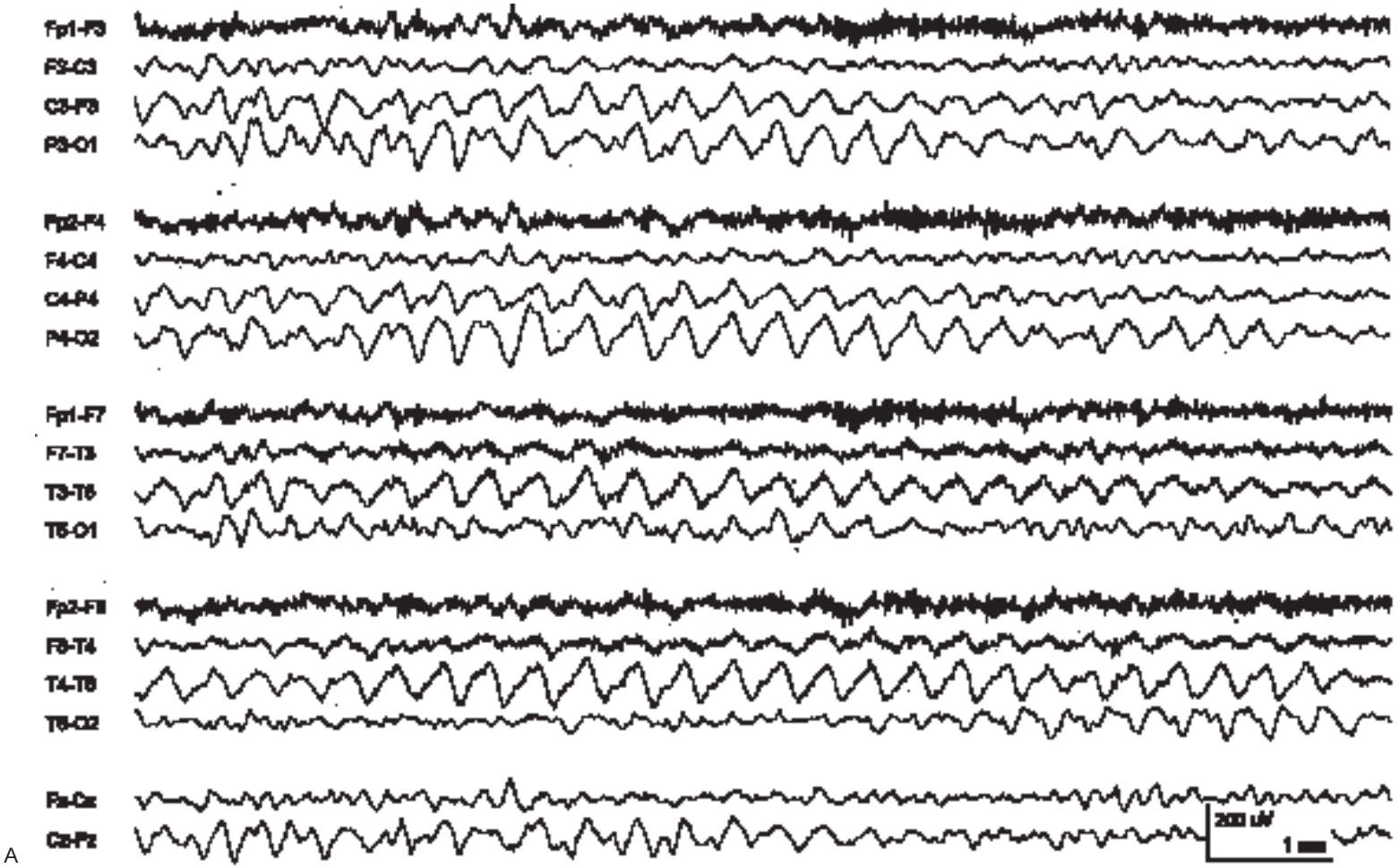


FIG. 17.6 Three-hertz (3Hz) spike-wave complexes in a 7-year-old girl with typical absence seizures. **Left:** While awake, the child had a spontaneous absence seizure. Her eyes fluttered, she did not respond to a test phrase, and she was unaware that she had had a seizure. **Right:** Generalized spike-wave discharges during NREM sleep. Note change in spike-wave morphological appearance during sleep (see text for discussion).



A

FIG. 17.7 EEG of a 9-year-old girl with childhood absence epilepsy. **A:** The EEG shows runs of 3-Hz bilateral synchronous occipital intermittent rhythmic delta activity (OIRDA). TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*

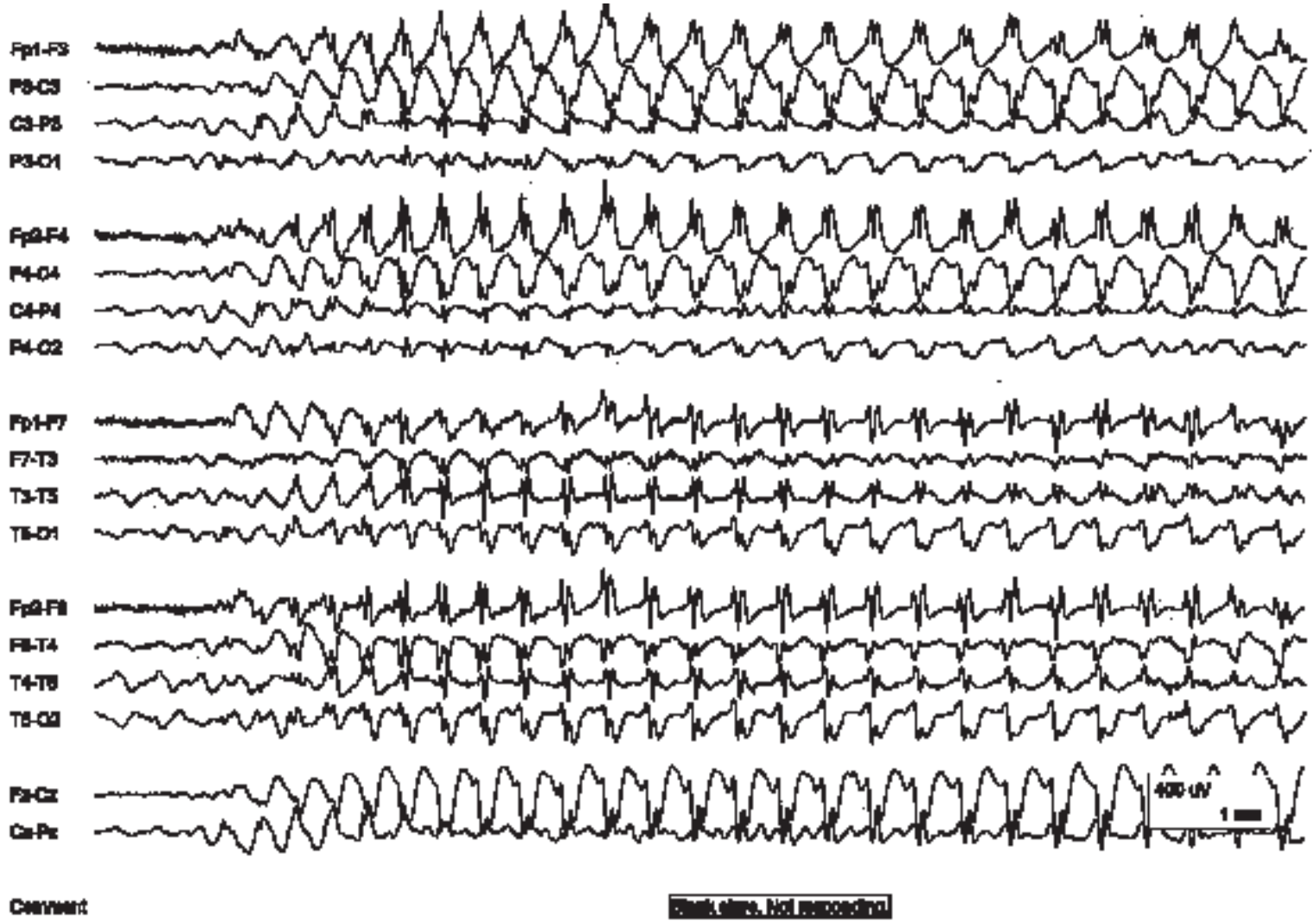


FIG. 17.7. *Continued.* **B:** Later in the same EEG recording, the patient had a typical absence seizure associated with generalized 3-Hz spike-wave activity. TC, 0.1 second; HFF, 70 Hz.

Benign Epilepsy of Childhood with Central-Midtemporal Spikes

Clinical Features

Benign epilepsy of childhood with central-midtemporal spikes (BECTS) is an idiopathic, localization-related epilepsy syndrome (228). It is also commonly referred to as *benign rolandic epilepsy*. It is one of the most common forms of childhood epilepsy, occurring in 16% to 24% of children with epilepsy (48,131).

BECTS is characterized by two defining features, one clinical and one electrographic:

1. Stereotyped partial seizures consisting of unilateral paresthesias of the tongue, lips, inner cheeks, and gums, accompanied by unilateral tonic or clonic activity of the facial and pharyngeal/laryngeal muscles, speech arrest (anarthria), and excessive salivation. Nocturnal secondarily generalized seizures are common and are often the first manifestation of the disorder. Seizures remit spontaneously during adolescence.
2. Interictal EEG demonstrating central-midtemporal spikes and otherwise normal background activity.

Onset of seizures usually occurs between the ages of 4 and 10 years, although the syndrome can occur as early as the age of 2 years and, rarely, begin as late as 13 years. In the majority of patients, nearly 80% in some series, seizures occur exclusively during sleep (174,180). In about 20%, seizures occur during both sleep and wakefulness. Seizures that occur solely during the waking state are least common (174,180). Seizures are usually infrequent, and 13% to 21% of patients have only a single seizure (174,180). Frequent seizures or seizure clusters are present in only 20% to 25% of cases (174,180). Early onset seems to be predictive of a longer active phase of seizures before remission (180). Partial status epilepticus is rare (61,91).

Electroencephalographic Findings

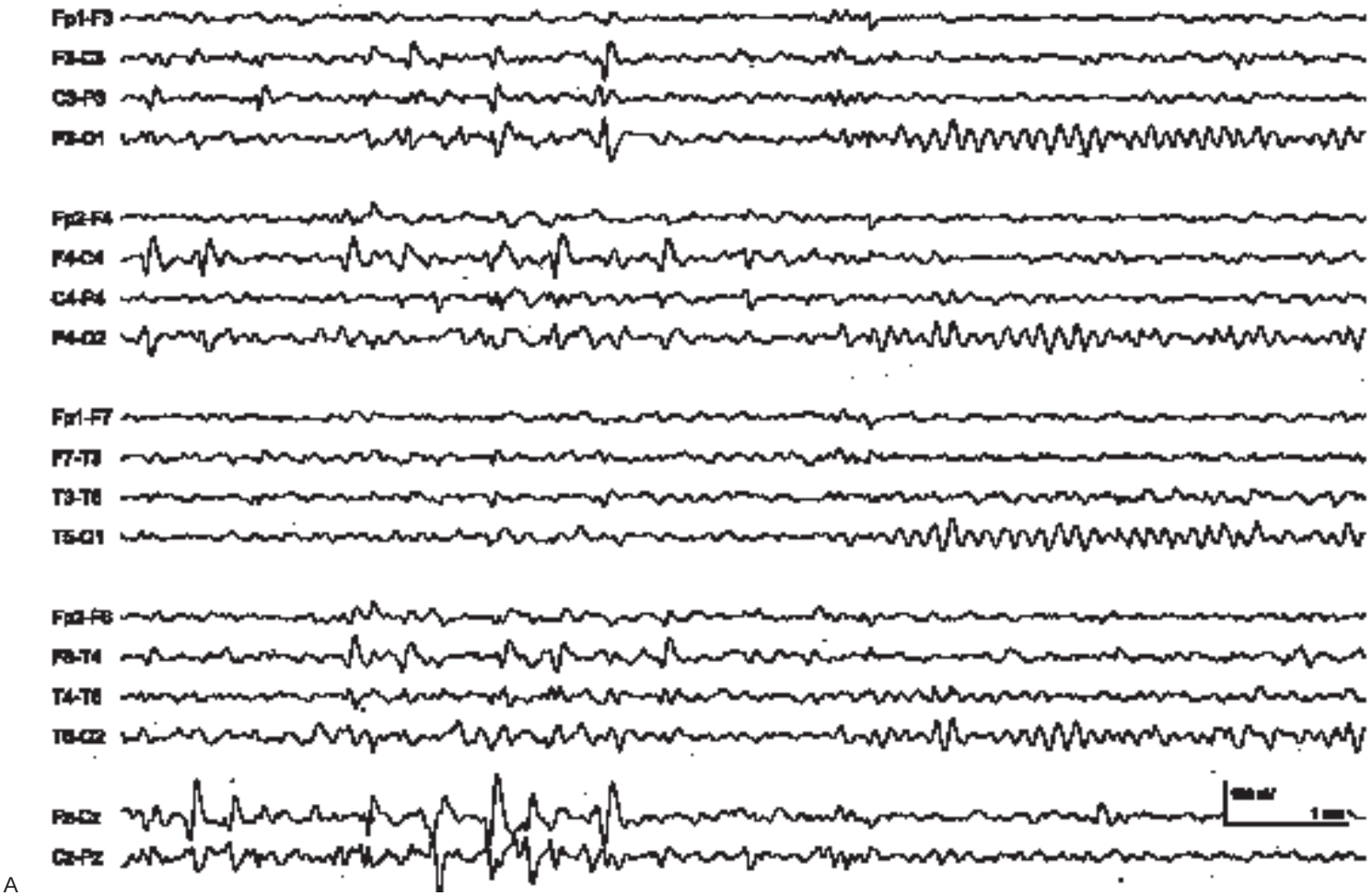
Interictal EEG. The interictal EEG demonstrates the characteristic central-midtemporal epileptiform discharges (Fig. 17.8). These are stereotyped, diphasic or sometimes triphasic sharp waves, usually followed by an aftergoing slow wave. The sharp waves average 100 to 300 μV in voltage. In bipolar recordings, the discharges most often show maximal voltage in the central (C3-C4) and midtemporal (T3-T4) areas. On occasion, the maximal voltage is displaced posteriorly, to P3-P4 or T4-T6. Discharges are usually seen simultaneously in both central and temporal regions, although they may be of higher voltage in one or the other of these. On occasion, they are confined to either the central or the temporal area. They occur bilaterally and independently in homologous areas of both hemispheres, but in a single recording, they may predominate on one side (see later discussion). The sharp waves occur either as isolated discharges or as runs of repetitive spikes. The latter is especially common during sleep. The frequency of spiking does not correlate with the frequency or severity of seizures. The EEG abnormality typically persists for some time after remission of clinical seizures. The EEG discharge also eventually disappears, almost always by late adolescence; in rare cases, they can be detected in subjects in their early 20s (4,174).

Legarda et al. (170) analyzed the spatial distribution of central-midtemporal spikes in detail, using additional "low central" electrodes (C5, C6) placed equidistant between C3-C4 and between T3-T4. When only standard electrode placements were used, 21 of 33 patients had discharges that were of maximal voltage at C3 and C4. In the rest, discharges were of highest voltage in the midtemporal region. However, when "low central" electrodes were included, all of the apparent T3-T4 loci, and half of the C3-C4 loci were actually of highest voltage at the C5-C6 sites. These data suggest that the term *central-midtemporal* may be a misnomer, because all such discharges actually localize to either high (30%) or low (70%) central regions. This observation is not surprising, inasmuch as the T3 and T4 electrodes actually overlie the junction of the rolandic and sylvian fissures.

Gregory and Wong (121) used digital spike averaging and computerized topographic mapping to analyze the spatial and temporal characteristics of central-midtemporal spikes in 10 children. All of the discharges had stereotyped waveforms that displayed a characteristic tangential dipole over the rolandic region: peak negativity was located over the central or midtemporal area with a lower voltage peak of positivity seen bilaterally over the frontal regions but maximal ipsilaterally. On the basis of these findings, Gregory and Wong postulated a single spike generator in the lower rolandic-sylvian area that was oriented tangentially to the cortical surface.

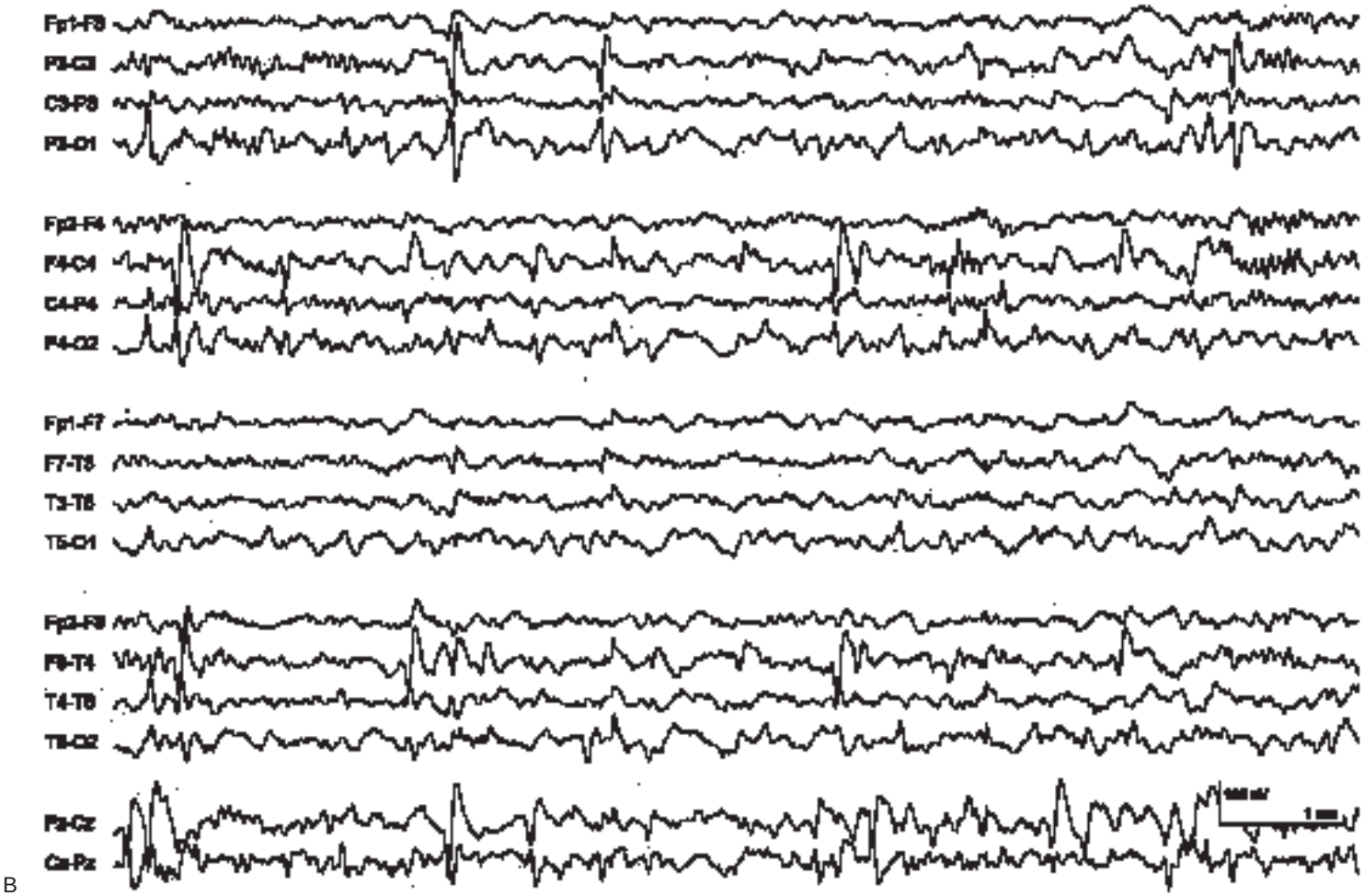
In many patients, epileptiform discharges occur unilaterally, in the same hemisphere on multiple EEG recordings. In other patients, spikes occur bilaterally and independently, either in a single EEG recording or in consecutive EEG recordings (19,32,174,173). When spikes are present bilaterally, the maximal voltage of the discharges is always in homologous areas (e.g., C3 and C4) (170).

Sleep enhances central-midtemporal discharges, often dramatically. In up to one-third of patients, spikes are seen only during sleep (31,181). This activation occurs in all stages of sleep, including the REM stage, but the effect is most pronounced in slow-wave sleep (27,58). Clemens and Majoros (58) found that the spike discharge rate was highest in stages 3 and 4, lower in



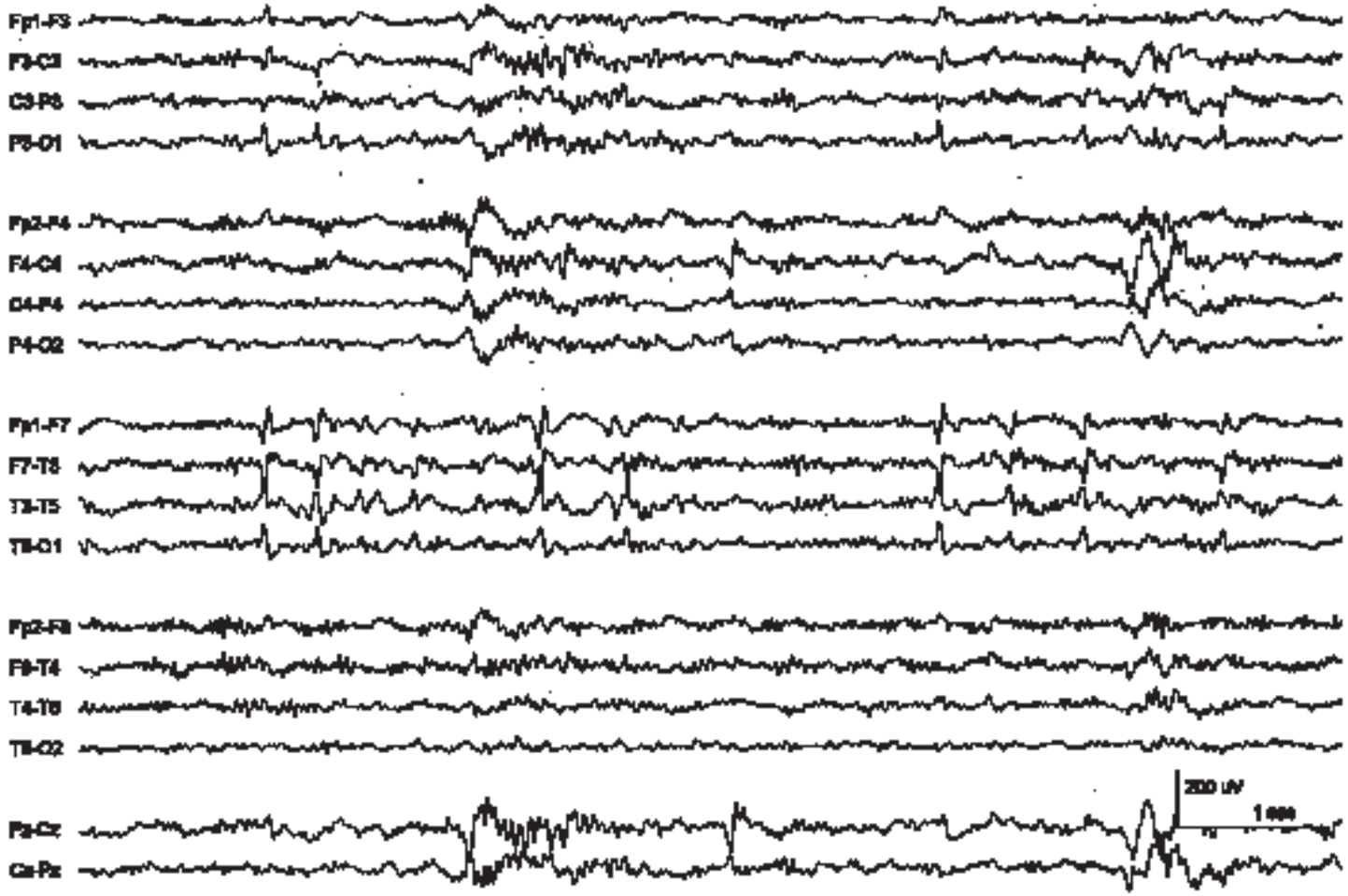
A

FIG. 17.8. **A:** EEG of a 6-year-old girl with benign epilepsy of childhood with central-midtemporal spikes (BECTS). She had infrequent seizures consisting of right face and arm clonus with drooling but without loss of consciousness. During drowsiness, the EEG shows frequent, stereotyped sharp waves occurring independently over the left (C3) and right (C4) central regions. Some of the right hemisphere discharges have a more extensive field that includes the temporal region (T4). Note that the vertex sharp transients are clearly distinct with phase reversals at Cz. After arousal, the discharges attenuated completely. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



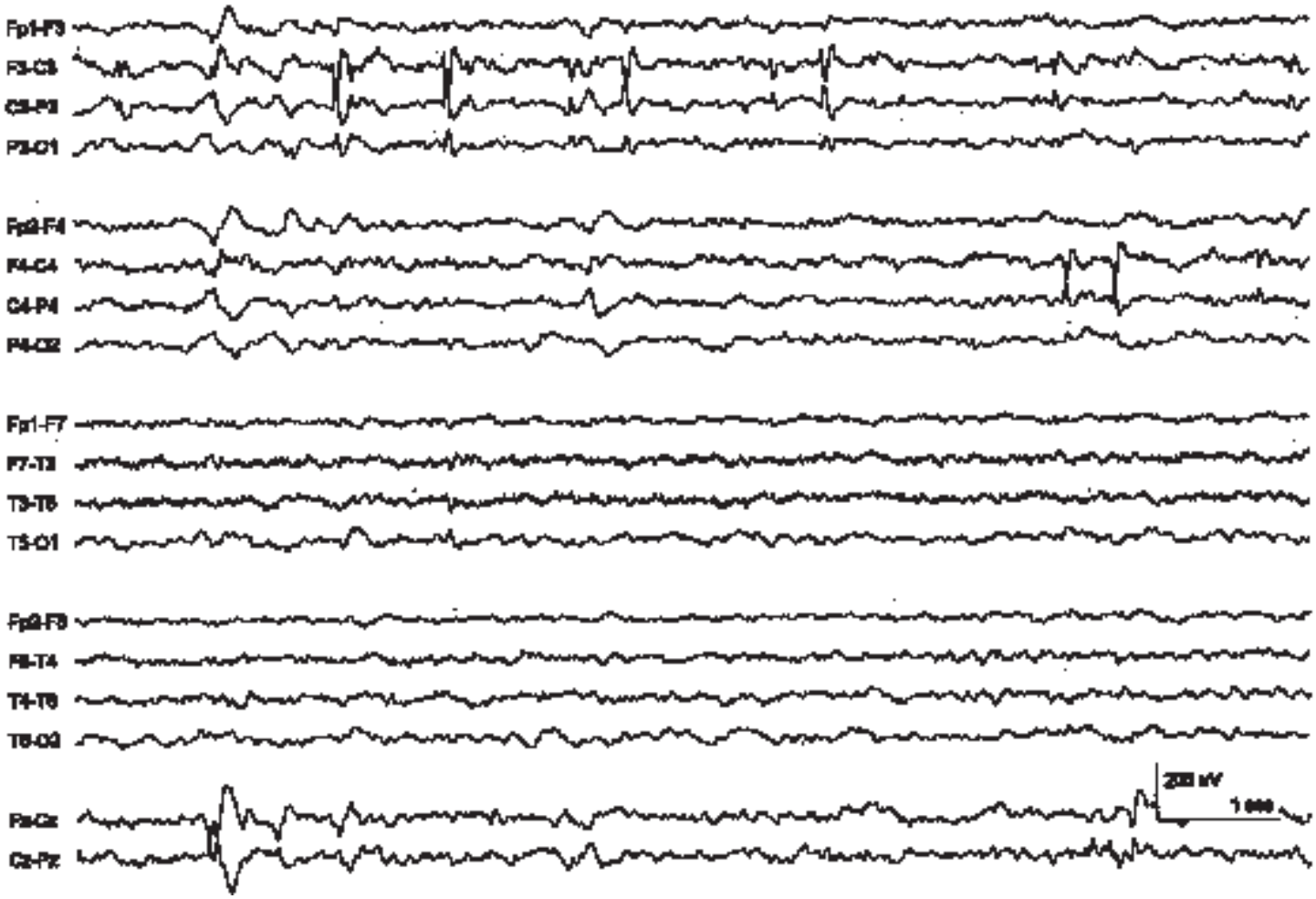
B

FIG. 17.8. *Continued.* **B:** Stage 2 sleep in the same patient. The discharges occurred more frequently and were more broadly distributed. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



C

FIG. 17.8. *Continued.* **C:** EEG of a 9-year-old boy with BECTS. In this child, the discharges are predominantly left-sided and mainly temporal in their distribution (see text). TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



D

FIG. 17.8. *Continued.* **D:** EEG of a 5-year-old boy with BECTS. There are independent left and right discharges localized to C3 and C4 without significant involvement of temporal electrodes. TC, 0.1 second. HFF, 70 Hz.

stages 1 and 2, even lower in REM sleep, and lowest in the waking state. Epileptiform discharges are also of higher voltage and have more extensive fields during sleep (17,170,195). Spikes that are unilateral during wakefulness often become bilateral during sleep (27). Although there is agreement that central-midtemporal discharges are most apt to be recorded during sleep, the actual sensitivity of this state-dependent effect has not been rigorously examined. Thus, single EEGs, even including sleep, can be normal in children whose clinical presentation is consistent with BECTS.

Hyperventilation and photic stimulation have no consistent effect on central-midtemporal epileptiform discharges (19,29).

In general, EEG background activity is normal in children with BECTS. However, when the discharges are frequent and repetitive, focal slowing can occur in the same distribution as the spikes as a result of summation of aftergoing slow waves.

Other electrographic abnormalities are present in a minority of patients. The most common of these are generalized, bisynchronous 3- to 4-Hz spike-wave discharges. These occur in about 7% of routine EEGs from patients with BECTS (19,174), but the incidence is much higher (up to 70%) with overnight or longer recordings (17,27). Unlike central-midtemporal spikes, the generalized spike-wave complexes can be activated by hyperventilation and, to a lesser extent, photic stimulation (32,195). Other focal spike discharges also occur, most often in the occipital and frontal areas (19), and multiple independent spike foci have also been reported (29). In such cases, the morphological appearance of these other focal spikes is often similar to that of the central-midtemporal discharges.

Ictal EEG. Ictal EEG recordings from patients with BECTS have been reported infrequently. Lerman (173) described the EEG correlate of a diurnal seizure as beginning with a focal decremental pattern followed by dense spikes in the central-midtemporal region during the tonic phase and then by spike-waves in the clonic phase. The ictal discharge remained localized, lasted less than 1 minute, and was not followed by postictal slowing. Bernardina and Tassinari (28) recorded a seizure during stage 2 sleep. The ictal event began with low-voltage (20- to 30-μV) 12-Hz activity over the central and temporal regions on one side, which increased in voltage (to 50 to 100 μV) with an enlarging field before becoming generalized with widespread 8- to 10-Hz rhythmic spike activity. The ictal pattern ended abruptly, and there was no postictal slowing. Interictal spiking was suppressed for 1 minute after the seizure.

Familial Occurrence

Bray and Wiser (36) were among the first to record central-midtemporal discharges in nonepileptic relatives of patients with BECTS. In a study of 40 patients with BECTS, 30% had at least one close relative with central-midtemporal discharges. Siblings and children were more likely to be affected (36%) than were parents (19%). Heijbel et al. (132) found central-midtemporal spikes in 34% of siblings, more than half of these (56%) did not have seizures. In a study of persons whose EEGs contained central-midtemporal spikes (not all of whom had epilepsy), Degen and Degen (66) found that a higher proportion of siblings had generalized epileptiform discharges (31.9%) than central-midtemporal discharges (4.3%). These findings are suggestive of a strong genetic component to the development of BECTS, perhaps a single autosomal dominant gene with age-dependent penetrance.

Differential Diagnosis

Not all patients with central-midtemporal discharges on EEG, however, have BECTS, inasmuch as typical discharges may be seen in several circumstances other than BECTS. The occurrence of central-midtemporal spikes in neurologically normal patients without epilepsy is well recognized (19,27,29,174,195). Cavazutti et al. (49) performed EEGs on 3,726 neurologically normal children 6 to 13 years of age who had no history of epilepsy. They found "rolandic or parietal" or "midtemporal" epileptiform discharges in 2.3% of the children. In a series of 386 neurologically normal children whose EEGs showed central discharges and normal background activity, Kellaway (158) found that only 57% had seizures. In another large series of 315 patients with centrotemporal discharges, Beaussart (19) found that 16% did not have epilepsy.

Central-midtemporal discharges have been recorded in patients with symptomatic forms of epilepsy. In Kellaway's (158) series of 335 patients with central discharges and seizures, only 66% had BECTS; the other 34% were classified as "lesional": that is, having a history of early brain insult or neurological impairment. Central-midtemporal discharges have also been described in patients with a variety of neurological abnormalities, including perinatal hypoxia, agenesis of the corpus callosum, callosal lipoma, congenital toxoplasmosis, Rett's syndrome, fragile X syndrome, cortical dysplasia, and cerebral tumor (74,163,164,201,203). In such cases, the association with BECTS may have several explanations:

1. The occurrence of BECTS is coincidental.
2. The associated neurological insult allowed emergence of rolandic seizures by further lowering seizure threshold in a patient geneticall y predisposed to BECTS.
3. The neurological lesion resulted in epileptiform discharges and/or seizures similar to those seen in BECTS. In these cases, careful analysis of the clinical features and EEG background may reveal atypical fea-

tures that bring the diagnosis of BECTS into question. In particularly difficult cases, careful topographic analysis of the epileptiform activity, as described by Gregory and Wong (121), may provide useful distinguishing features, such as the characteristic dipole seen in BECTS.

Despite the occurrence of central-midtemporal discharges in the foregoing situations, the characteristic EEG findings, in the absence of atypical features, are quite specific for BECTS.

Childhood Epilepsy with Occipital Paroxysms

Clinical Features

Gastaut (101) was the first to clearly delineate childhood epilepsy with occipital paroxysms (CEOP) as a distinct electroclinical syndrome. The 1989 International League Against Epilepsy (ILAE) Commission on Classification groups this syndrome among the idiopathic localization-related epilepsies (228). Since publication of the initial description, it has become evident that CEOP encompasses a heterogeneous group of patients whose disease is one of two subtypes: an early-onset variant, now termed the *Panayiotopoulos's syndrome,* and a late-onset variant that corresponds to the syndrome initially described by Gastaut (215).

Although there are no epidemiological studies of the incidence of CEOP, several case series indicate that it is two to three times less common that BECTS (46,207,212). The early-onset variant accounts for most cases (46, 207,212).

In addition to the EEG findings (see later discussion), the two variants of CEOP share several features. Children are neurologically normal and have normal computed tomographic and magnetic resonance imaging scans (104,212,213,228). Boys and girls are equally affected in both early- and late-onset variants (92,101,104). As in BECTS, genetic factors are clearly involved, although the pattern of inheritance has not been elucidated. A family history of epilepsy is evident in 37% to 44% of cases (104,273), and occipital spikes have been reported in 26% of nonepileptic relatives (165).

In the late-onset CEOP variant, seizures begin between the ages of 15 months and 17 years; the peak age at onset is between 7 and 9 years (104,215, 273). Seizures nearly always begin with visual symptoms (amaurosis, phosphenes, illusions, or hallucinations) and are typically brief, lasting only seconds, without alteration in consciousness (104,228). In the immediate postictal period, about one-third of patients develop a severe diffuse headache, often with associated nausea and vomiting (104). Seizures tend to occur frequently, but response to medication is usually good (104,273). Although details of prognosis remain unresolved, the long-term outcome of the late-onset variant CEOP is generally less favorable than that of BECTS.

In the early-onset variant, the peak age at onset is between 3 and 5 years (92,214). In contrast to the late-onset variant, seizures lack the characteristic visual phenomena. Rather, stereotyped seizures consist of lateral gaze deviation and ictal vomiting, with a varying degree of alteration in consciousness (92,214). Seizures are exclusively nocturnal in about two-thirds of cases and are typically prolonged (5 to 10 minutes or longer in duration) (92,214). Partial status epilepticus occurs in nearly half the patients (92, 214). Despite the long duration of seizures and the high incidence of status epilepticus, prognosis in the early-onset variant is universally excellent. Up to 30% of patients experience only a single seizure, and in the remainder, seizures occur infrequently. Ferrie et al. (92) found that the median number of seizures was two, and no more than 15 occurred in any patient. Duration of the disease is typically 1 to 2 years, and nearly all patients become seizure free by age 12 (92). In rare cases, atypical seizures, either generalized or rolandic, recur after remission (92).

Electroencephalographic Findings

Interictal EEG. EEG findings are indistinguishable in the two CEOP variants. The interictal EEG demonstrates normal background activity and occipital epileptiform discharges that are morphologically stereotyped (92,101,104). The characteristic discharge consists of a diphasic spike or sharp wave with a high-voltage (200- to 300-μV) surface-negative peak, followed by a low-voltage surface-positive peak and an aftergoing surface-negative slow wave (104,213) (Fig. 17.9). Although maximal in the occipital derivations, the discharges at times extend into the posterior temporal areas (104). In about 20% of discharges, the principal sharp component has a duration longer than 70 milliseconds. In a similar percentage of discharges, spikes occur without aftergoing slow waves (92).

Gastaut and Zifkin (104) reported that the epileptiform discharges disappeared promptly with eye opening in 94% of cases and returned within 1 to 20 seconds after the eyes closed. Ferrie et al. (92) found less impressive responses to eye opening: The discharges disappeared completely in 54% of instances. Partial attenuation occurred in 15%, and there was no effect in 19%. Panayiotopoulos (211) demonstrated that reactivity of the epileptiform discharges to eye opening and closure is actually determined by central visual fixation. When patients were recorded in darkness, the occipital discharges per-

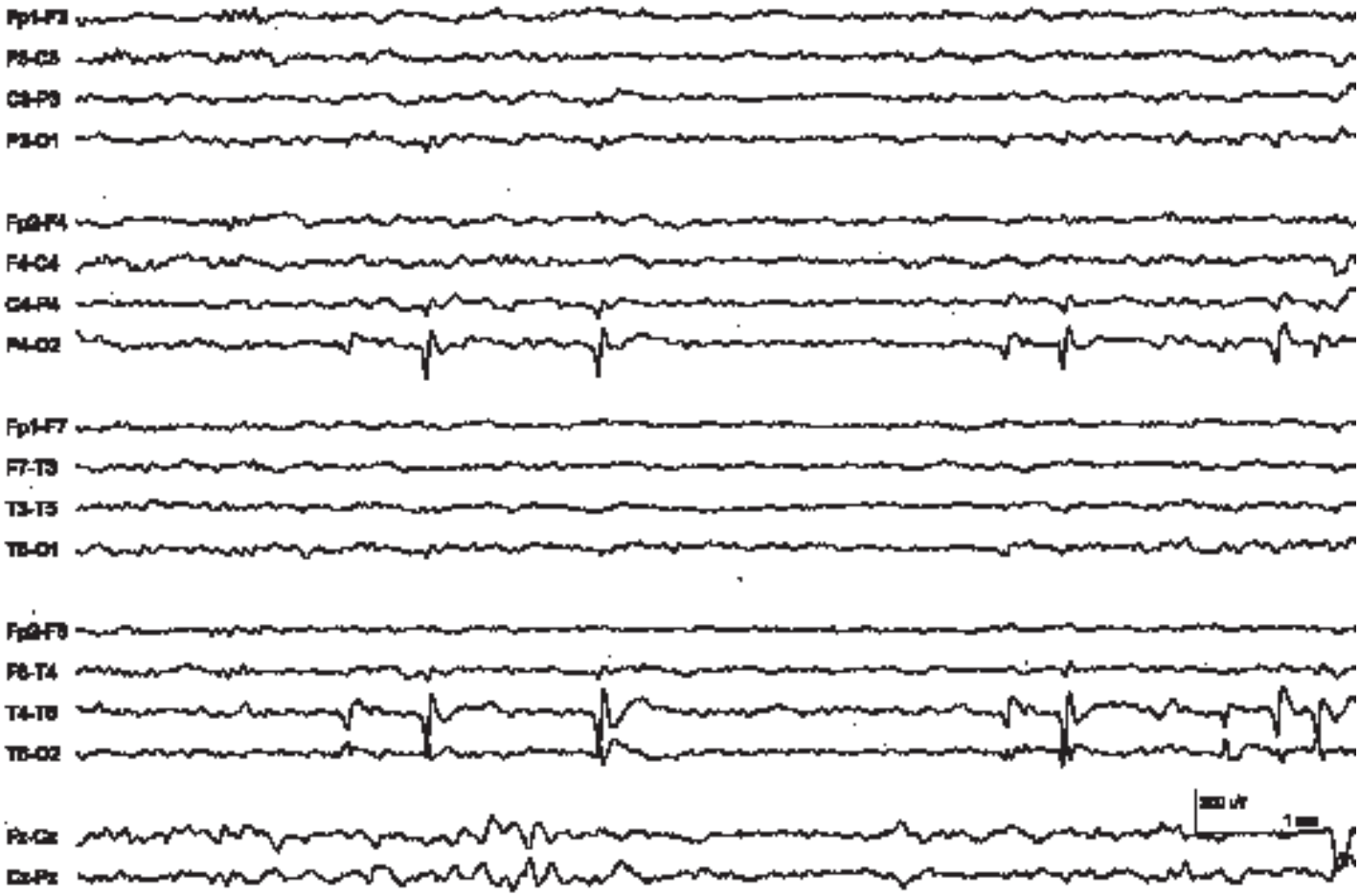


FIG. 17.9. EEG of a 10-year-old girl with childhood epilepsy with occipital paroxysms (CEOP). Her seizures consisted of lateral gaze deviation and vomiting with subtle impairment in awareness. The EEG shows normal background activity and high-amplitude occipital (T6/O2) spikes that have a stereotyped waveform. TC, 0.1 second; HFF, 70 Hz.

sisted, independently of whether the eyes were open or closed. When a small red light was used as a target for visual fixation in an otherwise dark environment, epileptiform activity attenuated promptly. This phenomenon of dependence on central visual fixation has been referred to as *fixation-off sensitivity* or *scotosensitivity*. These findings were confirmed later by Lugaresi et al. (185).

Occipital spikes can occur as isolated discharges, but they are seen most often as 1- to 3-Hz repetitive, semirhythmic paroxysms. At times, such discharges occur nearly continuously (101,104). Spikes may be unilateral or bilateral. When they are bilateral, the discharges on the two sides can be either synchronous or asynchronous (104). Bisynchronous discharges often differ in voltage, which raises the possibility of a single generator located within the medial surface of one occipital lobe with rapid propagation to the homotopic contralateral area.

Hyperventilation usually has no effect on epileptiform activity (104), although a few authors have reported activation (175,273). Similarly, in most patients, photic stimulation has no effect on epileptiform activity (92,104). In a few, however, however, photic stimulation can either activate epileptiform discharges (104,213) or inhibit them (212,213). The inhibition effect seems to occur mainly with high flash rates.

Occipital discharges are activated by NREM sleep and inhibited by REM sleep (92,175) In a minority of cases, occipital discharges may be evident only during sleep (104).

Occipital discharges are not invariably present in CEOP. In 5% to 6% of cases, rhythmic slow waves occur in the occipital regions in the absence of any spike or sharp-wave components (92,104). Interictal epileptiform abnormalities are especially likely to be absent at the beginning of the early-onset variant. For example, Guerrini et al. (125) described four children with early-onset CEOP who did not manifest epileptiform activity until several months after the first seizure.

In many patients—more than half in one series (92)—interictal epileptiform discharges persist after clinical remission of seizures, sometimes for several years.

As in BECTS, some patients have other epileptiform abnormalities as well. Gastaut and Zifkin (104) found generalized spike-wave or central-midtemporal discharges in 38% of their patients. Ferrie et al. (92) made similar observations: 25% of their patients had central-midtemporal spikes, 12% had generalized spike-wave discharges, and 7% had frontal discharges.

Ictal EEG. Ictal EEG recordings have demonstrated a rhythmic spike pattern, initially localized to one occipital region, which evolves into a rhythmic theta or delta frequency discharge. The ictal discharge spreads both anteriorly on the same side and into the contralateral occipital area, but it usually remains best defined and most prominent in the occipital regions. Beaumanoir (14) described the EEG activity recorded during a nocturnal seizure. Interictal occipital spikes disappeared just before seizure onset, replaced by 10-Hz spikes in one occipital region. The rhythmic spike discharged evolved into rhythmic theta activity that was maximal posteriorly. Vigevano and Ricci (287) recorded an EEG during a seizure typical of the early-onset variant. There were unilateral, high-voltage, sharply contoured, rhythmic 1- to 2-Hz waves intermixed with spikes over the occipital-posterior temporal region.

Differential Diagnosis

Occipital spikes by themselves do not indicate a diagnosis of CEOP. Occipital discharges typical of the condition, including scotosensitivity, can be seen in other circumstances as well. Occipital spikes can occur in normal children as the asymptomatic expression of a genetic trait. In a small case series, Kuzniecky and Rosenblatt (165) found occipital spikes in 26% of nonepileptic relatives of patients with CEOP. In a study of 100 children with epileptiform EEGs but no history of seizures, Lerman and Kivity-Ephraim (176) found that 19% had occipital spikes. Kellaway (158) studied children with congenital or acquired amblyopia and found that many of them had occipital spikes and otherwise normal or nearly normal background activity. Such spikes can be very fast and extremely sharp ("needle spikes"). Occipital spikes also occur in patients with idiopathic photosensitive occipital lobe epilepsy. These patients have light-induced seizures and photoparoxysmal EEG responses (126). Occipital spikes can be seen in patients with symptomatic localization-related epilepsy (62) (Fig. 17.10). The best examples of such patients are those with celiac disease, who have occipital seizures, reactive occipital spikes on the EEG, and calcifications in the occipital lobes (114,115). The initial course of seizures in these patients appears benign, but many patients subsequently develop progressively severe epilepsy. Occipital epileptiform discharges have also been reported in hyperglycemia (128) and mitochondrial diseases (6).

Juvenile Myoclonic Epilepsy

Clinical Features

Juvenile myoclonic epilepsy (JME) is the most common syndrome among the idiopathic generalized epilepsies: it comprises 4% to 6% of all types of

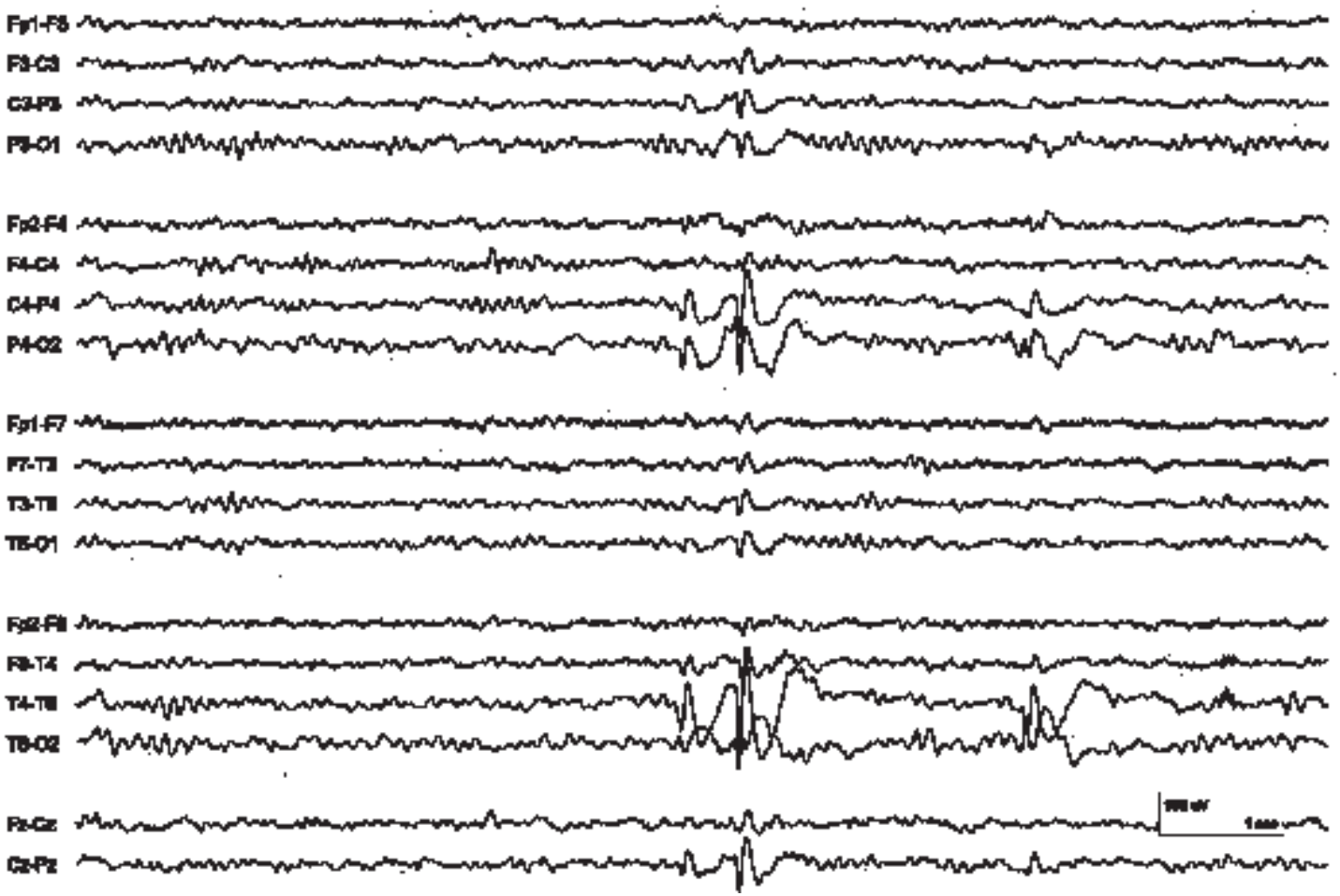


FIG. 17.10. EEG of a 13-year-old boy with intractable epilepsy resulting from heterotopic gray matter in the right temporal-occipital region. Note that the alpha rhythm is less persistent and poorly regulated on the right, and there is associated focal slowing of theta and delta frequencies. Note the similarity of the spike discharges in this example to those shown in Fig. 17.9.

epilepsy (8,148,200). Hereditary factors are clearly evident, and 40% to 50% of patients have a family history of epilepsy (8,67). Boys and girls are affected in equal numbers (67,150,216). Several groups of investigators have reported linkage to chromosome 6p (120), although this has been disputed by others (84,299). No single causative gene has been found, and polygenic factors are likely to be involved (76).

As its name indicates, this epilepsy syndrome usually begins in adolescence. Myoclonic seizures are present in 100% of cases as they are required for diagnosis. They may be the only type of seizure in 2% to 10% of cases (67,216,225). Typically, myoclonic jerks appear 2 to 3 years before the first generalized tonic-clonic seizure, although it is almost always the latter that brings the patient to medical attention. Generalized tonic-clonic seizures occur in more than 90% of patients. Both myoclonic and generalized tonic-clonic seizures occur most often within 1 to 2 hours after awakening. Myoclonus is especially marked in the setting of fatigue and sleep deprivation (216). Sometimes a crescendo of repeated myoclonic jerks terminates in a generalized tonic-clonic seizure (67). Absence seizures occur in about 35% of patients with JME (67,216,225). Sometimes, they may be the first manifestation of the disorder, even preceding the development of myoclonic jerks (8,217,216). Absence seizures in JME are typically less frequent and less intrusive than those seen in childhood absence epilepsy (pyknolepsy) and frequently go unnoticed (218,217).

Electroencephalographic Findings

Interictal EEG: Waking State. As in other idiopathic generalized epilepsy syndromes, the interictal EEG in JME is characterized by two main features:

1. Normal or near-normal background activity, with a well-modulated alpha rhythm (8,67,149).
2. Spontaneous bursts of generalized, bisynchronous epileptiform discharges.

Polyspikes and polyspike-wave discharges are characteristic of JME, although they are not pathognomonic, as initially believed by Janz and Christian (149). Such discharges are also common in other idiopathic generalized epilepsies. However, when polyspikes are abundant and are the predominant form of epileptiform activity, it is more likely that the patient has JME than another idiopathic generalized syndrome. The epileptiform discharge consists of a burst of generalized bisynchronous, symmetrical multiple spikes (polyspikes) that are of maximal voltage in the frontal and central regions, followed by high-voltage, irregular 2- to 5-Hz slow waves with intermixed spikes (148,149) (Fig. 17.11). The polyspike component is often evident only at the beginning of the epileptiform paroxysm. The number of repetitive spikes may be as high as 20; two to four spikes are more usual (148,149). Epileptiform activity can occur either as isolated polyspike-wave bursts or as prolonged paroxysms lasting up to 20 seconds (2). Spike-wave complexes and polyspikes without associated slow waves are also frequent and may sometimes be the only epileptiform abnormality (8).

The spike-wave and polyspike-wave discharges seen in JME are usually "fast"; that is, the repetition rate is higher than the 3-Hz spike-wave pattern seen in childhood absence epilepsy. The most common frequencies are 3.5 to 6 Hz, and the range is between 2 and 10 Hz (67,149,216). "Typical," stereotyped 2.5- to 3-Hz spike-wave discharges, indistinguishable from those seen in childhood absence epilepsy, are present in up to 25% of patients (67).

The sensitivity of the EEG for demonstrating epileptiform activity in patients with JME is widely accepted as being very high, but the actual data from different studies vary considerably in the percentage of "positive" EEG. For example, Delgado-Escueta and Enrile-Bacsal (67) reported epileptiform activity in 100% of patients, Janz and Christian (149) in 92%, Panayiotopoulos et al. (216) in 79%, and Aliberti et al. (2) in 73%. Although much of this variability may result from differences in recording methods, especially the length of the EEG and whether samples of both waking and sleep activity were obtained, antiepileptic drugs may also play a role. Jain et al. (147) found that the probability of detecting epileptiform activity was much greater in untreated (100%) than in treated (63%) JME patients.

Hyperventilation generally activates epileptiform activity (148,216), although there have been no quantitative studies of this effect. In a minority of patients, epileptiform activity is seen only during hyperventilation (2).

A relatively high percentage of patients, 27% to 41%, demonstrate photosensitivity (2,8,124,216,308). Photosensitivity is two to three times more common among girls with JME than among boys with JME (225,308). Like hyperventilation, photic stimulation may be the only way to elicit epileptiform activity in some patients (8). In a minority of patients, epileptiform activity is triggered by eye closure (8,216).

Other EEG abnormalities, including excessive amounts of theta activity and slower than expected alpha rhythms, have been reported in a minority of patients with JME (216). In the study by Panayiotopoulos et al. (216), seizures were uncontrolled at the time of study. Thus, the degree to which slowing of background EEG patterns reflected poorly controlled seizures or other factors is unknown.

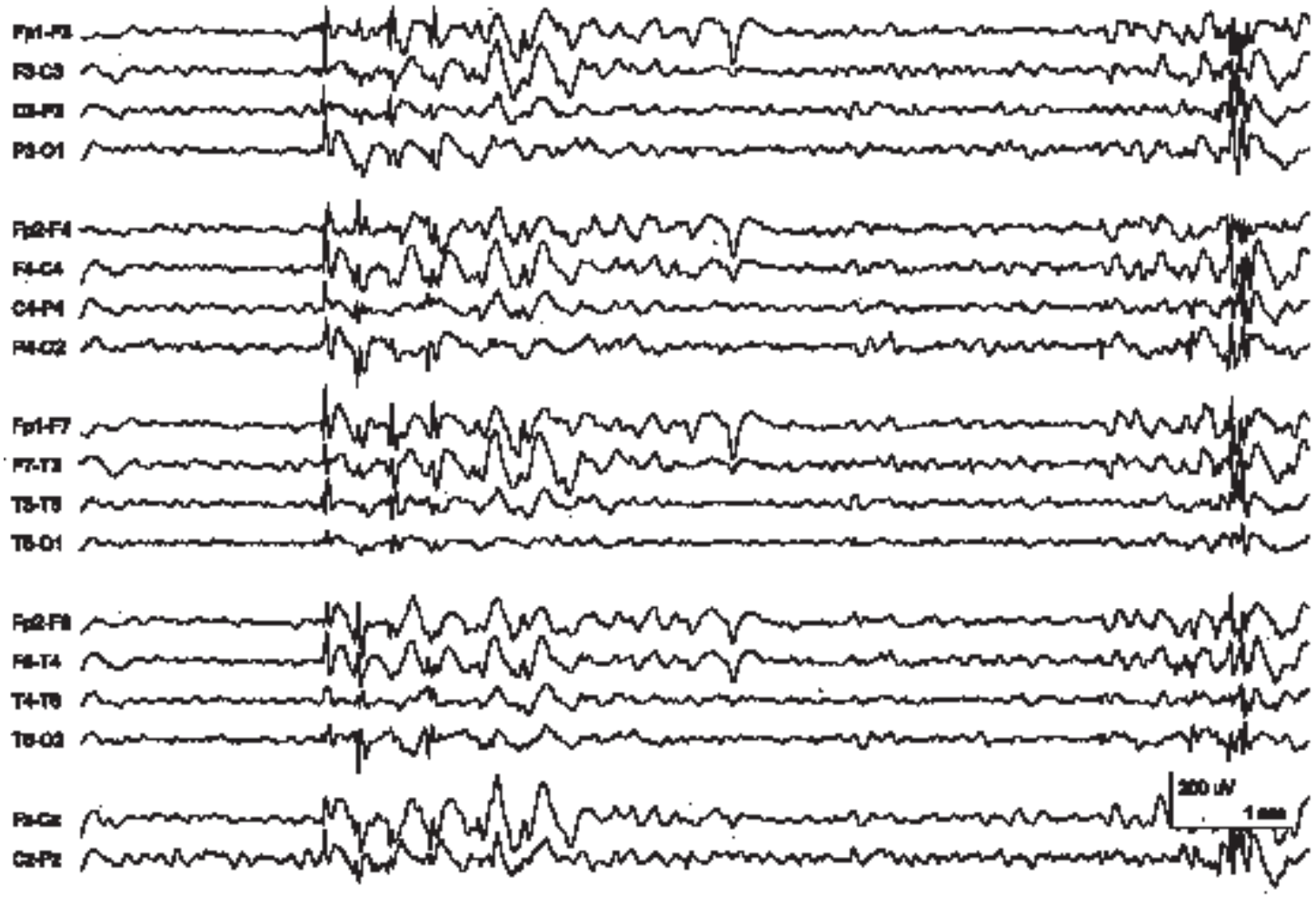


FIG. 17.11. EEG of an 18-year-old woman with juvenile myoclonic epilepsy (JME). The interictal EEG demonstrates generalized spike-wave and polyspike-wave discharges. TC, 0.1 second; HFF, 70 Hz.

Focal EEG abnormalities have been found in 16% to 54% of patients (2, 124,166,219,216). Although details are often lacking, inference of focal regions has usually depended on demonstrating asymmetrical spik e-wave discharges, unilateral or focal spik e-wave discharges, or unilateral or focal slowing. However, these were often described as inconsistent and shifting in laterality over time. The authors' experience suggests that a detailed anal y-sis would demonstrate that the majority of these "focal dischages" represent limited or fragmentary expression of a generalized abnormality (Fig. 17.12). This conclusion is reasonable when the "focal" discharges have a waveform that mirrors that of the generalized spik e-wave discharges, are of maximal

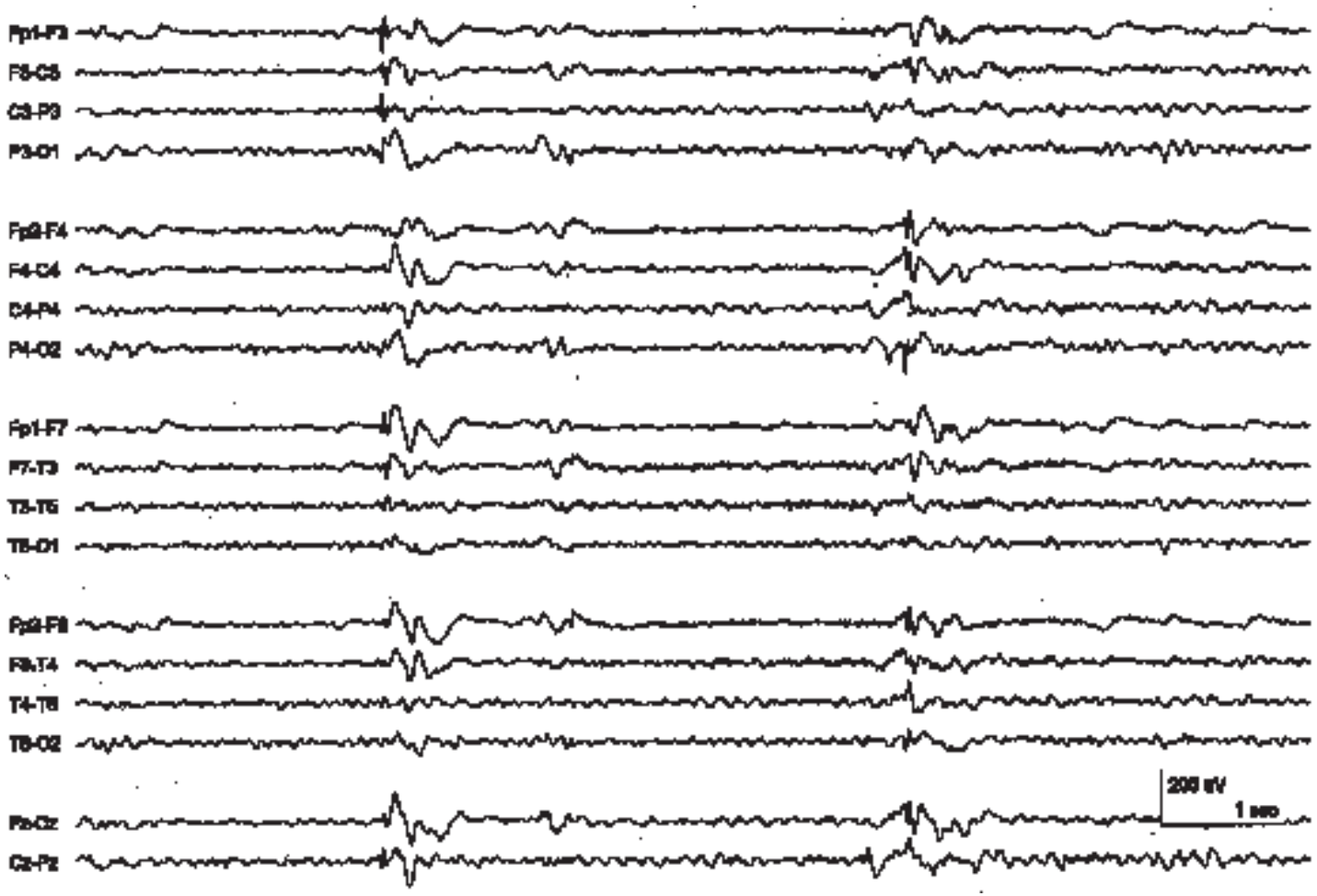


FIG. 17.12. EEG of an 18-year-old patient with juvenile myoclonic epilepsy (JME). Spike-wave discharges seem to shift from side to side during the recording. These asymmetrical fragments are often mistaken for evidence of a localization-related epilepsy syndrome (see text). TC, 0.1 second; HFF, 70 Hz.

voltage over the frontal and frontal-central regions, and lack associated focal slowing of background activity (see section on primary versus secondary bilateral synchrony).

Interictal EEG: Effects of Sleep. In polygraphic EEG studies of 33 patients with JME, Touchon (278) demonstrated that in stage 2 NREM sleep, epileptiform discharges were suppressed, in contrast to the activation seen with most other types of epilepsy. Discharge rates were equivalent during wakefulness and drowsiness, dropped significantly during REM sleep (although not nearly to the rate seen in NREM sleep), and increased markedly after awakening, especially when the arousal was externally provoked. Epileptiform activity

was most abundant after nocturnal and morning awakenings that followed sleepless nights. Sleep deprivation had similar effects and, in some patients, was necessary to elicit epileptiform discharges (8,124).

Ictal EEG. Myoclonic seizures are always associated with polyspike or polyspike-wave bursts (208) that are generally indistinguishable from those that are not accompanied by clinically detectable jerks. Sometimes the number of multiple spikes is higher (10 to 16 Hz) with ictal discharges, and the voltage may increase from the first spike to the last. The intensity of the myoclonic jerks correlates with a higher number of repetitive spikes (148, 149). The polyspikes are of medium to high voltage, maximally expressed over the frontal regions, and followed by high-voltage, 1- to 3-Hz rhythmic slow waves (67) (Fig. 17.13). While the jerk itself is extremely brief ("light-

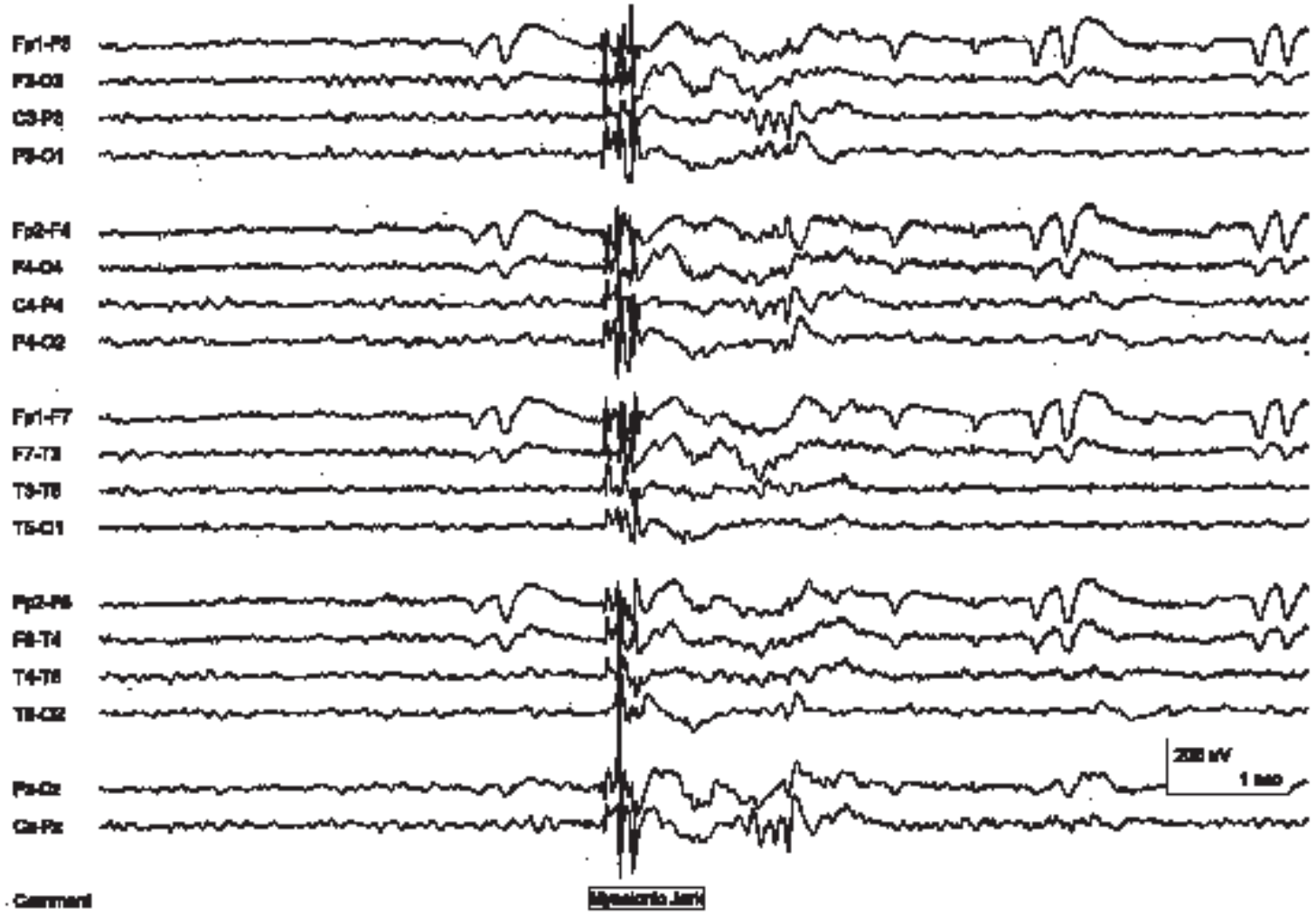


FIG. 17.13. EEG of an 18-year-old patient with juvenile myoclonic epilepsy (JME). A myoclonic jerk of the arms accompanies this burst of bilateral synchronous polyspikes. TC, 0.1 second; HFF, 70 Hz.

ning-like"), the associated EEG discharge is typically 1 to 2 seconds in duration and may last as long as 4 seconds (208).

Absence seizures in JME are associated with generalized, somewhat irregular 2.5- to 4-Hz spike and polyspike-waves that last several seconds and may be interrupted with discontinuities lasting 1 second or less. The repetition rate of the spike-wave and polyspike-wave discharges can range from 2 to 7 Hz. A classical 3-Hz spike-wave pattern is uncommon (217,218).

West's Syndrome

Clinical Features

West's syndrome is named for Dr. W.J. West, who first described the clinical features of infantile spasms in 1841, on the basis of observations of his own son (298). The syndrome consists of the triad of infantile spasms, arrest of psychomotor development, and a grossly abnormal EEG pattern termed *hypsarrhythmia.* Onset nearly always occurs in the first year of life, usually between the ages of 4 and 7 months (153,160,182). Nearly 90% of cases are associated with neurological abnormalities arising from a diverse array of structural, metabolic, and genetic disorders. Only 10% to 15% of cases are cryptogenic/idiopathic (140,159,190).

Electroencephalographic Findings

Interictal EEG. In 1952, Gibbs and Gibbs (108) described the classical EEG pattern associated with infantile spasms. They coined the term hypsarrhythmia, and their description cannot be improved upon:

> "It consists of random high voltage slow waves and spikes. These spikes vary from moment to moment, in both duration and location. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern....The abnormality is almost continuous...."

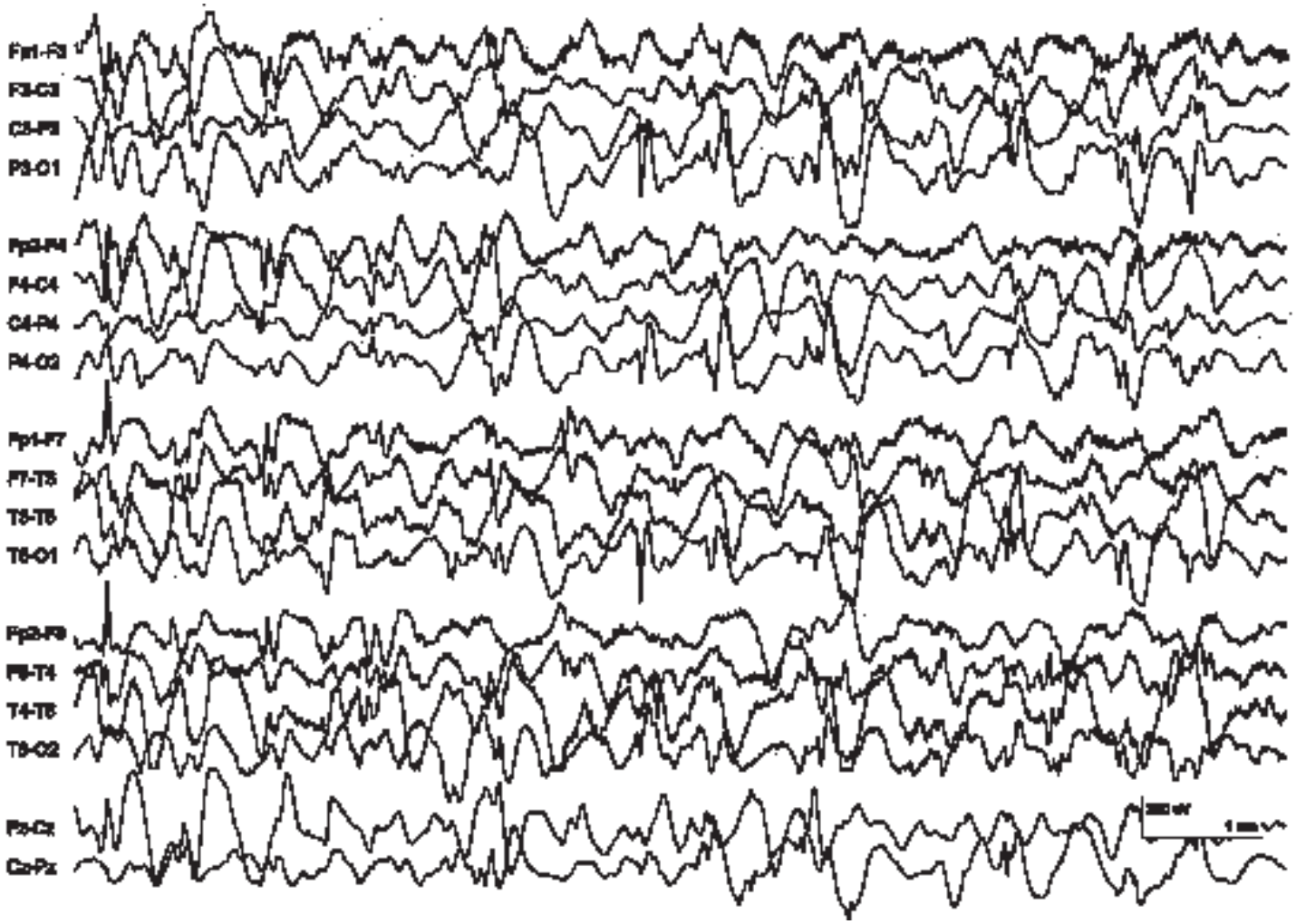
The chaotic, high-voltage, and asynchronous features of this abnormality, combined with an absence of virtually all normal activity, give the appearance of near-total disorganization of cortical voltage regulation (Fig. 17.14). This prototypic pattern, however, is usually seen in only the early stages of infantile spasms and most often in younger infants (159). Over time, the degree of abnormality seems to lessen, in that the EEG pattern becomes more organized, decreases in voltage, and shows greater interhemispheric synchrony and symmetry (159).

Hrachovy et al. (140) described five variations of the classical pattern. Each of these variants retained some of the major characteristics of prototypic hypsarrhythmia, and each had the same clinical and electrographic ictal features:

1. Hypsarrhythmia with increased interhemispheric synchronization, which appears as bursts of generalized spike-wave activity or as increased synchronization of the background theta and alpha frequency activities. This variation can evolve from classical hypsarrhythmia over weeks to months. These features sometimes appear only intermittently with frank hypsarrhythmia present at other times (Fig. 17.15*A*).
2. Asymmetrical hypsarrhythmia, in which there are consistent voltage asymmetries, either regionally or affecting an entire hemisphere. This pattern is seen most often when there are large cystic or atrophic defects of one cerebral hemisphere, such as porencephaly or encephalomalacia (see Fig. 17.15*B*).
3. Hypsarrhythmia with a consistent focus of abnormal discharge. In these cases, there is a persistent localized area of spike or sharp wave activity, in addition to the typical multifocal discharges. Focal electrographic ictal discharges can occur in the same region, but the background pattern of hypsarrhythmia is not affected by the focal seizure. Such localized abnormalities can persist after the hypsarrhythmia disappears (see Fig. 17.15*C*).
4. Hypsarrhythmia with episodes of generalized, regional, or lateralized voltage attenuation. These periods of attenuation last 2 to 10 seconds and sometimes occur in a periodic pattern (see Fig. 17.15*D*).
5. Hypsarrhythmia composed primarily of high-voltage, bilaterally asynchronous slow wave activity with relatively little epileptiform activity (see Fig. 17.15*E*).

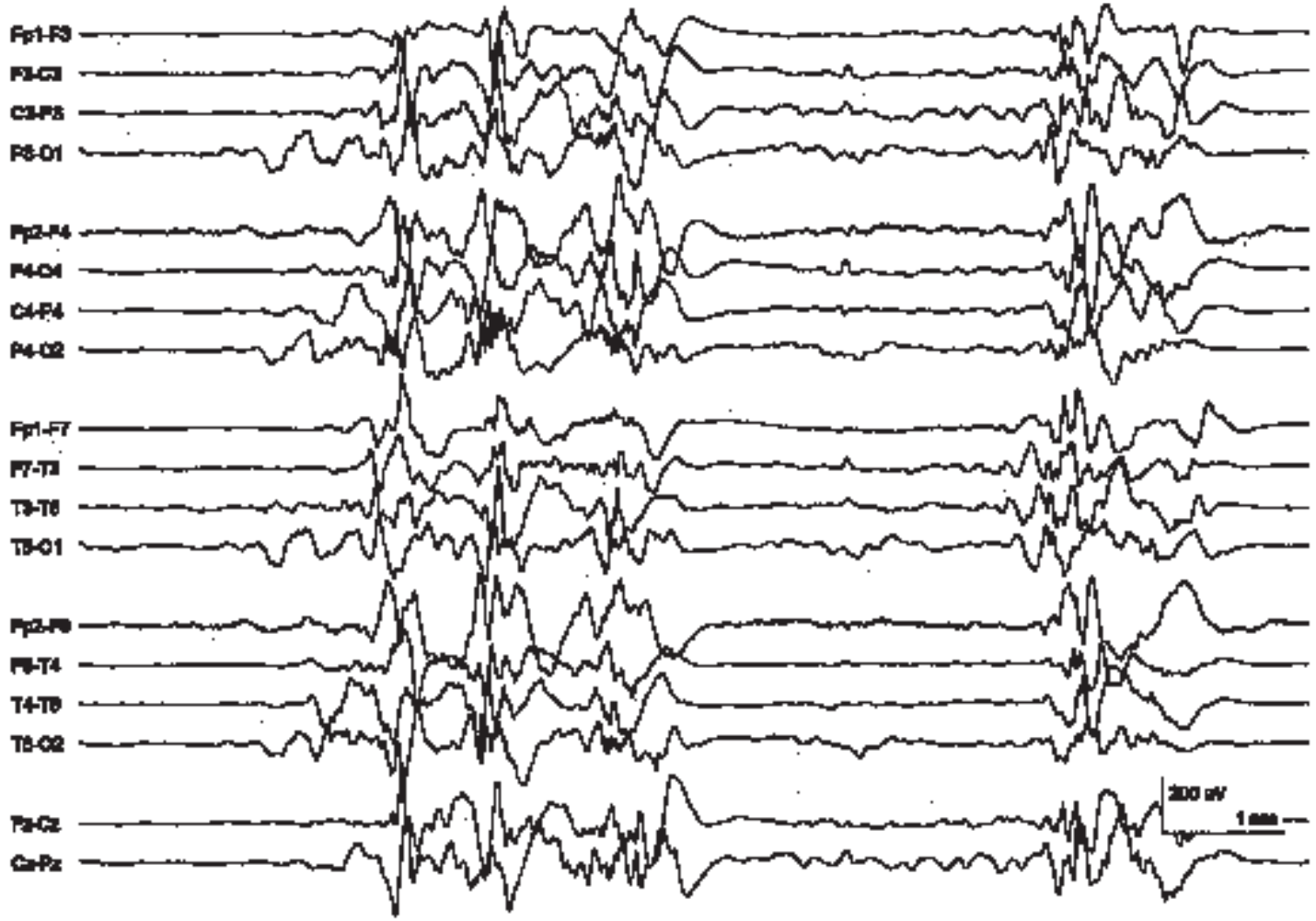
More than one of these variations may be present at the same time in a given patient.

Hrachovy et al. (140) considered the foregoing variations to be examples of "modified hypsarrhythmia," a term that had been used over the years by many authors to describe any deviation from what, in their view, represents "true" hypsarrhythmia. In fact, the boundaries of what constitutes hypsarrhythmia are not clearly defined, and experienced electroencephalographers have differing opinions about "how abnormal" an EEG must be, and with what constellation of features, before it can be classified accurately as hypsarrhythmia. The authors believe that it is more meaningful to consider hypsarrhythmia as a group of severe abnormalities that share many of the same



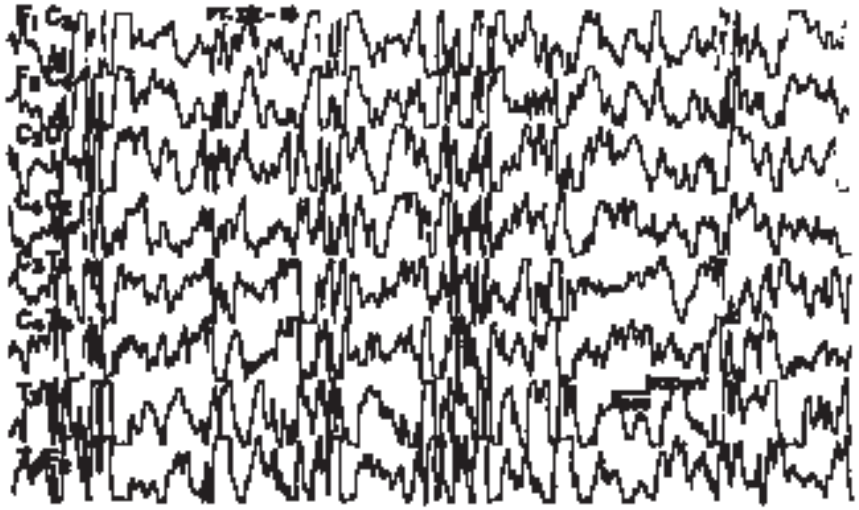
A

FIG. 17.14. **A:** EEG of an 8-month-old boy with infantile spasms and severe developmental delay. EEG during the waking state shows typical hypsarrhythmia. Note the high voltage, absence of spatial organization, and the multifocal spikes (F4, C3, P3, O1). TC, 0.3 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.14. *Continued.* **B:** EEG of a 3-month-old boy, also with West's syndrome. The EEG recorded during sleep demonstrates an episodic (burst-suppression) type of hypsarrhythmia pattern. TC, 0.3 second; HFF, 70 Hz.



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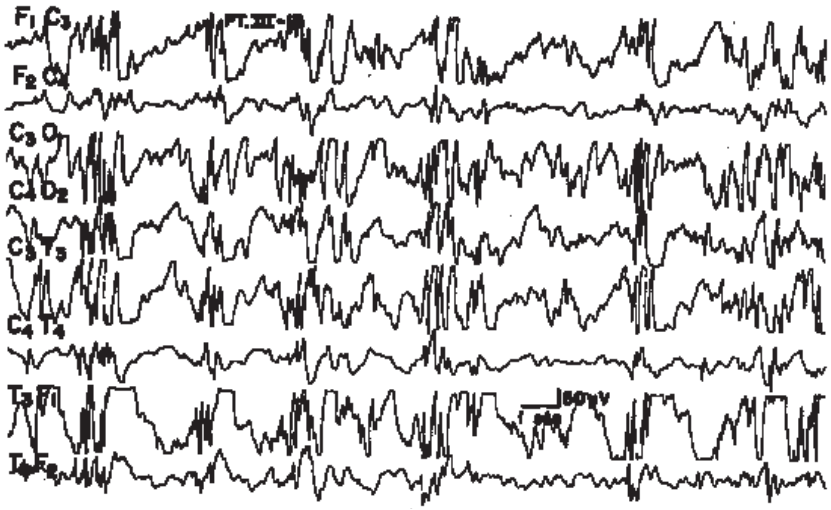

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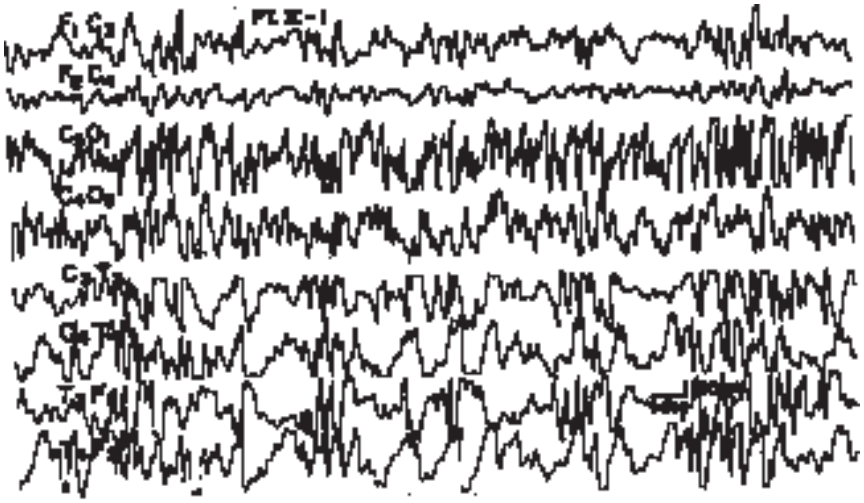


C

FIG. 17.15 A: EEG of an 8-month-old infant, showing hypsarrhythmia characterized by the presence of synchronous and symmetrical frontal-dominant spike and slow-wave and sharp-and-slow-wave activity. **B:** EEG of a 6-month-old infant, showing asymmetrical hypsarrhythmia. A head computed tomogram revealed a porencephalic defect in the right hemisphere. **C:** EEG of a 3-month-old infant, showing hypsarrhythmia with an identifiable focus of irregular spike and slow-wave and sharp-and-slow-wave activity in the left occipital region. *(Figure continues.)*

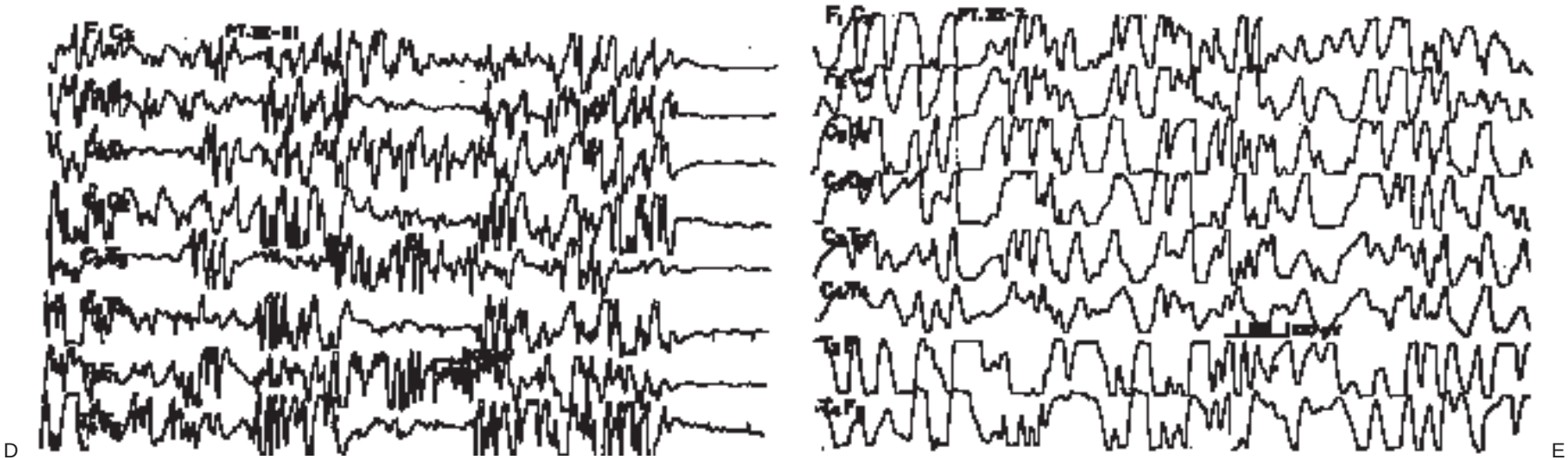


FIG. 17.15. *Continued.* **D:** EEG of a 9-month-old infant, showing hypsarrhythmia with episodes of lateralized and generalized voltage attenuation. **E:** EEG of a 13-month-old infant, showing hypsarrhythmia characterized by the presence of high-voltage, primarily asynchronous slow-wave activity with little spike or sharp wave activity. (From Hrachovy RA, Frost JD Jr, Kellaway P. Hypsarrhythmia: variations on the theme. *Epilepsia* 1984;25:317–325.)

features and exist at one extreme of a spectrum of age-dependent, abnormal EEG findings seen in infants and very young children with severe epileptic encephalopathies. It is not an entity per se, nor does it reflect any common underlying condition or pathological process. It is therefore understandable that physicians encounter considerable variability, including the variations just listed, at one time or another not only among patients but also over time in the same patient. In the authors' view, variations such as those listed are not "modified hypsarrhythmia"; they are simply different manifestations of the hypsarrhythmic type of abnormality.

Although it is characteristic, hypsarrhythmia is not seen in all patients with infantile spasms. *Aicardi's syndrome,* which consists of infantile spasms, agenesis of the corpus callosum, and chorioretinal lacunae, is associated with a distinctive EEG pattern. The interictal EEG is characterized by a background of burst-suppression activity that is completely asynchronous between the two hemispheres. The periods of EEG activity contain medium-voltage, very irregular theta and delta waves intermixed with multifocal spikes and sharp waves. There is complete absence of any semblance of normal sleep architecture (89). In a longitudinal study of patients with Aicardi's syndrome, Ohtsuka et al. (209) described similar EEG findings but also noted that this pattern may in turn evolve into hypsarrhythmia during the course of the disease. At the same time, not every infant whose EEG demonstrates hypsarrhythmia has infantile spasms. Hypsarrhythmia is sometimes seen in with other types of severe infantile epileptic encephalopathy (96).

In their initial description of hypsarrhythmia, Gibbs and Gibbs (108) described the abnormality as "...almost continuous, and in most cases [evident] as clearly in the waking as in the sleeping record." This description has had to be modified in light of more recent studies. Although the EEG pattern is indeed unreactive to photic or tactile stimulation, hypsarrhythmia commonly varies with changes in state. In a study of 82 children with clin-

ical spasms, Watanabe et al. (295) found that 99% had hypsarrhythmia during stages 2 and 3 NREM sleep, 86% during stage 1 sleep, and only 64% during waking periods. This finding emphasizes the importance of recording adequate samples of sleep to maximize the yield of "positive" EEGs. In slow-wave sleep, background activity voltage and the number of epileptiform discharges typically increase. In addition, background activity often becomes more periodic with intervals of diffuse voltage attenuation (138,140) (see Fig. 17.14*B*). In contrast, the hypsarrhythmia pattern tends to disappear during REM sleep (138,295). Immediately after arousal from either NREM or REM sleep, the EEG may transiently "normalize" before hypsarrhythmia reappears (140). Total sleep time and percentage of REM sleep time are significantly reduced in patients with West's syndrome (138). Of interest is that sleep spindles are commonly preserved even with otherwise profound disturbances in background activity and virtual absence of other normal sleep (138).

The natural evolution of hypsarrhythmia is known mainly from studies performed before 1958, when adrenocorticotropic hormone (ACTH) was introduced (268); treatment with either ACTH or corticosteroids subsequently became widespread. There is gradual modification of the abnormalities over time, with increasing organization and greater interhemispheric synchrony (159). Without treatment, about 25% of patients have spontaneous cessation of spasms with disappearance of hypsarrhythmia within 1 year of onset of the disorder (141). Livingston et al. (178), who studied 531 cases of infantile spasms with hypsarrhythmia, none of whom received corticosteroids, found that only 6% retained a hypsarrhythmic EEG after age 5, and in no case did the abnormality persist after the age of 7. Fewer than half the original patients continued to have spasms after the age of 3 (152); it is extremely rare for spasms to persist after the age of 5 (178).

Until the introduction of vigabatrin, most infants with West's syndrome were treated with ACTH. ACTH usually leads to rapid normalization of the EEG, with response rates ranging from 67% (139) to 97% (264) (Fig. 17.16). Resolution of clinical spasms usually parallels disappearance of hypsarrhythmia, but the two can be dissociated. Improvement in EEG activity is usually long lasting, but a substantial portion (31% to 47%) of patients develop recurrent spasms after being free of seizures for several months (139,264). Longer term follow-up studies have demonstrated that about half the patients develop a normal EEG background (153,154,178). About 35% to 40% develop persistent focal or bilateral abnormalities, and most of these are epileptogenic (153,154).

There is, unfortunately, little evidence that early resolution of spasms and hypsarrhythmia results in lasting, long-term neurological improvement (141). It is therefore important to emphasize that normalization of EEG activity is not necessarily correlated with neurological status and that nearly 90% of patients remain disabled by epilepsy and other neurological abnormalities, including severe mental impairment.

Ictal EEG. Although not all spasms are associated with hypsarrhythmia, spasms are, by definition, present in all cases of West's syndrome. In a video-EEG study, Kellaway et al. (160) reviewed the clinical and electrographic features of 5,042 infantile spasms in 24 infants. The most common electrographic pattern, seen in 37.9% of spasms, consisted of a high-voltage, frontally dominant, generalized slow wave transient, followed by diffuse voltage attenuation (electrodecremental event) (Fig. 17.17). They also noted ten other distinct electrographic ictal patterns:

Generalized sharp-and-slow-wave complexes (17.4%)
Generalized sharp-and-slow-wave discharge followed by a period of attenuation (13.2%)
Period of attenuation only (11.9%)
Generalized slow-wave transients (10.9%)
Attenuation with superimposed fast activity (6.9%)
Generalized slow wave followed by attenuation with superimposed fast activity (1.3%)
Attenuation with rhythmic slow activity (0.2%)
Fast activity only (0.2%)
Sharp-and-slow-wave complex followed by attenuation and superimposed fast activity (0.06%)
Attenuation with superimposed fast activity followed by rhythmic slow activity (0.06%)

The electrodecremental event was the most consistent electrographic feature; it was seen as a part of the ictal discharge in 71.7% of spasms. The duration of the ictal discharge was quite variable, ranging from 0.5 to 106 seconds.

In another video-EEG study, Fusco and Vigevano (98) found less variability in the ictal EEG patterns. All clinical spasms were accompanied by a medium- to high-voltage, positive slow wave that was maximal at the central and vertex regions. Very-low-voltage fast activity was often superimposed. These workers also noted that 70% of spasms were associated with an electrodecremental event but observed that this was a postictal, not an ictal, feature.

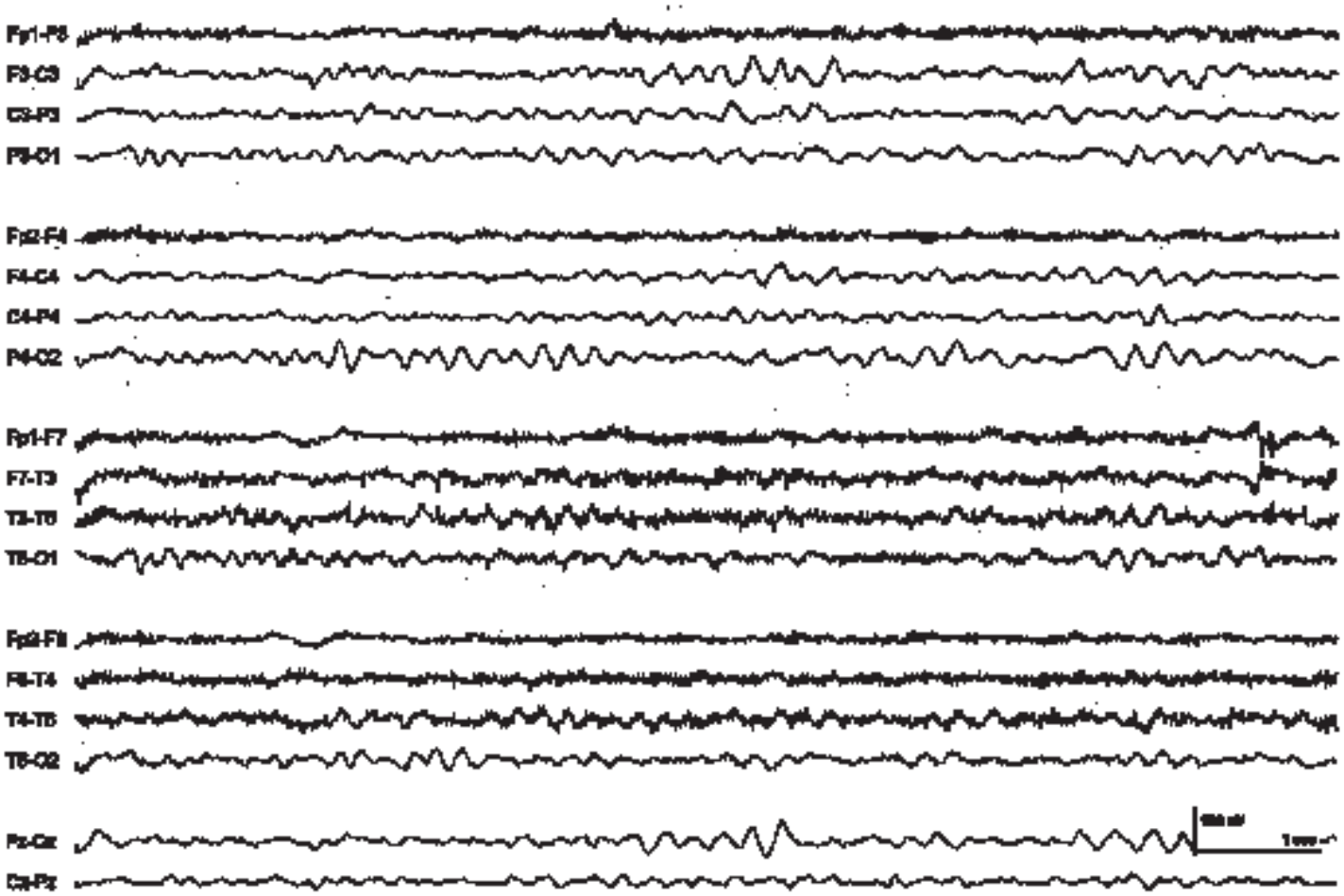


FIG. 17.16. EEG from the same 8 month-old child as in Fig. 17.14*A* obtained 1 month after treatment with adrenocorticotropic hormone (ACTH). Despite the resolution of both hypsarrhythmia and infantile spasms, the child remained severely impaired neurologically. TC, 0.1 second; HFF, 70 Hz.

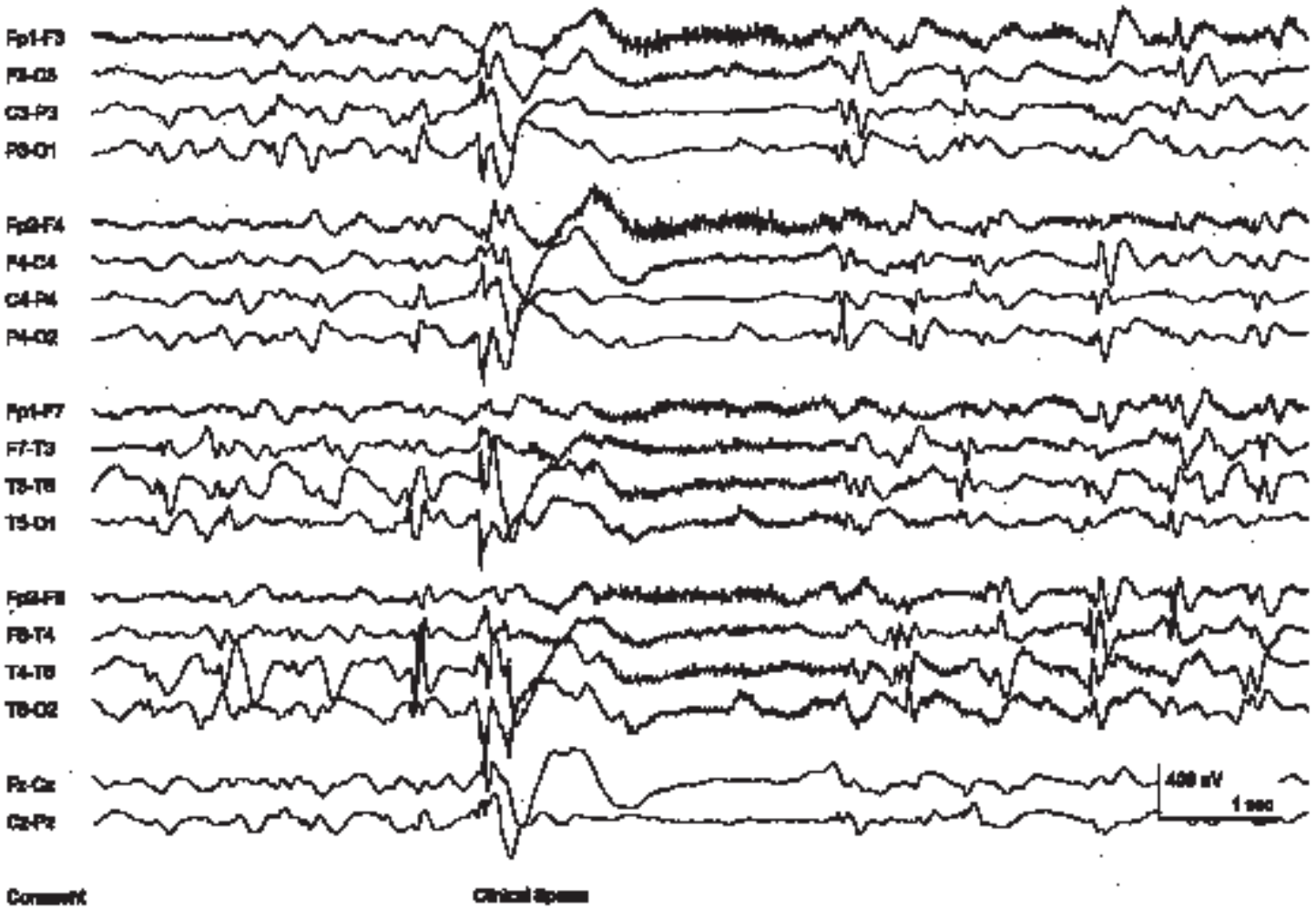


FIG. 17.17. Electrodecremental pattern associated with a typical spasm. There is a high-voltage slow wave followed by 3 seconds of greatly attenuated EEG activity. TC, 0.3 second; HFF, 70 Hz.

Lennox-Gastaut Syndrome

Clinical Features

William G. Lennox and, later, Henri Gastaut described the clinical and electrographic features of this disorder. The Lennox-Gastaut syndrome (LGS) encompasses a characteristic triad of severe generalized epilepsy, mental retardation, and an EEG pattern of slow-spike-and-wave discharges (103,171,172). Age at onset is usually between 1 and 8 years; most cases begin between the ages of 2 and 5 years. Onset after 10 years of age is rare (13,18,186).

The ILAE Classification of Epilepsies and Epileptic Syndromes (228) includes LGS among the generalized cryptogenic or symptomatic epilepsies. It is defined by the following criteria:

1. High seizure frequency; tonic, atonic, and atypical absence seizures are the most common. Myoclonic, generalized tonic-clonic, and partial seizures may also be present. As a rule, patients with LGS have multiple seizure types, and at least one episode of status epilepticus occurs in the majority (13).
2. Mental retardation, in general. More recently, some authors have argued that behavioral disorders, not accompanied by cognitive impairment, should be sufficient for diagnosis (105).
3. EEG demonstrating abnormal background activity with diffuse sharp-slow waves that have a repetition rate of less than 3 Hz. There are often multifocal spikes or sharp waves and, during sleep, frequent bursts of 10 Hz and faster frequencies.

LGS accounts for about 10% of all childhood epilepsies (3,102), although the actual prevalence may be much lower if rigorous criteria are used (13,18). Tonic, atonic, and myoclonic seizures can all result in the characteristic "drop attacks" seen in LGS, and differentiating among these on the basis of clinical features alone is often difficult. Moreover, there is significant overlap among the ictal patterns (see later discussion). Despite the consistent electroclinical triad, LGS cannot be attributed to a single cause or common pathological substrate. Diverse prenatal, perinatal, and postnatal disorders have been implicated. About two-thirds of cases are considered symptomatic, because a preexisting neurological condition can be identified. One-third of cases are classified as cryptogenic (54,103,186).

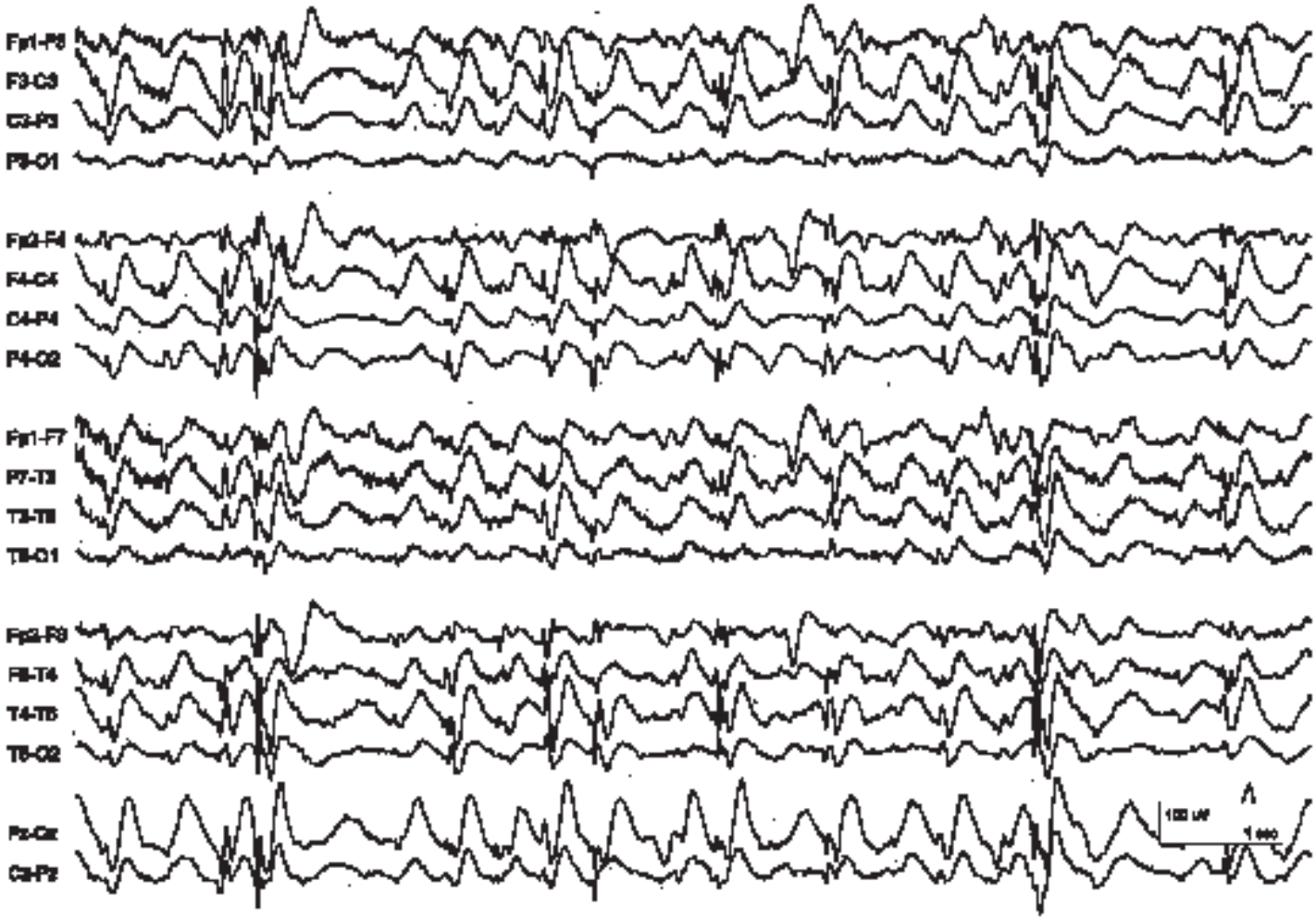
Electroencephalographic Findings

Interictal EEG: Slow-Spike-and-Wave Pattern. Gibbs et al. (109) were the first to describe the characteristic slow-spike-and-wave abnormality, a pattern they called "petit mal variant" to distinguish it from the stereotyped 3-Hz spike-wave discharge of childhood absence epilepsy. The slow-spike-and-wave discharge is more accurately described as a slow-sharp-and-wave (SSW) complex, because it consists predominantly of biphasic or triphasic surface-negative sharp waves of 150 to 200 milliseconds' duration followed by high-voltage (300- to 400-μV) negative slow waves, each lasting about 350 milliseconds (34,103,186). The SSW complexes are bilateral, synchronous, and symmetrical and of highest voltage over the frontal-central regions. These discharges occur repetitively in bursts or extended runs at frequencies of 1.5 to 2.5 Hz (103,186) (Fig. 17.18*A*). It is important to recognize, however, that there are many variations on this general theme. For example, SSW discharges can vary, both between and within individual bursts, in morphological appearance, distribution, voltage, and frequency. The repetition rate of SSW discharges can be quite erratic, with frequencies ranging from 1 to 4 Hz. The extended runs of SSW discharges commonly lack discrete onsets or terminations; sometimes they are nearly continuous during the greater part of an entire recording. Most SSW discharges are not accompanied by obvious clinical manifestations (34,103,186). Although usually symmetrical, SSW complexes sometimes show shifting asymmetries. Persistent focal or lateralized asymmetries of SSW discharges usually occur in symptomatic cases with focal neurological abnormalities (34,186). Asymmetries of SSW discharges usually include associated asymmetries in background activity (186).

Some authors have reported that hyperventilation increases the occurrence and duration of SSW bursts in more than 50% of patients (35,186), but this is disputed by others (34,103). Photic stimulation typically has no effect on SSW activity (18,34,103,186).

NREM sleep dramatically enhances SSW discharges in the great majority of patients (34,103,186). This effect is not universal, however, and in some patients, the discharges may actually decrease in both NREM and REM sleep (35,137). On occasion, SSW discharges are prominent during sleep even when they are infrequent during wakefulness, which underscores the importance of obtaining an adequate sleep recording (186). Polyspike-wave discharges may emerge during sleep (34,51,137). In a minority of patients, sleep causes fragmentation of SSW bursts and a pseudoperiodic or burst-suppression appearance, with 2- to 3-second paroxysms of SSW alternating with diffuse voltage attenuation of background activity (186).

Interictal EEG: Paroxysmal Fast Activity. Paroxysmal fast activity (PFA), the second defining electrographic feature of LGS, is present mainly or exclusively during sleep in nearly all patients (13). PFA consists of diffuse, bilaterally synchronous bursts of 15- to 20-Hz activity that last several seconds. It is of highest voltage in the frontal areas (51) (Fig. 17.19). The frequency of PFA



A

FIG. 17.18. EEG of a 29-year-old woman who had had Lennox-Gastaut syndrome (LGS) since early childhood. **A:** Interictal EEG recording demonstrating diffuse background delta frequency slowing and nearly continuous 1.5- to 2.0-Hz bilateral synchronous slow-spike-and-wave (SSW) discharges. During this time, the patient was attentive and interactive. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*

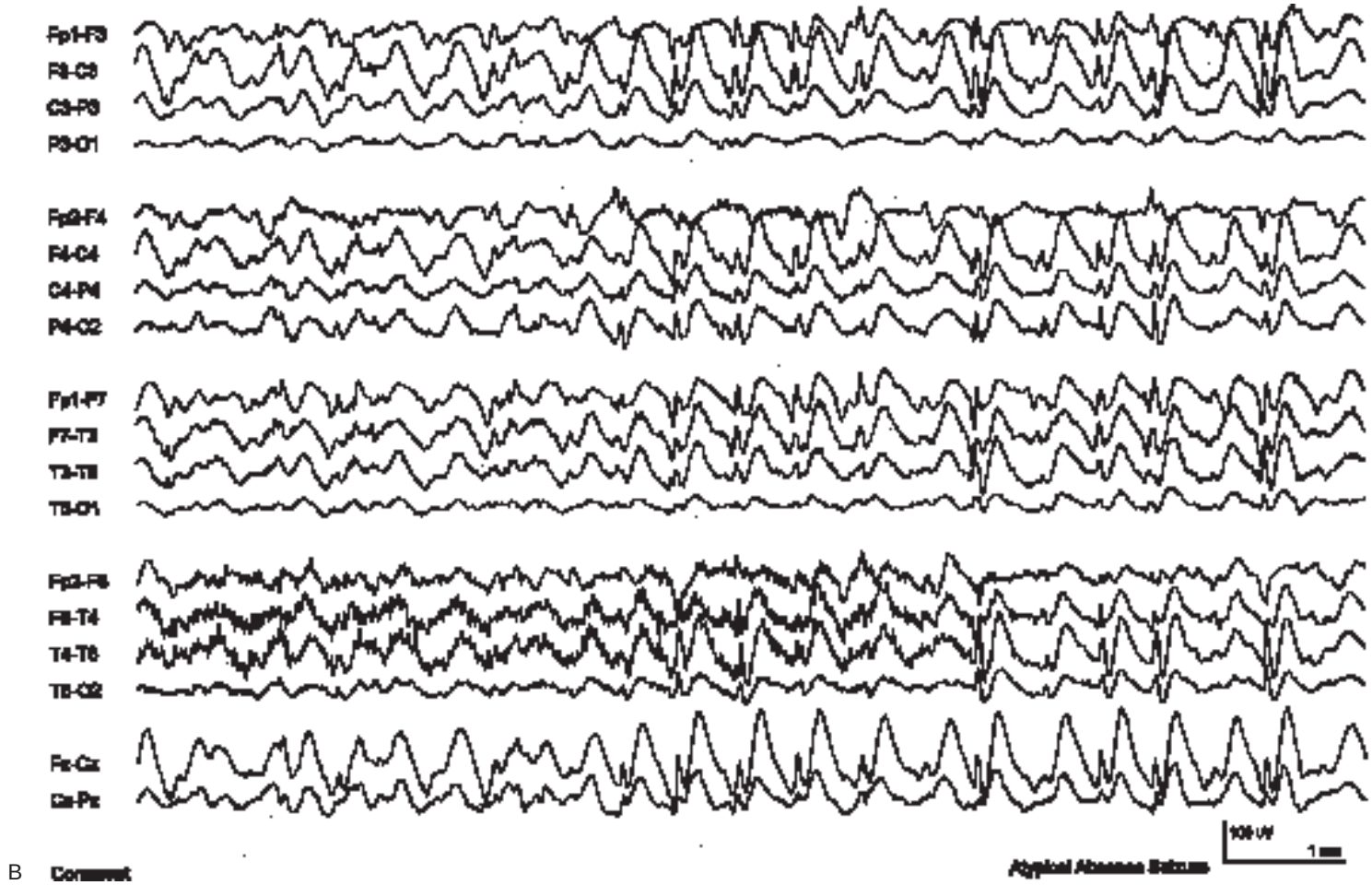


FIG. 17.18. *Continued.* **B:** Atypical absence seizure characterized by decreased responsiveness and gaze deviation to the right. Although very similar to the interictal recording shown in part *A,* the SSW discharges appear more organized and sustained at a consistent 2-Hz frequency. TC, 0.1 second; HFF, 70 Hz.

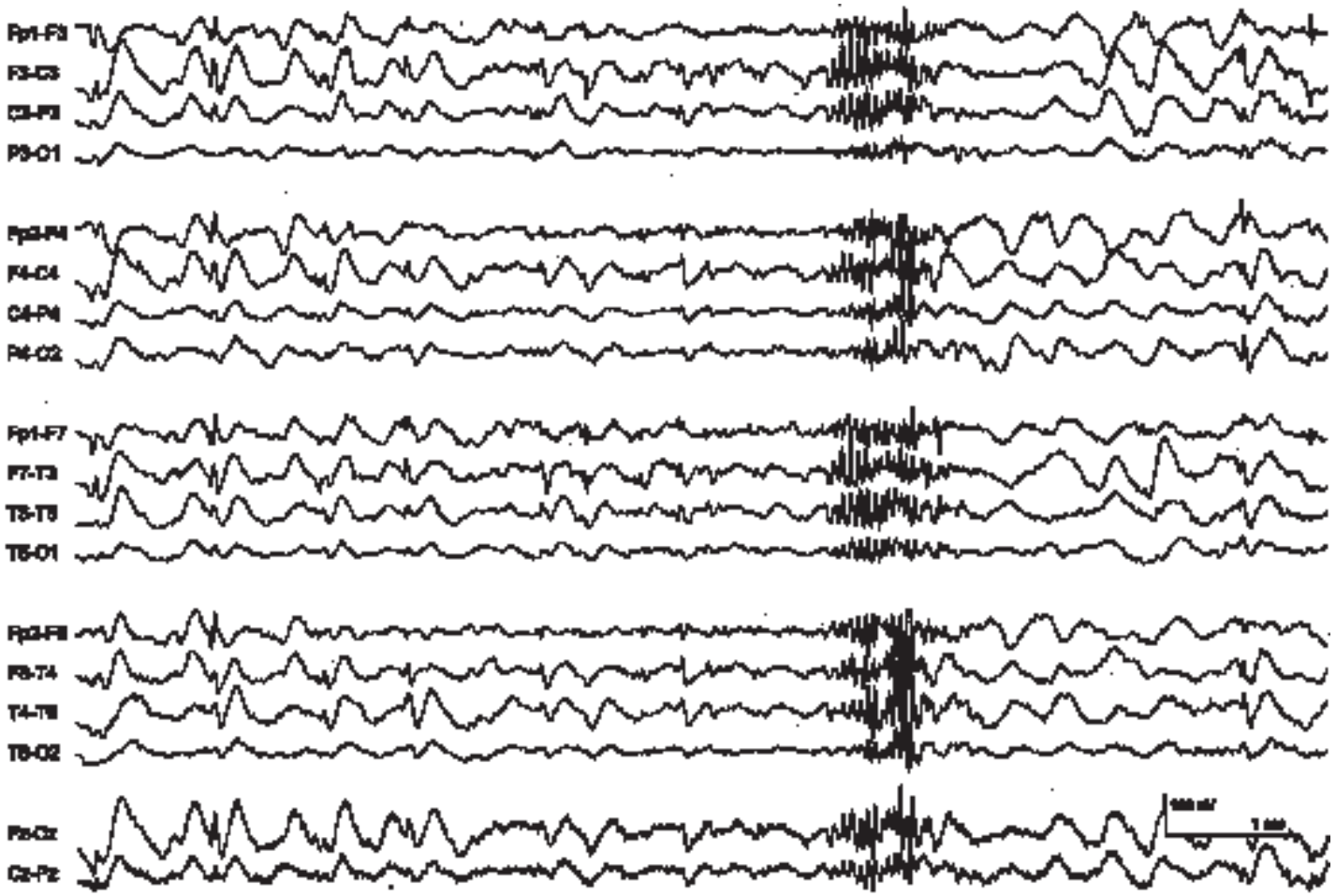


FIG. 17.19. Sleep EEG of a patient with Lennox-Gastaut syndrome (LGS). There are frequent bursts of diffuse 16- to 20-Hz paroxysmal fast activity (PFA) without any visually detectable clinical changes. TC, 0.1 second; HFF, off.

can vary from 7 to 30 Hz, and the voltage may vary from 25 to 250 μV. The duration of PFA bursts ranges from 2 to 12 seconds (51). Bursts of PFA occur up to hundreds of times each night, but only in NREM sleep; they are absent during REM (51).

Although indistinguishable from the ictal pattern associated with tonic seizures (see later discussion), the majority of PFA discharges are not accompanied by any visually discernible clinical changes. Chatrian et al. (51) reported absence of clinical manifestations, even from submental electromyographic electrodes, in 77% of 1,432 discharges. However, electrodes placed over the paraspinous muscles demonstrate subclinical tonic muscle activity that is correlated with bursts of PFA in a higher percentage of patients. Duration of PFA may be one important variable associated with clinical manifestations. Brenner and Atkinson (37) studied 20 patients with LGS and found that bursts of PFA lasting more than 6 seconds usually produced clinical changes, whereas those lasting less than 6 seconds were typically clinically asymptomatic. Autonomic changes, including tachycardia and apnea, can occur in association with PFA, even when motor manifestations are absent (51,137) Thus, it can be argued that PFA is not, strictly speaking, an interictal finding, although the ictal manifestations may be subtle and not visually detectable.

In addition to the characteristic SSW complexes, focal or multifocal epileptiform discharges occur in 14% to 18% of patients (35,186). Additional focal or lateralized abnormalities are present in 23% to 50% of LGS patients (10,186). Diffuse abnormalities of background activity occur in up to 90% of patients with LGS (10,54,103,186). In two-thirds of cases, background slowing is moderate to severe and is generally correlated with the degree of cognitive impairment (186).

Many patients have abnormal sleep architecture. In comparison to normal age-matched controls, REM sleep time in patients with LGS is nearly always reduced and can be absent completely (5,137). In extreme cases, there is complete lack of identifiable sleep stages, and only an undifferentiated pattern of NREM sleep is seen (51). Other patients develop such severe disorganization of background activity during sleep that a quasi-hypsarrhythmic pattern emerges (186).

In most patients with LGS, mental impairment and severe epilepsy persist throughout life. The characteristic electroclinical triad persists into adulthood in 75% of patients (10,13,177).

Ictal EEG. The electrographic correlate of a tonic seizure is the PFA pattern (Fig. 17.20). The discharge is usually of maximal voltage shortly after onset but fluctuates subsequently (51). Diffuse voltage attenuation or a burst of SSW discharges may precede the PFA discharge. After the seizure, baseline EEG activity returns rapidly (51).

Egli et al. (81) described a slightly different type of tonic seizure that they termed *pure axial spasm*. The spasm consists of a high-velocity muscle contraction lasting 0.5 to 0.8 seconds that produces prominent flexion of the neck, trunk, and hips. Consciousness is not impaired, and usually no change in EEG activity is recordable from scalp electrodes.

Atypical absence seizures have been reported in 32% (103), 79% (13), and 100% (310) of patients with LGS. The rising percentage most likely reflects the introduction of continuous video-EEG monitoring and recognition of the more subtle manifestations of these seizures. Although the distinction between typical and atypical absence seizures is not always clear-cut (135), several features tend to characterize the majority of atypical absences. First, impairment of consciousness is incomplete, and some purposeful activity may continue. Second, onset and termination are gradual, often making the seizures difficult to recognize, especially when there is marked cognitive impairment. Third, excessive salivation, eyelid or mouth myoclonus, changes in postural tone, and automatisms are common.

Several ictal EEG patterns have been associated with atypical absence seizures. Most often, there is diffuse, bisynchronous, high-amplitude, 1- to 2.5-Hz SSW activity, which may be difficult to distinguish from the interictal EEG pattern. However, ictal paroxysms tend to be more regular, more widely distributed, and of longer duration than interictal bursts (186) (see Fig. 17.18) . Less often, two other patterns are seen: (a) diffuse, bisynchronous, 7-Hz spike-wave discharge or (b) diffuse bursts of 10- to 20-Hz rhythmic activity similar to PFA (35,310).

Ictal EEG recordings during atonic seizures are also variable. Most often, there is a diffuse, high-voltage, bisynchronous burst of polyspikes or polyspike-waves similar to the discharge seen with myoclonic seizures. Less often, the EEG shows diffuse spike-wave, SSW, or generalized fast-frequency activity.

Association of Lennox-Gastaut Syndrome with Other Epileptic Encephalopathies

Blume (33) described a syndrome that is related clinically to LGS with mental retardation and severe generalized epilepsy, but with multiple independent spike foci on EEG. Unlike West's syndrome and LGS, however, this syndrome is not age-specific, and about one-third of patients are mentally normal.

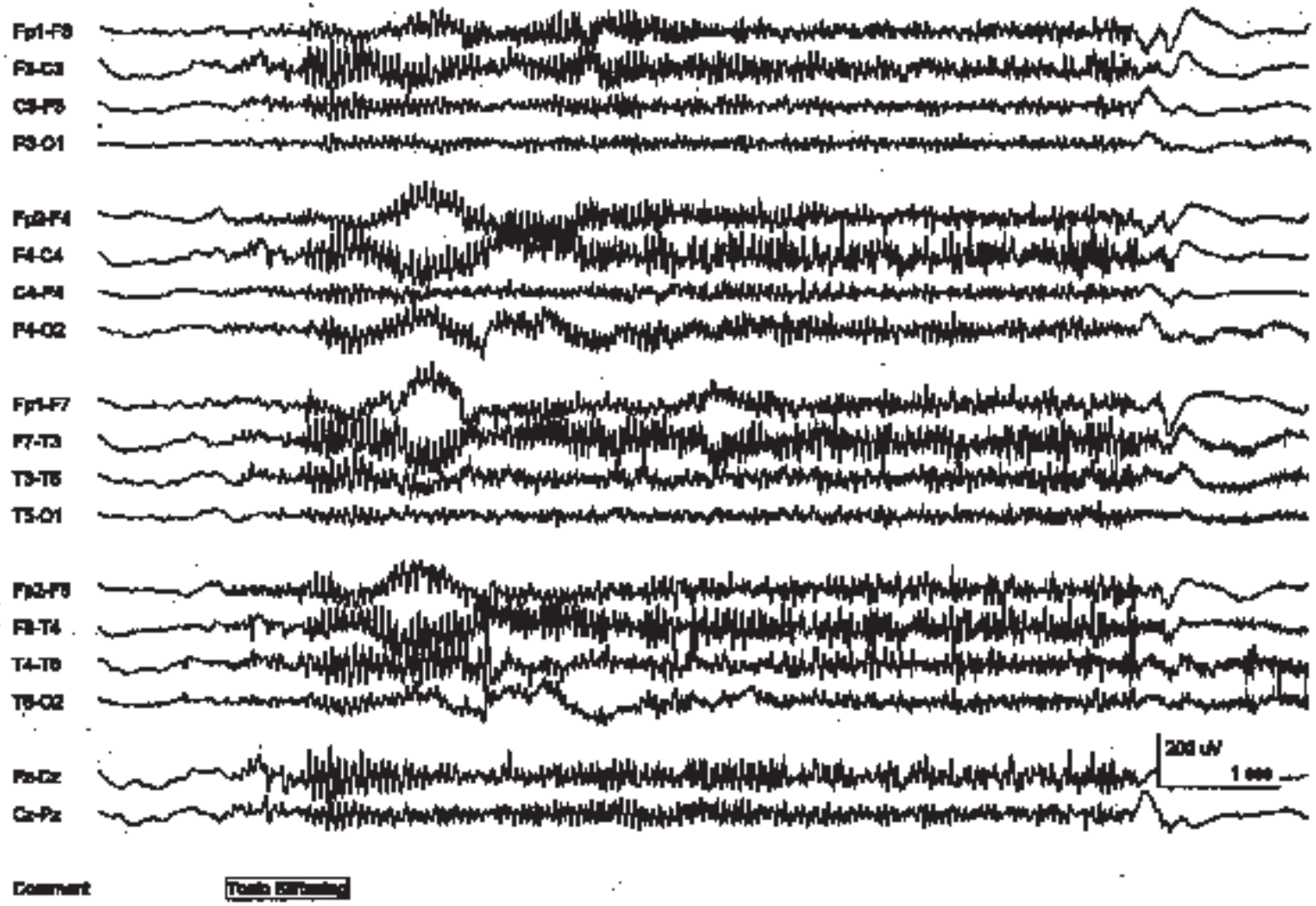


FIG. 17.20. Tonic seizure in Lennox-Gastaut syndrome (LGS). During sleep, the child exhibited abrupt onset of arm and neck stiffening, which lasted several seconds. The EEG shows an 8-second run of bilateral synchronous 16- to 20-Hz activity, which is the ictal discharge. TC, 0.1 second; HFF, off.

There are many associations among infantile spasms, LGS, and multiple independent spike foci. A history of infantile spasms with hypsarrhythmia can be obtained in 17% (13) to 20% (186) of children with LGS. In a few patients, different EEG patterns coexist. For example, in Markand's series (186), some patients showed multiple independent spike foci while awake but SSW during sleep, and nearly one-fourth of patients with SSW in the waking state had hypsarrhythmia during sleep.

Because none of these syndromes is specific with regard to either cause or pathological process, it is likely that the particular manifestations of severe epileptic encephalopathies reflect complex interactions of brain immaturity, developmental mechanisms, timing of brain injury, and pathological processes. When certain sets of clinical and EEG features occur together as the predominant abnormalities, individual clinical-electrographic syndromes can be identified. These groupings, however, show considerable overlap in clinical features and EEG findings, which indicates that although they may be clinically useful, they are fundamentally artificial.

Landau-Kleffner Syndrome and the Syndrome of Continuous Spikes and Waves during Slow Sleep

The Landau-Kleffner syndrome (LKS) and the syndrome of continuous spikes and waves during slow sleep (CSWS) are two rare electroclinical syndromes that have considerable overlap in both clinical and electrographic features.

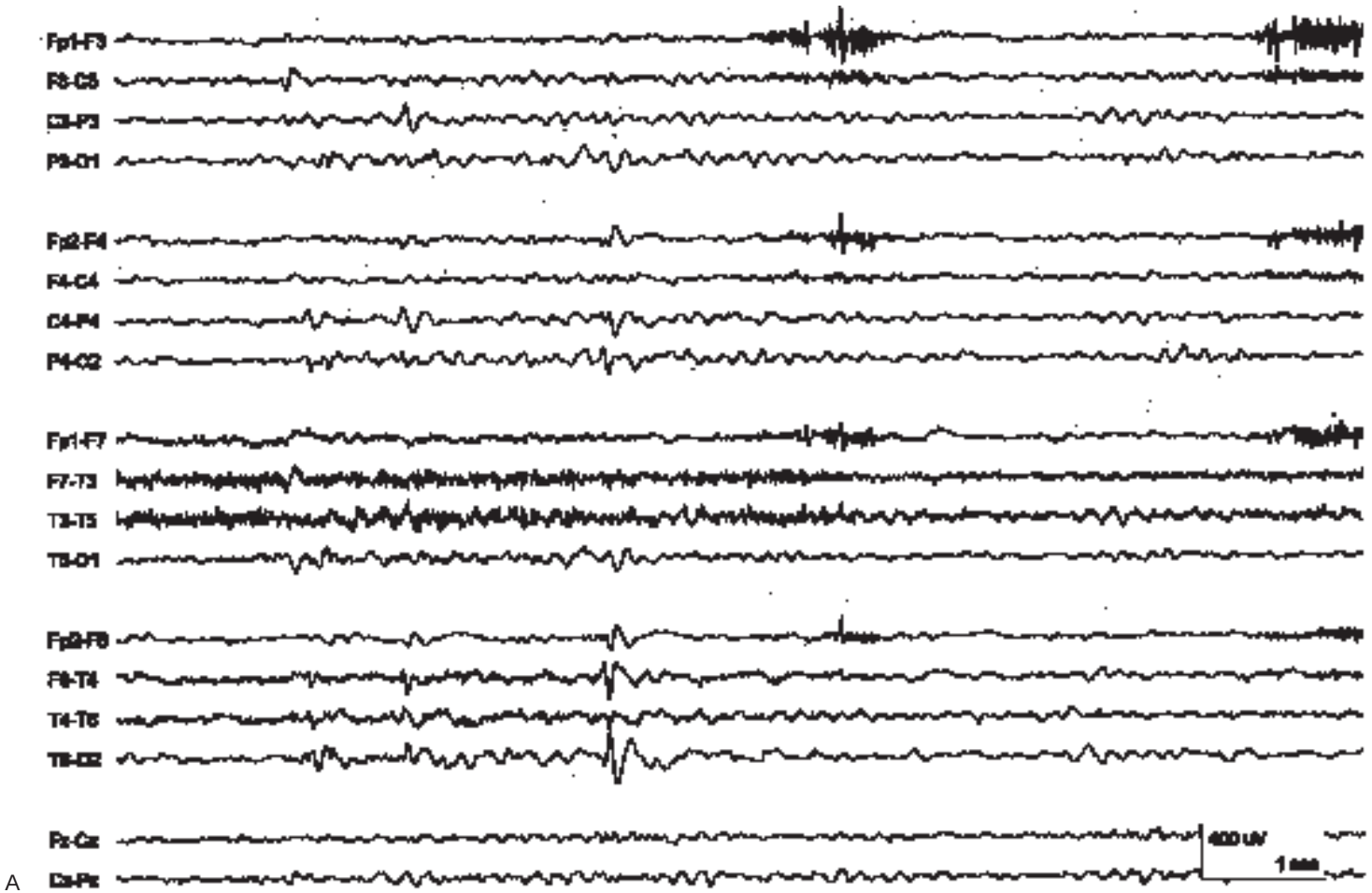
Landau-Kleffner Syndrome

Clinical Features. This syndrome, first described by Landau and Kleffner (167), is characterized by acquired aphasia associated with epileptiform activity on EEG ("epileptic aphasia"). Although the nature of this syndrome is controversial, it is probably not fundamentally an epileptic disorder. It occurs in previously healthy children between the ages of 3 and 9 years (peak incidence, 5 to 7 years) (15,42,134). The first indication of aphasia is verbal auditory agnosia (234), but language function continues to deteriorate. Some children become mute and do not respond even to nonverbal sounds (15,71). Hyperactivity and personality changes appear as the aphasia worsens (15). Seizures occur in about 70% of patients; they tend to be relatively infrequent, although status epilepticus has been reported. Partial motor, atypical absence, generalized tonic-clonic, and atonic seizures have all been reported (15,134). More subtle seizures, such as eyelid myoclonia, ocular deviation, and head drops also occur (198). Type and frequency of seizures are not correlated with outcome (16,198). Similarly, treatment with antiseizure drugs does not clearly affect aphasia, EEG findings, or prognosis. Although subpial transection (Morrell's procedure) has recently been used to eliminate epileptiform activity surgically (198), there are no controlled studies to show that this affects the natural history of the disorder. About two-thirds of children have residual language impairment; cognitive and behavioral abnormalities are less frequent consequences.

Electroencephalographic Findings. A paroxysmal EEG is one of the defining features of LKS, and epileptiform discharges are thus invariably present. Epileptiform activity is extremely variable in both location and amount. High-voltage multifocal spikes and spike-wave discharges occur both singly and repetitively (15). Discharges occur over the posterior temporal regions preferentially but are not limited to these areas (Fig. 17.21). Epileptiform activity can be unilateral or bilateral. When bilateral, the discharges can be diffuse and bisynchronous and either symmetrical or asymmetrical (15,134,198). In the early stages of the disorder, epileptiform activity may be limited to sleep. The EEG abnormalities vary considerably over time, so that the distribution, abundance, and topography may change from one tracing to the next (69).

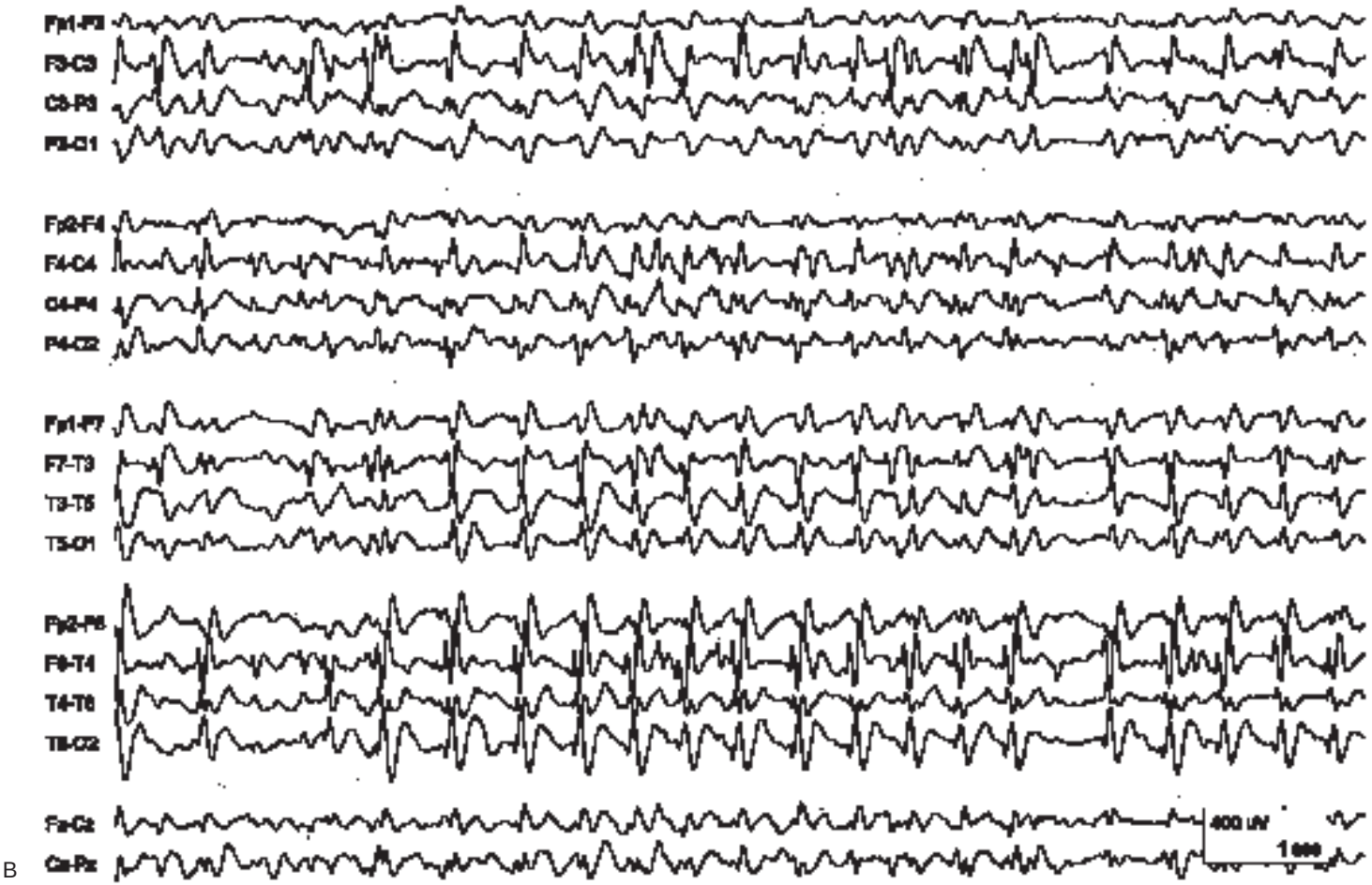
Morrell et al. (198) used a variety of specialized techniques, including the methohexital suppression test, intracarotid injection of amobarbital, and electrocorticography to show that some patients with LKS had a single epileptogenic focus in the perisylvian region. They proposed that bilateral discharges resulted from spread from this one epileptogenic area rather than being manifestations of generalized or independent abnormalities. This argument became the basis for using multiple subpial transections to suppress the perisylvian focus. Although Morrell et al. (198) reported dramatic and clinical improvement after surgery, a controlled study is necessary to confirm these data.

NREM sleep activates epileptiform activity, often to a marked degree. Epileptiform discharges exhibit larger fields, tend to become generalized, and occur repetitively at frequencies of 1.5 to 3 Hz (134). During REM sleep, the slow spike-wave pattern fragments and focal or multifocal discharges appear in a pattern similar to that seen in the waking state (30). Sometimes there is continuous (occupying more than 85% of sleep time) spike-wave activity that is similar to that seen in the syndrome of CSWS (134,220). In a study of five patients with LKS, Hirsch et al. (134) found that all of them showed continuous spike-waves during sleep at some point in their course. Similar findings by other researchers (69,198,220) indicate that this pattern is underrecognized and that perhaps most, if not all, patients with LKS demonstrate this pattern with extended polygraphic sleep recordings.



A

FIG. 17.21. EEG of a 6-year-old boy with Landau-Kleffner syndrome (LKS). He had been neurologically normal until 9 months previously, when he developed rapidly progressive loss of language skills. He had only three seizures, all generalized convulsions. Results of brain imaging, cerebrospinal fluid studies, and metabolic evaluation were normal. **A:** EEG in the waking state demonstrates mild slowing of background activity and infrequent right midtemporal spikes. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.21. *Continued.* **B:** EEG during non–rapid-eye-movement sleep shows nearly continuous spike-and-wave discharges. Although broadly distributed bilaterally, they are maximal over the right temporal region. TC, 0.1 second; HFF, 70 Hz.

Seizure remit and the EEG normalizes in nearly all patients by the end of adolescence (15,70), but some degree of language dysfunction persists in the majority (15,70,75). Most patients show improvement, but the degree of recovery is variable and unpredictable; some patients remain profoundly impaired.

Continuous Spikes and Waves during Slow Sleep

Clinical Features. This syndrome was first described by Patry et al. (222) as "subclinical electrical status epilepticus induced by sleep." It was later renamed because of the lack of typical clinical features associated with status epilepticus. The ILAE Commission on Classification (228) accepted the proposed name, continuous spike-waves during slow sleep, and described the syndrome as follows:

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

The syndrome of CSWS is a rare condition, accounting for fewer than 0.5% of cases of childhood epilepsies (197). Age at onset ranges from 1 to 12 years, but onset peaks between the ages of 5 and 7 years. Twenty percent of cases begin between the ages of 9 and 12 years (42). Two-thirds of patients are neurologically normal before onset of the syndrome (42,272).

In nearly all patients, seizures appear 1 to 2 years before the EEG abnormality of this syndrome (41,272). Simple partial motor and generalized tonic-clonic seizures predominate. Later, with appearance of the syndrome of CSWS, other seizure types emerge, including atypical absence seizures associated with atonia and falls (42,272). Most patients have frequent seizures, often multiple times in a week or even in a single day (272). Tonic seizures do not occur (30,41,196,272). With development of the syndrome, nearly all patients have a significant decline in IQ with deterioration in language, temporospatial disorientation, impaired memory, and reduced attention span. Behavioral changes such as aggressiveness or, rarely, psychosis also occur (30,41,272).

Electroencephalographic Findings. When seizures first appear, EEG findings are nonspecific. Background activity can be normal or abnormal. Occasional epileptiform discharges occur, and these become more frequent during sleep (41,272). Epileptiform activity consists of generalized spike-wave discharges, occurring singly or in bursts, and focal or multifocal spikes or sharp waves that are best developed over the frontal-central regions. Both focal and generalized discharges often occur in the same patient (41,272).

When the CSWS pattern appears, epileptiform activity in the waking state increases. Diffuse 2- to 3-Hz spike-wave discharges predominate, often occurring in runs (222,272). The CSWS pattern itself consists of continuous, generalized, 1.5- to 2.5-Hz slow spike-wave activity that is maximal frontally (222,272) (Fig. 17.22). Discharges of 3 to 5 Hz also occur in some patients (41). Spike-wave discharges can be asymmetrical, especially in patients with focal cerebral lesions (30,41,196). The continuous spike-wave pattern persists throughout NREM sleep, typically occupying more than 85% of the total NREM sleep recording (spike-wave index) (41,222,272). Beaumanoir (16) observed a subgroup of patients with the syndrome of CSWS who had spike-wave indices between 50% and 85%. In these patients, focal discharges continued to be seen during sleep (16). During REM sleep, the continuous spike-wave activity fragments and occupies only about 5% of REM sleep time, often disappearing completely (16,271,272). Occasional generalized spike-waves or focal spikes are seen in REM sleep (271,272).

The CSWS patterns persist for long periods, ranging from 1 to 3 years in most patients and up to 6 years in some cases (16,41,272). The electrographic pattern gradually resolves in all children, although focal abnormalities may remain somewhat longer. Long-term follow-up demonstrates normalization of the EEG, including sleep architecture, in the majority of patients (272).

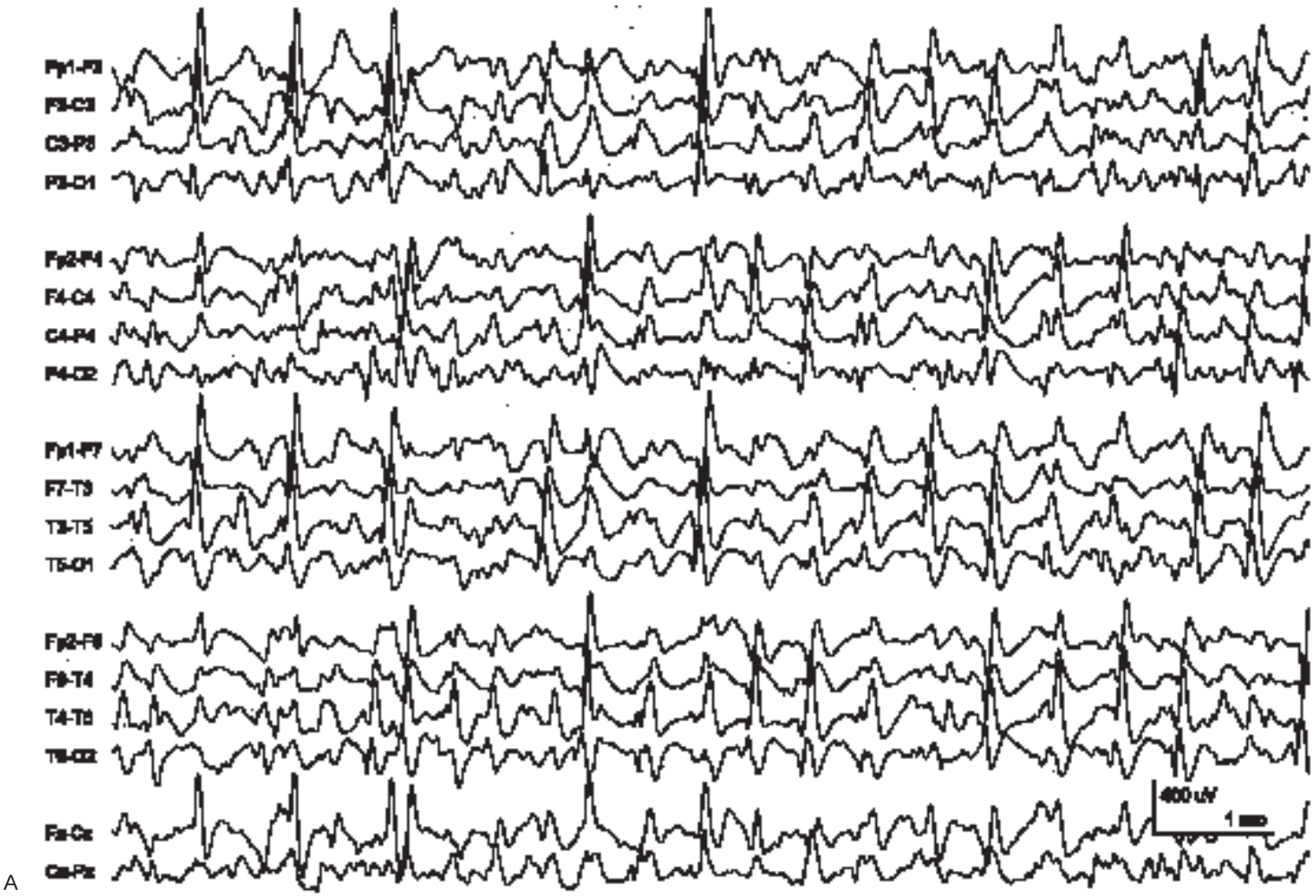
Seizures also remit spontaneously in all patients, regardless of their severity and frequency (41,196,272). EEG normalization and remission of seizures do not always occur simultaneously. In some cases, seizures cease while the CSWS pattern is still present, whereas in others, seizures persist after the CSWS pattern has disappeared (272).

Neuropsychological outcome is not as benign. All patients show neurological and behavioral improvement after the CSWS pattern remits, but recovery is slow and often incomplete (41,272). About half of the patients remain profoundly impaired (41,272).

Progressive Myoclonus Epilepsies

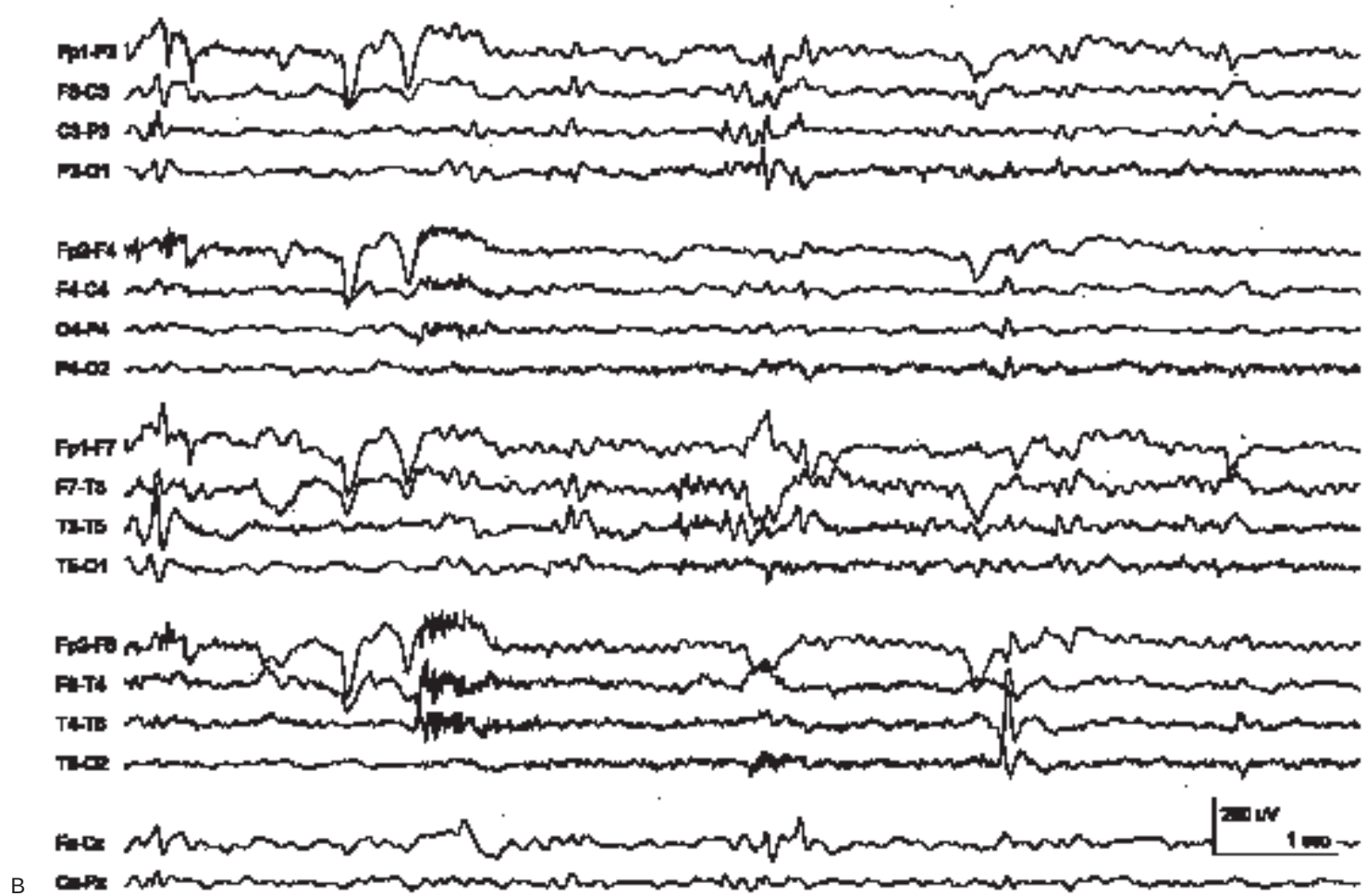
Clinical Features

The progressive myoclonus epilepsies (PMEs) are rare syndromes characterized by myoclonic seizures and progressive neurological abnormalities, especially ataxia and dementia. Five entities account for most of the PMEs: myoclonic epilepsy with ragged red fibers (MERRF), Unverricht-Lundborg disease, Lafora's disease, neuronal ceroid lipofuscinosis in its various age-



A

FIG. 17.22. The syndrome of continuous spikes and waves during slow sleep. EEG of an 11-year-old boy with global cognitive decline and seizures. **A:** During sleep, there was continuous sharp-and-slow-wave activity, which shows shifting laterality for waveform definition and voltage. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.22. *Continued.* **B:** The EEG in the waking state is strikingly different. Background activity is mildly attenuated with reduced complexity and occasional multifocal sharp waves (T6, P3, F7). TC, 0.1 second; HFF, 70 Hz.

related forms, and sialidoses (24). The clinical forms of each are characteristic. It is often possible to make specific diagnoses from careful review of clinical features, family history, biopsy of skin or muscle, and increasingly, genetic analysis (25). EEG and evoked potential studies help support a clinical diagnosis of PME and distinguish PME from other generalized epilepsies. However, only a few electrophysiological findings are sufficiently specific to indicate a particular syndrome.

Electroencephalographic Findings

EEG findings in PME were reviewed by Berkovic et al. (26). Background activity may be normal initially but inevitably slows as dementia develops. EEG features that distinguish the various sleep stages disappear. In all forms of PME, the predominant epileptiform abnormality consists of generalized spike, spike-wave, and polyspike-wave discharges, most often at a rate of 3 to 6 Hz. Occipital spikes and seizures occurring independently from both hemispheres are seen in all major forms of PME except the sialidoses; these are especially common in Lafora's disease. Photosensitivity and high-voltage, exaggerated somatosensory evoked potentials are also common in most of the PMEs (162,193). Visual and brainstem evoked potentials are usually normal. Prolonged central conduction times occur in late stages of Lafora's disease and MERFF (162,267).

Myoclonic jerks in PME can be generalized, fragmentary, and multifocal in the same patient. Action, or reflex, myoclonus (especially in response to light) is common. Polygraphic studies demonstrate that some, but not all, jerks are accompanied by epileptiform activity (23). Back-averaging techniques may demonstrate EEG potentials preceding muscle jerks that are not obvious with routine recordings. In view of the abundant evidence of cortical hyperexcitability in the PMEs, it is likely that most, if not all, myoclonus in these disorders is of cortical origin, although this has not been demonstrated in careful studies.

A few EEG findings suggest a specific PME syndrome. In the sialidoses, generalized spike-wave activity is infrequent or absent altogether. Instead, myoclonus is associated with characteristic trains of 10- to 20-Hz, low-voltage, positive spikes at the vertex (87,233). Runs of these vertex spikes also occur without myoclonus and are especially frequent during deep sleep. In late infantile and adult neuronal ceroid lipofuscinosis, single light flashes evoke giant potentials over the occipital and posterior scalp regions. Paradoxically, the electroretinographic pattern is greatly attenuated or altogether absent in late infantile and juvenile neuronal ceroid lipofuscinosis (233).

Temporal Lobe Epilepsy

The ILAE Classification of Epilepsy Syndromes (228) distinguishes between medial temporal lobe epilepsy and neocortical temporal lobe epilepsy. Both syndromes can be treated effectively by surgical resection, although the extent of the presurgical evaluation in each is substantially different. Thus, clinical and EEG criteria for distinguishing the two are increasingly important.

Medial Temporal Lobe Epilepsy

Clinical Features. Medial temporal lobe epilepsy (MTLE) is the most common form of localization-related epilepsy occurring in adults. A consistent clinical syndrome has been defined by careful analysis of surgical series (88,95). Onset occurs at the end of the first decade or during adolescence in most cases. Over 80% of patients have a history of at least one convulsive seizure in early childhood; the great majority of these are febrile seizures. Complex partial seizures are the predominant seizure type, with secondarily generalized seizures relatively infrequent or controlled with antiepileptic drugs. Auras, especially epigastric ones, are common. MTLE is highly associated with medial temporal sclerosis, which can be detected reliably by magnetic resonance imaging using appropriate anatomical orientation and imaging sequences (47,145). Anteromedial temporal lobe resection results in freedom from seizure in more than 80% of such patients.

Electroencephalographic Findings. Interictal EEG. Interictal EEG findings in MTLE are also consistent: anterior temporal sharp waves associated with intermittent temporal slowing (Fig. 17.23). Findings are summarized in Table 17.4. Voltage of the IEDs is usually maximal in temporal basal electrodes, such as sphenoidal or "true" anterior (T1/2) temporal electrodes. Because of this, the typical IEDs of MTLE are sometimes referred to as temporal-sphenoidal discharges. IEDs that are of maximal voltage over the lateral temporal area also occur in patients with MTLE, but these are exceptional (93,303). Topographic voltage analysis has demonstrated that most IEDs in MTLE show a relatively discrete region of electronegativity over the ipsilateral inferior temporal scalp that is accompanied by a more diffuse area of positivity over the contralateral central-parietal scalp (78). One-third of patients have bilateral IEDs that occur independently on the two sides (56,86,303). Independent bilateral temporal IEDs often appear during non-REM sleep. IEDs recorded during wakefulness and REM sleep are more often lateralized and closely associated with the area of seizure onset (249).

Ictal EEG. The characteristic ictal EEG pattern associated with complex partial seizures of MTLE is a unilateral, 5-Hz (or faster) temporal discharge

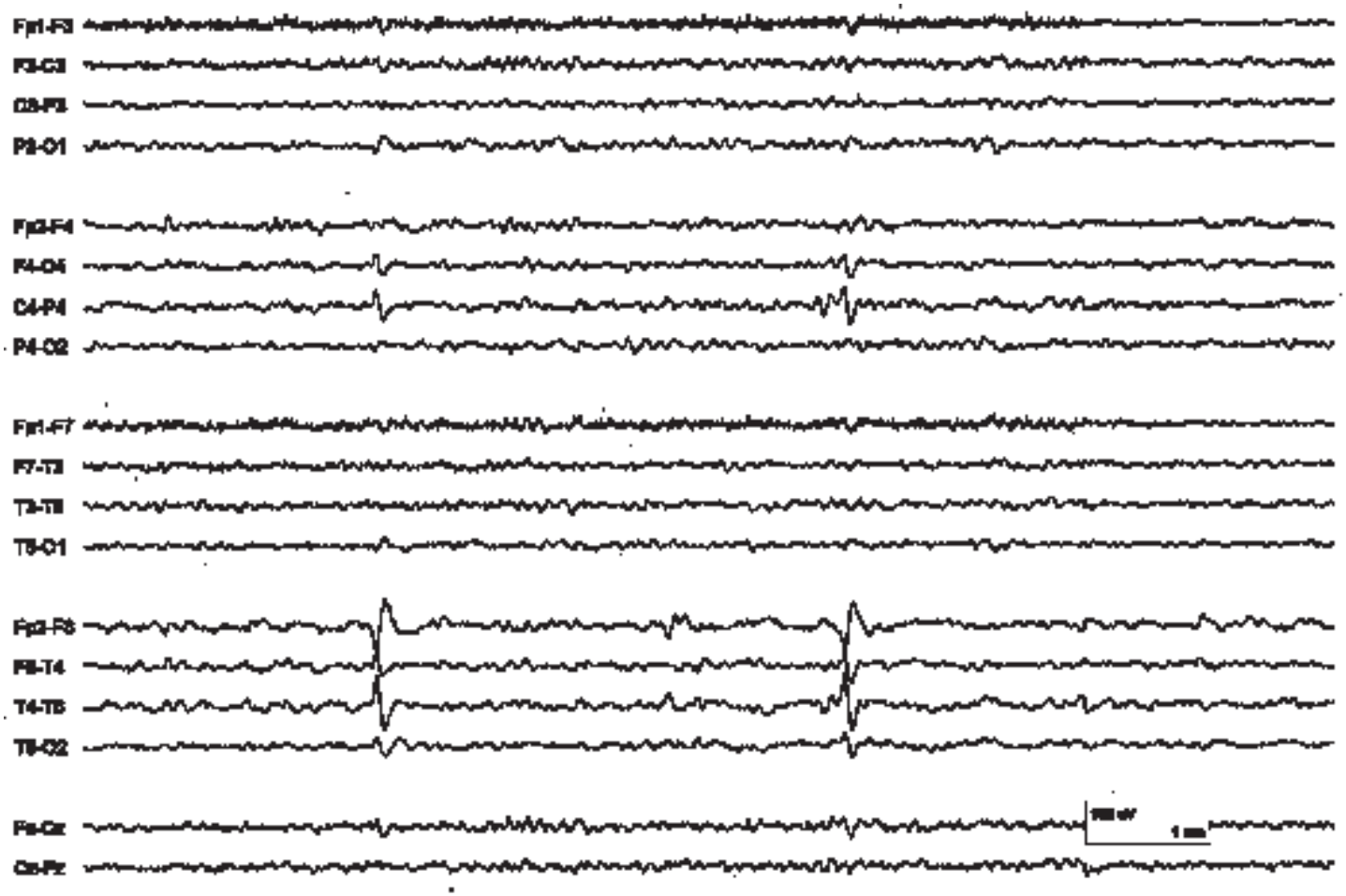


FIG. 17.23. EEG of a 33-year-old woman with complex partial seizures characterized by a rising epigastric sensation, oral automatisms, and impaired responsiveness. Brain magnetic resonance image showed right mesial temporal sclerosis. The interictal EEG shows right temporal polymorphic theta and delta frequency slowing and epileptiform sharp waves which phase reverse at F8. TC, 0.1 second; HFF, 70 Hz.

TABLE 17.4. *Patients with medial temporal lobe epilepsy: scalp EEG interictal paroxysmal activity*

Total number of patients	67
Present	64
Absent	3
Strictly unilateral	35
Concordant	33
Discordant	2
Anterior temporal	32
Midtemporal	1
Posterior temporal	2
Bilateral independent/anterior temporal predominant	28
Equal	7
Lateralized preponderance	21
Concordant	15
Discordant	6
Bilateral synchronous predominant	1

From Williamson PD, French JA, Thadani VM, et al. Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. *Ann Neurol* 1993;34:781–787.

that appears in anterior and inferior temporal scalp electrodes within 30 seconds or so after onset of clinical symptoms and signs (93,111,242,291) (Fig. 17.24). This finding occurs in 82% to 94% of patients with MTLE (242,291) and lateralizes seizure onset correctly in more than 95% (242,269,291). Table 17.5 summarizes the main ictal scalp findings. Ictal EEG changes are only rarely seen in scalp electrodes when clinical symptoms first appear. The ictal temporal-sphenoidal discharge has less lateralizing value in patients with bilateral temporal IEDs (269,290). Although quite sensitive, temporal-sphenoidal ictal discharges are probably less specific for MTLE than are the interictal discharges, which are also seen in temporal neocortical epilepsy (77,111) and, occasionally, in extratemporal epilepsy. Propagation of the ictal discharge from extratemporal to temporal areas presumably accounts for the latter observation. Focal slowing or attenuation, usually on the side of seizure onset, occurs postictally in about 70% of patients with MTLE (156,291). Postictal focal EEG findings are more common after partial seizures in MTLE than after partial seizures originating outside the temporal lobe (156,290).

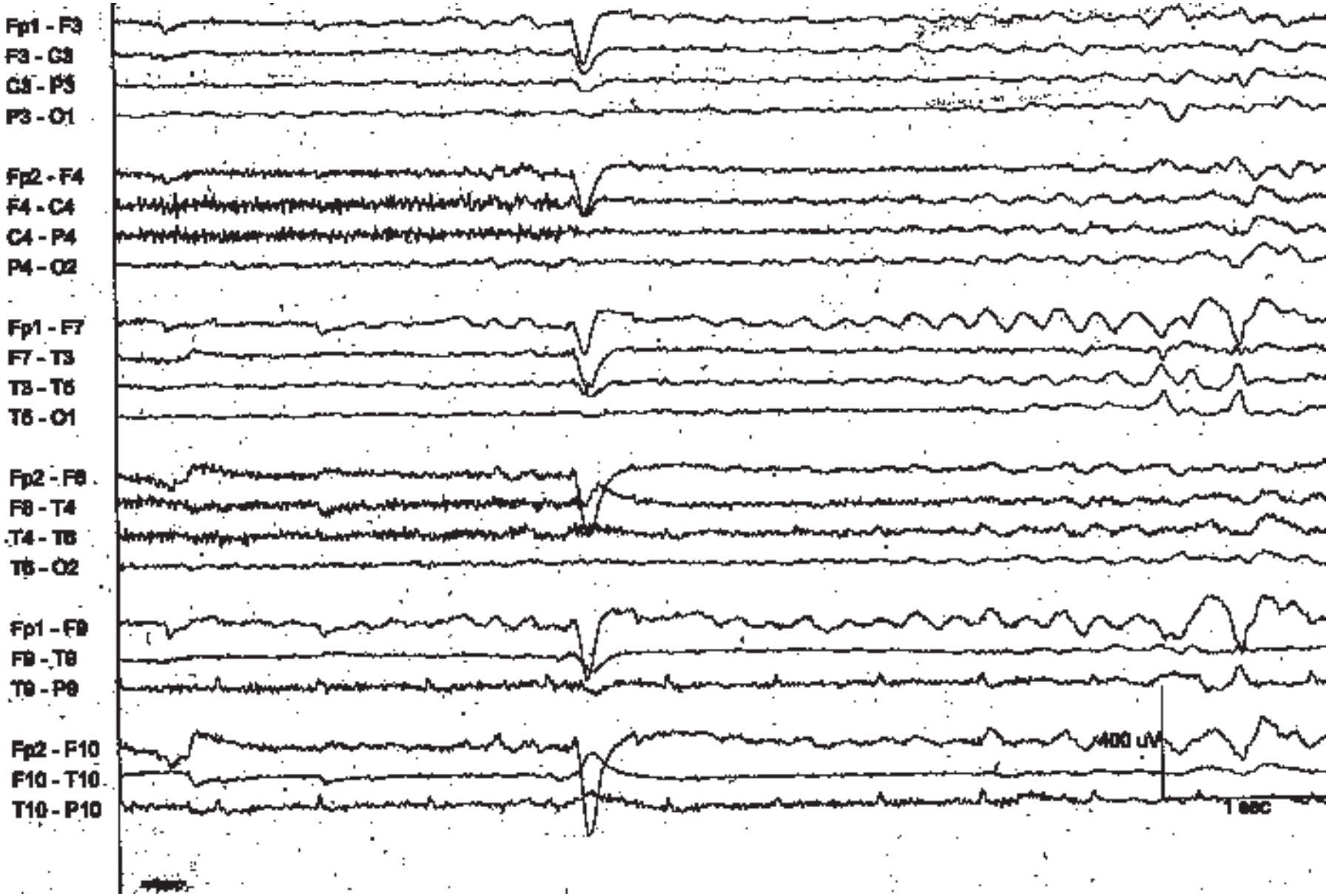
Neocortical Temporal Lobe Epilepsy

Clinical Features. Neocortical temporal lobe epilepsy (NTLE) has been more difficult to characterize because it is less common that MTLE and also because demonstrating a lateral temporal onset requires excluding a medial temporal onset, which can be a difficult challenge. Making the distinction often requires placement of intracranial electrodes. Descriptions of NTLE emphasize absence of features present in MTLE; there are few positive distinctive characteristics (93,111,288). Epigastric auras occur more often in MTLE, but they can also occur with NTLE, probably caused by medial spread of the ictal discharge (79,253). Early oroalimentary automatisms and asymmetrical limb behaviors (contralateral dystonic posture and ipsilateral automatisms) are infrequent in NTLE (111,253).

Electroencephalographic Findings

Interictal EEG. EEG features of NTLE are also less consistent and specific than those of MTLE. IEDs localize to the temporal region but tend to be more broadly distributed than in MTLE. Some researchers have found that IEDs of NTLE are less likely to be of maximal voltage in sphenoidal electrodes (93,226), but this difference has not been found by others (43). Topographic voltage analysis indicates that most IEDs seen in patients with NTLE have a relatively broad negative region over the ipsilateral temporal scalp and lack the contralateral central-parietal scalp positivity seen in MTLE (77). Focal slowing and independent bilaterally temporal IEDs appear to be equally prevalent in the two syndromes (43).

FIG. 17.24. EEG of a 31-year-old man with complex partial seizures consisting of impaired responsiveness, oral automatisms, dystonic posturing of the right hand, and postictal aphasia. Brain magnetic resonance image showed left mesial temporal sclerosis. The interictal EEG demonstrated left temporal slowing and epileptiform discharges. In this example, the ictal discharge appeared 9 seconds after onset of clinical symptoms. There is rhythmic delta activity (maximal at F7-F9), followed by repetitive sharp waves (maximal at F7-F9-T9) and evolution to rhythmic 6-Hz activity that was maximal in the inferior temporal electrode chain (F9-T9). TC, 0.1 second; HFF, 70 Hz.



1

(Figure continues.)

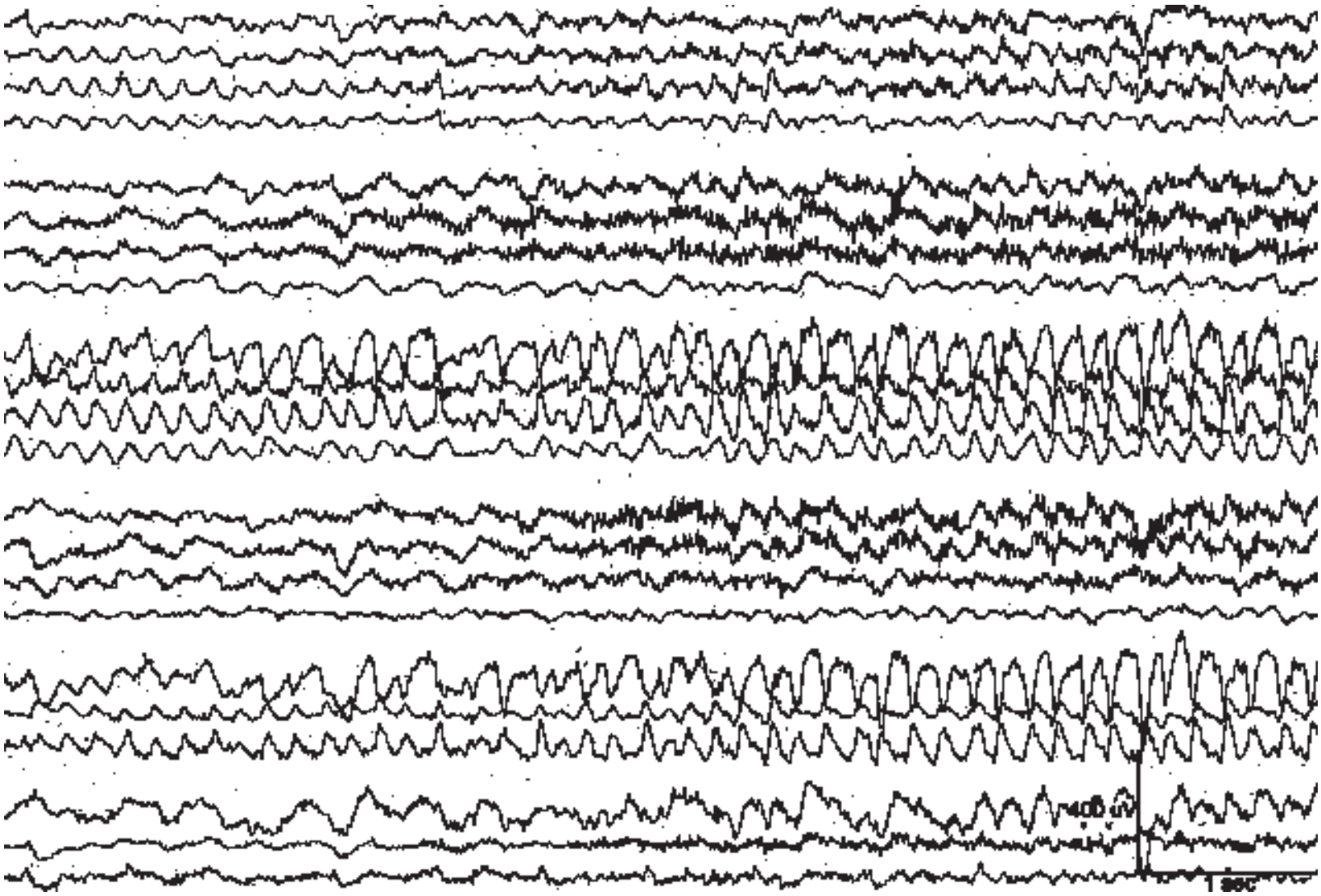
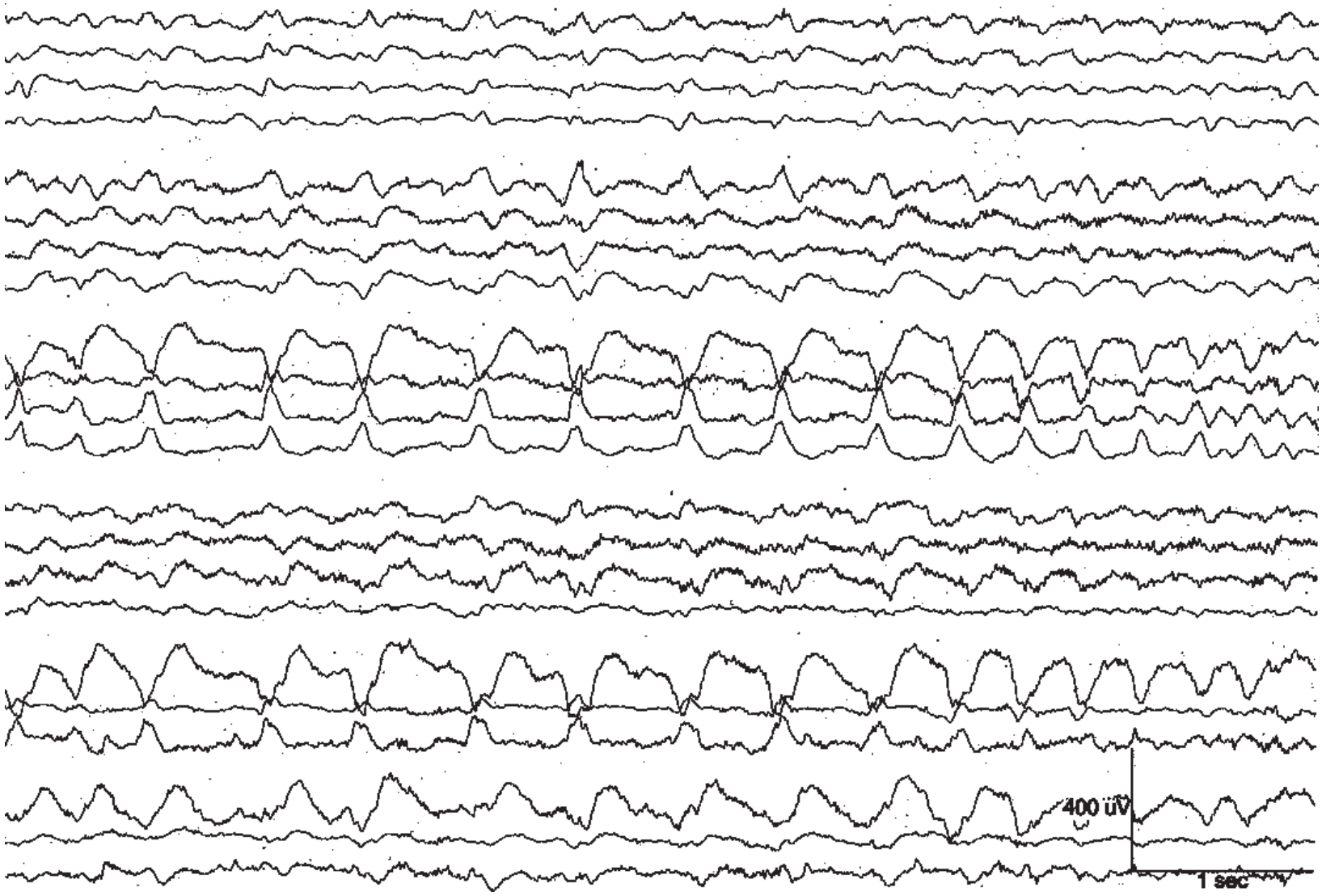


FIG. 17.24. *Continued.*



3

FIG. 17.24. *Continued.*

TABLE 17.5. *Patients with medial temporal lobe epilepsy: scalp EEG ictal changes*

Total number of patients	67
Bilateral ictal changes	13
Lateralized ictal onset	4
Concordant	4
Lateralized buildup (including four with lateralized onset)	54
Concordant	47
Discordant	5
Alternating bilateral	2
Lateralized postictal slowing	45
Concordant	45

From Williamson PD, French JA, Thadani VM, et al. Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. *Ann Neurol* 1993;34:781–787.

Ictal EEG. The temporal-sphenoidal pattern so common in MTLE appears less often in NTLE (93,111,289). Widely distributed, often hemispheric ictal discharges are much more common in NTLE. Other differences are (a) generally slower frequency, (b) less stability of frequency and voltage, and (c) appearance later in the evolution of the seizure (77,93). In two studies, researchers found that parasagittal spread, either ipsilateral or contralateral to the epileptogenic temporal lobe, was seen only in NTLE (93,289), but another report described this in MTLE (77). Absence of a scalp ictal discharge was much more common in NTLE than in MTLE (77).

The overlap in EEG findings between MTLE and NTLE precludes confident distinction of the two syndromes by ictal EEG alone.

Frontal Lobe Epilepsy

Clinical Features

Although neither the incidence nor prevalence of frontal lobe epilepsy (FLE) is known with certainty, large surgical series indicate that it is the second most common localization-related epilepsy, accounting for about 20% of patients undergoing epilepsy surgery (230,237,301). Unlike MTLE, seizure symptoms are heterogeneous, reflecting both the large size of the frontal lobe with its many functional and anatomical divisions, as well as the different pathways of propagation from different areas of the frontal lobe. As a result, several syndromes have been described as types of FLE referable to specific anatomical areas of presumed seizure onset within the frontal lobe. Although the ictal manifestations of frontal lobe seizures suggest particular localizations, no features are definitive for any. Recognizing significant overlap among the regions, the ILAE Commission (228) classified the frontal lobe epilepsies by anatomical areas that produce relatively characteristic seizure symptoms: supplementary motor, cingulate, anterior frontopolar, orbitofrontal, dorsolateral, opercular, and motor cortex.

All frontal lobe seizures share a number of features: (a) early and prominent motor manifestations, including clonic activity, asymmetrical tonic posturing, or complex semipurposeful, repetitive movements that often involve the legs (e.g., bicycling); (b) short duration with minimal or no postictal confusion; (c) occurrence in clusters; (d) frequent secondary generalization; and (e) predilection for occurring at night (304). Three manifestations are especially correlated with frontal lobe epilepsy:

1. Supplementary motor area seizures manifested by sudden asymmetrical tonic posturing of the limbs, usually with one arm extended upward, and contralateral head and eye deviation; consciousness may or may not be impaired.
2. Complex partial seizures with prominent motor activity, such as vigorous rocking, bicycling, circling, or vocalization; minimal or no impairment in consciousness; and no postictal confusion. Because of their frequently bizarre manifestations, nonepileptic psychogenic seizures are often first suspected. Although such seizures are typical of the medial frontal or orbital frontal areas, they may arise anywhere within the frontal lobe.
3. Simple partial motor clonic seizures, arising from regions within or adjacent to the primary motor cortex.

Electroencephalographic Findings

Interictal EEG. Diagnosis of FLE rests largely on clinical features, inasmuch as the EEG is often normal or nondiagnostic. This is largely because much of the frontal lobe, including the orbital-frontal cortex, interhemispheric convexity and cingulum, and the sulcal depths are relatively inaccessible to scalp EEG recording (229). Consequently, small epileptogenic foci may be missed entirely; conversely, epileptiform abnormalities may appear widespread because of the often large distances and intervening cortex between the epileptogenic area and scalp electrodes. Furthermore, functional networks permit rapid propagation within and outside the frontal lobes, which results in the appearance of diffuse (secondary bilateral synchrony), multifocal, or falsely localizing epileptiform abnormalities (229). In contrast to temporal lobe epilepsy, the placement of additional, closely

spaced scalp electrodes does not usually improve the localizing value of scalp EEG in FLE (123).

Interictal EEGs in FLE can demonstrate one of several patterns:

1. For the reasons just listed, epileptiform discharges are not identified on scalp EEG recordings in up to one-third of patients (199,247,305). This is most commonly seen in patients with medial frontal epilepsy (11,204,296).
2. Secondary bilaterally synchronous discharges may be seen in up to two-thirds of patients with FLE (235); these discharges are especially frequent with medial frontal foci. Tükel and Jasper (283) first used the term *secondary bilateral synchrony* in describing the bilateral discharges seen in patients with parasagittal epileptogenic lesions. Secondary bilateral synchrony is discussed in detail later in this chapter.
3. Focal epileptiform discharges occurring over one frontal lobe are seen in 42% to 63% of cases of FLE (169,235,247). When these arise from epileptogenic cortex in the medial frontal lobe, the discharges are of highest voltage at or adjacent to the vertex.
4. High-voltage (up to 300- μV), sharply contoured slow waves that are broadly distributed over the frontal regions but maximal at F3-F4 and Fp1-Fp2 are characteristic of orbital frontal foci. These discharges are almost always seen bilaterally to some extent, but they show voltage and field asymmetries that accurately indicate the epileptogenic hemisphere (184,275).

Ictal EEG. The ictal EEG is nonlocalizing in more than half the patients with FLE (169,199,247). Often, there is no electrographic correlate to be seen in scalp electrodes. Equally problematic, however, is that the early and prominent motor activity of many frontal lobe seizures produces large amounts of muscle and movement artifact that obscures EEG activity. False localization, particularly to the temporal lobe, also occurs as a result of frontal-limbic connections.

Although supplementary motor area seizures can be associated with a focal rhythmic discharge localized or adjacent to the vertex (199), most other seizures of medial frontal origin are not accompanied by a lateralized discharge; EEGs sometimes show only diffuse, bilateral frontal voltage attenuation (11,97,296) followed by bilateral frontal or diffuse rhythmic theta or delta activity (11,305) (Fig. 17.25). Although diffuse, bilateral frontal voltage attenuation is frequently correlated with onset of orbital frontal seizures, focal rhythmic alpha or beta frequency activity is sometimes seen in the frontopolar electrodes (184,275). Seizures of dorsolateral frontal origin are usually associated with a localizing ictal discharge. Bautista et al. (11) reported that focal and lateralizing rhythmic fast activity was associated with seizure onset in 80% of patients with dorsolateral frontal lobe seizures.

Parietal Lobe Epilepsy

Parietal lobe epilepsy is much less common than temporal or frontal lobe epilepsy; it accounts for about 6% of patients who undergo epilepsy surgery (236). As with FLE, scalp EEG is most often nonlocalizing and is sometimes falsely localizing. In a review of 11 patients with parietal lobe epilepsy, 10 of whom had undergone successful surgery, Williamson et al. (302) reported that scalp EEG correctly localized the seizure onset zone in only one patient. Interictal parietal epileptiform discharges were present in four patients (36%), and additional epileptiform abnormalities were noted in three of these. Five patients (45%) without focal parietal epileptiform discharges had other, falsely localizing abnormalities, including temporal and bisynchronous frontal spikes. Scalp ictal EEG was lateralizing in only three patients. There is little doubt that conventional scalp EEG is of limited utility for parietal lobe epilepsy.

Occipital Lobe Epilepsy

Discharges associated with occipital lobe epilepsy have been described in detail in the earlier section on childhood epilepsy with occipital paroxysms.

Focal Cortical Dysplasia

Magnetic resonance imaging, when used as a routine diagnostic procedure, has revealed that focal cortical dysplasia is a relatively common cause of intractable epilepsy, and it enables more thorough study of associated EEG findings, especially in patients being evaluated for epilepsy surgery. Barkovich et al. (9) proposed a useful classification.

EEG abnormalities are related to the extent and location of the lesions. Small lesions often do not disrupt normal background activity. Larger lesions result in ipsilateral or bilateral slowing of the alpha rhythm as well as focal slowing over the involved cortical area. Epileptiform discharges, usual focal, are present in more than 80% of patients (100,239). Generalized epileptiform activity can be seen with multifocal or more diffuse developmental malformations. Focal, bilateral, or generalized discharges can be seen with subependymal heterotopia (240). Epileptiform activity is frequently abundant; discharges occur in repetitive or near-continuous trains, especially during sleep (100,239) (Fig. 17.26). Such findings are especially

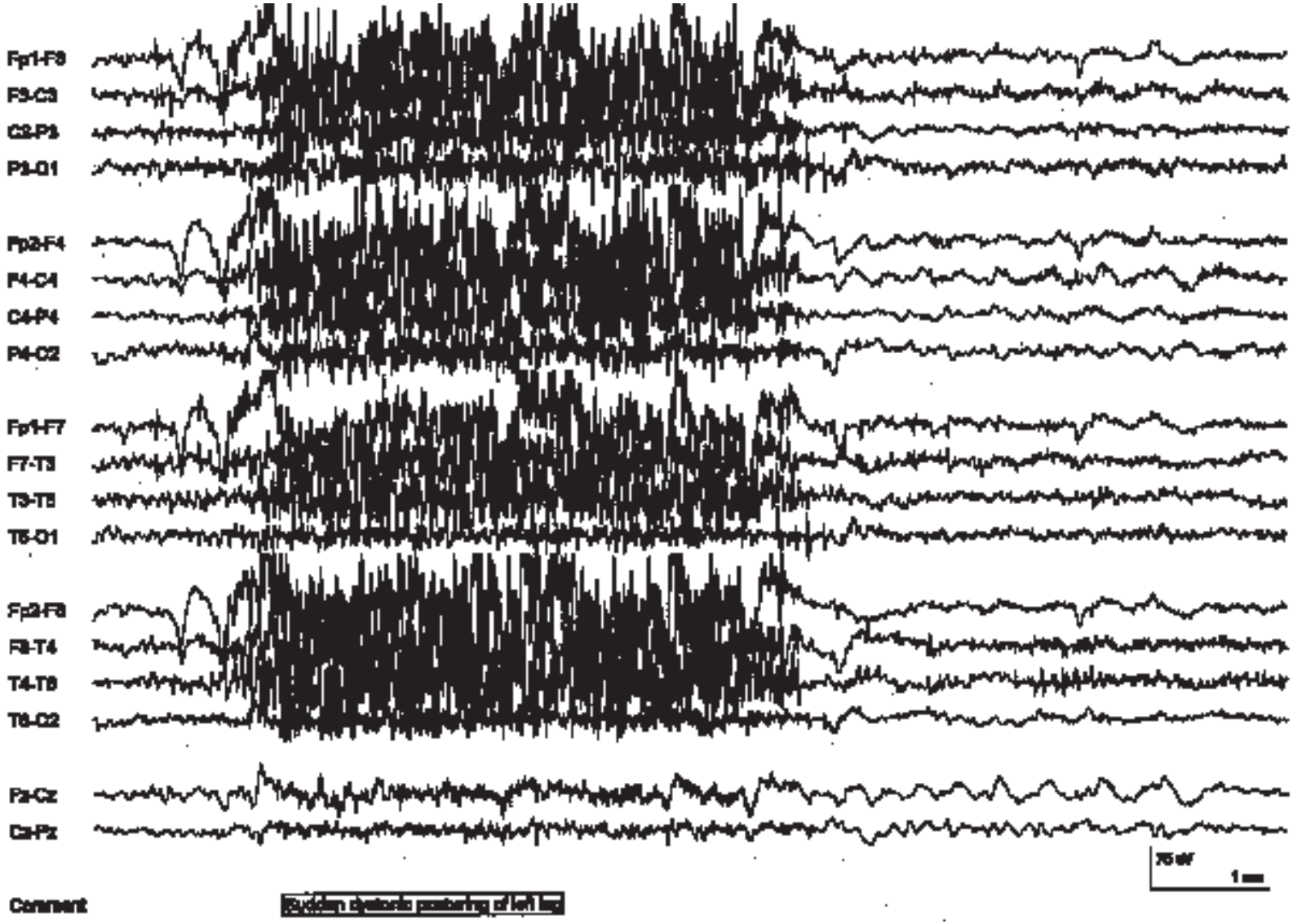


FIG. 17.25. EEG of a 27-year-old man with frontal lobe epilepsy. Seizures consisted of sudden dystonic posturing of the left leg followed by several seconds of large-amplitude clonic activity without loss of consciousness. In the immediate postictal period, there was subtle left leg weakness. The EEG is initially obscured by muscle artifact, but rhythmic 3-Hz delta activity is later seen over the right frontal (F4) and central (C4) regions. TC, 0.1 second; HFF, 35 Hz.

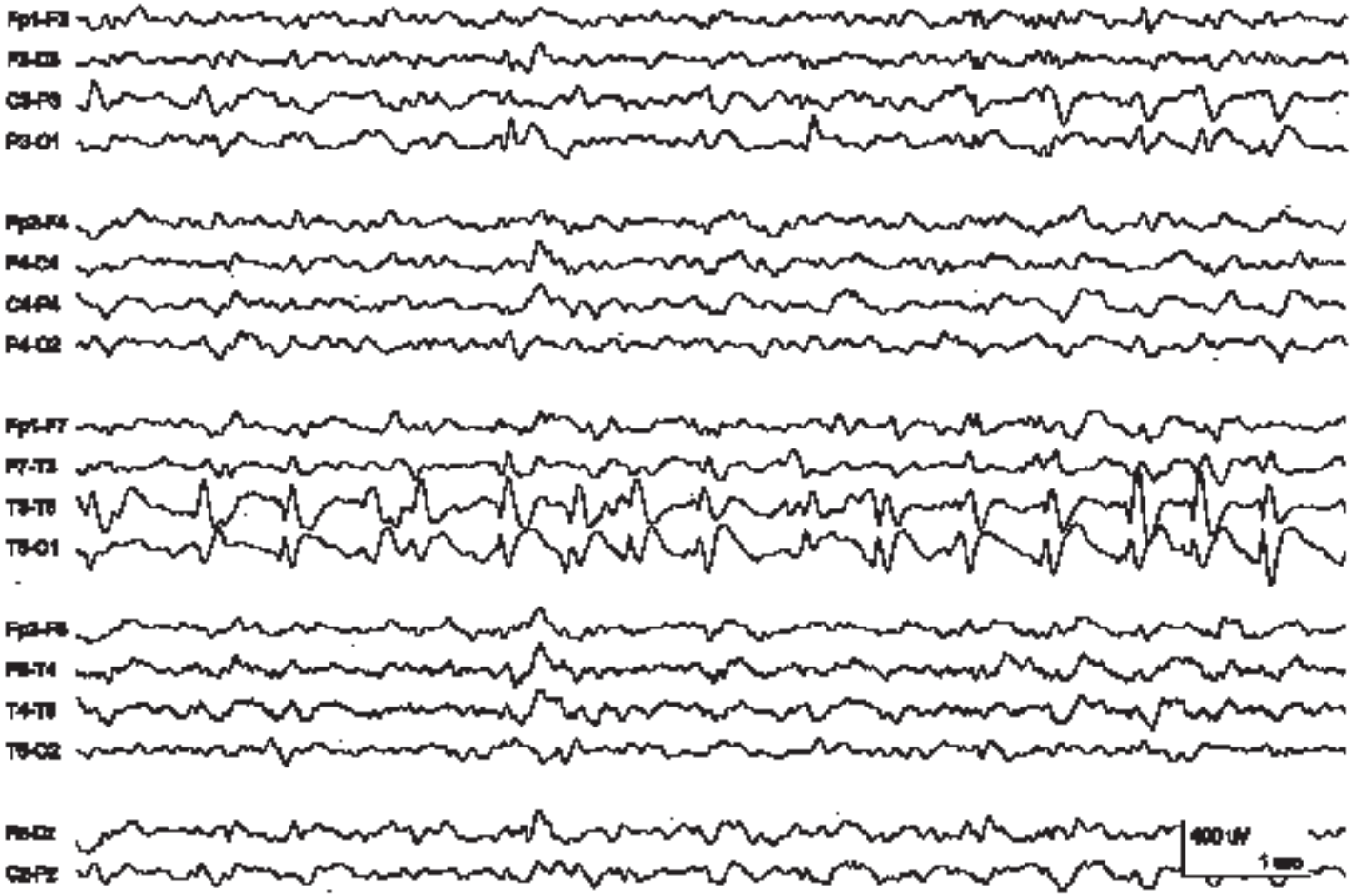


FIG. 17.26. EEG of an 8-year-old girl with intractable epilepsy. During infancy, she had spasms and hypsarrhythmia. Seizures at the time this EEG was obtained consisted of repetitive flexion of the right shoulder and neck, with speech disruption and decreased attentiveness. Brain magnetic resonance image showed signal abnormalities consistent with a large region of cortical dysplasia in the left posterior hemisphere. The EEG recorded during sleep demonstrates nearly continuous high-voltage epileptiform discharges at T5 (note calibration). These discharges persisted throughout sleep, but there were no visible clinical changes. TC, 0.1 second; HFF, 70 Hz.

characteristic of large neocortical areas of malformation (238) and are strongly suggestive of cortical dysplasia rather than other structural lesions (100). Electrocorticographic recordings in such patients demonstrate continuous rhythmic spiking or repetitive electrographic seizures (210). These patterns, too, are uncommon with other types of lesions and have been considered evidence of the intrinsic epileptogenicity of dysplastic cortex (146). There is often relatively sharp demarcation between epileptogenic and normal cortex, which thus providing a useful guide in determining the extent of surgical resection (210).

EXAMPLES OF USES OF ELECTROENCEPHALOGRAPHY TO AID IN CLINICAL DIAGNOSIS

Seizures with Quiet Staring

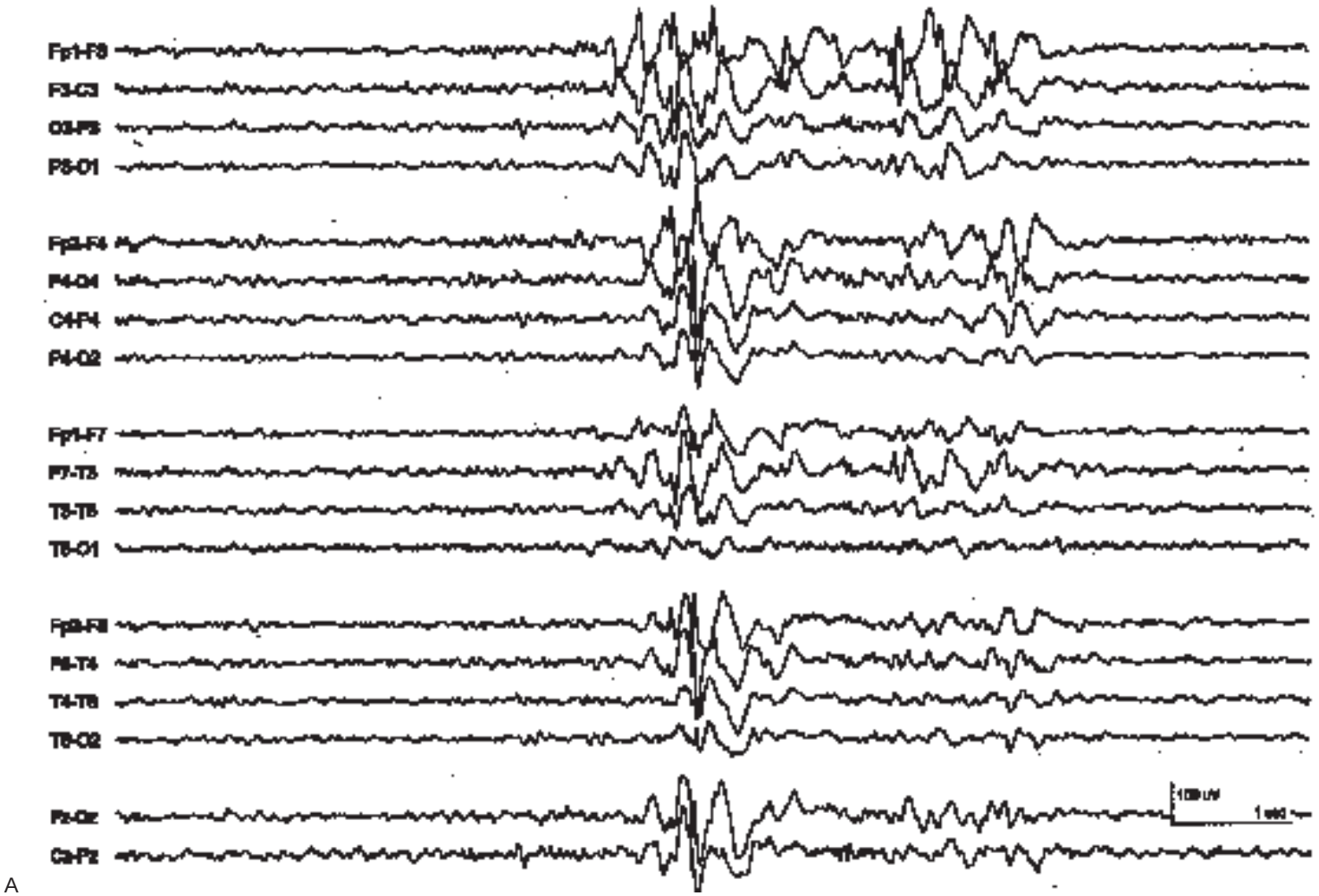
Seizures characterized by quiet staring with amnesia but without obvious automatisms are common, especially during childhood, and can occur with such diverse disorders as childhood absence epilepsy, LGS, and temporal lobe epilepsy. EEG findings can provide critical information that aids in diagnosis and management. Generalized 3-Hz spike-wave activity accompanied by staring is pathognomonic of idiopathic absence epilepsy. Generalized sharp-slow wave discharges at a frequency of less than 2.5 Hz and diffusely slow background activity are characteristic of the atypical absence seizures of LGS. Focal IEDs over the anterior temporal region are suggestive of complex partial seizures caused by temporal lobe epilepsy.

Primary Generalized Versus Secondarily Generalized Tonic-Clonic Seizures

Many patients with epilepsy are unaware of the nature of their condition or do not seek medical attention until they have a generalized tonic-clonic seizure. The first manifestations of a seizure are often not witnessed and, even if observed, are not remembered, because the experience of observing a generalized tonic-clonic seizure is often accompanied by panic, fright, and a sense of helplessness. Therefore, it is frequently impossible for the physician to determine whether the convulsion was a symptom of primary generalized epilepsy or of localization-related epilepsy in which rapid secondary generalization occurred. Clinical features such age at onset, history of previous absence or complex partial seizures, and family history are helpful, but not always reliable, in distinguishing the two. In such circumstances, EEG provides critical additional diagnostic information. Generalized IEDs indicate primary generalized epilepsy, and specific features of the generalized discharges can point to a specific epilepsy syndrome. Focal IEDs or focal slowing, in contrast, are most consistent with localization-related epilepsy. Because treatment and prognosis are usually different for these two groups of syndromes, accurate diagnosis is essential for optimal management.

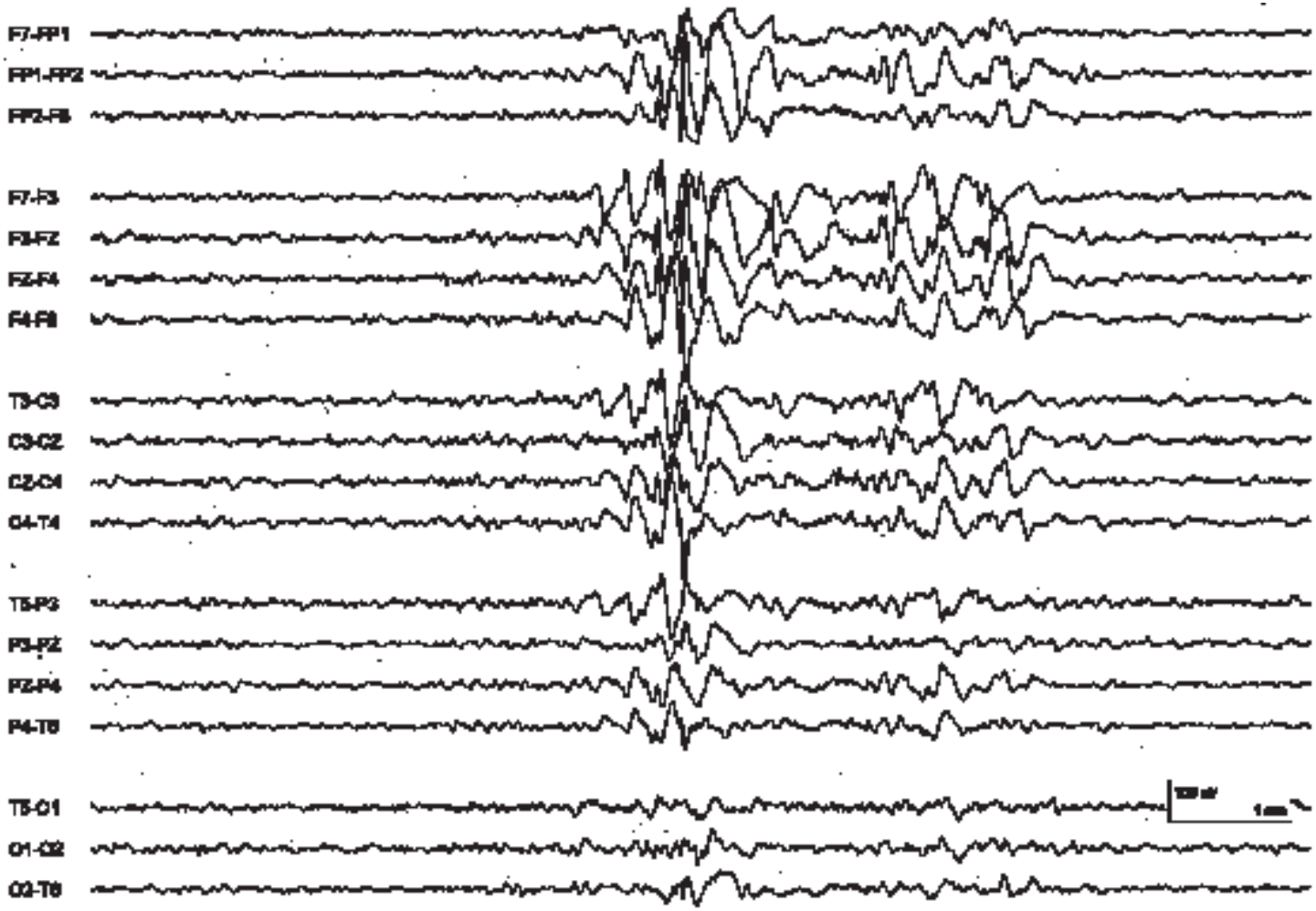
Primary Versus Secondary Bilateral Synchrony

It is sometimes difficult to distinguish between spike-wave activity that is generalized from the outset and spike-wave activity that reflects rapid generalization from one or multiple foci (*secondary bilateral synchrony*) (Fig. 17.27). The first pattern indicates primary generalized epilepsy, whereas the second implies localization-related epilepsy and raises the possibility of a structural lesion. Sometimes generalized spike-wave activity is expressed incompletely or asymmetrically (see Fig. 17.27). This occurs most often over the frontal regions and during sleep. In such cases, these "focal" aspects are transient and have a morphological pattern that is very similar to that of more typical widespread bursts. Because the IEDs of primary generalized epilepsy are not always perfectly synchronous and symmetrical, subtle asymmetries should be interpreted conservatively and not interpreted as secondary bilateral synchrony. It is useful to remember that the overall appearance of the epileptiform activity in such cases is typical of primary generalized epilepsy. The following criteria for secondary bilateral synchrony helps avoid errors of overinterpretation: (a) Focal IEDs, when present, occur persistently in one area; (b) the morphological pattern of the focal IED is more variable and differs from that of the generalized IEDs; and (c) focal IEDs clearly and consistently precede and initiate most or all of the bursts of generalized IEDs. Simple EEG procedures, such as increasing paper speed or time base, also help distinguish primary from secondary bilateral synchrony. Subtle time differences between IEDs in different regions can be resolved or clarified by the use of special montage designs, such as reference subtraction (151). At one time, the differential effect of intracarotid injections of amobarbital on the spike-wave bursts of each hemisphere was used to recognize secondary bilateral synchrony (113,183). Anesthesia of the dependent hemisphere did not affect contralateral epileptiform activity, whereas anesthesia of the epileptogenic hemisphere suppressed discharges bilaterally. This technique is only rarely used today.



A

FIG. 17.27. EEG of a 41-year-old woman with nocturnal generalized convulsive seizures. Seizures began with right arm dystonia and forced head deviation to the right with rapid secondary generalization. **A:** Interictal EEG shows frontally predominant bilateral synchronous spike-wave activity that consistently has a left frontal (F3) lead-in, which is consistent with secondary bilateral synchrony. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.27. *Continued.* **B:** The F3 lead-in is even clearer in a coronal bipolar montage (compare with part *A*). TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*

C

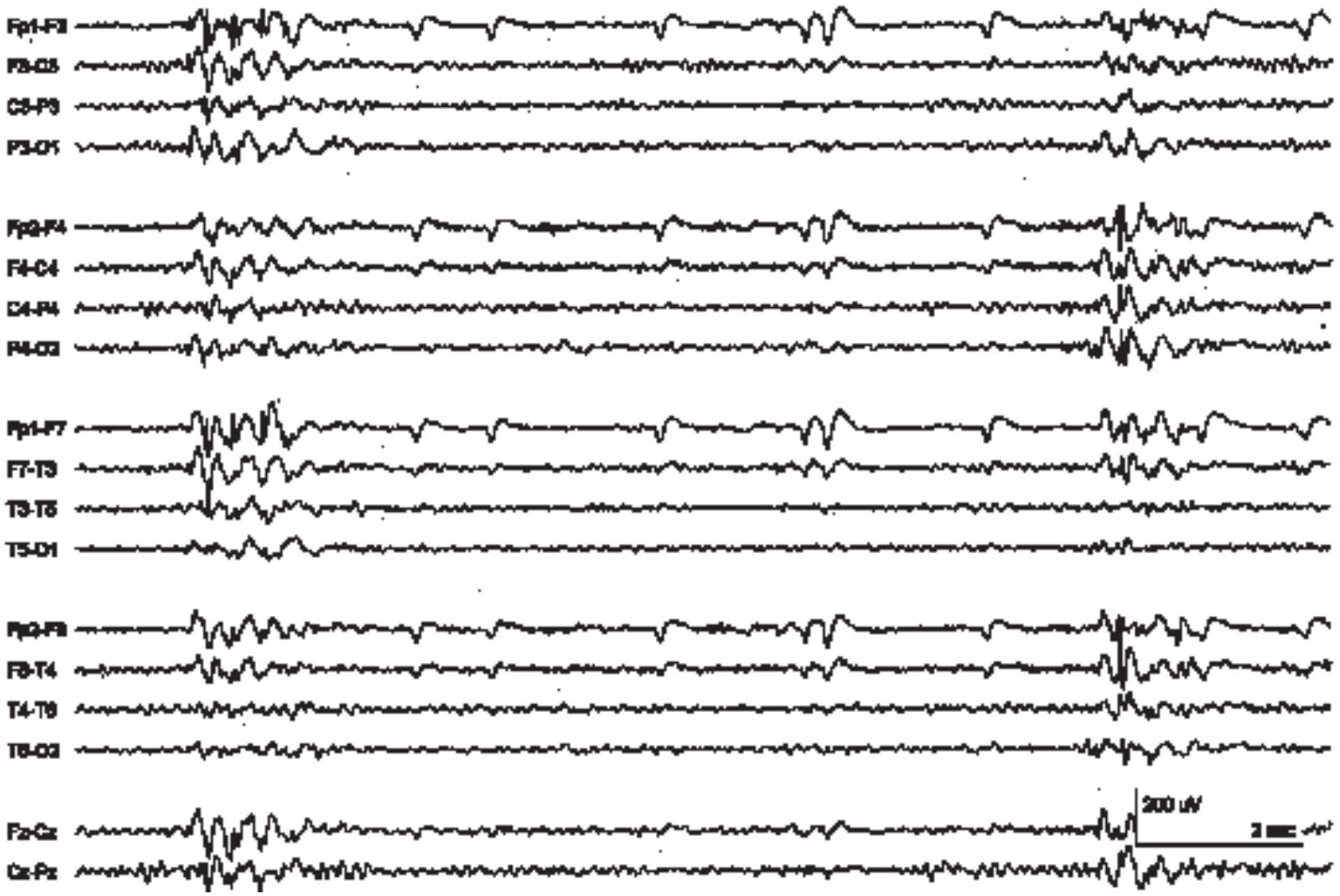


FIG. 17.27. *Continued.* **C:** EEG of a 21-year-old woman with juvenile myoclonic epilepsy. The EEG shows fragments of primary generalized spike-wave discharges that shift in laterality over the course of a recording, rather than demonstrating a consistent focal onset. TC, 0.1 second; HFF, 70 Hz.

Nocturnal Drooling Attacks in Children

Physicians are sometimes asked to see children with a history of nighttime drooling and facial twitching with or without unresponsiveness. Diagnostic possibilities include the rolandic seizures of benign focal epilepsy with central-midtemporal spikes and either simple or complex partial seizures that are a manifestation of symptomatic localization-related epilepsy. Although the clinical symptoms of the two types of seizure are quite different, historical details may be incomplete or ambiguous because of the child's age and because the seizures occur during sleep. The EEG can provide definitive information. A central-midtemporal spike discharge supports a diagnosis of benign rolandic epilepsy, whereas an anterior temporal location is indicative of temporal lobe epilepsy. In this case, however, the distinction may not always be straightforward, because not all patients with central-temporal spikes have benign rolandic epilepsy (74,132,158,191). How often central-temporal spikes are associated with symptomatic localization-related epilepsy is not known.

Differentiating Benign Rolandic Spikes from Other Spikes Occurring in the Same Areas

Differences in several EEG features help distinguish discharges of benign rolandic epilepsy from those of perirolandic symptomatic localization-related epilepsy. In the rolandic form of benign focal epilepsy, the IED dipole is oriented tangentially to the cortical surface, with the negative pole near the junction of the rolandic and sylvian fissures and the positive pole more broadly distributed over the frontal regions bilaterally (121,132,181). In symptomatic perirolandic epilepsy, IEDs have a radial distribution (121). In benign rolandic epilepsy, the topographic distribution of the IEDs is typically stereotyped, whereas the distribution of IEDs in symptomatic perirolandic epilepsy is more variable. Focal slowing is absent in benign rolandic epilepsy (except when discharges are so frequent that the after going slow waves summate), but it is often present in symptomatic perirolandic epilepsy. These electrographic differences interpreted within the particular clinical context usually allow firm distinction between two very different types of epilepsy.

Distinction between anterior temporal and centrotemporal spikes usually poses little difficulty. However, distinguishing between benign centrotemporal discharges and midtemporal IEDs that have some suprasylvian representation can be more difficult. The T3/4 electrode placements of the international 10-20 system actually lie near the junction of the sylvian and rolandic fissures, and the short interelectrode distances used in routine longitudinal and bipolar montages do not facilitate assessment of voltage differences in this region. Placement of additional electrodes is frequently very helpful. Recording to an inactive reference and use of the expanded 10-20 system invariably demonstrates that the voltage of IEDs that is characteristic of benign rolandic epilepsy is maximal over C3/4 or C5/6 rather than T3/T4 (170). Similarly, in patients with midtemporal symptomatic epilepsy, the IEDs are of highest voltage when recorded from electrodes below the standard temporal 10-20 placements.

NON-CONVULSIVE STATUS EPILEPTICUS

Non-convulsive status epilepticus is often difficult to diagnose clinically, and it may be confused with dementia, metabolic or toxic encephalopathy, or a psychiatric syndrome. EEG is often the only method for making an accurate diagnosis. The literature has traditionally distinguished between complex partial status epilepticus with lateralized seizure activity occurring continuously or in cycles and generalized non-convulsive status epilepticus with predominantly symmetrical, bilateral synchronous IEDs. However, studies have emphasized practical difficulties in making these distinctions, especially if EEG and clinical findings are followed longitudinally. Consequently, investigators have advanced classifications based on syndromic and etiologic (261), as well as EEG, criteria.

Epilepsia partialis continua is most often characterized by unremitting motor seizures involving part or all of one side of the body. Although the seizures are of cortical origin, correlations between clinical manifestations and EEG changes are inconsistent. One series reported focal discharges in only 22% of affected patients (60). In another, with more aggressive sampling, researchers found focal discharges in 71% of patients, usually in the form of irregular spikes and sharp waves (276). In that series, PLEDs occurred in 14% of patients. More comprehensive neurophysiological investigations demonstrated a relationship between scalp-recorded discharges and muscle jerks in 37% to 45% of patients (60,276). Completely normal EEGs occur in fewer than 10% of cases of epilepsia partialis continua, but focal epileptiform discharges can be demonstrated by electrocorticography (276). In such EEG-negative cases, the discharging cortical region is presumably either oriented unfavorably with regard to scalp electrodes or too small to allow detection at the scalp. PLEDs have been found in 8% to 14% of cases of epilepsia partialis continua (52,256,276), and in these patients, a diagnosis of partial status epilepticus is justified. Most authorities, however,

do not believe that PLEDs, by themselves, are a form of non-convulsive status epilepticus. Although mental status is often impaired in patients with PLEDs, this can usually be attributed adequately to the acute structural or metabolic disturbance causing PLEDs, rather than to the PLEDs themselves. PLEDs that occur in the absence of structural lesions or metabolic disturbances may be associated with recurrent episodes of confusion that respond to carbamazepine (274). This unusual situation probably represents a peculiar form of non-convulsive status epilepticus in the elderly.

Initial descriptions of complex partial status epilepticus emphasized recurring periods of automatic activity attributed to partial seizures. These intermittent automatisms with "concomitant cycling of the EEG patterns" were said to be present even in the most advanced stages (279). In one analysis of a large series of EEGs in partial status epilepticus, researchers did, in fact, find that EEG changes remained focal throughout the course of the status epilepticus episode (119). However, in most patients with frontal lobe complex partial status epilepticus, scalp EEGs eventually showed bilateral sharp-slow activity (306). Furthermore, most patients who develop non-convulsive status epilepticus in later life have generalized spike-wave or polyspike-wave discharges during most of the course of the episode (83,168) (Fig. 17.28). The majority of these patients do not have a history of absence seizures, and focal, not generalized, IEDs are recorded subsequently. In these patients, generalized discharges stop altogether or become focal after treatment with phenytoin, and phenytoin also prevents subsequent episodes of status epilepticus (83,168). Such observations provide strong support for the view that non-convulsive status epilepticus occurring later in life and associated with generalized ictal discharges is a localization-related seizure disorder. When confusional episodes in adults are accompanied by generalized ictal discharges, careful inquiry should be made regarding manifestations of primary generalized epilepsy earlier in life. If such history is lacking, brain imaging is mandatory, and treatment with drugs that are effective against partial seizures is reasonable.

Serial EEGs during and after convulsive status epilepticus have demonstrated a wide variety of patterns. It is important to recognize these, because only one of them may be seen during a single EEG study. Treiman et al. (280) proposed that EEG changes occur in a progressive sequence during convulsive status. Seizures occur (a) discretely at first and then (b) gradually merge with waxing and waning voltage and frequency. This is followed by (c) a period of continuous rhythmic ictal discharge. Subsequently, (d) a continuous monorhythmic discharge is punctuated by periods of attenuation. Finally, (e) GPEDs are seen against a severely attenuated background (Fig. 17.29). It is not clear where clinical convulsive activity ends in this sequence and what effect treatment has on these patterns. It is also unclear which of these patterns are related to electrographic seizures rather than to the results of cortical injury, whether from the seizures themselves or from the underlying cause of the seizures. Subsequent studies have reported that non-convulsive status (patterns as through d proposed by Treiman et al. [280]) occurred in approximately one-third of patients after convulsive seizure activity had ceased (68). Each of the patterns of Treiman et al. occurred in some patients, but many patients exhibited only a few of the patterns, often out of the sequence proposed (68,202). Non-convulsive status epilepticus accompanied by any of these patterns was associated with a higher rate of mortality, even after investigators accounted for the effects of age and etiology of status epilepticus (68). In contrast, brief electrographic seizures occurring more than 30 minutes after cessation of convulsive activity were not associated with increased rates of mortality (68). GPEDs occurred more often in the elderly and tended to correlate with poorer outcome in one study (202) but not in another (143).

EEGs obtained to rule out non-convulsive status epilepticus sometimes demonstrate a pattern of continuous sharp-slow wave activity or GPEDs. Distinguishing between the more or less continuous sharp-slow wave pattern seen in non-convulsive status epilepticus and the triphasic wave pattern of metabolic or toxic encephalopathies is usually not difficult (see Chapter 12). Distinguishing between GPEDs that occur during or after status epilepticus from those seen in the setting of diffuse anoxia is more problematic. Subtle or overt myoclonus often accompanies GPEDs (155,262,311), and this leads to further confusion. Husain et al. (143) compared GPEDs related to status epilepticus with those caused by other entities. In cases of status epilepticus, GPEDs were of longer duration and of higher but more variable voltage. However, the intergroup variability was too great to formulate clinically useful rules. When status epilepticus is suspected and the EEG shows GPEDs, it is important to review the clinical situation carefully. If the patient has had previous seizures or serial convulsions, vigorous treatment is indicated, because it is possible that the patient has a late stage of status epilepticus. Most experts would probably not use barbiturate anesthesia or a midazolam drip, because it is most likely that the GPEDs represent cerebral aftereffects of the status epilepticus rather than ongoing seizure activity. If the patient has sustained a severe anoxic or other significant cerebral insult, the GPEDs are much more likely to result from the brain injury than from ongoing seizures. In such cases, even aggressive antiepileptic drug treat-

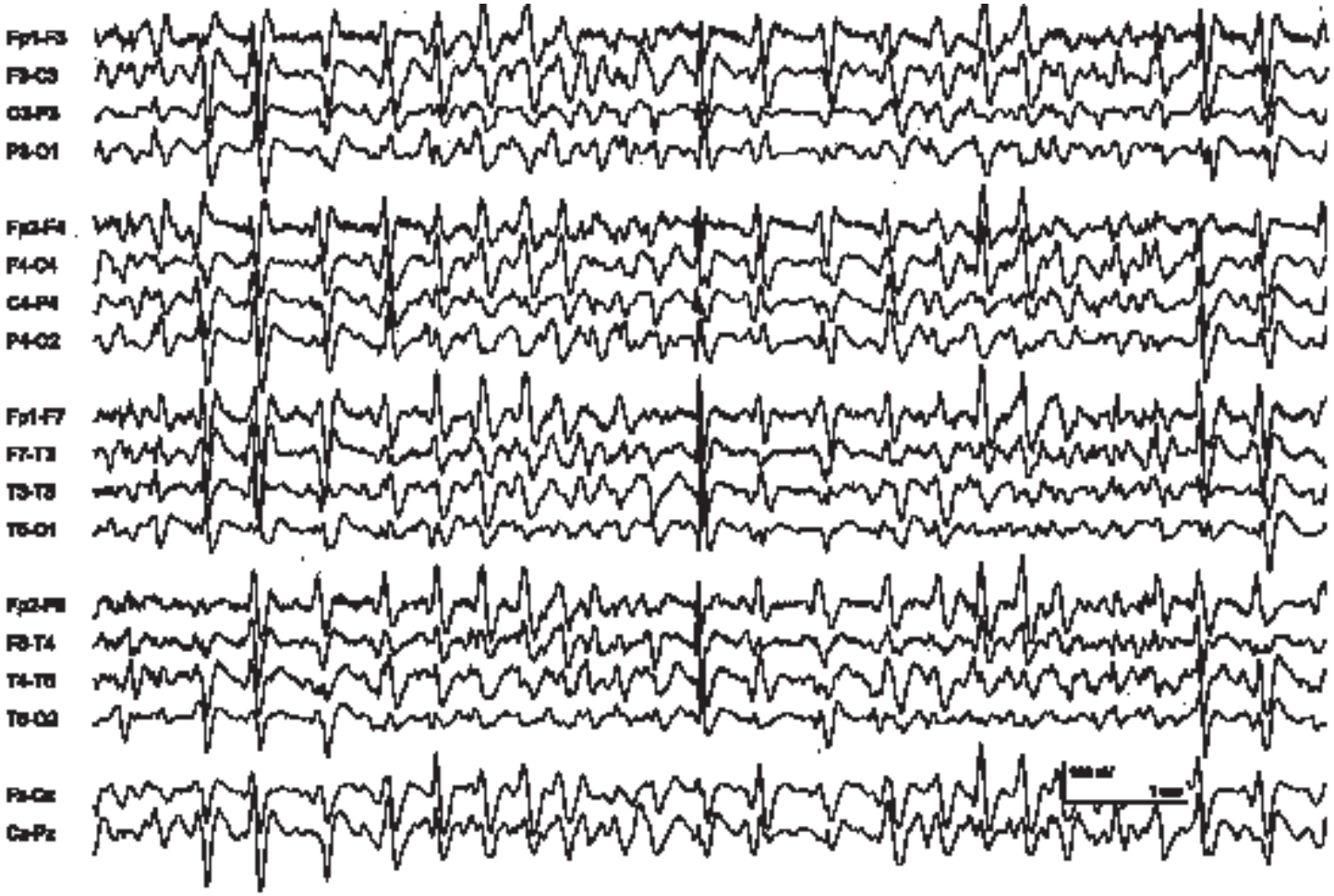
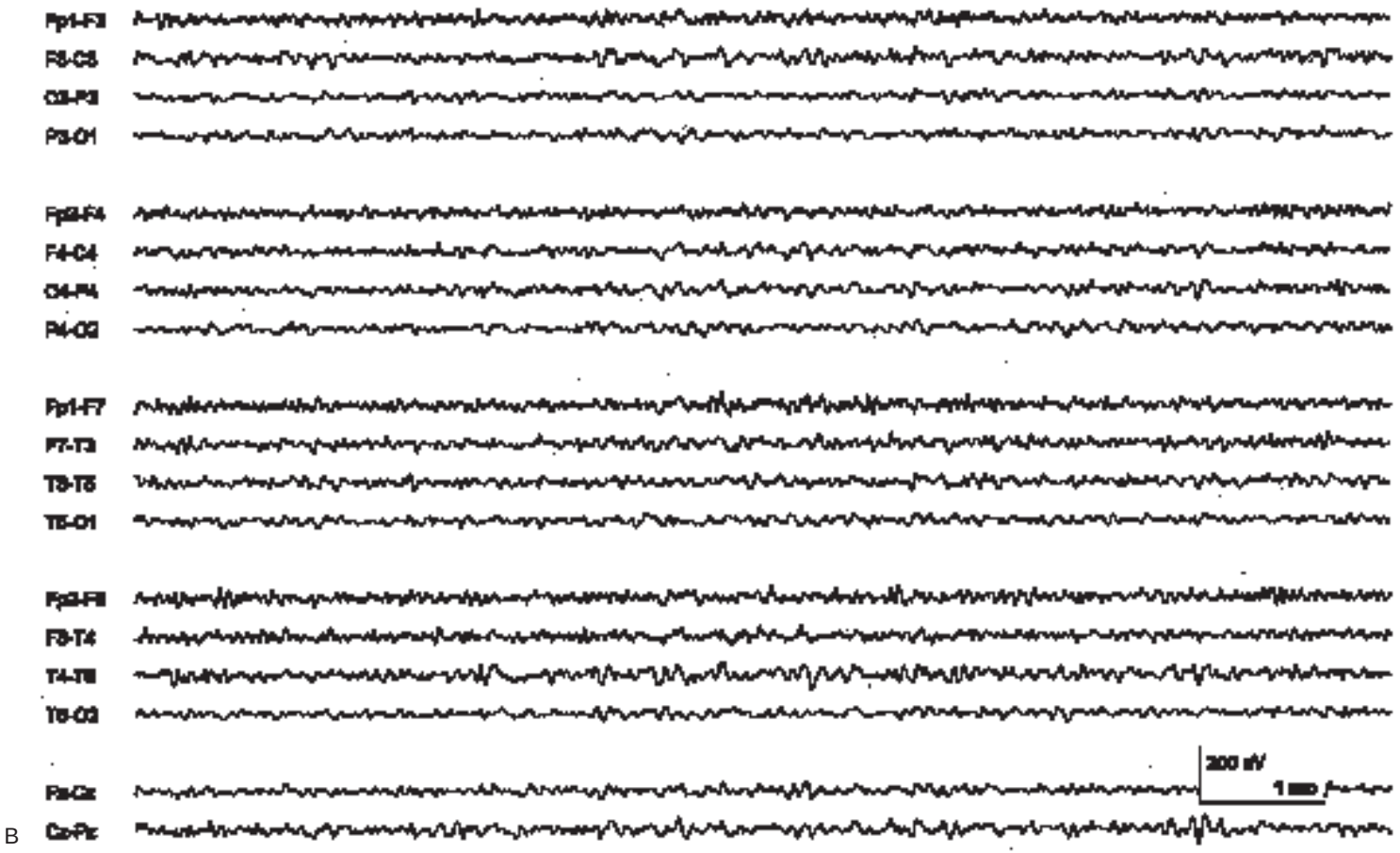
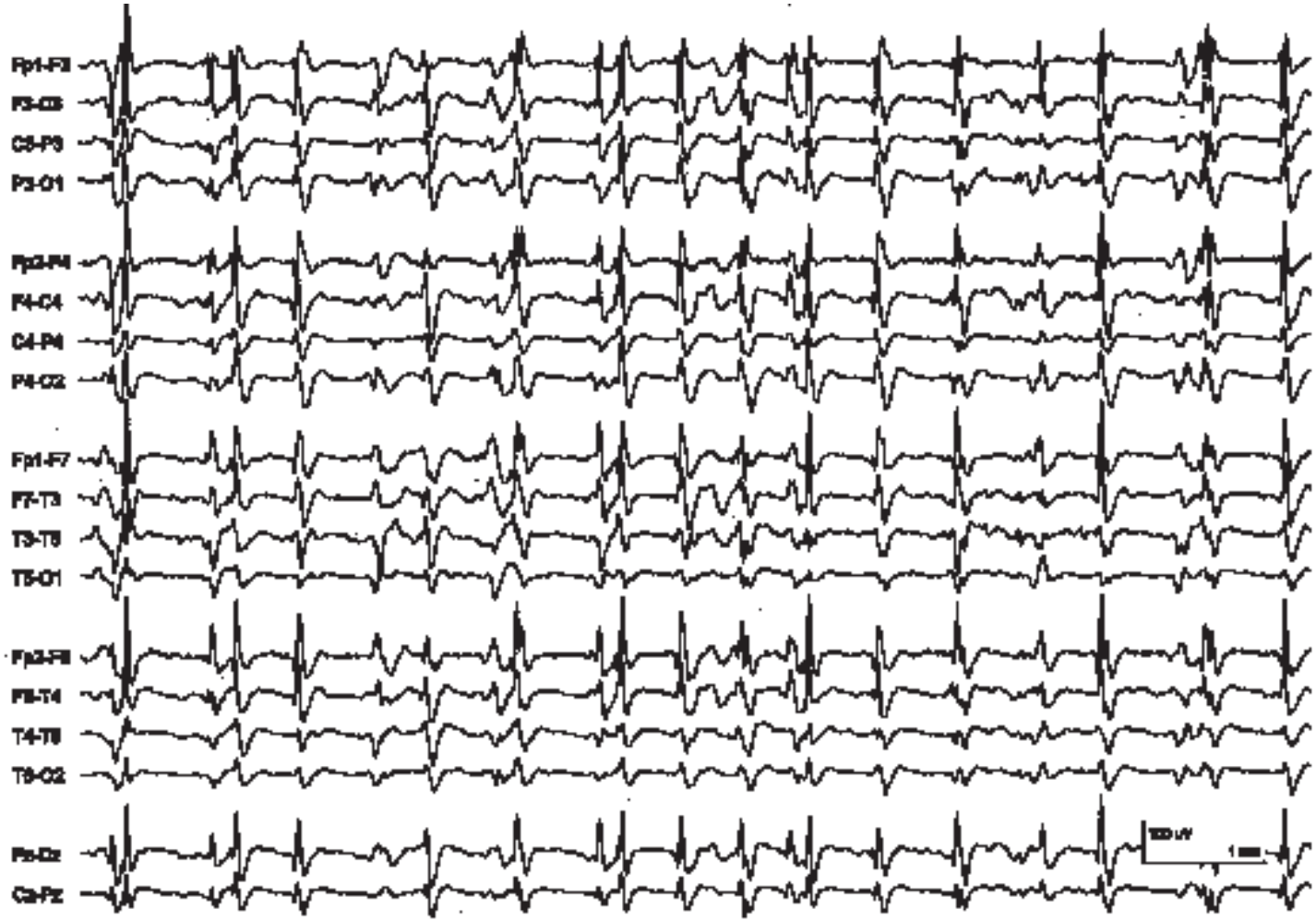


FIG. 17.28. Non-convulsive status epilepticus in a 75-year-old woman with a history of complex partial seizures. On the evening before admission, she had a generalized convulsive seizure. The following morning, she was found staring and poorly interactive. **A:** The EEG shows repetitive bilateral synchronous 2- to 3-Hz spikes and sharp waves. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



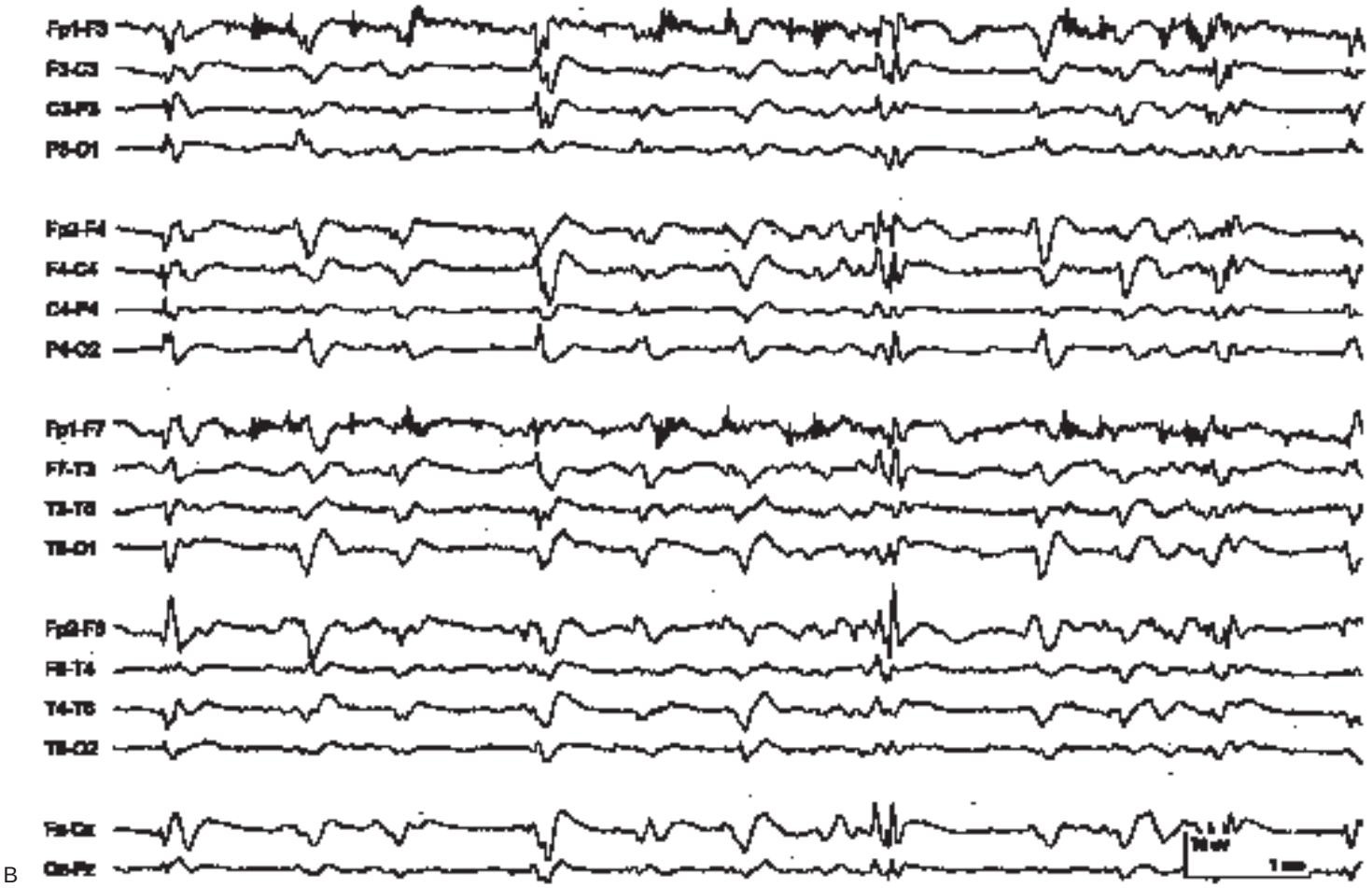
B

FIG. 17.28. *Continued.* **B:** Fifteen minutes after receiving intravenous lorazepam, she became more responsive, although she remained inattentive. The EEG demonstrates resolution of epileptiform activity and is now notable only for moderate diffuse background slowing. She received a phenytoin loading, and she gradually returned to her baseline neurological status over the next 24 hours. TC, 0.1 second; HFF, 70 Hz.



A

FIG. 17.29. EEG of an 86-year-old woman with refractory non-convulsive status epilepticus after a cardiorespiratory arrest. She remained comatose despite treatment with multiple anticonvulsant medications. She died shortly after the EEG recording shown in *B* was obtained. **A:** EEG demonstrates 1- to 2-Hz generalized periodic epileptiform discharges (GPEDs). Background activity seen between epileptiform discharges is markedly attenuated and undifferentiated. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*



B

FIG. 17.29. *Continued.* **B:** EEG recorded 1 day later. Background activity remains severely attenuated and undifferentiated. GPEDs have much broader morphological patterns and occur at a slower repetition rate. TC, 0.1 second; HFF, 70 Hz.

ment, including barbiturate anesthesia, is almost always futile, and hypotensive side effects may actually worsen the situation. The prognosis is extremely poor (155,262,311).

EEG interpretation after status epilepticus is sometimes difficult, as indicated in the foregoing section. However, because of the high prevalence of late non-convulsive status epilepticus and the possibility of obtaining useful prognostic information, follow-up EEG should always be obtained after convulsions are controlled, if continuous EEG monitoring is not being used.

ELECTROENCEPHALOGRAPHY AND THE RISK OF SEIZURE RECURRENCE

The likelihood of seizure recurrence is the most important factor in deciding whether to initiate treatment after a first epileptic seizure. EEGs demonstrate IEDs in 10% to 39% of adults after a first seizure and in 32% to 59% of children after a first seizure (45,136,161,259,285). An EEG obtained within 24 hours of the seizure is more likely to yield epileptiform activity (232,285) than is one obtained later, and sleep deprivation increases the yield even further (161,285). Various EEG abnormalities have been associated with increased risk of seizure recurrence (Table 17.6). Three studies found that IEDs were predictive of recurrent seizures (232,130,285). All IEDs were associated with seizure recurrence in two of these studies (232,285), whereas only generalized IEDs were found to increase risk of further seizures in the third (130). A metaanalysis concluded that EEG findings provide useful prognostic information, especially in children, beyond that already obtained by diagnosis of the epilepsy syndrome, which is itself strongly influenced by EEG results (21).

TABLE 17.6. *EEG predictors of recurrence after first unprovoked seizure*

Study	Age	IEDs	Non-IED abnormality	Any abnormality
Annegers et al. (7)	Mixed	NR	NE	+
Hopkins et al. (136)	Adults	0	0	0
Shinnar et al. (258)	Children	0	NR	+
Hauser et al. (130)	Mixed	+	0	0
FIRST Group (232)	Mixed	+	NR	NR
Van Donselaar et al. (285)	Adults	+	+	+

+, factor associated with increased risk; 0, factor not associated with increased risk; IED, interictal epileptiform discharge; NR, effect of factor not reported.

Febrile seizures represent an exception to the foregoing statements. After a febrile seizure, many children have nonspecific EEG abnormalities, usually generalized slowing that is maximal over the occipital areas, for several days to a week (94,270). Neither slowing nor IEDs have prognostic significance for additional febrile seizures or development of epilepsy (94,277, 282). Serial EEGs obtained for febrile seizures reveal generalized epileptiform discharges in 35% to 45% of children who are older than 2 years, especially between the ages of 3 and 5 years (73,94,281,282). EEG has no role in the evaluation of children with typical febrile seizures.

Determining the probability of seizure relapse also plays a role in deciding whether to discontinue antiepileptic drugs after an appropriate seizure-free period. Most studies have found that an abnormal EEG obtained at the time of drug withdrawal is associated with a greater chance of seizure relapse (relative risk, about 1.5). Results of four of these studies are summarized in Table 17.7. In two of the studies, researchers also examined the value of specific EEG findings. The Medical Research Council (231) found that only generalized IEDs were correlated with recurrent seizures; focal or diffuse abnormalities of background activity were not prognostic. With univariate analysis, Shinnar et al. (258) found that both IEDs and focal or diffuse background abnormalities were associated with a greater chance of recurrence. Using multivariate analysis, they discovered that four of six variables predicting relapse were EEG related: association between age at first seizure and background slowing; presence of IEDs; presence of background slowing; and EEG improvement between seizure diagnosis and antiepileptic drug withdrawal. As is the case with first seizures, epilepsy syndrome also plays an important role in estimating risk of relapse after discontinuation of antiepileptic drugs. For example, benign epilepsy of childhood with central-midtemporal spikes has a uniformly good prognosis (72), whereas in juvenile myoclonic epilepsy, relapse is probable when antiepileptic drugs are stopped (106). It is thus not clear whether the EEG contribution to predictions of seizure relapse exists because EEG findings are a measure of "seizure susceptibility" or an indication of epilepsy syndrome. Berg et al. (22) reported that focal slow wave abnormalities, epilepsy syndrome, and seizure frequency were independent predictors of persistent seizures and lack of response to antiepileptic drugs. This finding supports the conclusion that the utility of EEG in predicting seizure recurrence is greater than its role in diagnosing epilepsy syndromes.

TABLE 17.7. *EEG predictors of relapse after withdrawal of antiseizure drugs*

Study	Population	Definition of abnormality	Relapse risk when abnormality present	Percentage with abnormality suffering relapse
Medical Research Council trial (231)	Mixed	Features analyzed individually	+	NR
Callaghan et al. (44)	Adults	IED, focal slowing	+	70%
Shinnar et al. (260)	Children	Features analyzed individually	+	35%
Emerson et al. (85)	Children	IEDs, focal slowing	+	57%

+, factor associated with increased risk; IED, interictal epileptiform discharge; NR, effect of factor not reported.

CONCLUSIONS

Even in the era of high-resolution anatomical and functional imaging, EEG continues to play a critical role in the evaluation of patients with known or suspected seizures. Because EEG is a physiological test, its results are optimally useful only when considered in the relevant clinical context. This is similar to interpreting findings on neurological examination. Two patients, each with a hemiplegia, may look the same, but if the hemiplegia developed abruptly in one case but evolved slowly over 2 weeks in the other, the diagnostic considerations would be substantially different. The interpretation of epileptiform discharges similarly depends on context. Accurate interpretation and meaningful clinical-electrographic correlations require careful analysis of a spike's voltage distribution on the scalp, the frequency and regularity of its repetition rate, its response to activating procedures, and any alteration that occurs with changes in physiological state. The degree of associated disturbances in EEG background activity must also be taken into account. Finally, when an EEG is "normal," it is important to know whether it was the first EEG or one of several, whether sleep was included in the recording, whether the patient was sleep deprived, and whether appropriate activating procedures were used. Only when these important variables are taken into account is EEG information optimally useful in answering the questions posed in Table 17.1.

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Chapter 18

Video-Electroencephalographic Monitoring

Eli M. Mizrahi and Ronald P. Lesser

Instrumentation and Recording
The Electroencephalograph
Polygraphic Variables
Video Recording
Synchronization and Data Display
Monitoring Environment
Role of Technical Personnel in Monitoring
Strategies of Monitoring
Sleep and Sleep Deprivation
Hyperventilation
Photic and Other Methods of Sensory Stimulation
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Infantile Spasms
Seizures in Infancy
Childhood Epilepsy
Epilepsy Surgery
References

Video-electroencephalographic (video-EEG) monitoring is a valuable tool in the diagnosis and management of those patients suspected of having seizures, from the neonate (71) to the elderly (18). Basic techniques, strategies of recording, and interpretations of findings of video-EEG monitoring are similar for all patients, regardless of age and suspected etiology of the underlying disorder. However, there are also critical differences in the monitoring of certain patients, and the recognition and understanding of these differences will ensure that these studies have a high probability of yielding clinically relevant and valid information.

Technical similarities include EEG and video instrumentation, the requirement for time synchronization of EEG and video, the need for a relatively controlled monitoring environment, the critical role technologists play in recording, and the necessity to prospectively individualize the plans and objectives of each monitoring session. Technical differences relate to requirements, especially in certain pediatric patients, for additional recording sensors; age-dependent instrumentation adaptations; alterations in the recording environment to meet the needs of certain patients, especially young children; and the development of age-dependent strategies for monitoring newborns, infants, and children. Also critical in the monitoring of pediatric patients is the understanding by technologists, referring physicians, and neurophysiologists of the various paroxysmal clinical events that may occur in young patients, in order to determine their significance if or

when they are recorded. Finally, it should be emphasized that accurate interpretation of the EEG is the cornerstone of all such studies.

In other reviews and reports, various terminology has been used to describe the simultaneous recording of EEG and video: long-term monitoring, closed-circuit television monitoring, telemetry, and EEG–polygraphic–-video monitoring. Here, these techniques are all referred to as "monitoring"—additional information about the specific techniques is provided as needed.

INSTRUMENTATION AND RECORDING

The basic components of monitoring are the electroencephalograph, the polygraph, video recording instruments, and a device to synchronize and display the data. Although these various components have undergone development over the past several years based on contemporary technology, their basic configuration and purposes have not changed. The components are arranged for the simultaneous recording of EEG and clinical events to determine their temporal relationships and to characterize and classify them. Each clinical laboratory may configure instrumentation differently; the physical plant, instrumentation vendor, resources of individual institutions, or preferences of the interpreting neurophysiologist may dictate this. Whatever the configuration, policies and procedures are typically in place to achieve the same clinical objectives: capture clinical events and determine their significance for individual patients. Specific technical guidelines for long-term monitoring have been developed by the American Clinical Neurophysiology Society (for merly the American Electroencephalographic Society) (1).

The Electroencephalograph

Digital units are rapidly replacing analog units in most laboratories, and this is particularly the case for video-EEG monitoring. Critical to the application of either type of EEG recording device are the ability to be synchronized to video; the ability to record a full compliment of EEG channels, at times with several channels of polygraphic data (see below); and the ability to display all channels in a manner that can be visually resolved for analysis. A large number of channels may be needed in particular situations. For example, 128 channels are often needed in patients with implanted subdural electrodes.

Various pediatric age groups pose special challenges in the interpretation of their EEGs (70). Age-dependent features of the EEG exist for premature infants, adolescents, and young adults (41,44; see Chapter 5), including the character of the background of the waking and sleep recordings, the significance of interictal sharp transients, and the characteristics of electrical seizure discharges. For example, not all interictal sharp-wave transients are considered epileptiform in the neonate and young infant. In addition, other transients, including those sometimes called normal variants, may be confused with interictal epileptiform activity, when, in fact, they are variations of normal, sometimes occurring in specific age groups (67). Similarly, other rhythmic activity in adults may be benign and not epileptic activity (97). Therefore, these findings should be interpreted with caution.

The EEG signal can be transmitted to the recording instrument by radio transmission or by hardwired connections. There are strengths and limitations to each technique. Radio transmission allows more freedom of movement for patients, but there is an increased likelihood of movement outside the video camera range, and there is the potential for interference with other radio signals in the vicinity of the EEG recording location. Also, hardwiring will limit patient activities; this may be a concern during long-term monitoring of older children and adults, but is less of a concern for neonates and young infants. However, there may be greater fidelity of signal transmission with the technique. Many laboratories, including our own, prefer hardwired transmission (43,60).

On-line EEG montage and recording variable (filter settings, paper speed, instrumentation sensitivity) selection may be an important consideration in recording, depending on the instrument used. Analog recording instruments and some digital-based instruments require prerecording of montage selection and recording parameters. Many instruments that digitally record EEG allow for initial on-line referential recording and off-line remontaging of the EEG during analysis. If the instrumentation used requires on-line montage selection, it is often best that a single montage be selected for neonates and young infants, to record all wake–sleep states with the same "view" of the electrical activity of the brain (2). It is important that digital devices allow montaging and remontaging to occur in a simple way. There should be a simple way to share montage information between machines—for example, between the instrument used to acquire the EEG data and that used for later review.

Electrode Type and Placement

Although the international 10-20 system remains the benchmark for electrode placement during EEG monitoring, placement of additional

electrodes, often using the so-called 10% system (85), can frequently add important information in this setting. These additional electrodes are interpolated between the standard 10-20 electrodes and also placed lower on the scalp, so as to record from the base of the cerebral cortex. Sphenoid electrodes, or the somewhat more invasive foramen ovale electrodes, also can be used (100). Although various electrodes and electrode placements have their proponents, the important question is not which electrode is superior but rather which combination of electrodes is best able to resolve a particular clinical problem. Additional electrodes can help verify a finding that might otherwise occur at only one electrode, can help to record a signal of as high an amplitude as possible, and can aid in determining the field of projection of the discharge, which can in turn help determine its underlying source (15,22,23).

"10%" Electrodes

Electrodes placed between and below the standard positions of the routine EEG electrodes can help to more precisely localize regions of seizure origin. This is particularly important in the case of events originating from the cortical base, because these signals are poorly detected and may not be recorded at all from standard electrodes (64). In one study (75), amplitudes of epileptiform activity were maximal at the standard electrodes 27% of the time and at the "extra" electrodes 61% of the time. Such extra electrodes include zygomatic (cheek) or periorbital electrodes.

Semi-invasive Electrodes

Nasopharyngeal electrodes were widely used at one time to evaluate complex partial seizures arising from the inferior or mesial temporal regions or from the orbitofrontal cortex, but are now used infrequently if at all (29,91). Sphenoid electrodes are more commonly employed. These are thin, flexible wires placed via a needle near the lateral angle of the jaw and directed to the region of the foramen ovale, near the greater wing of the sphenoid bone (78,87). Anterior placements are close to the amygdala and posterior placements close to the hippocampus. However, in practice, there are no clear differences in actual recordings that appear to distinguish various placements. This suggests that the major advantages of the use of sphenoid electrodes are their basal position and subdermal placement. The use of so-called mini-sphenoidal electrodes has been described, and they have been found to provide data similar to that obtained from traditional sphenoidal electrodes, although recorded waveforms are lower in amplitude (54).

Invasive Electrodes

Invasive electrodes include depth electrodes and subdural electrodes in arrays of strips and grids. They are placed in patients thought to be candidates for seizure surgery and are discussed below in the section on "Epilepsy Surgery."

Polygraphic Variables

Polygraph measures displayed as waveforms or alpha-numeric values in synchronized fashion with an EEG can assist in differentiating epileptic from nonepileptic paroxysmal events and in characterizing these events fully, whatever their pathophysiology. For example, in neonates, paroxysmal changes in heart rate or blood pressure may be investigated during monitoring to determine whether they are part of epileptic seizures or of nonepileptic, yet abnormal, events. In addition, parameters required for sleep staging are recorded in order to characterize events that may be associated with normal sleep or may be abnormal events best categorized as sleep disorders. In older children and adults, heart rate monitoring may detect syncope, and oxygen saturation and respiration measures may detect and characterize apneic episodes. Physiological parameters may be displayed as waveforms along with the EEG or may be displayed on the video screen numerically. The selection of the physiological parameters to be recorded depends on the clinical questions to be addressed during monitoring.

Electrocardiogram

The electrocardiogram is recorded with electrodes placed on the chest. Changes in rate or rhythm, which may occur in isolation or in association with other motor, autonomic nervous system, or behavioral changes, may provide critical data for diagnosis. For example, cardiac syncope may be detected and differentiated from syncope resulting from respiratory arrest in infants and children (65). In addition, syncope resulting from cardiac arrhythmias, alterations in blood pressure, or metabolic changes may occur both in children and in adults and requires differentiation from loss of consciousness associated with epilepsy.

Electro-oculogram

The electro-oculogram (EOG) is recorded to assist in the staging of sleep states and to help in the differentiation of EEG transients recorded by scalp electrodes from electrical potentials generated by eye movements. The EOG electrodes must be placed in order to detect both horizontal and vertical eye movements. This can be done by placing electrodes at both the inner and outer canthi, and both above and below an eye. Alternatively, one electrode can be lateral to and above one eye and the other electrode lateral to and below the other eye.

Respirations

The characterization of respirations is often a critical finding during monitoring studies—particularly those performed in younger infants or those patients suspected of having abnormal events during sleep. Respiratory effort is recorded in a number of complimentary ways: It may be measured by an impedance pneumograph attached to the chest with standard EEG electrodes or by a strain gauge placed around the chest. Abdominal movements associated with respiration are recorded with a strain gauge placed around the abdomen. Airway flow is measured by a thermistor or a thermocouple device placed at the mouth or nares. With these measurements—chest movements, abdominal movements, and airway flow—changes in respiration and the effectiveness of respiratory effort can be determined. Other respiratory parameters that may be recorded include systemic oxygenation and end-tidal carbon dioxide measurements recorded by pulse oximetry from nasal sensors. Regardless of the measurements taken, they must be recorded and displayed synchronously to each other, to the EEG, to other polygraphic parameters, and to the video in order to be clinically useful.

Electromyogram and Triaxial Accelerometry

The movements of selected muscle groups may be documented by using surface electrodes placed over the designated areas with the resultant electromyogram (EMG) recorded and displayed synchronously with other parameters, the video, and the EEG. To assist in identifying sleep stages, a submental EMG is typically recorded. EMGs of other muscle groups may be recorded if these muscle groups are thought to be involved in abnormal clinical events and the correlation of their movements is needed to determine their precise relationship to EEG activity. However, reliance on EMG electrodes to detect limb movement may be limiting because the movement of interest may not require the muscle group that the EMG electrodes are monitoring. Another sensor device, the triaxial accelerometer, can overcome this limitation (26). This compact sensor can be placed on a limb to detect movement in any plane; changes in movement can be represented by a deflection on a polygraph channel.

Systemic Blood Pressure

Continuous recording of systemic arterial blood pressure (SABP) during monitoring is not often performed—it is technically difficult and the clinical relevance of its interpretations is often not clear. However, continuous recording of SABP with other parameters, often including both video and EEG, can address specific clinical questions in the intensive care unit (ICU) setting, such as whether paroxysmal elevations in blood pressure are associated with EEG seizure activity. This parameter usually is measured when an intra-arterial pressure transducer already has been placed for clinical purposes. Values from this transducer can be displayed in parallel with the clinical bedside ICU monitors as a polygraphic analog tracing, or numerically in the video image, simultaneously with other parameters.

Video Recording

The equipment—including cameras, lens, camera mounts, remote control devices, videocassette recorders (or digital video storage media), and lighting—the recording formats, and the method of utilization all can affect the quality of the recorded data and, in turn, the validity of interpretation of the findings. The cameras may record in color or black and white. It may be more difficult to maintain a stable color image over time, and details of the video image may not be as crisp as with black-and-white recording. However, a color image provides clinical information that black-and-white images may not, including, obviously, changes in color of the patient—pallor, flushing, cyanosis, and vasomotor changes. Black-and-white recording is most effective in low-light areas or during nocturnal studies with standard lights out and with the use of infrared or ultraviolet light. The considerations may change with rapidly evolving technology, including the development of cameras that automatically select color or black-and-white recording modes, depending on lighting conditions. The type of questions to be answered will dictate the number of cameras used. A full compliment may include up to four cameras: two color cameras may be used for recording in daylight and

two black-and-white cameras for recording in the dark, with one of each pair of cameras used for a full view of the entire body and the other used for a close-up of the face. However, recordings of good quality can be performed using a single camera, carefully adjusted by staff. Lights remain on in the patient's room at night to facilitate continuous color recording.

As with any camera, the lens will determine whether the patient's entire body is on the film (when considered with respect to the distance between camera and patient), whether there is any distortion of the body, and whether there is a capability to obtain close-up views of the face or body parts. Most camera and lens units have the capability for autofocus and automatic monitoring and maintenance of stable color; however, these features must be confirmed for each unit.

Remote control of camera movement and focus is critical in the conduct of accurate monitoring. Many patients, in particular infants and children, move frequently during monitoring. Adults may change locations, such as from bed to chair. Many patients move dramatically during seizures. It is essential that the patient remain on camera at all times in order to capture clinical seizures. Remote control of camera movement, using pan-and-tilt devices, and of camera focus helps ensure this. This control must be accomplished by a technologist assigned to conduct the monitoring; automated sensing devices, placed on the patient and designed to have the camera follow the patient, have not been satisfactory thus far.

For adults, cameras are mounted toward the top of the wall of the monitoring room and directed down toward the bed. This camera placement is appropriate for adults because most of their time is spent in bed or in a chair often watching a television mounted next to the camera. Care must be taken in camera placement so that visitors cannot block the recording; because they may first greet the patient by standing at the front of the bed, visitors' heads may obscuring the full camera view of the patient. Although high-wall mounting may be appropriate for some children, it may be inadequate for others. Infants and young children may sit in bed and play or interact with family. A camera mounted near the ceiling of the monitoring suite will provide a continuous view of the top of the child's head but not the facial features, which may be crucial in the characterization of a seizure. Thus, for monitoring some children in a laboratory, camera mounting ideally should be flexible to meet specific needs of patients. Bedside monitoring poses different challenges in camera mounting. This type of monitoring is often performed on newborns and infants in neonatal or pediatric ICUs. Mounting the camera directly over the infant, rather than to the side or at a diagonal, allows the most accurate view of the infant without distortion or obscuration of face, limbs, hands, or feet. Other challenges in this setting include securing the camera so that movement near it does not cause the camera to jitter, and placing the camera so that staff or family will not obscure a view of the patient. Regardless of age of the patient or camera placement, visitors and staff must be educated to stay clear of the camera line of site, particularly during a seizure.

The particular videocassette recorder utilized is often dictated by the vendor of the system(s) installed, but it is often a standard, commercially available unit. Most recently, devices have become available with the capacity to store video images on computer hard drives or compact disks, although this currently requires a significant amount of disk recording space. To accommodate this problem, some configurations allow for simultaneous recording on videotape and hard drive—a complete study is recorded on videotape and significant clinical events are saved on disk. For recording on videotape, the modes of recording (standard vs. extended play) will affect the duration of time it may take to review the video during analysis and may also determine overall quality of the video image if segments are duplicated for teaching. Use of extended-play mode will allow a longer amount of recording on a single videotape and quicker review of the entire video during "fast forward" surveys of the tape compared with recordings made in standard-play mode. However, duplication of video segments obtained during extended-play mode will result in more degraded images than with those obtained during standard play. Fluid, full-motion, digital video, recorded onto computer disk simultaneously with digital EEG, may eliminate these concerns once the recording technology and data storage methods are perfected.

Lighting should be installed in EEG laboratories in order to avoid shadows, particularly on the patient's face and around the eyes. Portable supplemental lighting can be helpful, particularly when recording infants, but may also generate some heat, in addition to shadows, and may cause the patient to sweat, thus compromising EEG recording. Such lighting also can impede movement around the bedside.

Synchronization and Data Display

Synchronization devices are critical to monitoring, providing the basis for the temporal correlation of electrical changes with any clinical events that may be recorded. Time–date generators may be freestanding instruments used in an assembly of analog EEG instrumentation and video equipment or may be embedded within the computer of a digital monitoring unit. The manner of data display will also determine the validity of the interpretation

of monitoring. Time–date data must be displayed both on the video image and on the EEG–polygraph. It is often also helpful to display selected channels of EEG on the video image. Digital video can be superimposed on the digital EEG. This has both limitations and strengths. In viewing a small image, subtle movements may be overlooked; however, some instruments have the capacity to expand the image to full screen for more detailed analysis. It can be helpful to see the EEG and video simultaneously on a single screen, although, in interpreting the data, one generally looks at one piece of information at a time and then correlates the two.

With the development and increasing popularity of digital recording devices, the quality of data display, including resolution of waveforms, interchannel distances, and number of displayable channels, has become a significant issue. Because of the limitations of computer monitors, on-screen waveform resolution of EEG is not equal to that available with analog recordings onto paper. Interchannel distances may be too narrow for adequate analysis when utilizing enough channels to record EEG and polygraphic data. For example, the amplitude of the EEGs of children recorded at the scalp may be higher than that of adults, and the number of polygraphic channels recorded may be greater. The display on a monitor may become visually crowded, and greater care may be needed in analysis, particularly among those neurophysiologists who are making the transition from analog to digital recordings. Digital EEG instruments usually can print onto paper using laser or ink-jet printers. The best devices produce very sharp and accurate images, without the problems of pen misalignment occurring with analog machines.

MONITORING ENVIRONMENT

Monitoring suites, often called epilepsy monitoring units, can be located in the clinical neurophysiology laboratory, away from an inpatient hospital unit, or may be placed within an inpatient hospital setting. Regardless of its location or designation, the monitoring facility should be appropriately equipped and staffed.

Children in the laboratory setting have special needs in terms of care, recreation, education, visitation, general activities, and medical attention. Each child must be assessed individually so that the environment is conducive to optimal monitoring. Some laboratories modify cribs with transparent sides in order to record video at a level perpendicular to a sitting or standing infant (21). Other accommodations may include a playroom with video recording capabilities, which will allow the child to roam freely and be more active during monitoring. Although this is an engaging notion for the family of the patient and may be less frustrating for the child, it also increases the chances that the child may be off camera or have critical body parts obscured during a seizure. In such instances, additional events must be recorded for accurate analysis. Thus what may seem an enlightened amenity for children may lead to unnecessarily prolonged monitoring studies in some cases. Monitoring in a more restrictive environment may provide the basis for a more focused and efficient study, but also presents its own sets of challenges in terms of child care.

Bedside monitoring poses different challenges. This technique has been successfully utilized in the monitoring of neonates and children (8,10,71, 83,84) and adults. Bedside recordings are typically requested for newborns and infants who are too ill to be transported to the laboratory. Recording techniques must be adapted to the current status of the individual patient. At times, bedside monitoring is relatively brief in duration compared to epilepsy monitoring unit studies, in part because of limitations of resources, personnel, and instrumentations and in part because the abnormal paroxysmal clinical events that are of most concern in young patients tend to occur more frequently or may be provoked by stimulation of the patient. Thus the yield of brief ICU monitoring in a sick neonate or infant is relatively high compared with a similar study in older patients. Longer studies occur when there is concern that patients may be experiencing unrecognized events, or when the EEG pattern is to be monitored for response to therapy. In the ICU, all the essential instrumental components for monitoring are transported to the bedside. Monitoring is initiated and conducted with the understanding that the clinical care of the patient must continue unimpeded.

ROLE OF TECHNICAL PERSONNEL IN MONITORING

With emerging automated technology, the financial pressures imposed on neurophysiology laboratories, and efforts to "cross-train" hospital personnel, there is a current, and unwelcome, trend to diminish the role of the technologist in monitoring. This role, however, is critical and irreplaceable. The technologist is trained in EEG monitoring, has particular expertise in the recording of EEGs, and is frequently registered by the American Society of Electrodiagnostic Technologists (ASET). The technologist's tasks may include assisting in the planning of the monitoring study; selecting appropriate EEG montages and polygraphic parameters; discussion of the monitoring study with family and other caregivers; conducting a premonitoring visit for the family and, depending on the age of the patient, orienting the

patient and family once in the monitoring suite; obtaining accurate historical data; applying electrodes and appropriate sensors for EEG and other polygraphic measurements; initiating and conducting the monitoring study; completing the study; and ending the recordings and removing the electrodes after the study has been completed.

Patient observation, interaction, and testing are important tasks of the technologist. The technologist assures that the patient is constantly on camera and that the EEG and polygraphic measurements are being recorded adequately. (For example, pediatric patients can move quickly off camera and can be very effective and efficient at dislodging recording electrodes.) Adults may suddenly turn and reach for a ringing telephone or, impulsively, try to get out of bed to go to the bathroom. In addition, clinical events can be documented and characterized on a log maintained by the technologist.

Also, during long-term monitoring, patients will require assistance with activities of daily living and, depending on medical necessity, will need recording of vital signs, medication administration, and medical assessments. Technologists may perform some of these tasks; nursing staff must perform others. Policies and procedures should be developed in advance of monitoring studies that delineate the roles of the technologist and nurse in patient care. When children are subject to prolonged monitoring, child-life specialists are helpful in developing age-appropriate activities, education, and recreation.

For bedside monitoring in the ICU, technologists must be available to initiate and conduct studies around the clock, weekdays and weekends, in order to maximize the yield of studies. Studies performed in a timely fashion have a greater likelihood of providing useful clinical information. It is also essential that trained technologists staff the epilepsy monitoring unit whenever patients are monitored.

The purpose of monitoring is to record transient, fleeting clinical events. The malfunction of instrumentation, even for a short time, may cause such events to go unrecorded and thus unnecessarily prolong monitoring. Therefore, dedicated biomedical engineering and computer specialist staffs are critical to the successful operation of a monitoring unit. Regular maintenance is, of course, needed. However, less obvious is the need for on-call biomedical engineering personnel in order to keep monitoring equipment operational around the clock. With new computer-based instrumentation, it is essential that adequate technical support be available to resolve problems rapidly.

The so-called economy of reducing support personnel for monitoring is problematic and, most often, shifts the cost of the study to the patient. Studies conducted with no technologist present, with cameras mounted on the wall with no means of remotely following patients, with little supervision of the patient by knowledgeable personnel, or with the burden of event identification shifted to parents or other care givers only serve to prolong monitoring unnecessarily, because clinical events may be missed and the patient must be monitored for additional time.

The clinical neurophysiologist is responsible for directing all aspects of the monitoring study and its interpretation. Often, medical issues complicate monitoring, including alteration of antiepileptic drugs (AEDs), intercurrent illnesses, and the management of seizures. There are number of strategies for dealing with these issues. Usually a number of physicians are involved with the patient during an inpatient stay, and comprise an ad hoc team for medical management of these patients. Monitoring, whether within a monitoring unit, in the neurophysiology laboratory, or at the bedside, will require around-the-clock availability of the attending clinical neurophysiologist. In instances in which several physicians are involved in the care of a monitored patient, delineation of responsibilities before recording is important—particularly in regard to management of acute seizures. There is also a tendency for physicians on rounds to review interesting portions of recordings. However, without benefit of the interpretation of the complete study by the neurophysiologist, the specific implications of the study for each patient cannot be determined. Discussion of segments of a study may provide premature information to the patient and may be at odds with the final reported findings.

STRATEGIES OF MONITORING

The strategy of monitoring for each patient is typically individualized and determined prior to monitoring. The type, character, and timing of the clinical events suspected of being abnormal will determine the best strategies for monitoring. This plan may change once monitoring is underway and initial findings are analyzed. The monitoring protocol is devised after consultation with the ordering physician. EEG montages, physiological sensors, and environment should be selected so as to provide for an efficient study and for the highest diagnostic yield during the study. The goal is to conduct a monitoring study that answers the clinical question in the least amount of time, with the least inconvenience and expense.

In addition, the timing of the suspected clinical events may suggest special strategies of timing. For patients with nocturnal events, monitoring must occur at night; monitoring during daytime napping typically cannot be substituted. Some seizure types may occur on arousal from sleep; for example, infantile spasms may occur in a cluster on arousing. Thus monitoring should include recording of a wake–sleep cycle. In addition, specific provocative agents, activities, stressors, or events may trigger a clinical seizure or behavior; these should be included during monitoring.

Sleep and Sleep Deprivation

Sleep activates the occurrence of seizure discharges in about one-third of patients with epilepsy (24). Sleep deprivation also has long been used to activate the occurrence of seizure discharges in patients with suspected seizure disorders (7,82). The technique is effective 30%–70% of the time and can increase the diagnostic yield even if sleep itself does not occur (25). Deprivation can be complete (e.g., no sleep in 24 hours) or partial (e.g., 2–4 hours of sleep the previous night).

Hyperventilation

Hyperventilation commonly produces EEG slowing as a result of hypocapnia and ensuing vasoconstriction and, in some patients, can activate both seizure discharges and actual seizures. This is particularly the case in patients with absence epilepsy but also can occur in patients with complex partial seizures. Hyperventilation is commonly used during routine EEG recordings but also can be useful during video-EEG monitoring. Only generalized or focal spikes on the EEG during hyperventilation should be considered epileptiform (see Chapter 5).

Photic and Other Methods of Sensory Stimulation

In selected patients, photic stimulation can activate epileptiform activity (81), or even seizures, when other modalities will not. However, generalized seizure discharges can occur at times during withdrawal of alcohol, illicit drugs, or medications, including AEDs. Standard flash equipment and flash frequencies are usually used, but special photic devices or activation methods are helpful in some cases (28).

Auditory, cutaneous, and behavioral stimuli can be used in the rare cases in which they are identified as causing seizures to occur (99,108). Startle can activate events in some cases, as can certain games, mental activities, or even eating (17).

Induction of Psychogenic Seizures

From the perspective of video-EEG monitoring, the finding of a normal EEG during a period of unresponsiveness is indicative of a seizure disorder of emotional origin (34,49,52,107). However, certain caveats must be kept in mind. First, seizure activity restricted to very localized areas of the cortex, particularly in adults, may not be reflected at the scalp (but essentially never produces episodes of loss of consciousness). Second, on occasion epileptic seizures can occur during attempts to induce psychogenic seizures immediately following epileptic events (16,59).

Many find it helpful to induce psychogenic seizures under controlled laboratory conditions (6,95). When this is done, the patient is told that a particular technique (e.g., infusion of intravenous saline, an applied tuning fork vibration) will induce a seizure. It has been suggested that hypnotism may be utilized to induce nonepileptic events (4). It is often helpful to review the videotape with the patient and family to ensure that the episode recorded is representative of those occurring spontaneously. If activating techniques are used, they should be employed in a respectful manner. Similarly, when a diagnosis of psychogenic seizures is made, findings must be discussed tactfully with the patient and family. Some patients with psychogenic seizures also have epilepsy (53). If the combination is suspected, it is important to try to make a positive diagnosis of each, so that treatment can be based on an empirically documented disease.

DATA ANALYSIS AND MANAGEMENT

Studies that are short in duration are interpreted by visual analysis. Studies conducted over a long period of time will generate large amounts of data. Typically, these data are also analyzed visually. However, there is a trend to utilize automated EEG spike-and-seizure detection programs. These computer programs have been useful in the analysis of EEGs of older children and adults (30,32,33), and have been applied to neonates and young infants with varied success (30,31,51). The application of spike detection computer programs is confounded by the fact that detection programs can miss seizures. Further-

more, there may be a high number of false positives resulting from detection of artifact or of normal variant patterns; an example of the latter is spike-and-sharp-wave complexes in the neonate, which may not be considered epileptiform (31). Because of these concerns, computer analysis and detection should be followed by human validation of the detected and analyzed data, with the understanding that some interictal and, perhaps, ictal events may be missed.

OVERALL CONSIDERATIONS FOR SYSTEM DEVELOPMENT AND IMPLEMENTATION

Among the principles the user should consider when planning and purchasing a monitoring system are the following (63). The system should be flexible and expandable so that more or fewer channels can be used to assess a given patient or a given problem. Second, breakdowns occur in monitoring equipment; redundancy should be planned into the system so as to account for this, at least some of the time. Third, the system should use standard and interchangeable parts so as to facilitate the flexibility and redundancy already mentioned. Fourth, the system should be modular, enabling separation of data acquisition, analysis, and storage. This facilitates maintenance of the system and allows evaluation of patient data to take place while new data are acquired. Communication between these modular parts should take place using standard methods and protocols. There should be methods of data analysis, data storage, and data reduction that are simple for the average end user.

ROLE OF MONITORING IN CLINICAL MANAGEMENT

The most effective application of monitoring is when it is conducted to answer a specific clinical question for an individual patient (55). Often the goal is to quantify seizures and various aspects of epilepsy (43,58,63,66,69). Applications may be age specific, because a greater variety and range of clinical events may occur in younger patients, events not seen when patients are older. Thus an important aspect of the analysis of pediatric monitoring is the anticipation of the type of clinical events that may occur at various ages.

Neonatal Seizures

Monitoring of neonates is most effectively and most often performed at the bedside (73). Instrumentation that synchronizes EEG, polygraphic parameters, and video is brought to the nursery for monitoring and used without disrupting the care of the neonate. The differential diagnosis of abnormal clinical paroxysmal events includes normal movements of the waking preterm or full-term infant, normal movements of sleep, nonepileptic apnea and bradycardia, obstructive or central apnea, gastroesophageal reflux, abnormal nonepileptic events such as jitteriness, and epileptic and nonepileptic seizures. The clinical events may occur spontaneously, may be provoked, or both. Thus, in order to characterize any of these events, the full range of polygraphic–physiological sensors is typically applied and recorded with video and EEG. In addition, the duration of recording should be sufficient to include complete wakefulness–sleep cycles and to allow adequate time to capture clinical events, including periods in which maneuvers are performed to provoke them.

The accurate interpretation of the neonatal EEG will allow a more comprehensive understanding of the pathophysiology of the clinical events recorded and, in the absence of any such recorded events, may still provide important information concerning the degree and distribution of brain function (73). The character of the background EEG is conceptional age specific. The findings of serial EEGs, rather than those of a recording from a single point in time, will give the most accurate information concerning prognosis.

Interictal sharp waves are typically not considered epileptiform. Electrical seizure activity may be unifocal or multifocal. It may be confined to one region of the brain (Fig. 18.1), may migrate gradually, or may suddenly change location (Fig. 18.2). When the seizures are multifocal, they may occur simultaneously, but asynchronously in the two hemispheres. The amplitude, frequency, and morphology of the electrical seizures themselves may vary within a single seizure and from seizure to seizure. Electrical seizures may occur in association with clinical events ("electroclinical seizures") or they may occur with no clinical accompaniment ("subclinical seizures"). The latter seizures may occur in infants with significant brain injury and are characterized as seizure discharges of the depressed brain (41) and as alpha seizure discharges (50,96,101). In addition, electrical seizures may occur in the absence of clinical seizures following the treatment of electroclinical seizures with AEDs. In this situation, the clinical seizures are controlled while the electrographic seizures persist, a situation known as "decoupling" (71,72) (Fig. 18.3). Electrical seizures may also occur in the absence of clinical events when the infant is pharmacologically paralyzed for respiratory care.

A number of systems for characterization and classification of neonatal seizures have been proposed and updated (71,73,93,94) (Table 18.1). Clinical

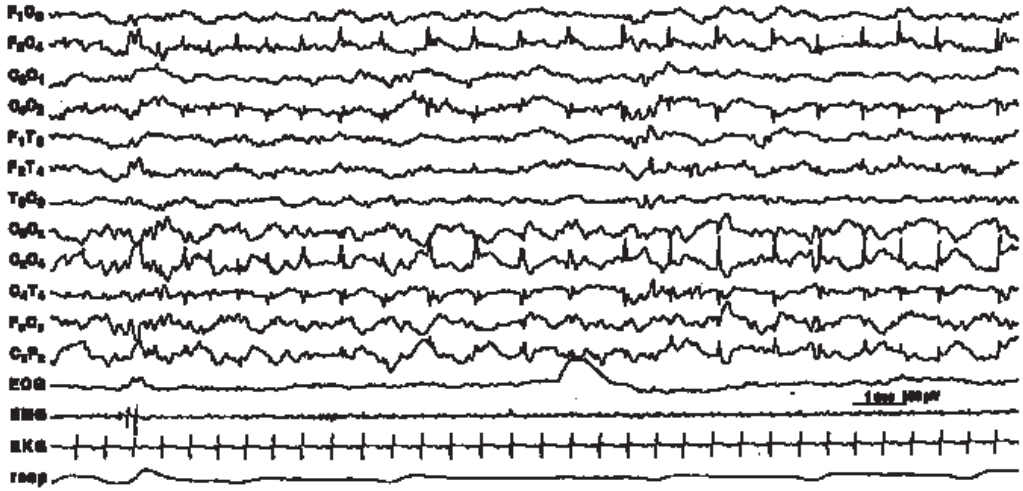


FIG. 18.1. Highly localized neonatal electrical seizure. Seizure discharges arising from the right central region of a 7-day-old, 40-week gestational age female infant with the diagnosis of group B streptococcal meningitis and cerebral infarction of the right temporal-occipital region, demonstrated by contract-enhanced computed tomography. Rhythmic focal clonic activity of the left foot occurred in close association with each seizure discharge. (From Mizrahi EM, Kellaway P. Neonatal electroencephalography. In *Diagnosis and management of neonatal seizures.* New York: Lippincott–Raven Publishers, 1998:99–143, with permission.)

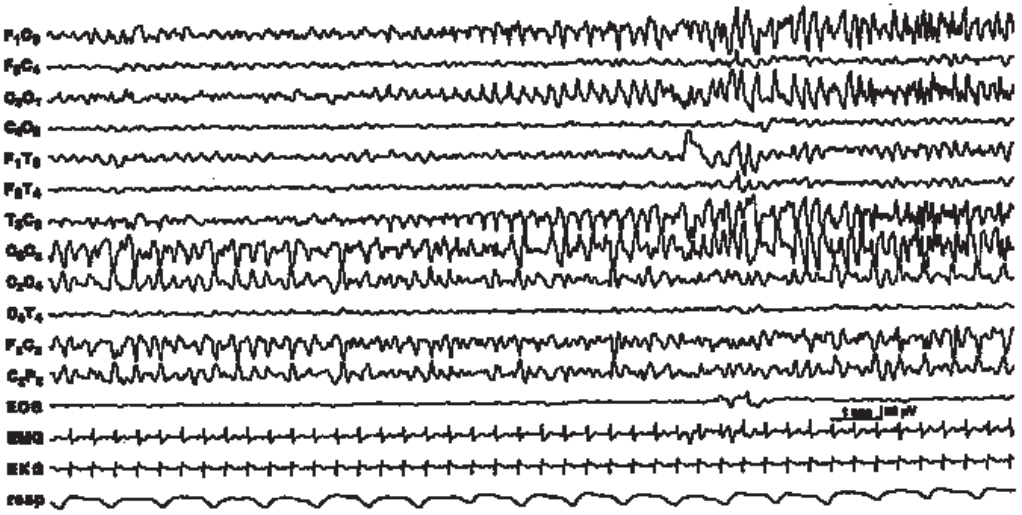


FIG. 18.2. Spread of electrical seizure activity in the neonate. Electrical seizure activity begins in the midline central region, then shifts to the left central region. As the electrical discharge spreads, the midline region becomes uninvolved, just as the left central region was uninvolved at seizure onset. No clinical seizures were associated with this electrical seizure discharge. This recording was obtained from a 4-day-old, 40-week gestational age female infant with hypoxic-ischemic encephalopathy. (From Mizrahi EM, Kellaway P. Neonatal electroencephalography. In *Diagnosis and management of neonatal seizures.* New York: Lippincott–Raven Publishers, 1998:99–143, with permission.)

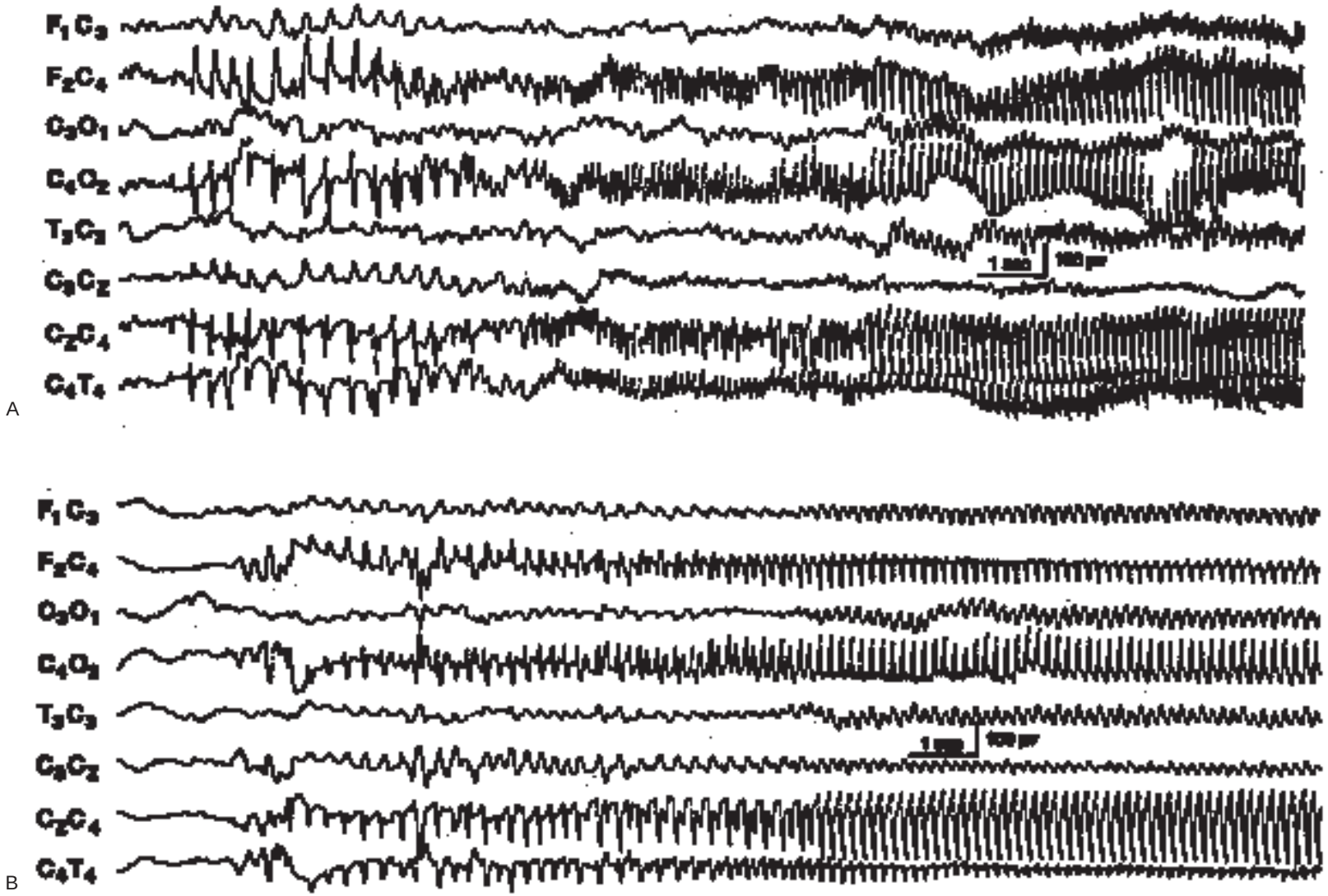


FIG. 18.3. Response to AED therapy in the neonate. **A:** Electrical seizure activity arises in the right central region, clinically associated with focal clonic seizures of the extremities on the left. Recording was obtained prior to AED therapy in this 1-day-old, 40-week gestational age female infant with focal cortical dysplasia in the right central region. **B:** Following administration of a loading dose of phenobarbital (20 mg per kilogram intravenously), no clinical seizures were present, although electrical seizures recurred in the same region as that prior to AED therapy. Thus the clinical seizures had been "decoupled" from the electrical seizures. Both figure parts show selected channels from a 12-channel EEG recording. (From Hrachovy RA, Mizrahi EM, Kellaway P. Electroencephalography of the newborn. In: Daly D, Pedley TA, eds. *Current practice of clinical electroencephalography*, 2nd ed. New York: Raven Press, 1990:201–242, with permission.)

TABLE 18.1. *Clinical characteristics, classification, and presumed pathophysiology of neonatal seizures*

Classification	Characterization
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on one side of the body May occur simultaneously but asynchronously on both sides Cannot be provoked by stimulation or suppressed by restraint **Pathophysiology:** Epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetrical posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint **Pathophysiology:** Epileptic
Generalized tonic	Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor–flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning **Presumed Pathophysiology:** Nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation **Presumed Pathophysiology:** May be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor–flexor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint **Pathophysiology:** Epileptic
Motor automatisms	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation **Presumed Pathophysiology:** Nonepileptic
Oral–buccal–lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation **Presumed Pathophysiology:** Nonepileptic
Progression movements	Rowing or swimming movements Pedalling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning **Presumed Pathophysiology:** Nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation **Presumed Pathophysiology:** Nonepileptic

seizures are characterized as clonic (focal or multifocal), tonic (focal or generalized), myoclonic (fragmentary, focal, or generalized), spasm, and motor automatisms (movements of progression, oral–buccal–lingual movements, ocular signs, and paroxysmal purposeless movements) (71). Some of these clinical events have a clear and consistent association with electrical seizure activity, and can best be described as neonatal seizures of epileptic origin. Typically, these are clonic, focal tonic, and some types of myoclonic events. Other clinical seizure types occur without electrographic seizure activity, and the clinical events can also be provoked by tactile stimulation and arrested by restraint. In addition, these types of clinical events have other features that also suggest that they are based in reflex physiology and are best referred to as "brainstem release phenomena" or nonepileptic neonatal seizures (47,71).

Thus the monitoring of neonates for suspected seizures should include a log of suspected clinical events that is well maintained by the technologist, efforts to provoke suspected events by stimulation of the infant, and, when clinical events do occur, efforts to stop them by restraint. These responses are considered in visual analysis of monitoring. In addition, the relationship of clinical and electrical events is given close scrutiny. Because so-called nonepileptic seizures may occur in infants who have also had subclinical electrical seizures unassociated with clinical events, the simple reporting of the occurrence of a clinical event in such a monitored infant may falsely identify that event as epileptic in origin.

The response of electroclinical seizures to treatment with AEDs has been discussed above. However, decoupled, subclinical electrographic seizures in the neonate may be very resistant even to vigorous AED treatment, and, even if eliminated, the discharges may recur. Thus new strategies for treatment and for continued EEG surveillance are needed. Typically, first- and second-line AEDs (phenobarbital and phenytoin) are given in dosages to attain high therapeutic serum levels, with additional dosages of benzodiazepines given. Further AED treatment is often not pursued because it can be associated with adverse effects such as hypotension, bradycardia, apnea, and central nervous system depression (79).

Other needs for new strategies of management concern methods of EEG surveillance for electrical seizures in AED-treated infants, in infants at risk for electrical seizures unassociated with clinical seizures, and in those pharmacologically paralyzed for respiratory care. The latter setting may be ideal for the application of computer-assisted, automated seizure detection systems. In these instances, the infants are relatively immobile and the chance of the occurrence of intrusive movement-induced artifact is minimized.

Infantile Spasms

Monitoring has been successfully utilized to characterize and classify infantile spasms and to assess the efficacy of various therapies (27,38–40, 48). The clinical spasms may be extensor, flexor, or mixed extensor–flexor. Electrographically, a generalized-voltage, slow–sharp transient or an episode of generalized voltage attenuation with low-voltage fast activity superimposed may accompany them (36) (Fig. 18.4). The occurrence of infantile spasms typically has been associated with the interictal EEG finding of hypsarrhythmia background activity, although modified hypsarrhythmic patterns, other abnormal types of EEG background activity, and even normal EEG background activity may occur in infants with spasms (36,37).

Monitoring is effective in establishing the diagnosis of infantile spasms. The duration of monitoring needed for diagnosis is variable, although prolonged recordings are not often needed, particularly in an infant with hypsarrhythmia or a modified pattern. However, additional information may be gained from monitoring these infants because they may also experience other seizure types (77). Thus a child with infantile spasms may also experience recurrent simple or complex partial seizures. Monitoring is critical in the documentation of the various seizure types an infant may have because therapies for each vary and are type specific.

Monitoring is also essential in children with infantile spasms in order to determine the effectiveness of therapy—traditional hormonal treatment with adrenocorticotropic hormone or prednisone, and more recently, new AEDs. Monitoring is more effective in this regard than is parental observation (36). Parents often underestimate spasm frequency or the presence of spasms. A comparison of parental observation with 24-hour monitoring of patients with infantile spasms demonstrated that the infants were actually experiencing several (often unrecognized) events per day. In addition, some parents may report that spasms are occurring when monitoring fails to reveal such events.

Seizures in Infancy

The concerns associated with the monitoring of neonates are also associated with the monitoring of infants suspected of having seizures in the first year of life—seizure types with similar underlying pathophysiology persist, but at relatively different frequencies (67,68). In addition, other seizure types emerge within the first year of life and become more prominent. These include

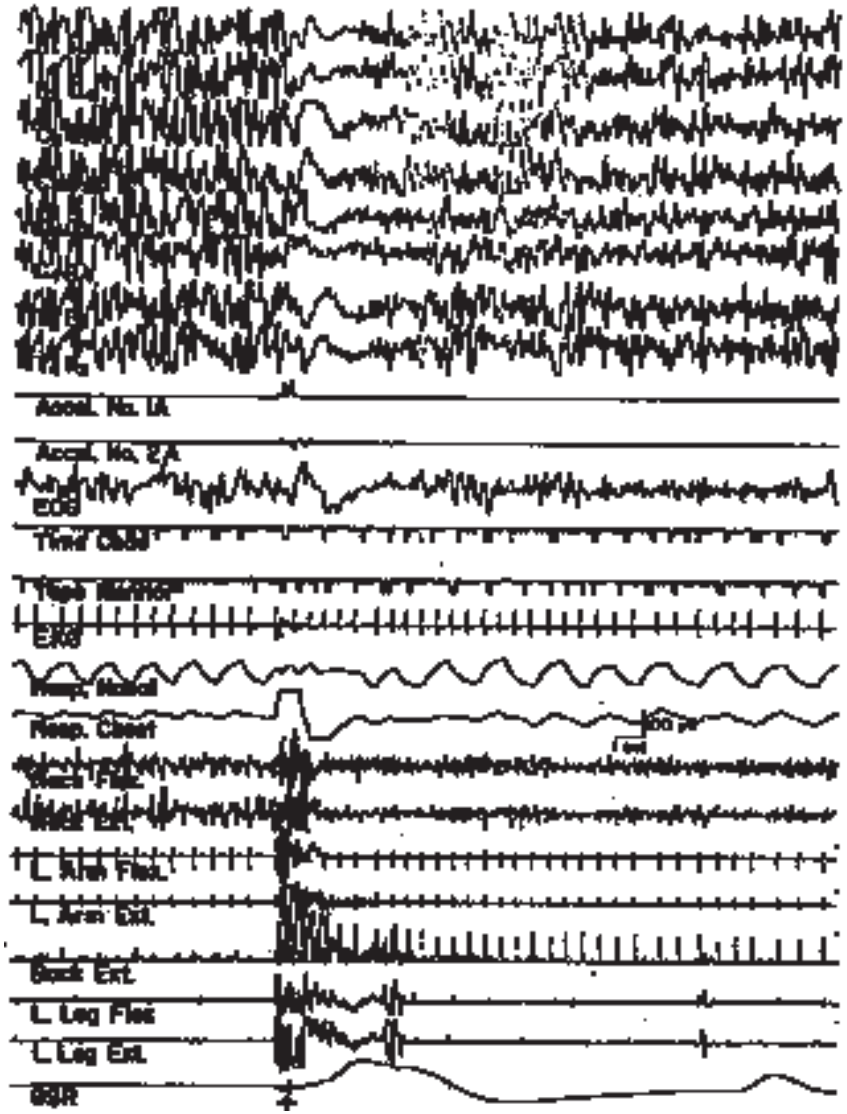


FIG. 18.4. Ictal and interictal recording of infantile spasms. Twenty-four channel EEG and polygraphic recording of an infant with clinical spasms. The preictal EEG background activity demonstrates hypsarrhythmia; the postictal EEG demonstrates relative normalization, which may occur follow electroclinical spasms. The clinical spasm is flexor–extensor, occurring in association with an ictal generalized, high-voltage slow-wave transient, followed by superimposed generalized fast activity. Polygraphic channels that record EMG, accelerometry, and respiration characterize the clinical event and its precise relationship to EEG. Video, capturing the clinical event, was also recorded, and synchronized to the EEG–polygraph with the time code channel.

infantile spasms and other generalized myoclonic events, complex partial seizures, and generalized tonic, generalized tonic–clonic, and generalized clonic seizures (19,76). It should be noted that this period may be characterized by the emergence of generalized epileptic seizures; however, the precise age at which they consistently appear is unknown and may extend beyond the first year of life.

Problems in semiology similar to those with neonatal seizures have led some investigators to develop an additional classification system of seizure for infants, utilizing monitoring (76). Some seizure categories were retained: clonic, tonic, spasms, and myoclonic events. Others added were not part of the seizure classification of older children or adults (11,12). *Astatic seizures* are described as sudden loss of muscle tone of one or more muscle groups or the entire body. *Behavioral seizures* consist of an abrupt change in behavior without other overt features, sometimes with a sudden cessation of movement. *Versive seizures* consist of version of the eyes only—without head or limb turning.

Complex partial seizures in infancy represent an important clinical problem (19). Their characterization and classification by monitoring is the first step in diagnosis and management. Partial epilepsy that presents in infancy and early childhood is considered by some investigators to be a catastrophic disorder that may eventually be associated with profound neurological deterioration (86) and, without effective therapy, a poor prognosis for mental or motor development (9). The diagnosis of complex partial seizures in infants may be difficult, and, because of its association with a poorer prognosis and perhaps the need for more aggressive initial AED therapy, monitoring may be a valuable tool in the management of these patients.

Childhood Epilepsy

The differential diagnosis of suspected seizures in older children may include movement disorders (tics, dystonia, ballismus); sleep disorders (apnea, paroxysmal leg movements, sleep myoclonus, night terrors, other parasomnias) (102); behavioral disorders; pseudoseizures; childhood migraine; cardiac or vagal syncope; esophageal reflux; reflex behaviors; and normal, although, perhaps, unusual behaviors. In addition, childhood seizures themselves can more easily be classified according to the international classification of seizures and, with additional information, epileptic syndromes (11,12). Thus monitoring can provide the basis for the diagnosis of a wide range of paroxysmal clinical events, some caused by epilepsy and some not, and for the classification of epileptic seizures (70).

Prolonged monitoring in childhood also allows for the quantification of epilepsy in the assessment of therapy. Certainly, capture of clinical or electrical seizure activity during monitoring may indicate that AED therapy is not effective. The quantification of EEG interictal generalized spike-and-wave activity during prolonged, overnight recordings in children with generalized seizures has been shown to predict future seizures effectively (45,46,48). In serial monitoring studies, the abundance of generalized spike-and-wave activity has been quantified during 12-hour epochs of EEG before and after therapy with ethosuximide in children with epilepsy characterized by absence seizures and concurrent atonic, myoclonic, or tonic–clonic seizures and 3-Hz generalized spike-and-wave activity. There was a direct relationship between the occurrence of seizures and the amount of interictal spike-and-wave activity. Reduction of the spike-and-wave abundance by AEDs predicted reduced seizure occurrence. At serum levels at which spike-and-wave activity during wakefulness or rapid-eye-movement sleep was

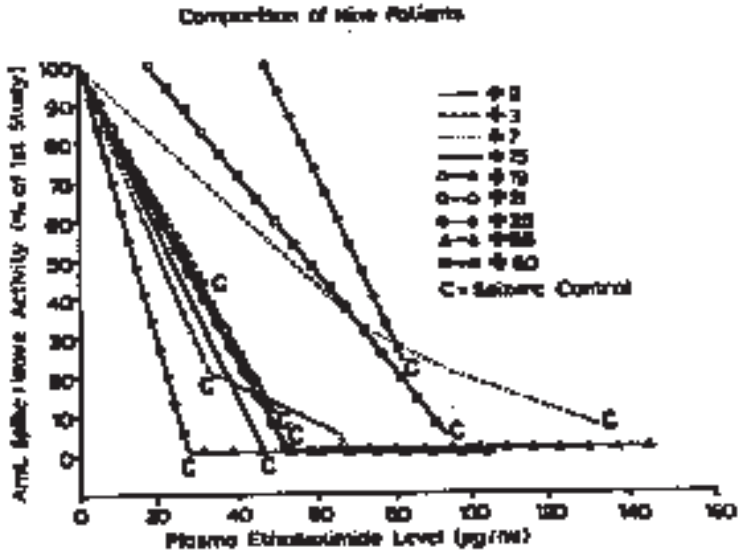


FIG. 18.5. Relationship of interictal generalized spike-and-wave activity, AED serum levels, and clinical control of absence seizures. Control of childhood absence epilepsy associated with 3-Hz spike-and-wave activity is attained with reduction of the amount of spike-and-wave activity during a 24-hour video-EEG monitoring period, compared to a baseline recording. See text for details.

abolished, the seizure types of absence, myoclonic, or atonic did not recur. However, if any spike-and-wave activity was present in a prolonged EEG sample (12–24 hours), the potential persisted for generalized tonic–clonic seizures to recur. Thus prolonged EEG monitoring of patients undergoing AED treatment for some generalized childhood epilepsies may be helpful in the early prediction of eventual seizure control at specific serum levels of AEDs (Fig. 18.5).

Epilepsy Surgery

Prolonged monitoring is an important part of the presurgical evaluation of patients with medically intractable seizures (3,5,20,35,42,56,74,89,105,106). The general principles of monitoring for nonsurgical candidates apply: maintenance of quality recordings, investment in support staff, time synchronization of all recording modalities, and observation for age-specific clinical seizure types.

There are two principle types of invasive leads: depth electrodes and subdural electrodes. The former are thin cylinders with multiple contacts along their length. They can be placed anywhere but are primarily used to record from mesial temporal structures such as the hippocampus and amygdala and from the mesial frontal lobe. They may be surgically placed in a posterior-to-anterior orientation or a lateral-to-mesial (orthogonal) orientation (90). Subdural electrodes are metal disks embedded in plastic. They can be linear "strips" of several electrodes, or larger arrays, often called grids, with several rows of evenly spaced disks. Some strips may be placed through burr holes, whereas other strips and grids require craniotomies. Both stainless steel and platinum–iridium electrodes are used. Depth electrodes (88) are particularly useful when the goal is to determine in which hemisphere seizures of likely mesial temporal lobe origin originate (Fig. 18.6). Subdural strips can be selectively placed: below the basal temporal and frontal lobes (103,104) or over specific cortical regions (Fig. 18.7). Subdural grids can be used to determine the extent of the epileptogenic region over an area of interest and to perform functional localization studies: evoked potential studies or cortical stimulation used to localize cortical regions subsuming motor, sensory, language, or other functions (57,62,64,92). Intracranial electrode utilization is considered safe, with potential benefits outweighing

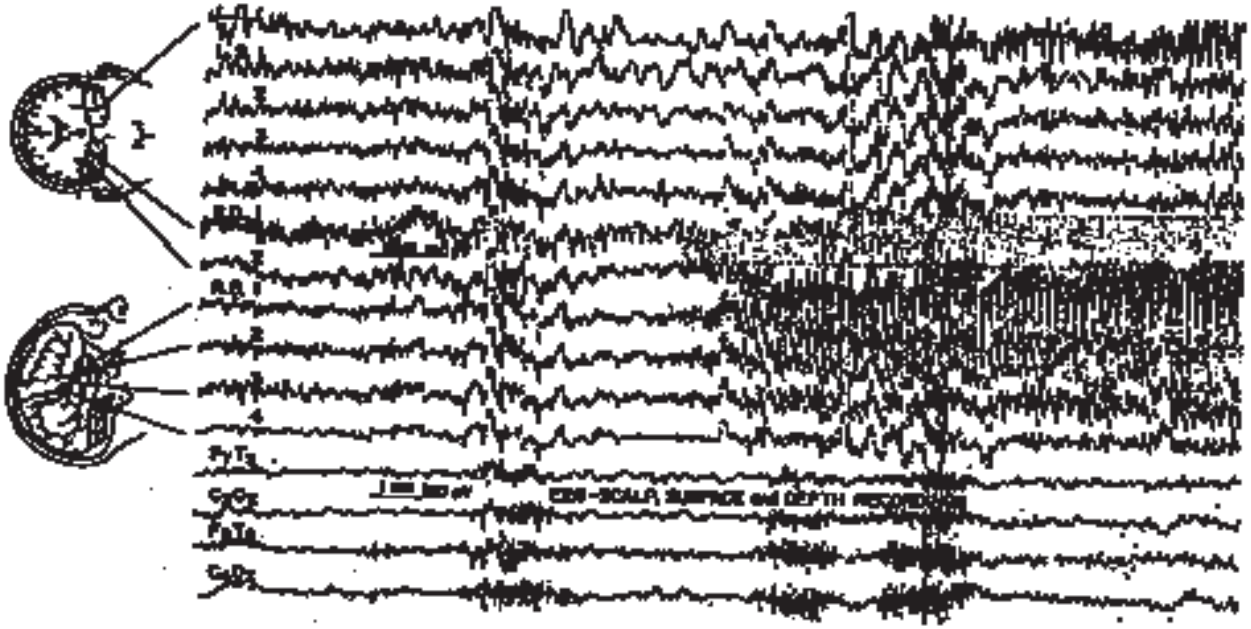
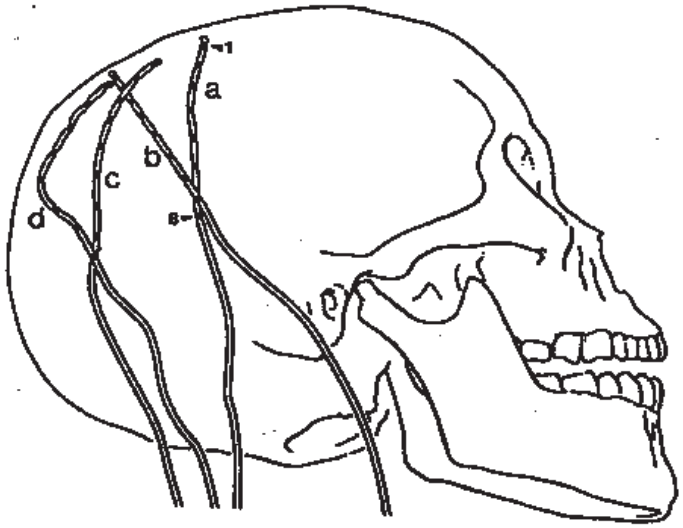


FIG. 18.6. Ictal depth recording in a 35-year-old man with complex partial seizures. Depth electrodes were implanted orthogonally, in lateral-to-medial orientation, into the left and right temporal lobes. Through the same bur hole, additional electrodes were situated over the posterior surface of the temporal lobes in anterior-to-posterior orientation. Electrical seizure activity arises in the depth of the right temporal lobe (*R.D.*) with eventual spread to the right temporal surface (*R.S.*) and finally to the left temporal region (*L.D.*), but there is no representation from the left temporal surface (*L.S.*). Selected EEG channels from scalp electrodes demonstrate no initial focal or lateralizing features. Following right anterior temporal lobectomy, pathology examination demonstrated mesial temporal sclerosis. (From Mizrahi EM, Kellaway P, Grossman RG, et al. Anterior temporal lobectomy and medically refractory temporal lobe epilepsy of childhood. *Epilepsia* 1990;31:302–312, with permission.)

A



B

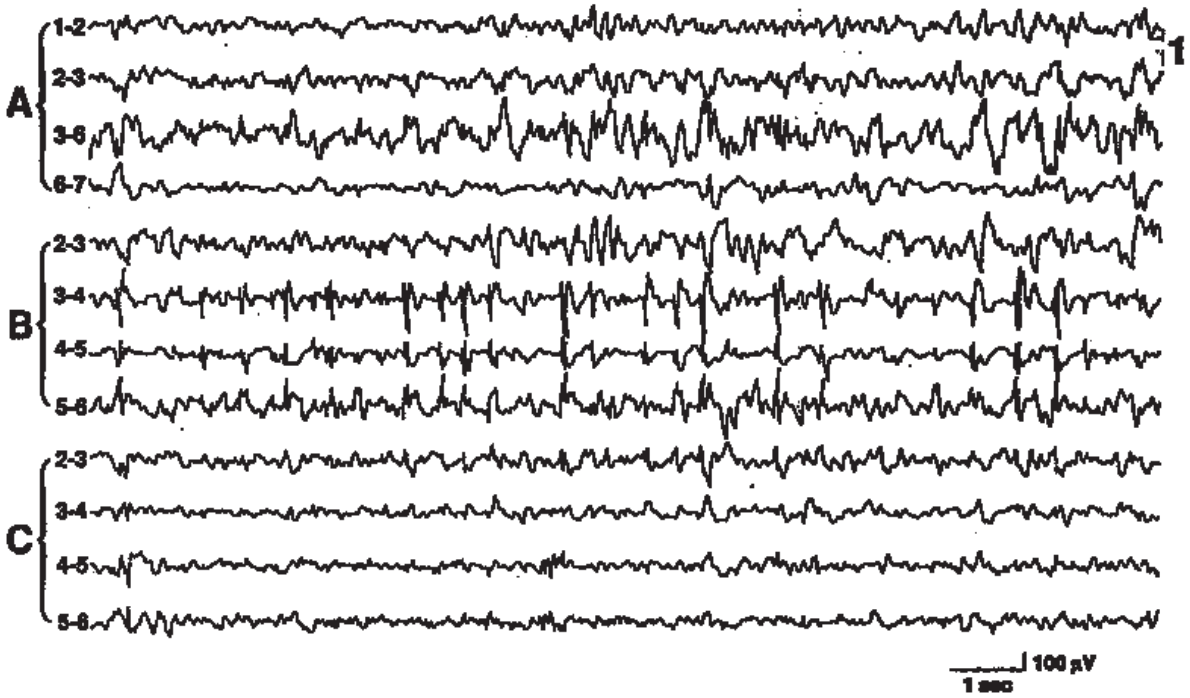
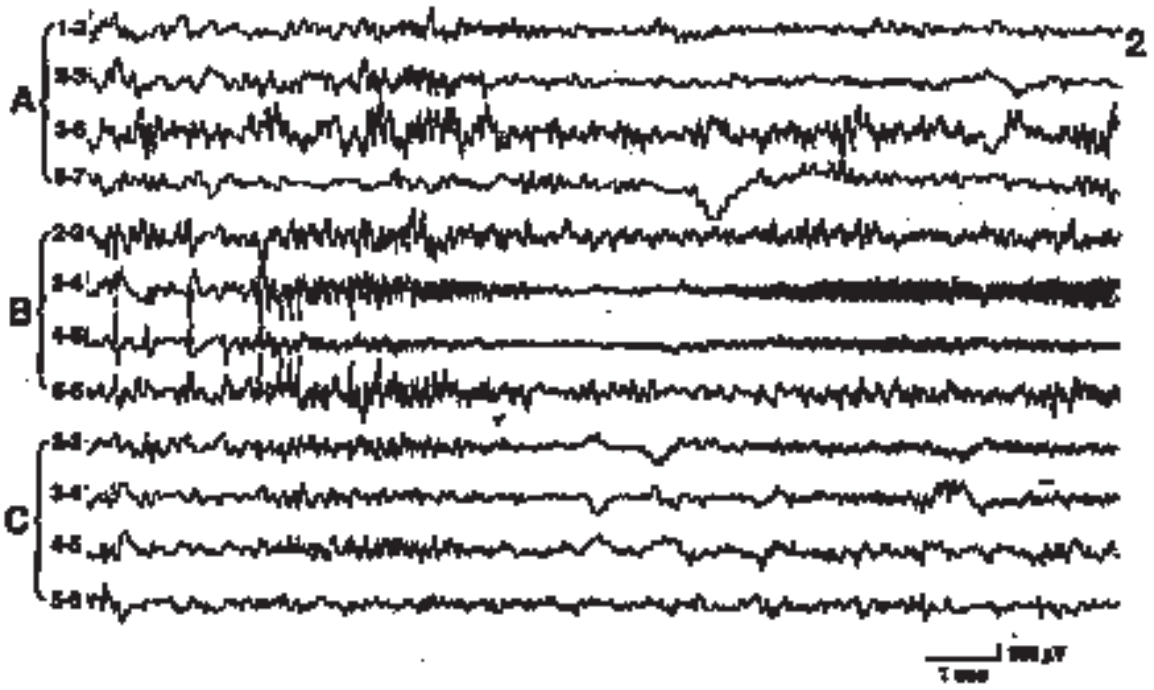


FIG. 18.7. Subdural strip electrode recordings. Four electrode strips, in this case arrays originally designed as depth electrodes, were inserted through two bur holes over a cortical region suspected of being the epileptogenic zone in an 11-year-old boy with recurrent, brief partial seizures characterized by initial sensory disturbance of the dorsum of the left hand, followed by transient tonic posturing of the left shoulder and arm, then focal clonic activity of the left arm and hand. **A:** Schematic of skull radiograph indicating location and numbering of electrodes. Electrodes were inserted through two bur holes at the sites of the crossing of each pair of electrodes. The recordings are sequential (labeled 1–5); capital letters on the recordings correspond to lower-case letters on the electrode diagram; and electrode contacts are labeled numerically. **B:** Segment 1. Interictal discharges localize to electrode B5 (calibration: 1 second; 10 µV per millimeter). *(Figure continues.)*



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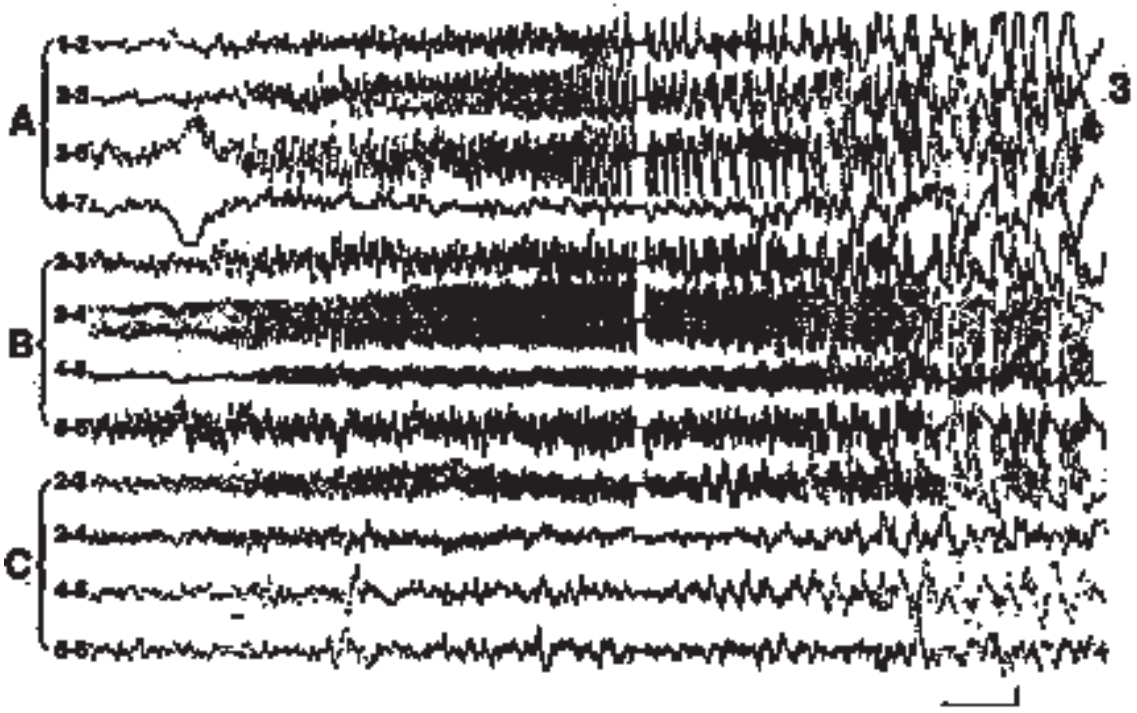

D

FIG. 18.7. *Continued.* **C:** Segment 2. High-frequency, low-amplitude seizure discharge arises from electrode B5 with involvement of B4 (calibration: 1 second; 10 μV per millimeter). **D:** Segment 3. Electrical seizure activity evolves in morphology and spreads (instrumentation sensitivity is changed, over halfway through this segment, from 10 to 15 μV per millimeter, marked by 0.2-second interruption in recording).*(Figure continues.)*

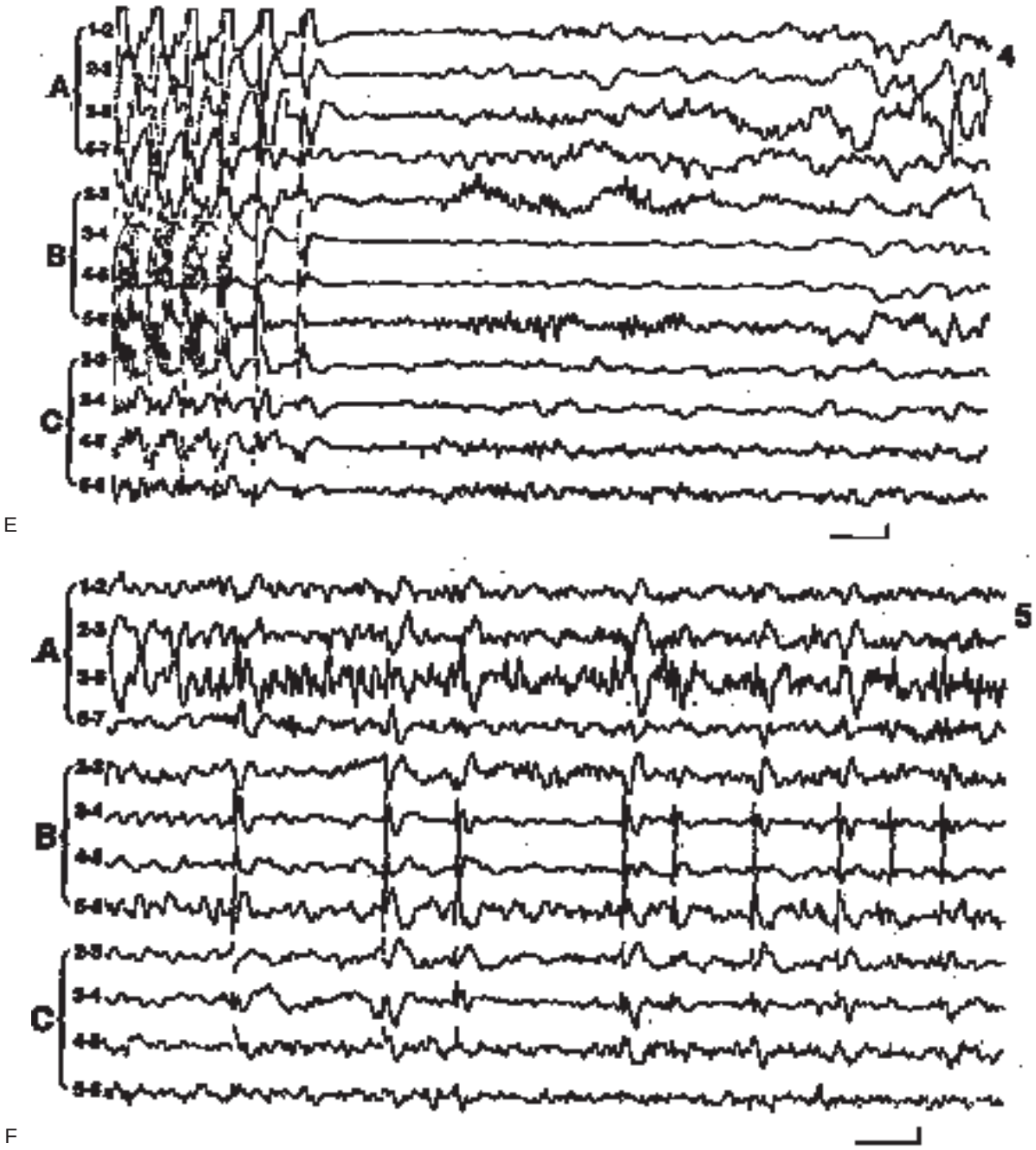

FIG. 18.7. *Continued.* **E:** Segment 4. Termination of the electrical seizure, followed by focal postictal depression (calibration: 1 second; 15 μV per millimeter). **F:** Segment 5. Resumption of interictal spike discharges (calibration: 1 second; 15 μV per millimeter). The cortical resection, guided by these recordings and intraoperative electrocorticography, was confined to a small region. Pathology examination demonstrated focal cortical dysplasia characterized by microdysgenesis.

potential risks. However, there have been reports of complications, including infection (98).

In the monitoring unit, cortical stimulation should be optimized at each stimulation site; actual currents used can vary from electrode to electrode and from day to day (61). If this is not done, false negatives can occur from stimulating at too low a current. Conversely, afterdischarges can be produced, and these can confuse the interpretation of any findings produced by stimulation. In addition to cortical stimulation, evoked potentials can be obtained. Somatosensory evoked potentials—to identify the rolandic fissure—have been the most frequently utilized, but visual and auditory evoked potentials also can be obtained, and event-related modalities show great promise for the future (13,14).

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Chapter 19

Ambulatory EEG Monitoring

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Historical Perspective
Technical Aspects of Ambulatory Recordings
Indications for Ambulatory EEG
Generalized Epilepsies
Partial Epilepsies
Neonatal and Childhood Seizure Disorders
Presurgical Evaluation
Sleep Disorders
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Overall Clinical Yield
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References

Ambulatory EEG was developed to fill the diagnostic gap that exists between routine electroencephalography (EEG) and intensive inpatient monitoring in the evaluation of paroxysmal disorders. The brief EEG provided by standard laboratory studies is not well suited to the identification of abnormalities that are infrequent, such as interictal spikes and, in particular, seizures. Prior research indicated that a single 30-minute EEG without sleep deprivation identifies abnormalities in about 50% of patients with epilepsy (1). Sleep deprivation, pharmacological sleep induction, and repeated EEG studies may increase the sensitivity to 70%–85% (1). The remaining patients with unexplained clinical events will not have abnormalities on EEG to support a clinical diagnosis. For this reason, inpatient epilepsy monitoring units evolved to provide long-term EEG recording. Despite widespread acclaim for this form of evaluation, there remain the inherent disadvantages of hospitalization, restricted patient mobility, insufficient availability, and expense. The need continues for a more convenient, mobile, readily available, and less expensive means of obtaining long-term EEG data.

HISTORICAL PERSPECTIVE

The concept of prolonged monitoring of physiological data on mobile patients by means of a portable tape recorder was first introduced by Holter (51) in the electrocardiographic (ECG) evaluation of arrhythmias. This scheme was not immediately applicable to EEG, because the early recorders were limited to one channel, the EEG signals required considerable additional amplification, and there was no efficient method for analyzing the data once recorded. When a four-channel miniature cassette recorder became available (77), Ives and Wood showed that recording EEG on it was feasible (61). Development of a solid-state, on-head preamplifier chip solved the second problem (88), and the introduction of a rapid video–audio

playback device solved the last (105). Complete four -channel ambulatory cassette systems were commercially available by 1979. Four-channel cassette recorders were standard analog devices utilizing four recording heads. Tape speed was reduced to approximately 2 mm per second so that a standard C120 cassette could record at least 24 hours of continuous EEG. Recorders weighed approximately 1.5 pounds and were easily worn by belt or strap on most patients, including small children. P aginated rapid video playback was the conceptual breakthrough that made ef ficient analysis of long-term ambulatory cassette tape recordings practical. The first playback units incorporated a video displa y of data at selectab le page lengths and speeds of replay, plus a simultaneous audio reproduction of the EEG data. At the fastest replay speed, 60 times real time, 24 hours of recording could be reviewed in 24 minutes.

In 1983, a cassette system capable of recording eight channels of continuous EEG, as well as digital real time and event markers, came on the market (26,96). A new recording method called "b locked analog" was developed in order to record eight channels of physiological data plus real digital time and e vents on 1/8th-inch tape. The size of the earl y eight-channel recorders was only slightly larger than the four-channel version. The eight-channel playback units provided not only a means of displa ying additional physiological data, but also a number of improved operational features.

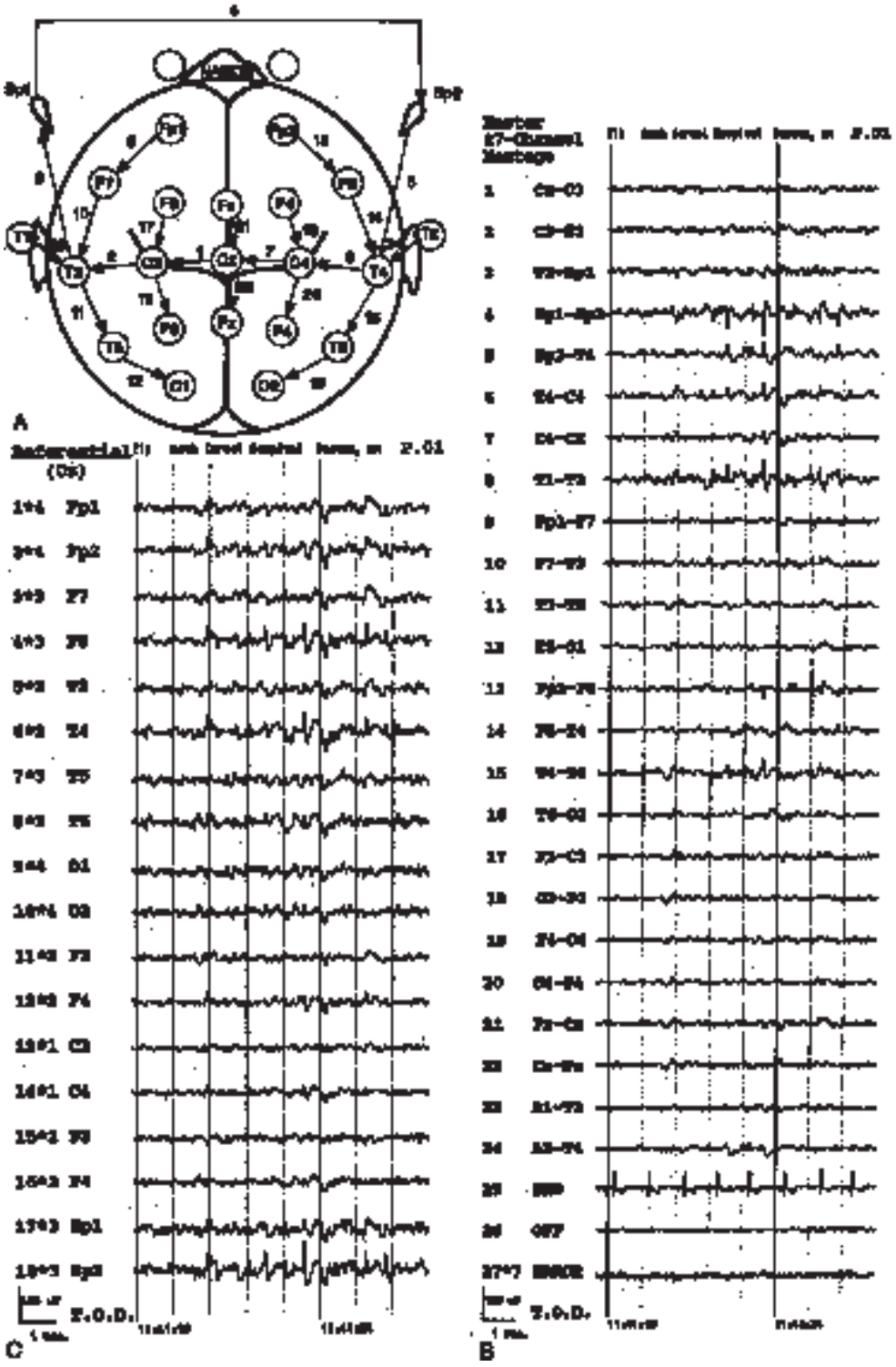
In 1988, a personal computer (PC)–based replay system made its debut, and 16-channel continuous EEG recordings became possib le by electronically linking two cassette recorders. The development in 1996 of a 17-channel continuous recorder w as made possib le with the use of lar ge-capacity removable hard dri ves originally designed for notebook computers. With this new recorder, 16 channels of EEG and 1 channel of ECG could be recorded for 24 hours (at a 200-Hz sampling rate). Montage reformatting was possible during replay. EEG analysis could be performed by rapid video review, audio transformation of signals from selected channels (up to 120 times real time), or of f-line, computer-assisted spike-and-seizure detection.

Several different 24- to 32-channel continuous recorders ha ve since been introduced that use either miniature hard dri ves or flash memor y technology. Various schemes have been devised for analyzing the data. Most systems use off-line spike-and-seizure detection software. Direct, on-line patient monitoring is now also possible with some systems. Isolation electronics built into the replay unit allow the ongoing EEGs of patients who are attached to recorders to be displayed on the replay screen as scrolling waveforms. Alternatively, an optional laptop computer has also been conf igured to ser ve as a displa y of ongoing EEG. Several systems also have the capability of displaying, editing, and analyzing (either manuall y or automaticall y) polysomnographic data, including oximetry.

Ambulatory EEG also de veloped along another line, namel y the discontinuous or epoch recorder. The original concept in this e volution was that more channels could be recorded at a higher sampling rate if only discrete epochs of EEG were recorded rather than continuous data. Ives introduced the first such recorder in 1982 (53). The recorder was like a commercial Walkman and used standard tape speed in order to achie ve the frequency response necessar y to record f aithfully 16 multiple xed channels. The recording was done in selectable periodic epochs, such as 15 seconds every 10 minutes over 24 hours, or the recorder could be tur ned on by a push b utton that the patient acti vated when he or she e xperienced a spell. An electronic buffer memory allowed recording of the EEG prior to the button push. Approximately 45 minutes of EEG could be recorded on a tape. Both the amplifiers and the multiplexing device were incorporated into one small box that was usually worn on the patient's head and secured by a gauze turban. The 16-channel epoch recorder did not usea video playback device; instead the recorded epochs w ere transcribed onto paper in real time. Analysis was like that of standard EEG.

Many of the deficiencies of intermittent and push-button EEG sampling were overcome by linking the epoch recorder to a portable computer (54). This device monitored the ongoing EEG and used spik e-and-seizure detection programs to identify se gments of abnor mal EEG that w ere stored to its hard drive. Although these computers were portable, they were not truly ambulatory because the y required mains po wer. They were appropriate for use in a setting where the patient moved only a limited distance, such as from bed to chair.

Presently, the most common discontinuous system records 16 channels of EEG and 2 channels of other ph ysiological parameters, such as ECG, elec - tromyography (EMG), and electro-oculography (EOG). Up to 15 hours of data can be recorded on the attached portable computer. This includes push-button actuations (with 2 minutes recorded before and after the b utton push), periodic sampling, and spik e-and-seizure detections. The EEG is recorded in one of three bipolar montages, including a standard "doub le banana" montage. These systems can also be conf igured with more pol y-graphic channels, in lieu of EEG channels, in order to record pol ysomnographic data. Data are routinel y printed out on a laser printer and re viewed like standard EEG or burned on a compact disk for review with EEG display software on any PC. An enhanced version of this 18-channel recorder has


A
C
B

been developed that contains within the waist-worn recorder sufficient computing power to perform the spike-and-seizure detection. It is no longer necessary to attach the recorder to a portable computer in order to obtain online EEG analysis. Discontinuous recorders of 27 and 32 channels have also been developed. They offer the possibility of remontaging the output using referential reconstruction from bipolar recordings (Fig. 19.1) (57). The 27- and 32-channel systems include all of the standard electrodes in the 10-20 system plus two basal temporal electrodes (55,58–60). Built-in, on-line spike-and-seizure detection is currently being implemented in these recorders also. Most recently, a digital video recording system with a wide-angle lens has been added to this line of discontinuous recorders. It is synchronized to the recorder to provide on-line monitoring of behavior just as with inpatient monitoring.

It is clear that these two lines of ambulatory recording technology are converging. Given recent increases in the capacity of digital storage devices and decreases in their size and power consumption, continuous recording of 24 or more hours of 24–32 channels of EEG is now reality. A similar evolution of central processing units soon will allow simultaneous on-line spike-and-seizure detection to be done routinely within the confines of a small, truly ambulatory recorder. With these future devices, both detections and their continuous EEG record will be available at the end of a recording session, as is currently the case with inpatient monitoring units. At this point there will be essentially no difference between inpatient and outpatient monitoring technology for EEG. Only greater channel numbers (e.g., 64–128 channels) will differentiate the two.

TECHNICAL ASPECTS OF AMBULATORY RECORDINGS

One of the advantages of ambulatory EEG is that long-term recordings can be obtained without the need for continuous supervision by technical personnel. However, this also means that electrode problems or mechanical failures can go undetected until after the monitoring session. For this reason, proper application of electrodes and faithful maintenance of recorders are of critical importance in minimizing the number of technically inadequate recordings (18).

Application of disk electrodes by collodion technique is currently the only method that will ensure stable long-term recordings. For emergency recordings of several hours' duration on nonambulatory inpatients, self-adhering "stick-on" electrodes, such as those commonly used for nerve conduction studies or pediatric ECG recordings, have been shown to be useful when employed in a subhairline montage (13,29); however, these electrodes are not secure enough for ambulatory outpatients. For outpatients, as well as for most inpatients, it is both convenient and worthwhile to continue the recording for at least 24 hours, including an overnight sleep period. For continuous recorders, battery and/or tape changes are usually needed every 24 hours. Discontinuous recorders commonly run unattended for 48–72 hours.

FIG. 19.1. A: The montage wiring diagram for the master 27-channel system. All of the 10-20–based electrodes are incorporated into a remontageable bipolar array. The Sp1-Sp2 contacts are for additional basal electrode recording and can use any of the standard electrodes employed for that purpose. Channel 8 is dedicated to the monitoring of horizontal eye movements. Channel 25, likewise, is for the monitoring of the cardiac rhythm. Channel 26 is shown as shorted but can be wired for additional noncerebral recordings such as the blood oxygen saturation levels (SPO_2). **B:** Playback of an 8-second epoch of EEG displaying all 27 channels. The time of day (*T.O.D.*) is shown along the bottom margin of the paper along with the 1-second marker and the voltage display. **C:** This remontaged display shows 18 channels of EEG for the same 8-second epoch. Each channel is mathematically recalculated so that it is referenced to the Cz electrode. (From Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999;16:116–129, with permission.)

In hospitals, the conveniences of ambulatory EEG recording can be combined with portable video recording to create a mobile intensive monitoring system. Combined ambulatory EEG and video recording of outpatients can similarly be accomplished in physician's offices, in hotel rooms, or at home, so that the inconvenience and expense of hospitalization can be avoided. The only technical necessity is that the EEG and video recordings must be synchronized so that temporal correlations can be made. This is most easily accomplished by adding the same time code to each recording. Both continuous and discontinuous ambulatory recording systems now offer this option.

The design of the recording montage was particularly important with four- and eight-channel ambulatory systems. Montages had to maximize the likelihood of detecting abnormal EEG features and to display the data in a pattern that was conducive to perception of these abnormalities on rapid video playback. Standard EEG montages are commonly used with recorders of 16 or more channels, particularly those with remontaging capability. An increased number of recording channels improved the localization and characterization of interictal and ictal features more than it did detection probability. Figures 19.2 through 19.5 illustrate the same EEG abnormalities viewed with ambulatory EEG montages of 3, 8, 16, and 26 channels.

Discontinuous ambulatory EEGs are sometimes printed out on paper. Such printouts do not have the same flexibility as EEGs reviewed on a computer screen because gain, filters, and montages cannot be changed to assist in interpretation. Most computer-based EEG replay units offer a variable display gain, simulating sensitivities that are comparable to those of routine EEG. Sensitivity should be varied during playback as required to view ongoing activity clearly. This means using a lower gain during active wakefulness and deep sleep to reduce the visual clutter of high-amplitude artifacts and sleep complexes, respectively, and using a more normal gain during quiet wakefulness and light or rapid-eye-movement (REM) sleep. A rapid review speed of 40–120 times real time may be used in scanning for ictal events. Such high rates of review are not recommended for detecting isolated interictal discharges. Slower scanning rates of 10–40 times real time are more appropriate for perceiving isolated and focal events.

Listening to an audio transformation of ongoing EEG channels can be very useful for detecting abnormalities (24). Seizures, interictal discharges, and various normal transients and artifacts all have characteristic sounds that can be used for event detection and differentiation. Stereo aural monitoring of the EEG from the left versus the right hemisphere further enhances detections. When deriving an audio output with a channel mixer, one should include only every other channel of a linked montage in order to avoid audio cancellation of phase-reversed activity coming principally from one electrode.

Analysis of ambulatory EEG during active wakefulness should be aimed principally at the detection of seizures (see Fig. 19.4). Individual epileptiform transients, even if present, are difficult to recognize or differentiate during periods when activity artifacts are common. The exception may be prominent generalized interictal discharges. Stages 1–3 of sleep, when artifacts are minimal, are the most reliable and productive periods to identify interictal epileptiform abnormalities. Both discontinuous and continuous recording systems have become increasingly dependent on spike-and-seizure detection software, developed originally for long-term monitoring to screen the massive amount of accumulated EEG data for epileptiform abnormalities. Most systems employ variations of the algorithms developed by Gotman and colleagues (43,45–47). More recent investigations have shown that a properly prepared neural network can identify seizures better than standard software detectors, but not as well as traditional video–audio review of the data (41,42).

INDICATIONS FOR AMBULATORY EEG

Generalized Epilepsies

Ambulatory EEG has been most useful in the evaluation of seizure disorders (22,23,25,28). Many of the early investigative efforts were directed at the generalized epilepsies because the electrographic patterns of the abnormalities were distinctive and thus easily recognized even with a reduced number of channels (see Fig. 19.2*A*). Furthermore, in the case of absence seizures, the behavioral manifestations of the seizures were so minimal that ambulatory recordings provided a very convenient way of identifying and quantifying the discharges over a long period. Baseline seizure frequency, circadian or intraday patterns, effects of environmental factors, and changes in medications could be documented in a way far more accurate than by counting clinical seizures.

Numerous clinical reports began appearing in the literature soon after ambulatory EEG equipment became available. Most attested to the usefulness of ambulatory EEG in the differential diagnosis of epilepsy (16,20,49,56,86,92,93,104,111), particularly 3-Hz spike-and-wave or generalized tonic–clonic ictal episodes (90). Objective measurement of drug efficacy in reducing the frequency of interictal and ictal discharges was also

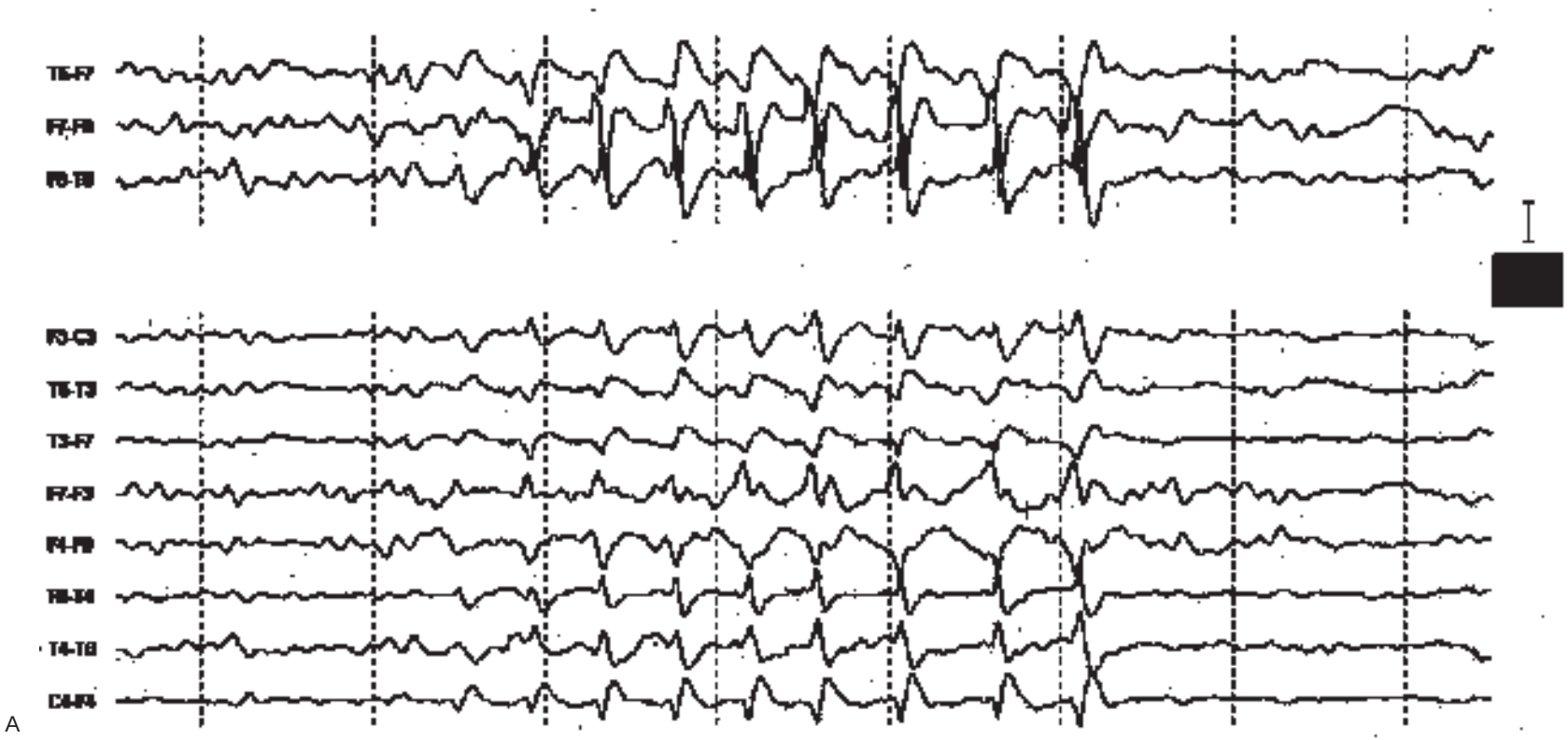
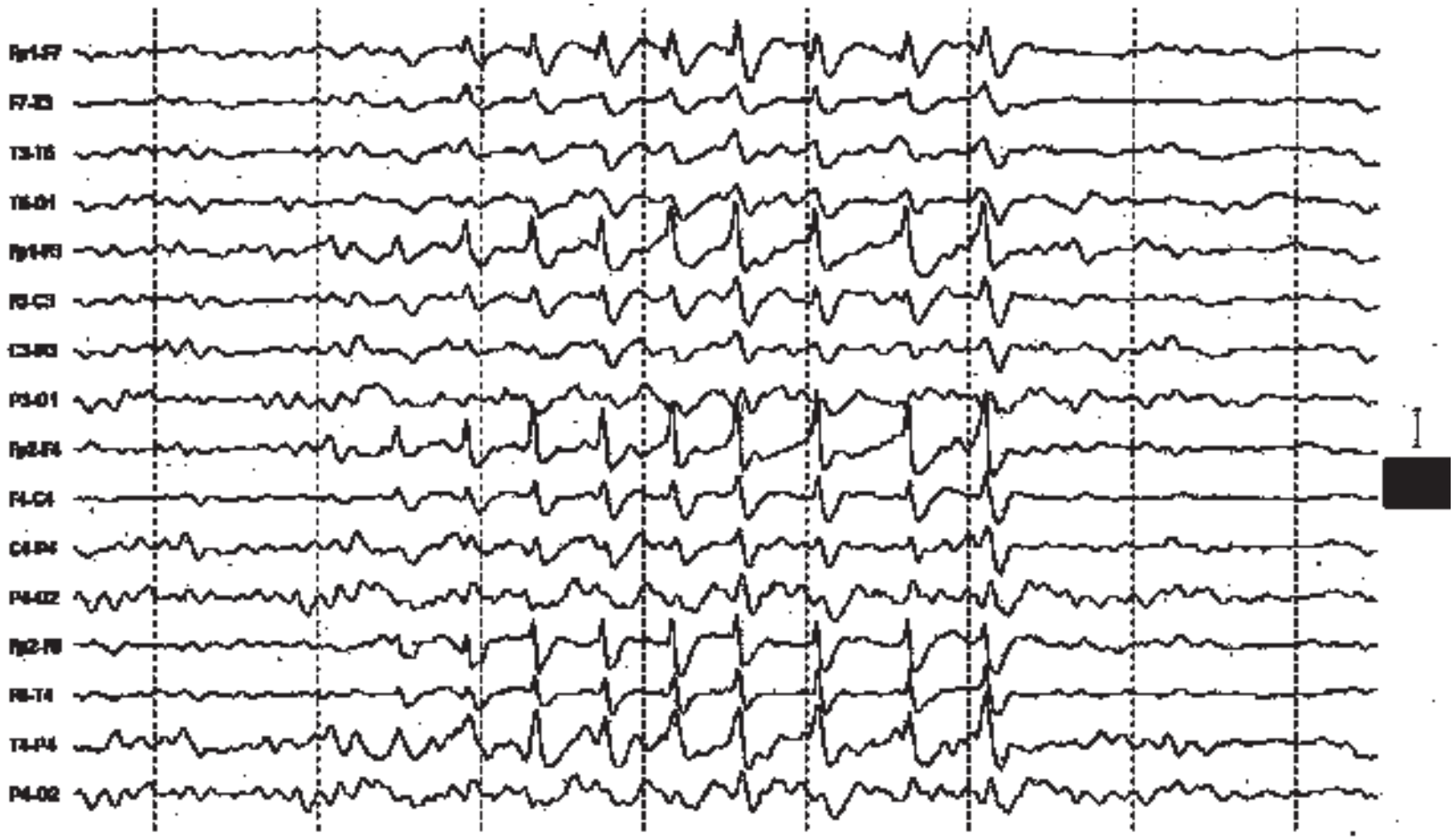
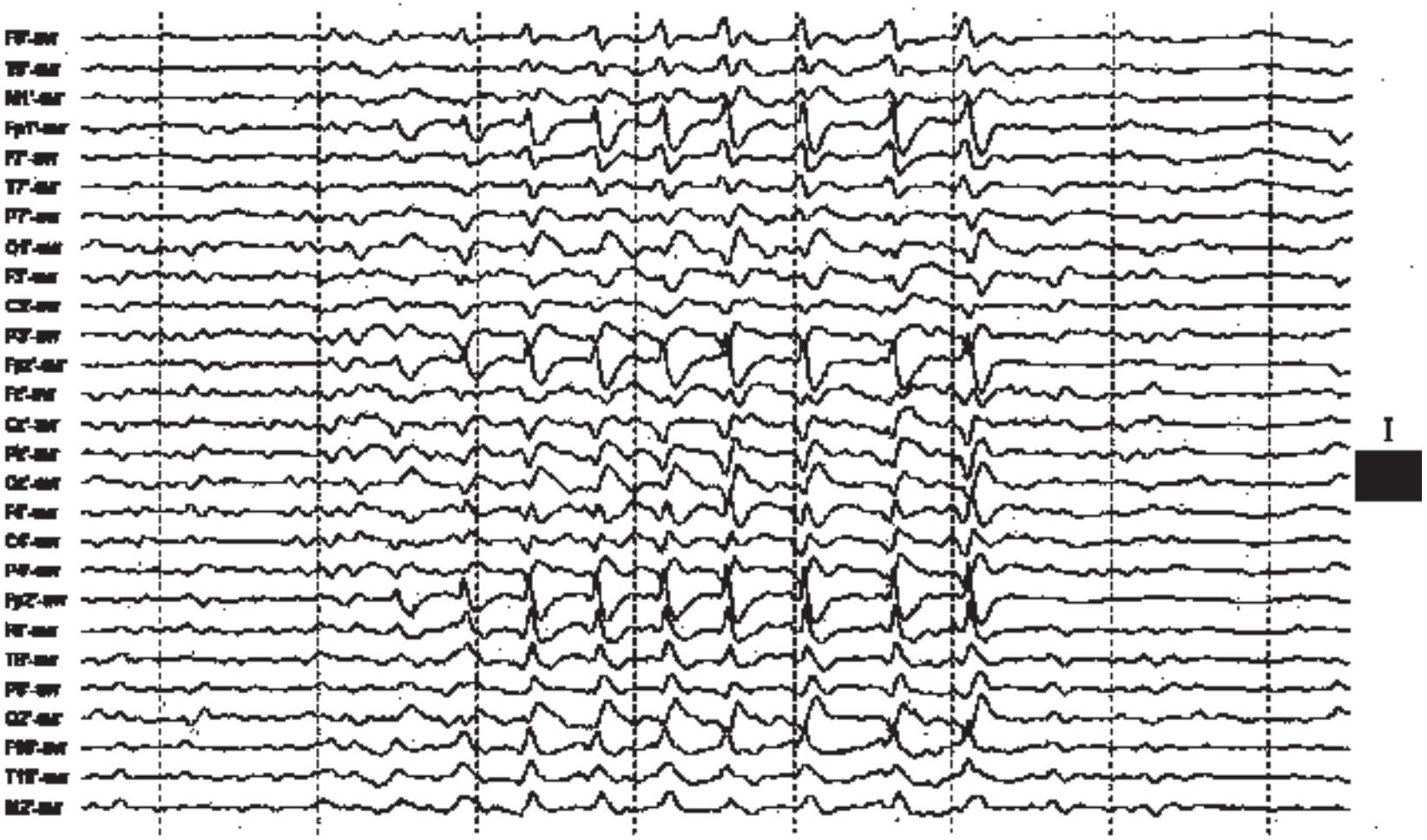


FIG. 19.2. Two-hertz bifrontal spike-and-wave discharges are depicted in 3-channel and 8-channel ambulatory EEG montages **(A)** as well as in 16-channel longitudinal bipolar **(B)** and 26-channel average reference **(C)** montages. Reduced channel number prevents accurate localization of frontopolar spike maxima in ambulatory EEG montages, but identification of the abnormality is easily accomplished with all montages. *(Figure continues.)*



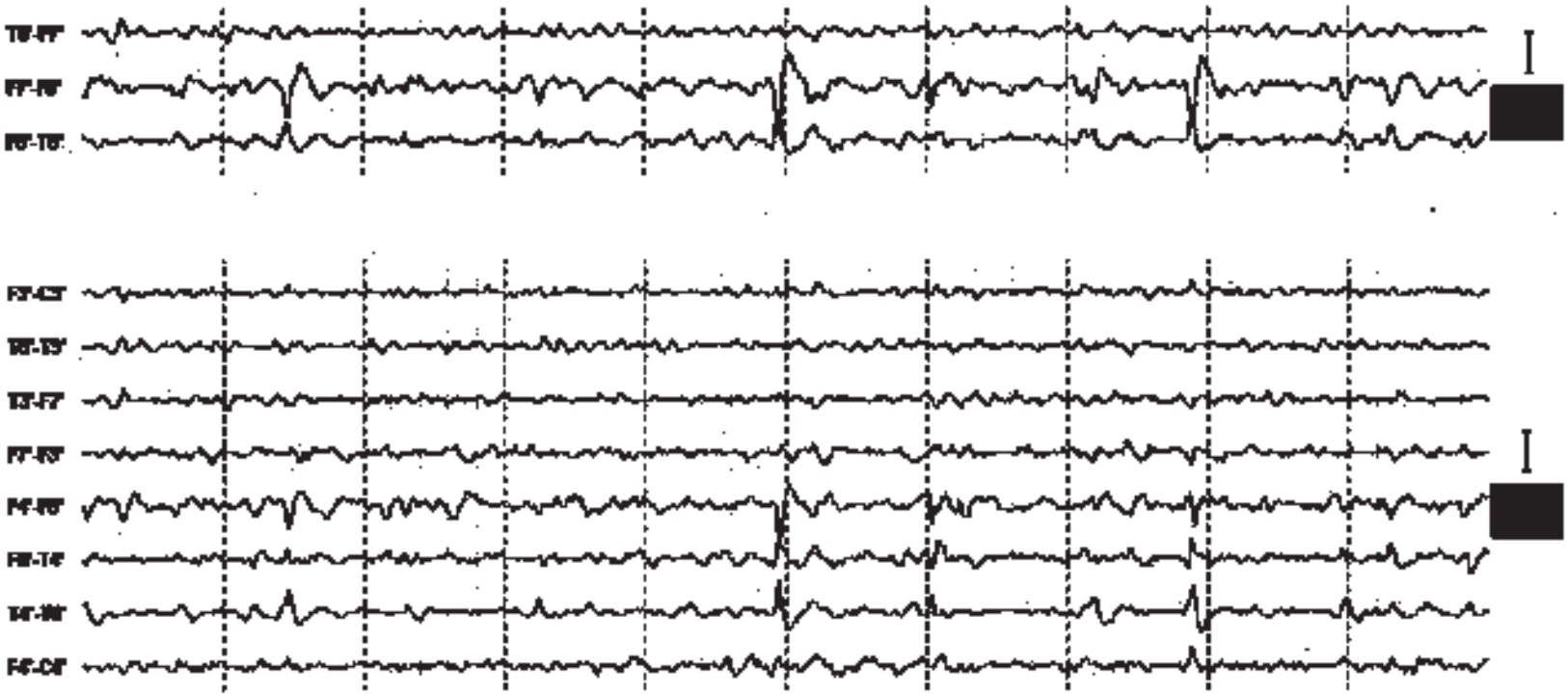
B

FIG. 19.2. *Continued.*



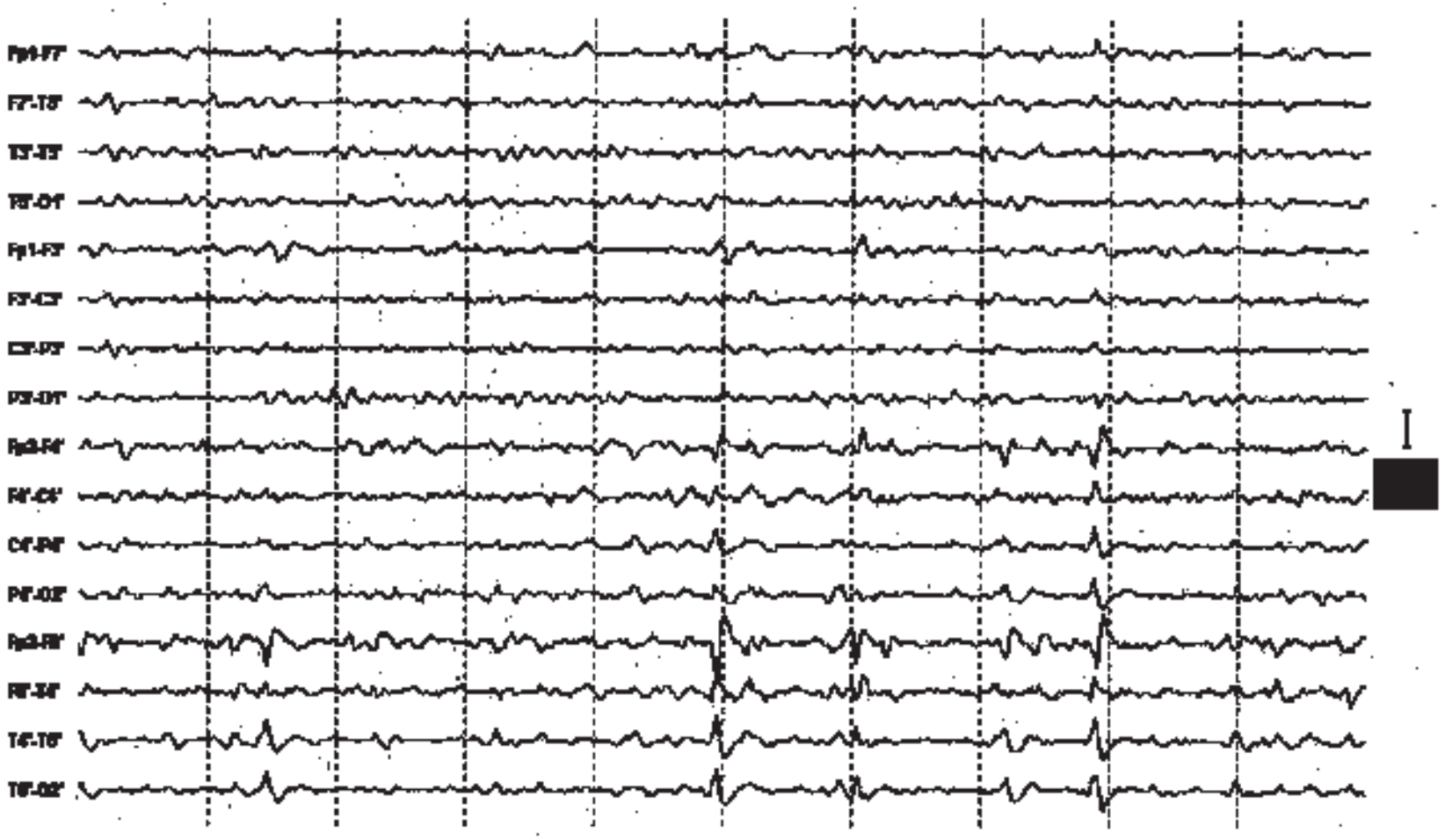
C

FIG. 19.2. *Continued.*



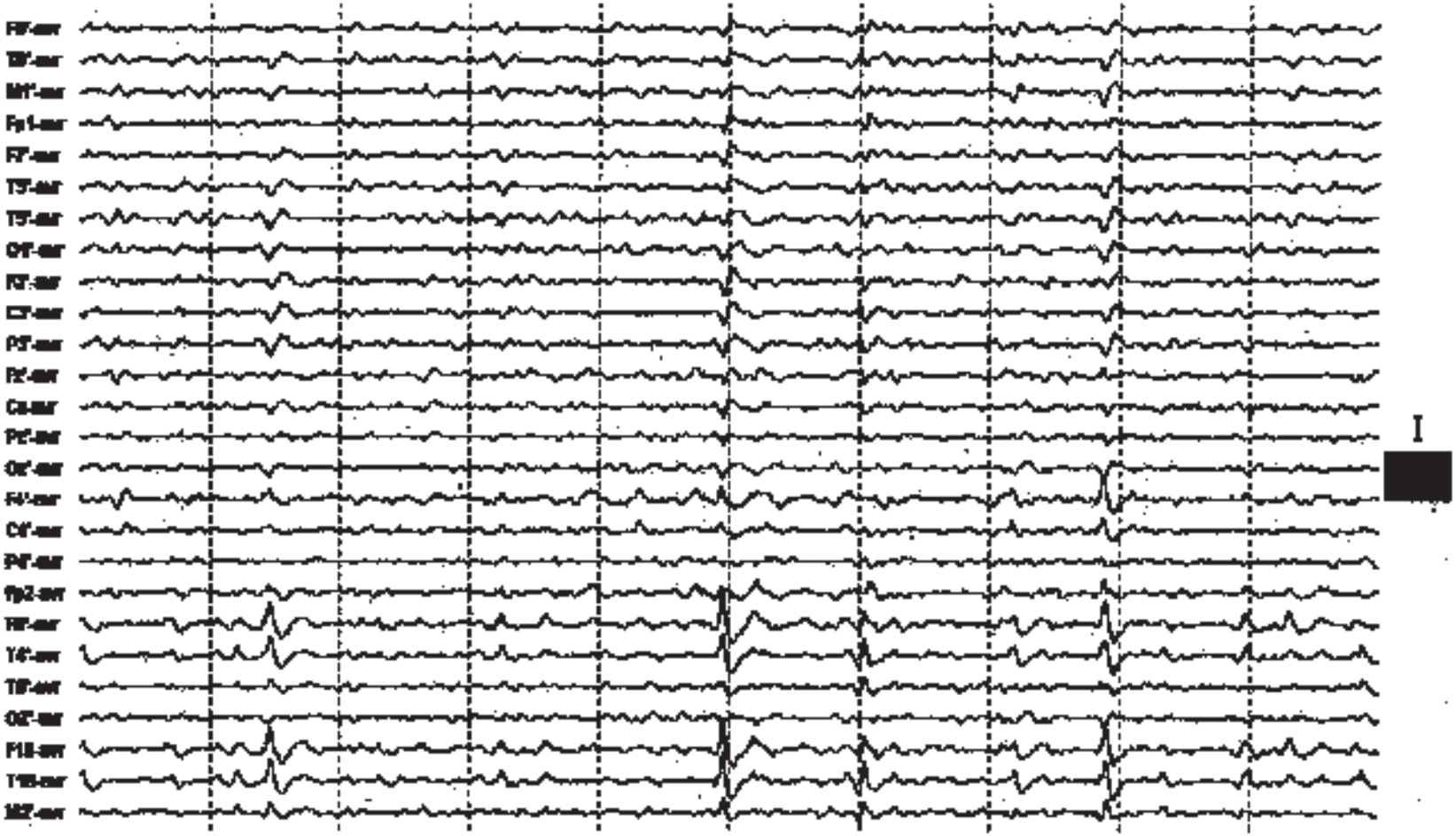
A

FIG. 19.3. Right anterior temporal spikes are depicted in 3-channel and 8-channel ambulatory EEG montages **(A)** as well as in 16-channel longitudinal bipolar **(B)** and 26-channel average reference **(C)** montages. F8 phase reversals in all the bipolar montages, including the 3- and 8-channel ambulatory arrays, easily identify the abnormality. The 26-channel common average reference montage reveals that the spike negative maximum is more inferior and includes electrodes F10 and T10. *(Figure continues.)*



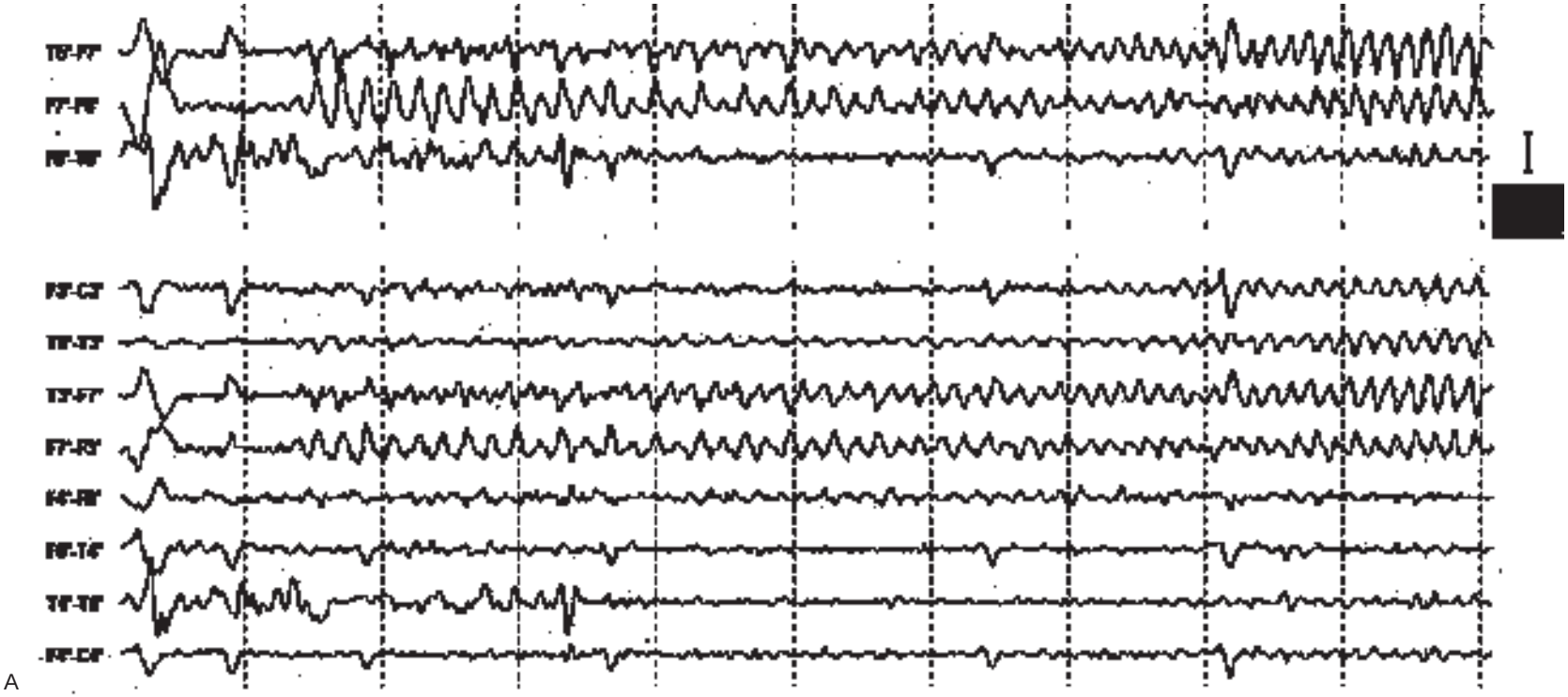
B

FIG. 19.3. *Continued.*



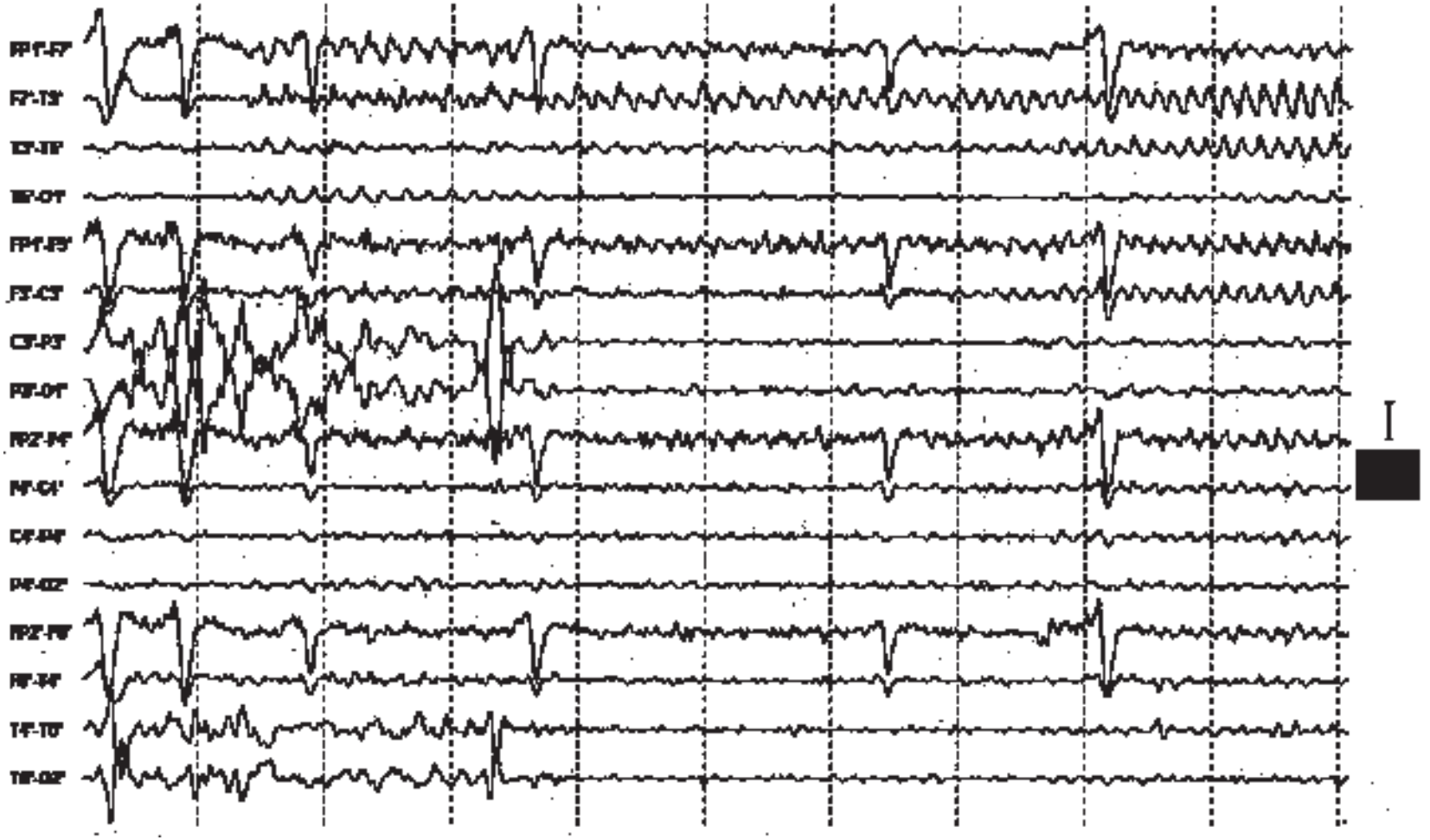
C

FIG. 19.3. *Continued.*



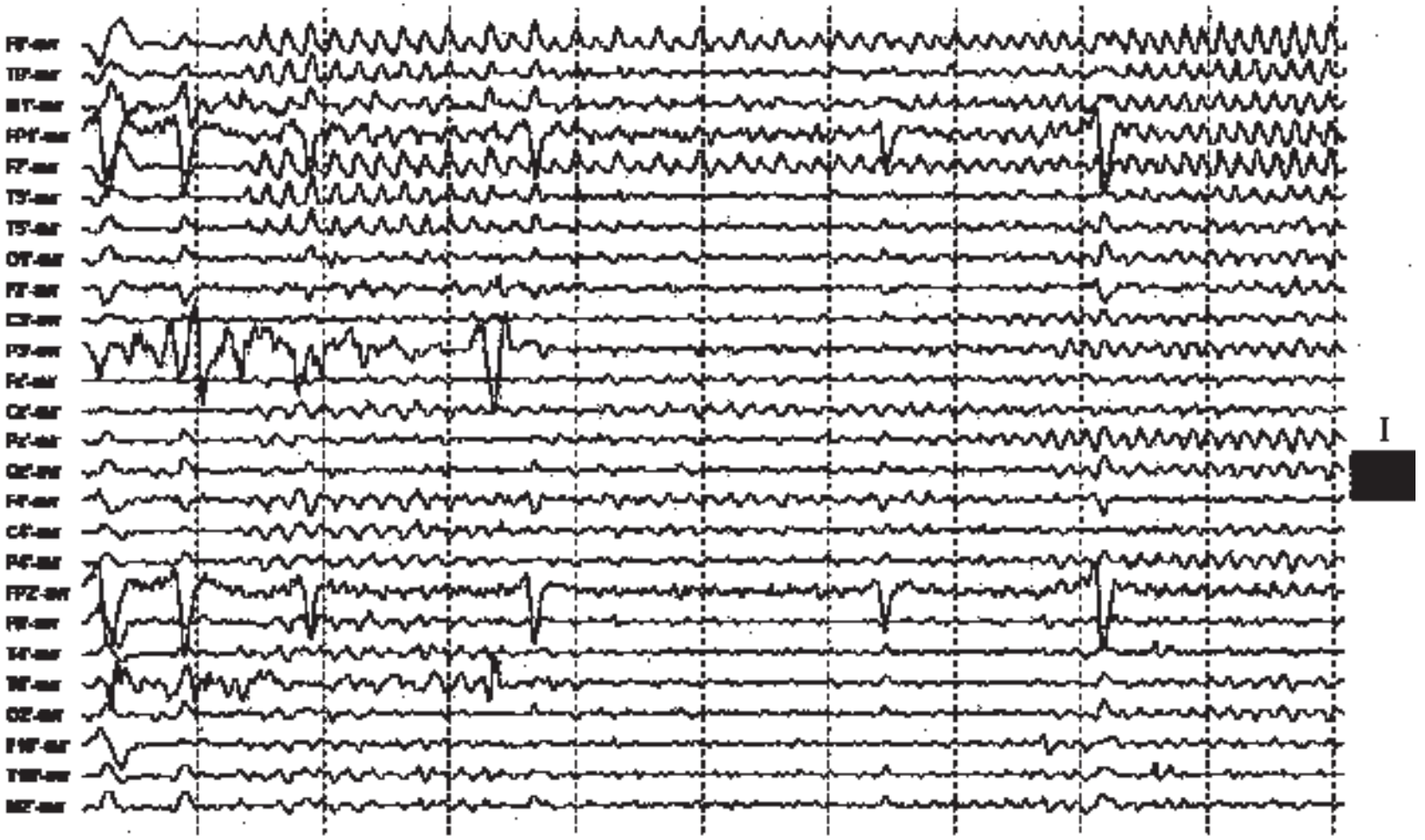
A

FIG. 19.4. A left anterior temporal seizure is depicted in 3-channel and 8-channel ambulatory EEG montages **(A)** as well as in 16-channel longitudinal bipolar **(B)** and 26-channel average reference 1 **(C)** montages. Anterior temporal location of the seizure is identifiable with all montages. Broad-field ictal discharge makes phase reversals less distinct at seizure onset with bipolar montages that have standard interelectrode distances (8 and 16 channels). Phase differences among temporal channels in these bipolar montages produce a "sham" 11-Hz frequency rhythm that is not apparent in the 26-channel common average reference display. *(Figure continues.)*



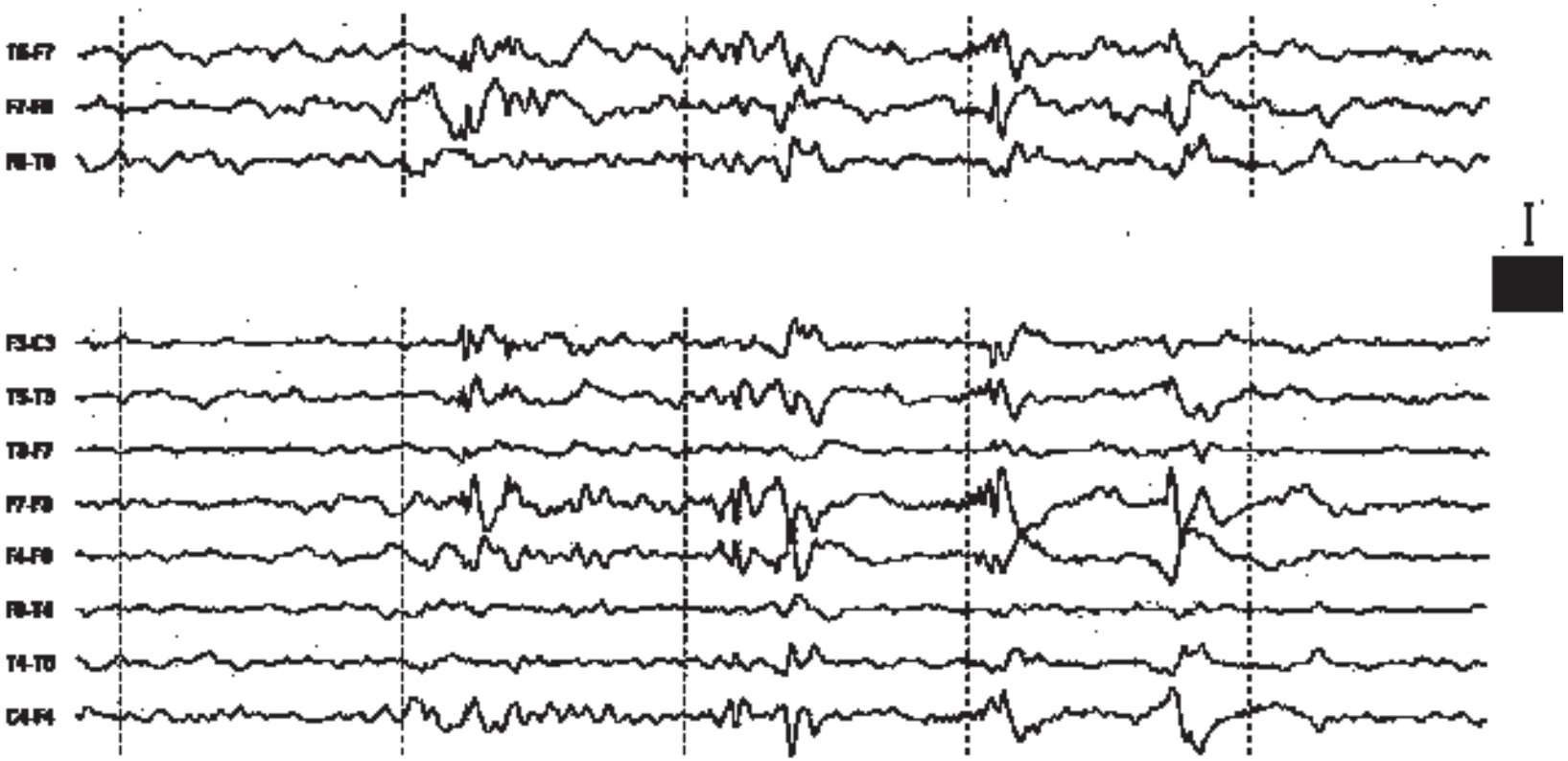
B

FIG. 19.4. *Continued.*



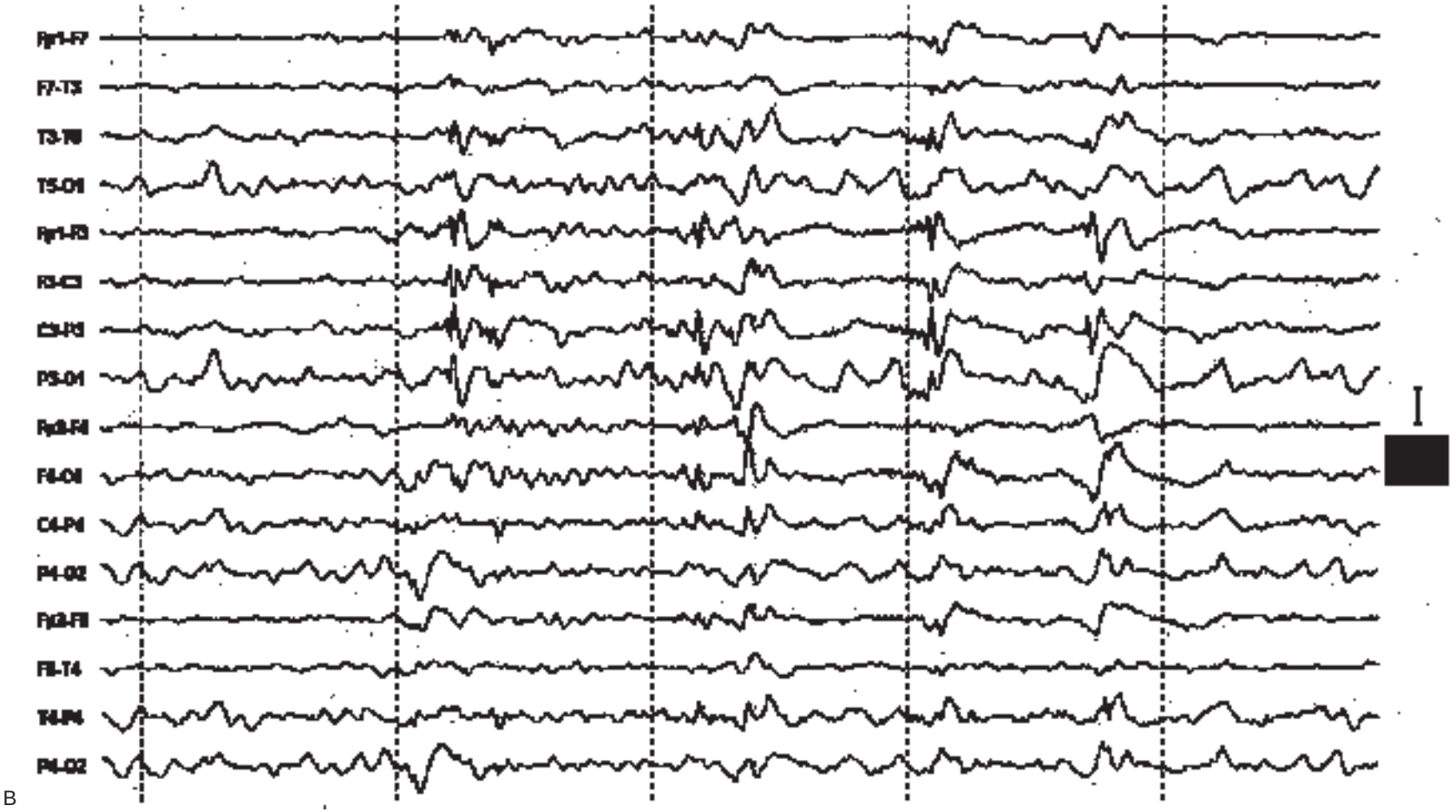
C

FIG. 19.4. *Continued.*



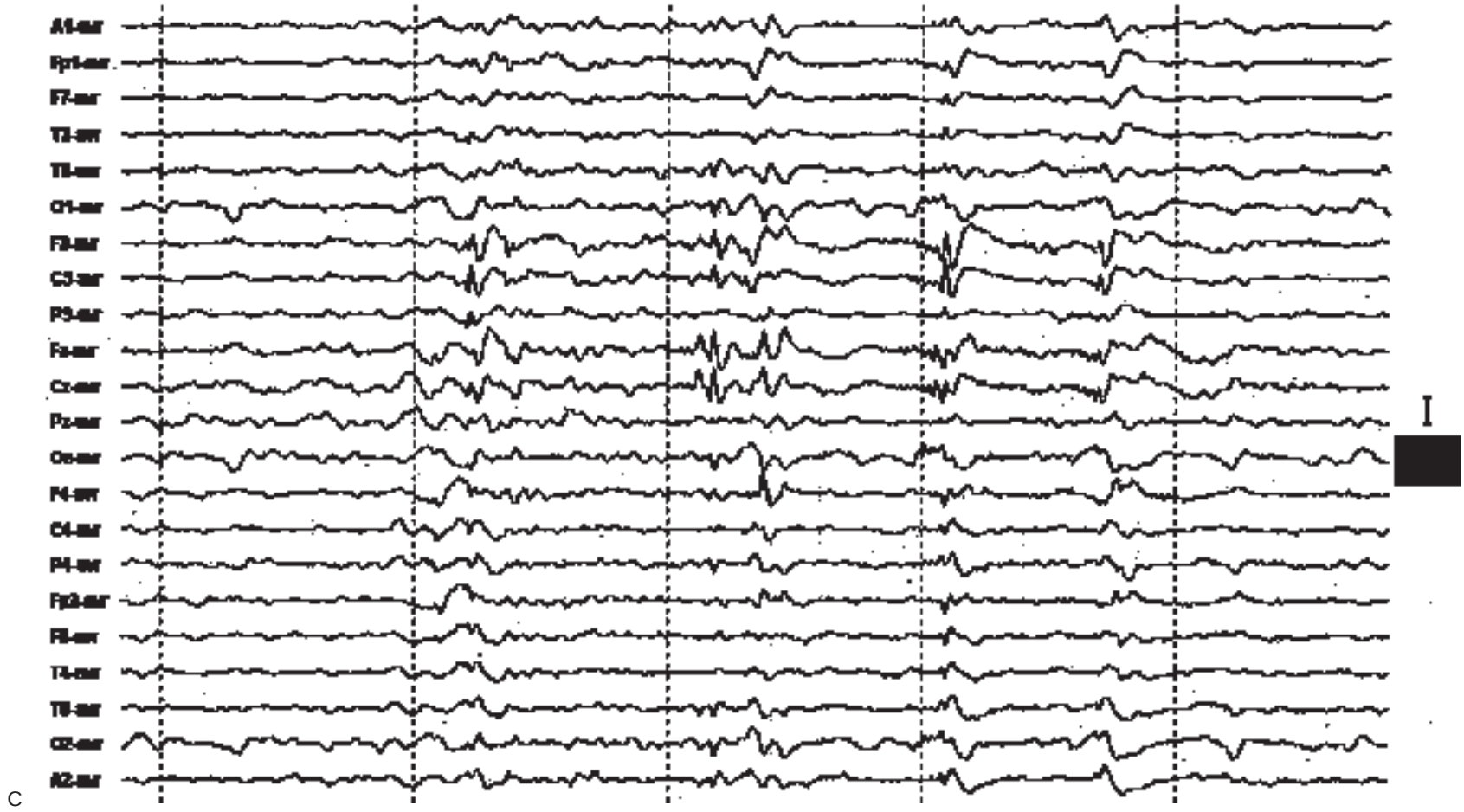
A

FIG. 19.5. Right frontocentral spikes are depicted in 3-channel and 8-channel ambulatory EEG montages **(A)** as well as in 16-channel longitudinal bipolar **(B)** and 26-channel average reference **(C)** montages. These spikes are not well defined with the 3-channel montage, and localization is difficult with the 8-channel montage. The variability of spike maximum is easiest to appreciate in the 26-channel common average reference montage. Complex phase reversals make this more difficult with the 16-channel bipolar montage. *(Figure continues.)*



B

FIG. 19.5. *Continued.*



C

FIG. 19.5. *Continued.*

shown to be feasible (81,102). In nearly all the above studies, improved diagnostic yield over routine EEG recordings was reported. The regular and rhythmic patterns of the generalized epilepsies were also the most promising place to attempt to develop automated means of analyzing recorded data. Generalized spike-and-wave discharges are to date the most common epileptiform features that have been identified and quantitated by automated means (Fig. 19.6) (7,15,44,69,89,107,109,110).

Partial Epilepsies

Many of the patients who would logically be referred for ambulatory EEG because they possess an atypical history and a normal or equivocal routine EEG are likely to have complex partial seizures. Ives and Woods demonstrated with only four EEG channels the feasibility of cassette monitoring for the lateralized ictal discharges of partial seizures (62). Ebersole and Leroy (30,31,72) later developed ambulatory EEG montages that were designed specifically to maximize the detection of the most common focal, as well as generalized, epileptiform features. They demonstrated that 24 hours of ambulatory EEG could provide identification of most focal (79%) and all generalized interictal abnormalities that were noted on simultaneous eight-channel long-term monitoring, which was the norm at that time. When performed before 4 days of long-term monitoring, 24 hours of ambulatory EEG identified 83% of interictal and ictal abnormalities later found by inpatient EEG recording (12). This diagnostic yield was 2.5 times that of previous routine EEG. The greatest advantage of intensive inpatient monitoring over ambulatory EEG was not its EEG

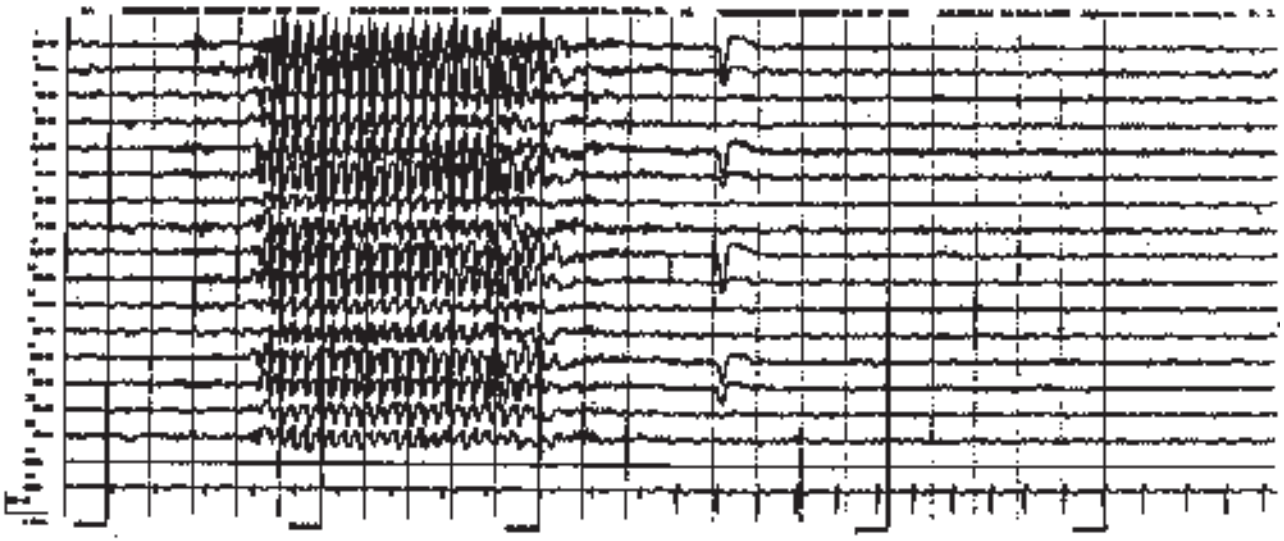


FIG. 19.6. This SZRF***.W18 file represents an automatic seizure detection. In this case, the patient suffered from juvenile absence epilepsy. She had recently experienced a recurrence of events and had undergone a medication change. At the time of this recording, she had rare clinical seizures but was having difficulty with school performance. The tracing did capture silent seizures such as the one shown here. However, extremely few events were detected and no clinically symptomatic events were recorded. This led the treating physician to conclude that the experienced educational difficulty was not secondary to frequent absences. (Tracing and clinical history courtesy of James J. Riviello, M.D., Children's Hospital, Boston, MA. Reprinted from Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999;16:116–129, with permission.)

superiority, but the additional information obtained through video monitoring of behavior and the ability to withdraw antiepileptic medications under medical observation.

The evaluation of partial epilepsies benefited from the introduction of eight-channel ambulatory EEG systems. Compared to simultaneous 16-channel cable telemetry records, both 3- and 8-channel ambulatory EEG reviews correctly identified 93% of the records as either normal or epileptiform (27). Lateralization of abnormalities was equally good with either cassette system, but more detailed characterization was achieved with eight-channel ambulatory EEG. Although 100% of seizures were detected on both systems, there were more false-positive errors when only three data channels were available.

Neonatal and Childhood Seizure Disorders

Ambulatory EEG is particularly useful in pediatric practice because epilepsy is a common neurological affliction of childhood, and these small patients do not tolerate well traditional EEG or especially inpatient long-term monitoring (103). The small size of ambulatory recorders, the resultant mobility, and the outpatient setting make this technique well suited to the pediatric patient. The utility of this method in children, particularly those with absence and other generalized epilepsies, was demonstrated early in the development of the technique (50,52,104,106). Its usefulness in documenting the nature of "spells" of uncertain etiology in children has also been shown (2,6).

Compact recording systems designed for ambulatory outpatients also offer a means of obtaining extended EEG recording in the neonatal intensive care unit with minimal disruption to nursing functions and no limitations of access to the patient being recorded (35). The utility of cassette EEG for seizure detection in neonates has been assessed in several studies (36,38). Extended cassette EEG recording, even when restricted to three EEG channels, can result in substantially increased detection of seizures over routine recordings. Ambulatory EEG can also provide a means of monitoring brain activity in neonates pharmacologically paralyzed in order to improve ventilatory support (37). Given the variable and sometimes localized distribution of neonatal seizure activity, as well as the need for correlative monitoring of other physiological variables, it is likely that newer recorders with multiple polygraph channels will receive greater application in this area.

Presurgical Evaluation

Epilepsy can be diagnosed and its type classified by ambulatory EEG with limited channel numbers. This is not the case with the evaluation of surgical candidates (Table 19.1). Detailed EEG characterization and localization of spikes and seizures are essential. At least 16 and preferably 24–32 scalp EEG channels sampled at a standard 200 Hz are required (see Figs. 19.3 through 19.5). Off-line data manipulations such as remontaging and filtering, as well as more sophisticated analyses such as voltage mapping or source modeling, are often very useful. Video recording of ictal behavior is also considered mandatory at most epilepsy surgery centers. Fortunately, the newest generation of ambulatory recording systems has all these capabilities. In fact, at several epilepsy centers the same recording equipment is used for both inpatient and outpatient monitoring (Figs. 19.7 and 19.8) (97). In the hospital setting, the "ambulatory" recorders are linked to fixed video recording systems, whereas in the outpatient setting they are linked to portable digital video recorders. With responsible patients, sphenoidal electrodes can also be used in home recordings. Withdrawal of antiepileptic medication is perhaps the only part of the normal inpatient scalp EEG evaluation that cannot be performed as an outpatient procedure. For patients with frequent seizures this is not a major consideration.

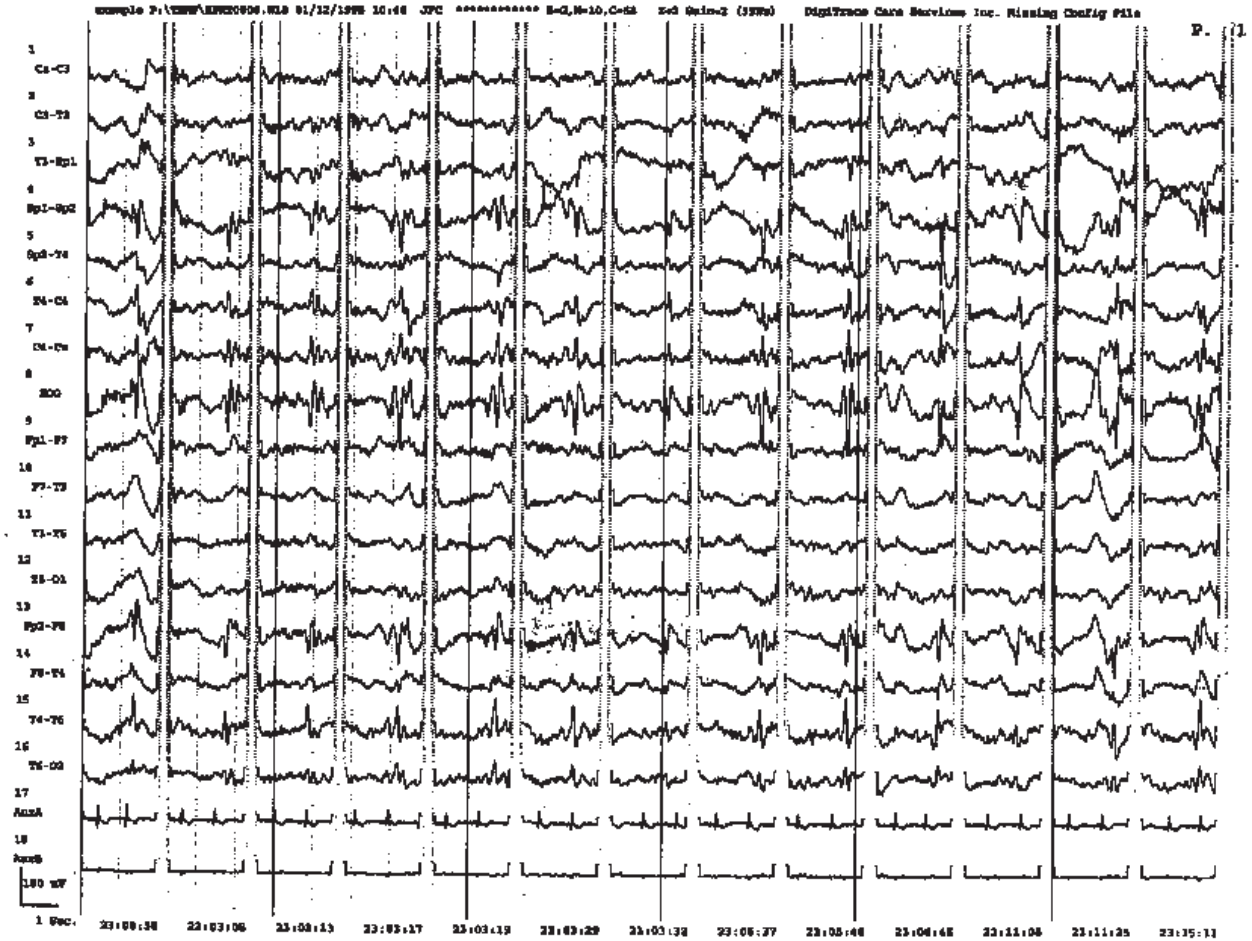
Sleep Disorders

The capability of recording multiple channels of electrophysiological data over long periods of time also lends itself to the diagnosis or evaluation of sleep-associated disturbances. Sleep staging is easily accomplished using combined video–audio analysis of recorded data (94). Computer programs have been developed that produce sleep statistics and hypnograms from data entered by the reader during such rapid review (32,33). Automated sleep analysis of data from ambulatory recorders has also been introduced and is being progressively refined (19,34,68,75,78).

TABLE 19.1. *Ambulatory EEG usefulness by channel number*

Channels	Use
3–8	Diagnosis, classification, rough localization
16–18	As above plus better localization
24–32	As above plus presurgical localizatio

The physiological parameters other than EEG that are most commonly used for sleep studies with ambulatory recorders are the ECG, EOG, EMG, and partial pressure of oxygen (PO_2). These are used to define disturbances of sleep architecture such as those seen, for example, in the hypersomnias (14). The EMG and movement data from the extremities can be used to identify nocturnal periodic movements and myoclonus (5,91). Measures of respiration by means of strain gauges, impedance pneumography, or thermistors, as well as PO_2, may be added in order to investigate paroxysmal disorders of breathing, such as sleep apnea (3,5), sudden infant death syndrome, and neonatal apnea. Monitoring all these sleep parameters in an inpatient setting is now commonplace, but their full utilization in ambulatory cassette recording is just evolving (4,79,80,83,95,108). Being able to monitor



A

FIG. 19.7. A: The file demonstrated here shows interictal epileptiform discharges detected by an automated spike detection algorithm. The discharges were increased by sleep. All of the discharges were from the right temporal lobe, where phase reversals were noted in the right sphenoidal lead, suggesting that the origin was from the more inferior temporal region. *(Figure continues.)*

B

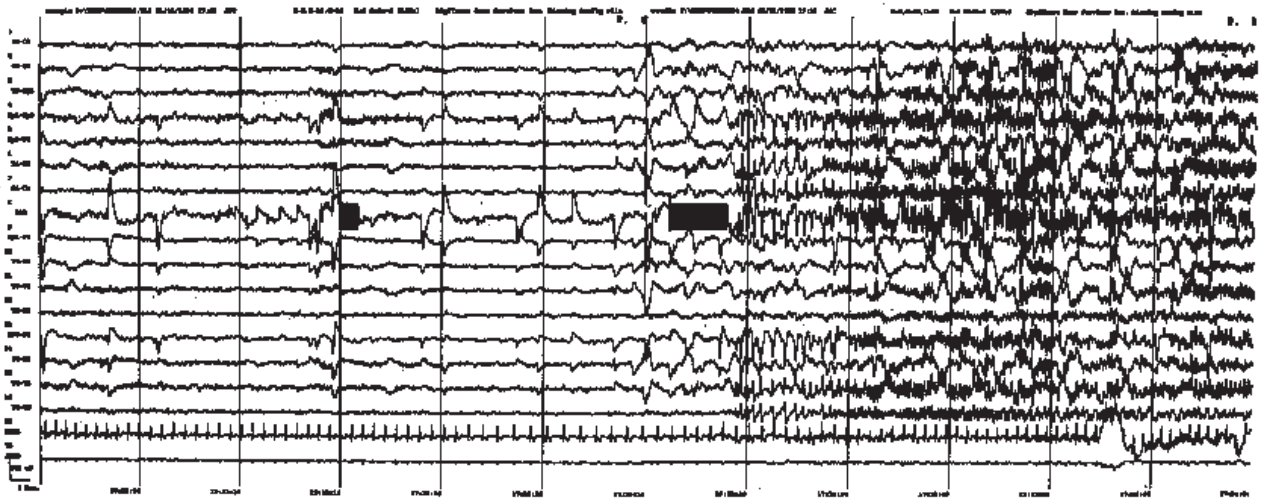


FIG. 19.7. *Continued.* **B:** The PB***.W18 file presented here is a recording made during a typical seizure. The origin appears also to be from the right inferior temporal lobe region, as noted with the interictal files shown above. The time of onset was determined to be 17:33:09 when this file was expanded and enlarged. (From Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999; 16:116–129, with permission.)

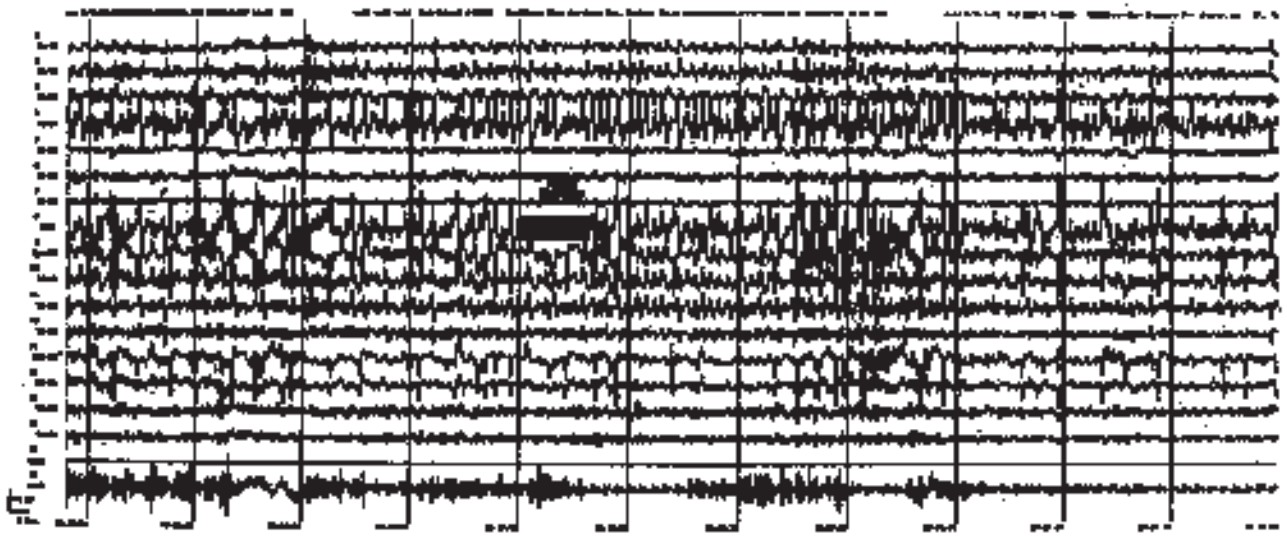


FIG. 19.8. Demonstration of the recording of an "event." The McSR***.W18 file name at the top of the recording identifies it as a waist-worn file of a "push-button" –based recording. In this specific case, the patient had been experiencing episodes of dizziness and aphasia. Channel 8 shows the superimposed artifact for the push-button marking of the time at which the patient felt symptomatic. There is a clear sustained seizure discharge present broadly over the left inferior and lateral temporal area, associated with the symptoms. Previous EEG recording demonstrated only slow-wave activity from the left temporal region. Subsequent to this recording and as a result of the finding of frequent focal left temporal seizures, the patient had repeat magnetic resonance imaging that demonstrated a newly defined left temporal structure that proved to be a glioma. (Case courtesy of Bruce H. Price, M.D., McClean Hospital, Belmont, MA. Reprinted from Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999;16:116–129, with permission.)

patients in their own homes not only is convenient, but also avoids the necessity of habituating the patient to a new environment. Sleep apnea (84,98) may also be associated with behavior that is confused with an ictal event (21,63,70). The new 16- to 32-channel systems are obviously better suited to multiparameter studies (Figs. 19.9 and 19.10). Ambulatory monitoring shows great promise in facilitating the evaluation of all forms of sleep-related disorders.

Syncope and Dizziness

Paroxysmal loss of consciousness or spells of dizziness are common diagnostic problems for neurologists. Ambulatory recordings provide a convenient way to monitor both the ECG and the EEG for a long enough period of time to be likely to record an episode. Several studies have shown that this form of combined monitoring can be useful in clarifying an etiology (8,17,48,66,67,71). Cardiac-related events are the most likely, given the relative infrequency with which epilepsy is uncovered in patients presenting with syncope (80). One study showed that only 1.5% of ambulatory recordings from patients complaining of syncope or dizziness contained epileptiform abnormalities (10,11). Although there continues to be a concern that an increased incidence of sudden death among people with seizure disorders may be related to cardiac arrhythmias, a combined ambulatory EEG and ECG study showed no increase in cardiac rhythm disturbances among known epileptics when compared to nonepileptics (64,65,67). ECG abnormalities may indeed accompany seizures (9,64). In most instances these consist of ictal tachycardia and at times abrupt changes in rate, rather than dangerous rhythm disturbances. Cardiac arrhythmias may, however, masquerade as seizures (Fig. 19.11) (40,66,71).

Nonepileptic Seizures and Psychiatric Disorders

The role of ambulatory EEG in the differential diagnosis of behavioral episodes has also been investigated. Its utility in adults and children has been acclaimed, particularly in documenting those attacks that were seizures rather than spells of psychiatric origin (39,85,99–101). Observing no electrographic changes on recordings made during episodes of apparent total loss of consciousness or major motor convulsions can provide support for a diagnosis of pseudoseizures. A lack of ambulatory EEG findings during reported episodes of only altered consciousness or behavior is less diagnostic. It lends some support to the possibility that the spells are functional, but these negative data cannot rule out the possibility of simple partial seizures, for which there may be no surface EEG manifestations. In the evaluation of pseudoseizures, observation of behavior is essential. Ambulatory EEG monitoring can be combined with video recording to provide the objective documentation necessary for these differential diagnoses (73).

In the case of psychiatric disorders that have no paroxysmal features, the yield for detecting underlying epilepsy has been very low, and in one investigation was zero (11). Ambulatory EEG monitoring may, however, be useful in identifying and quantitating disturbances in sleep architecture, particularly REM onset latency, that purportedly are observed in patients with depression and that resolve with drug treatment (76).

OVERALL CLINICAL YIELD

The usefulness of ambulatory EEG in general practice is dependent on the appropriateness of the question being asked and the likelihood of answering the question, even if appropriate. Rates for recording the attacks or spells by means of ambulatory EEG vary dramatically with the clinical frequency of these episodes, as would be expected. A 77% success rate was achieved in patients with one or more seizures daily (20), whereas only 16% of unselected patients had spells recorded (8). A 50% capture rate could be attained in patients who had only one attack per week by allowing at least 3 days for monitoring each of them (87).

Similarly, the yield for documenting epileptiform abnormalities is quite variable in the literature and is most likely due to differences in patient populations. Early reports of continuous four-channel recordings in unselected patients showed a positive yield of evidence to support a diagnosis in the range of 10%–15% (49,92). Of attacks recorded in several series, the proportion that was identifiable as seizures has ranged from 23% to 73% (16,56). In a series of 500 consecutive patients ages 2 months to 82 years who were undergoing eight-channel ambulatory EEG for the first time (11), seizures, interictal epileptiform abnormalities, or both were detected in 17.4%. This represented a 64% increase in the yield of interictal epileptiform abnormalities and a 21-fold increase in seizure recording as compared to a preceding laboratory EEG. A particularly high yield (34.9%) of epileptiform abnormalities was identified in recordings from patients diagnosed as epileptic. The positive yield was 15.3% in patients referred with a wide vari-

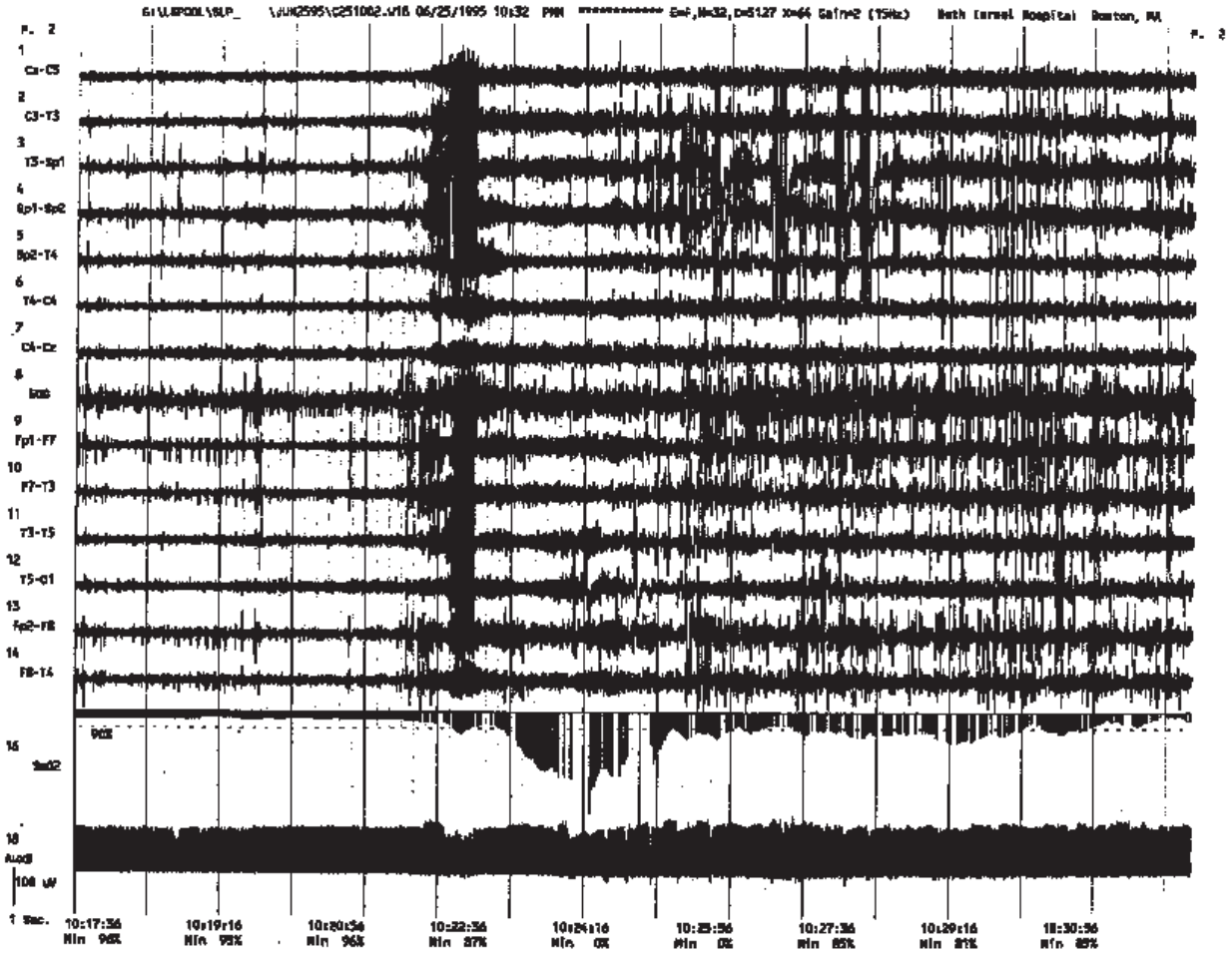


FIG. 19.9. This tracing represents part of a continuous recording done with additional equipment to monitor blood oxygenation levels (SPO_2) on the index finger. This file is compressed for better display of the SPO_2 data. The page shown here represents approximately 15 minutes of recording. From other files, we know that this patient experienced the sensation of a partial seizure at about 10:22:36. He never lost consciousness with this event but, as demonstrated by the SPO_2 monitor, there was a significant drop in his blood oxygen saturation for many minutes. Review of the video recording taken around this event shows that the SPO_2 pulse oximeter was intact. The *dotted line* represents the 90% saturation level. Before the seizure, the patient's oxygen levels were normal, in the 95%+ range. After this simple partial event, the levels dropped approximately to the 70% range. The patient was seemingly unaware of this drop. It took several minutes for the patient to reset his respiratory drive to return his levels to the normal range. (From Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999;16:116–129, with permission.)

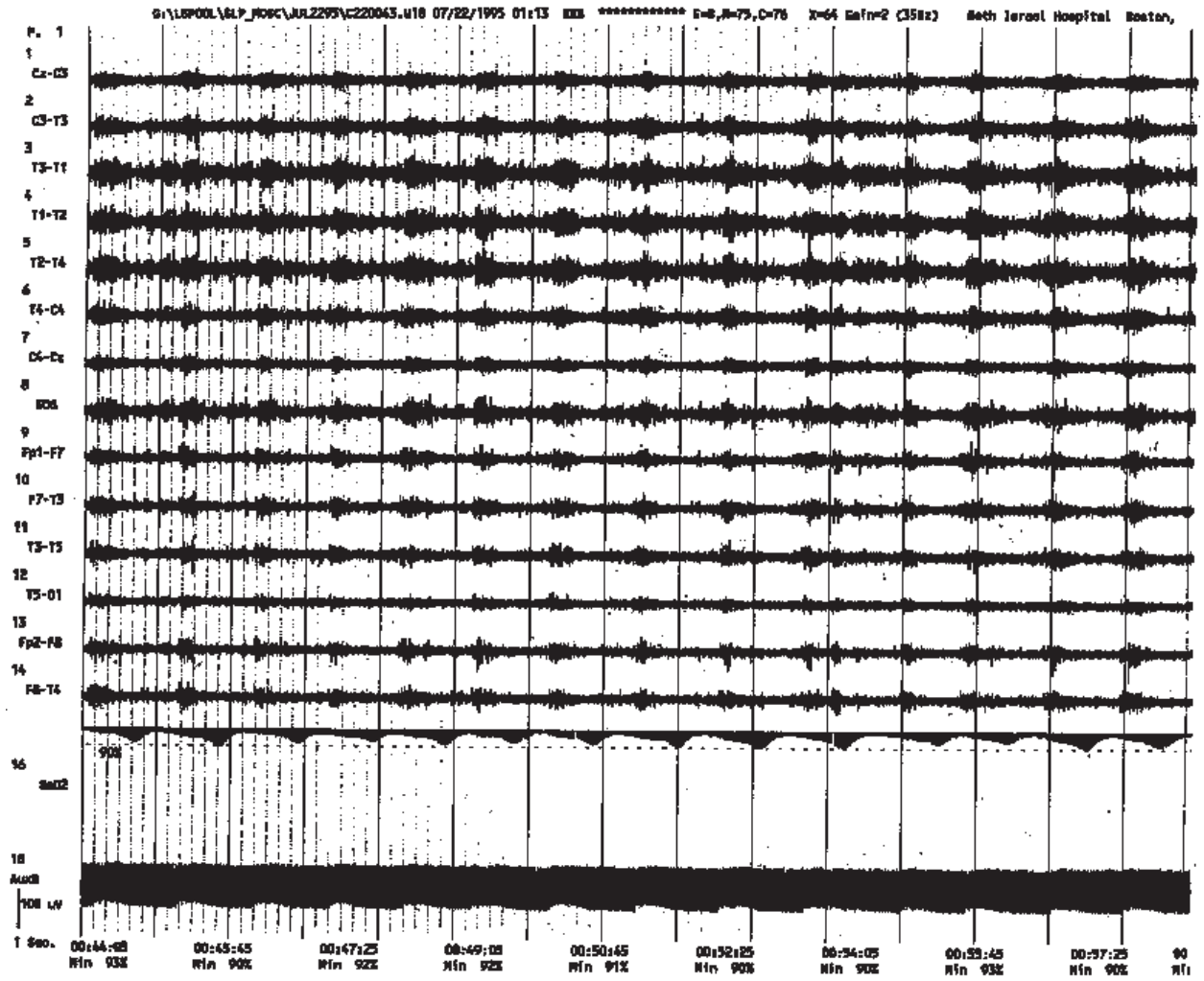


FIG. 19.10. As with the previous tracing, this playback is from a continuous recording with the addition of SPO_2 monitoring. This tracing came from an elderly woman with a history of rare epileptic events. She had experienced a subacute decline in mental status, and the referring physician was concerned that she was having unrecognized seizures, perhaps while asleep. The tracing failed to detect any electrical evidence for such seizures, but it did demonstrate the presence of this Cheyne-Stokes respiratory pattern. The regularly recurring fluctuation in the SPO_2 with about 90-second intervals is classic. The treating physician used this finding to reassess the patient. He found her to be in mild and previously unrecognized cardiac failure. Treatment was instituted and there was a significant improvement in her mental status. (From Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999;16:116–129, with permission.)

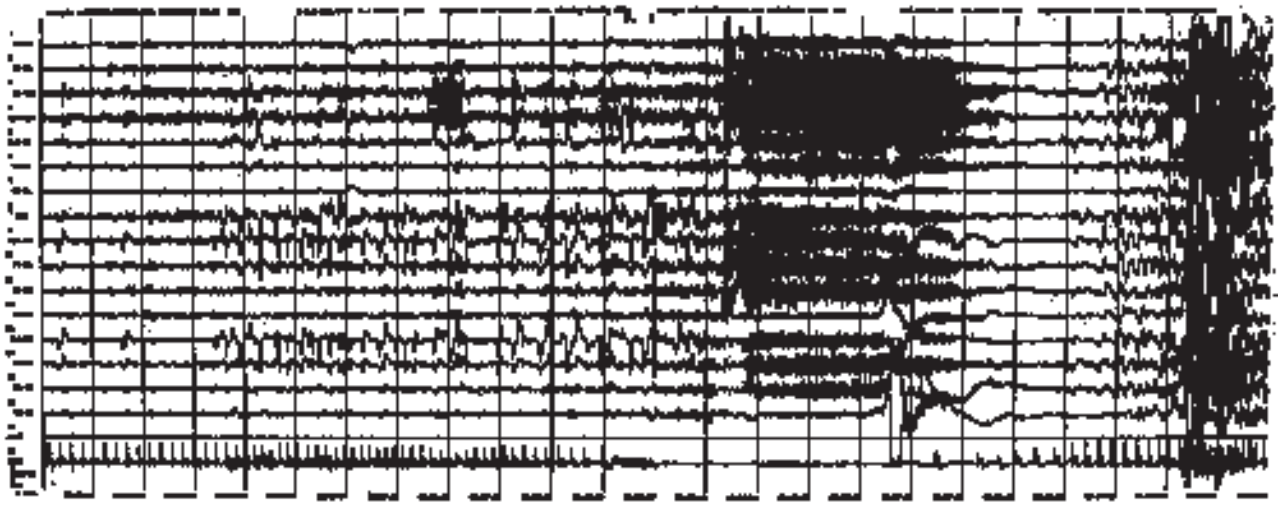


FIG. 19.11. G.H. was a 45-year-old man with a long-standing history of partial epilepsy. He was now having events during his sleep. His wife described being awakened once a week by his abnormal movements, of which he was completely unaware. He had not had any daytime seizures for many months. His recordings revealed the presence of a brief left temporal lobe electrical seizure associated with a profound bradycardia. He was without a pulse for 36 seconds. A cardiology consultant believed that a pacemaker was indicated. This was implanted, but additionally his anticonvulsant regimen was altered because this was believed to be a seizure-driven asystole. (From Shomer DL, Ives JR, Schachter SC. The role of ambulatory EEG in the evaluation of patients for epilepsy surgery. *J Clin Neurophysiol* 1999;16:116–129, with permission.)

ety of episodic alterations of behavior, perception, sensation, or motor function thought possibly to represent seizures. To the contrary, EEG yield was very low in patients with syncope, dizziness, and particularly nonepisodic behavioral alterations without a history consistent with seizure (10,11). These results underscore the need for appropriate clinical judgment in the application of ambulatory EEG.

In 1994, Morris et al. completed a study of the clinical usefulness of 16-channel discontinuous, but computer-assisted, ambulatory EEG recording (82). A total of 344 patients were recorded for an average of 1.4 days using a 16-channel bipolar montage. Push-button events plus spike-and-seizure detections and periodic samples were recorded on a portable computer attached to the recorder. Epileptiform abnormalities (seizures or spikes) were identified in 38% of patients (26% by computer only) and in 25% of patients with previously normal EEGs. Seizures were identified in 12% of patients. The higher overall yield in this study versus previous eight-channel studies may be related to improved detection of EEG abnormalities with the additional channels or to differences in patient population. It is noteworthy that computer assistance is very important in identifying interictal abnormalities with a discontinuous recording system. A full two-thirds of patients had abnormalities identified only by on-line spike-and-seizure detection analysis and not by push-button events or intermittent time samples. Push-button events without associated EEG changes were recorded in 36% of patients. The authors reported "an overall clinical usefulness of 74%" by adding the two yields together.

More recently, Liporace et al. (74) compared the utility of computer-assisted 16-channel, 24-hour ambulatory EEG to routine 30- to 60-minute sleep-deprived EEG in 46 patients using similar recording equipment. Electroencephalographers who were unaware of clinical information on the

patients reviewed records independently. Epileptiform abnormalities were found in 33% of ambulatory EEGs and 24% of sleep-deprived EEGs. Statistically significant, however, was the fact that seizures were recorded in 15% of ambulatory EEGs but in none of the routine EEGs.

THE ROLE OF AMBULATORY EEG

What, then, is the current role for ambulatory EEG in the diagnostic spectrum from routine laboratory EEG to inpatient long-term monitoring? In the past the answer to this question was technologically constrained, but this is no longer the case. Ambulatory and fixed EEG monitoring systems have nearly the same capabilities. Cost effectiveness is currently a major factor. Elective hospital admissions for diagnostic purposes are increasingly difficult to justify to insurers despite the fact that, in most situations, inpatient monitoring will provide better quality data. This has mostly to do with the controlled monitoring environment where electrode integrity is maintained and the patient is being watched and carefully recorded on videotape, and where antiepileptic medications can be more safely withdrawn to induce seizures. Conversely, there are few diagnostic situations in which outpatient ambulatory EEG cannot be considered a perfectly reasonable and potentially cost-efficient initial procedure. At present there are few controlled clinical comparisons of ambulatory versus inpatient monitoring. Numerous studies have shown that ambulatory EEG is clearly superior to routine EEG, particularly when seizure recording is essential. Although there are no official guidelines for ambulatory EEG, clinical experience would support the diagnostic flow charts in Tables 19.1 and 19.2.

TABLE 19.2. *Scalp EEG evaluation of patients with seizure-like spells*

Step 1: Routine laboratory EEG
Step 2: Sleep-deprived EEG or ambulatory EEG
Step 3: Ambulatory outpatient EEG
Step 4: Ambulatory outpatient EEG with video
Step 5: Long-term inpatient monitoring

Patient	Recording montage
New patient with no previous EEGs	Start at Step 1
Referred patient with previous normal or equivocal EEGs	Start at Step 2
Seizure classification/characterization needed	Start at Step 3
Presurgical workup	Start at Step 4

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Chapter 20

Intracranial Electroencephalography

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Although easily recorded from scalp electrodes, recording the electroencephalogram (EEG) directly from the cerebral cortex, termed *electrocorticography*, sometimes offers critical advantages (21). Cortical EEG recording is now mainly used for two reasons, planning epilepsy surgery and assessing the brain's electrical activity during cortical mapping sessions (Table 20.1). Planning epilepsy surgery accounts for most cortical recordings by far, although the proportion of surgical patients who require this technique has steadily decreased as noninvasive evaluation methods, such as magnetic resonance imaging (MRI), single-photon emission computed tomography, and positron emission tomography have improved. Monitoring of cortical function during electrical stimulation of the brain is the other major indication for cortical EEG recording. Cortical EEG recording is used to verify that the stimulus remains local and that afterdischarges are not provoked.

This chapter reviews the intracranial EEG, its benefits, and its pitfalls. In many respects, it resembles the extracranial EEG. Some dilemmas posed by extracranial EEG are eliminated with cortical recording, though new difficulties are introduced. The usual waveforms are readily visible, only more so. The intracranial EEG is not filtered by the scalp and skull, and, consequently, ordinary rhythms look different from usual. Normal rhythms sometimes appear sharper and less benign, and waveforms that are not seen in the scalp EEG are sometimes discernible. Definitive answers to clinical questions are not always gained, and, at times, the data are overwhelming. Nonetheless, the intracranial EEG can be immensely rewarding for the

TABLE 20.1. *Intracranial EEG recording objectives*

Define interictal abnormalities
Epileptiform
Nonepileptiform
Define ictal onset zone
Demonstrate site of onset of different seizure types
Establish reliability of seizure onset pattern
Demonstrate routes of seizure propagation
Monitor EEG during mapping of cortical function
Establish lack of afterdischarge during electrical stimulation

patient who derives benefit from its use, and intellectually stimulating to the neurophysiologist who employs it.

WHEN IS INTRACRANIAL EEG INDICATED?

The intracranial EEG may be recorded for a brief time during a neurosurgical procedure or for a longer time in a monitoring suite after electrode insertion in the operating room. Acute intraoperative EEG recording can be done quickly with a minimum of inconvenience and risk. Chronic recording is more complex, expensive, and riskier, and requires greater justification.

Chronic Intracranial EEG Recording

Two requirements must be satisfied before chronically indwelling intracranial electrodes should be used when evaluating someone for epilepsy surgery. First, localization should not be possible through safer noninvasive means or with acute recording during a neurosurgical procedure. The major objective of the presurgical evaluation process is to establish whether a single epileptogenic structural lesion exists that can be safely excised or transected. The widespread adoption of MRI and other ancillary techniques, including positron emission tomography and magnetic source imaging, permits most patients to have surgery without intracranial electrodes. Only when these noninvasive methods yield conflicting data or are insufficiently localizing should intracranial electrodes be employed (17,21,22,25). Second, before placing intracranial electrodes, one must have a reasonable hypothesis regarding the location of the epileptogenic zone; intracranial electrodes should not be placed in the absence of a clear idea of where seizures most likely originate.

The indications and rationale for performing intracranial EEG in epilepsy can be concisely summarized. Intracranial EEG helps establish whether there are one or more well-localized epileptogenic zones, helps demarcate the boundaries of a single zone, and establishes the function of the tissue within and adjacent to that zone. In practice, this means (a) determining the laterality of the focus, (b) localizing the focus to a specific lobe, and (c) defining its location within that lobe. It is also necessary to (a) determine whether there are multifocal epileptogenic areas (which might militate against surgery); (b) confirm that seizures are partial rather than generalized (occasionally, a frontal focus may appear as a generalized spike-and-wave discharge in the scalp EEG); and (c) confirm the diagnosis of epilepsy and define a focus for excision in those rare patients in whom the scalp EEG is negative.

Indwelling intracranial electrodes also provide a unique research opportunity. The electrodes can be utilized for experimental purposes to explore normal and abnormal brain physiology. EEG, evoked potentials, and single neuronal recordings can all be obtained in a passive state or under active experimental conditions, yielding new insights in brain function.

Rarely, chronic indwelling intracranial electrodes are placed for the sole purpose of mapping cortical function. This is generally done in complex cases in which the mapping procedure is expected to last so long that it would not be safe or tolerable to do it in the operating room. For example, most children and some adults cannot remain awake during surgery, so electrodes are inserted and electrical stimulation is performed over the next day or two outside the operating room (30,31). The electrodes are removed after cortical mapping is completed.

Acute Intraoperative Recording

Acute intraoperative electrocorticography is used for identical purposes, to reveal abnormal discharges and to monitor the EEG if electrical stimulation is performed (6,9,14,28,29) (see also Chapter 21 for a more detailed discussion). However, the surgeon must have identified the area for excision with reasonable certainty prior to surgery, and the intraoperative corticogram serves merely to refine the excision margins about a known lesion. Because the recording time is limited, expectations are different and quick decisions must be made.

The same types of electrodes, recording techniques, montage design, and methods of interpretation apply in the operating theater as in chronic recording; therefore, the discussion below is applicable to both acute and chronic recording. The only differences lie in duration of recording, types of ar ti-

facts, and potential confounding effects of anesthetic agents during the two types of recording session. Operating suites contain electronic and mechanical equipment that may introduce artifacts in the EEG. Several measures must often be taken to eliminate or reduce extraneous artifacts, ranging from disconnecting some pieces of equipment to conducting a thorough electrical engineering evaluation of the building's grounding cables with appropriate later engineering modifications. Many anesthetics, such as isoflurane and related compounds, propofol, benzodiazepines, and barbiturates, can either provoke or suppress interictal spikes and seizures. These agents are best avoided during intraoperative electrocorticography. Most neurophysiologists prefer to rely on a combination of narcotic medication, such as fentanyl, and nitrous oxide if general anesthesia is used. Local anesthesia provides perhaps the ideal combination of pain control and lack of EEG effect, but is neither suitable nor desirable for all patients.

ELECTRODES

Different types of electrodes can record the intracranial EEG (Table 20.2), including depth electrodes, subdural electrodes, epidural electrodes, and foramen ovale electrodes. Each electrode type has unique advantages and disadvantages, and their use depends on the question being posed in an intracranial evaluation. Often, multiple electrode types are used simultaneously to maximize the yield of an intracranial EEG recording session.

Depth electrodes are constructed as wires or catheters, and pierce the substance of the brain (Fig. 20.1) (13,21). Contacts are placed at regular intervals along the wire. Because depth electrodes penetrate the brain, their contacts lie within the cortex, in contrast to the other types of intracranial electrodes,

TABLE 20.2. *Intracranial electrodes*

Electrode type	Recording characteristics
Depth electrodes	Record from buried cortex (e.g., amygdala, hippocampus), although may be used for superficial or basal cortex; provide limited sampling
Subdural electrodes	Record from superficial, interhemispheric, or basal cortex; ideal for broad sampling
Epidural electrodes	Record from superficial or basal cortex; have dura interposed between electrode and cortex
Foramen ovale electrodes	Record from mesial temporal cortex; extradural location

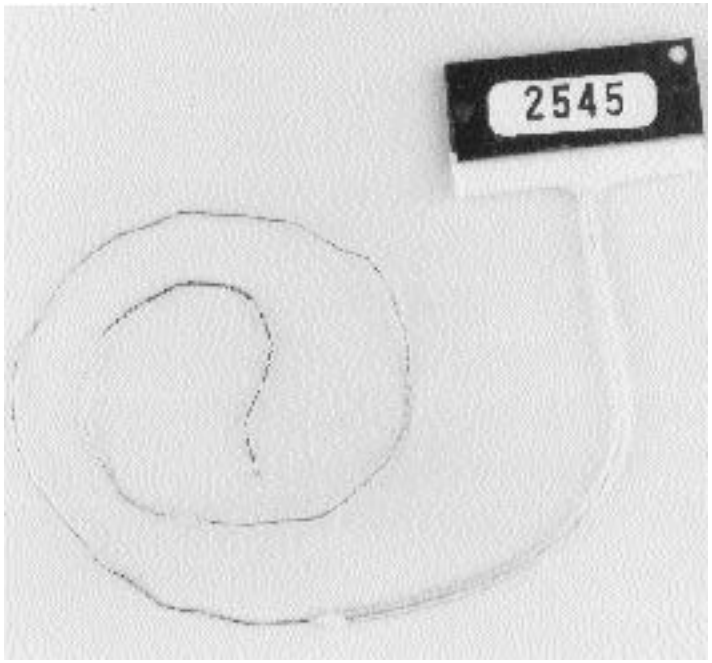

FIG. 20.1. This flexible depth electrode contains eight contacts, spaced every 5 mm beginning at the electrode tip. It is inserted while attached to a trocar insertion device that is removed after the electrode is placed.

which record from the pial or dural surface. Depth electrodes are ideally suited to record from buried, otherwise inaccessible nuclei such as the amygdala, hippocampus, and sulcal depths. At times, they are used to record from the orbitofrontal cortex, though this area can easily be reached by subdural electrodes as well. Limited numbers of these electrodes are used in any one patient to avoid excessive brain punctures; consequently, sampling is limited. They have also been utilized to record from diencephalic nuclei during surgery for Parkinson's disease or tremor.

Subdural electrodes are constructed as thin plastic (Silastic) sheets with embedded electrode contacts (Figs. 20.2 and 20.3). The contacts can be arranged in any pattern, spaced at any interval. The most common electrode types are referred to as strips and grids. Subdural strips have a single or double row of contacts placed in a straight line. Subdural grids are rectangular or square arrays of contacts spaced at regular intervals. Subdural electrodes are placed directly on the pia mater and are not inserted into the brain. They record

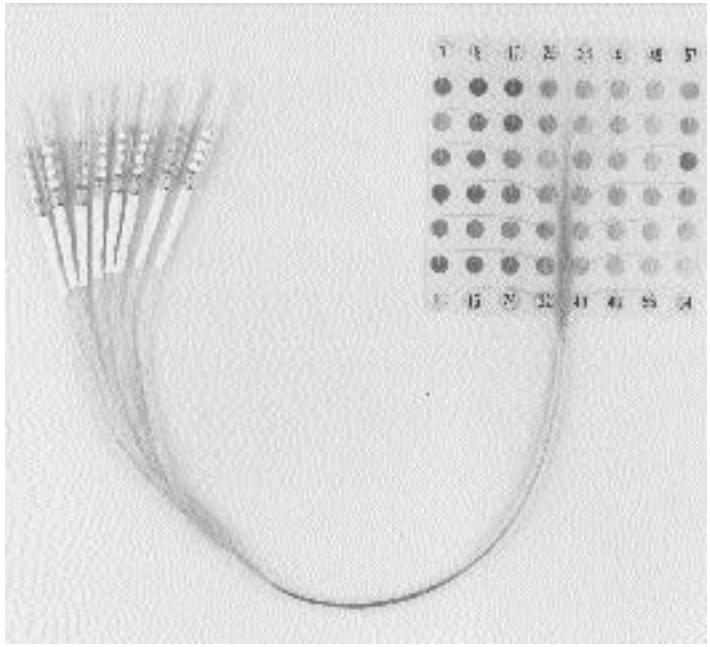

FIG. 20.2. In a subdural grid electrode, the contacts are spaced at 1-cm intervals in an 8-cm by 8-cm array. This electrode requires a craniotomy for placement and is placed in the subdural or epidural space.

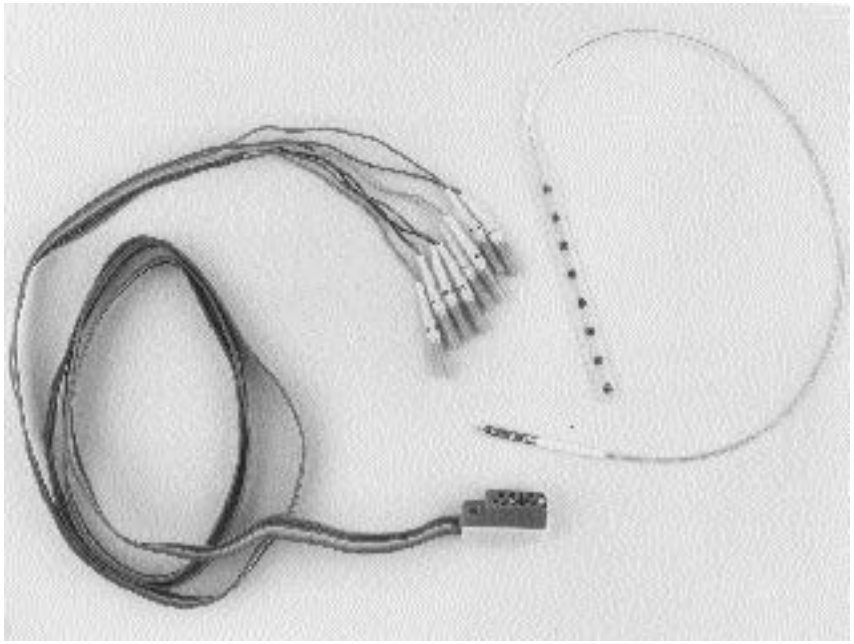

FIG. 20.3. This strip electrode has eight contacts spaced at 1-cm intervals, and can be inserted through a burr hole in the subdural or epidural space.

from the gyral surface and can be placed extensively over cortex to sample widely from one or more lobes (64,70). The same electrodes are used for epidural recording as for subdural recording, but they are placed over rather than under the dura. Epidural EEG recording is less precise than subdural recording, and is mainly reserved for patients who have dural scarring that prevents subdural electrode placement. However, some neurosurgeons prefer an epidural electrode location even in the absence of scarring, and the choice of technique must ultimately rest with the responsible physician.

Foramen ovale electrodes consist of wires with multiple contacts and are similar to depth electrodes (27,68,69). They are inserted via the cheek through the foramen ovale to rest in the epidural space adjacent to the mesial temporal lobe. They were developed as a substitute for depth electrodes. It is not clear that they carry a lower morbidity, though the insertion technique is simpler and less expensive.

ADVANTAGES AND DISADVANTAGES OF INTRACRANIAL ELECTRODES

Intracranial electrodes have several advantages over scalp electrodes (44). They lie in direct proximity to the cortex, so the EEG signal is neither attenuated nor altered by overlying skull or scalp tissue. The scalp and skull act as a frequency-dependent filter, and preferentially pass lower frequencies more readily than higher frequencies (21). Practically speaking, this means that beta and gamma frequencies are attenuated more than delta or theta frequencies, and that the fast components of interictal and ictal spikes are more greatly attenuated. In addition, the EEG signal cannot be obscured by electromyographic artifact when using intracranial electrodes; this is often an insurmountable problem when recording seizures with scalp electrodes. Intracranial electrodes record signals from small pools of neurons that do not generate a sufficiently strong signal for scalp electrode detection. Consequently, intracranial electrodes detect seizures earlier and more often than

scalp or sphenoidal electrodes, and hippocampal seizures are usually detected earlier with depth electrodes than subdural electrodes (8,56). Interictal spikes are detected in greater number and in more locations with intracranial electrodes than scalp electrodes. Focal disruptions of normal rhythms are more readily apparent with intracranial electrodes too, because the spatial averaging properties of the scalp are eliminated.

However, these advantages are accompanied by some disadvantages. Only a limited amount of cortex can be sampled by intracranial electrodes, and clinically important signals that are generated at a distance from the electrode may not be detected (21). Because the amplitude of any EEG signal is proportional to the solid angle of the dipole of any potential, potentials with a tangential orientation might not be detected. However, this limitation applies to scalp EEG as well. Signals that derive from the depths of sulci are typically not recorded by intracranial electrodes either, because the usual placement is over the superficial gyral surface. Finally, because the skull and/or dura must be breached to place intracranial electrodes, patients are exposed to risk and significant discomfort. Although the risk of a major complication such as hemorrhage, infection, or herniation is small, the potential for short- and long-term adverse consequences restricts the use of intracranial electrodes.

TECHNICAL CONSIDERATIONS

Depth Electrodes

Depth electrodes may have a variety of designs (see Fig. 20.1). They may be flexible or rigid, have a varying number of contacts, be constructed from different metals, be inserted from different approaches, and be used chronically or acutely in the operating room. The electrodes have blunt tips to avoid severing neural tissue during insertion. Most surgeons prefer to use flexible electrodes because they are safer than rigid electrodes. Flexible electrodes are inserted with a semirigid stylet or introducer placed in a hollow core of a cannula-type electrode or alongside a wire. These electrodes can deviate through natural tissue planes around structures such as arteries, which on occasion leads to less precise placement but a reduced chance of hemorrhage. Once the electrode is placed, the stylet or introducer is removed, leaving the flexible electrode behind. It is possible that removal of the introducer could displace the wire, but this rarely poses a significant problem. With flexible electrodes, a blow to the head cannot cause movement of the electrode through brain tissue with resultant injury. The electrodes are easily removed at the bedside with little discomfort when they are no longer needed. Rigid electrodes are placed somewhat more precisely in the targeted cortical region. However, caution must be taken to avoid any trauma to the exposed portion of the electrodes so as to avoid movement of the electrodes in the brain.

Commercially produced electrodes typically have multiple contacts placed at regular intervals, either 5 or 10 mm along the course of the electrode, to allow for sampling along the entire course of the electrode. Electrodes can also be fabricated to any desired specification for customized contact spacing. Contacts are usually several square millimeters in area, though size can be varied according to the neurophysiologist's preference. Contacts are typically made of nickel–chromium alloys (nichrome) or, less often, platinum–iridium alloys because these are nonmagnetic and compatible with MRI. In the past, stainless steel, gold–chromium alloy, and other metals were used, but these create more artifact in the MRI scan than does nichrome. Silver and copper cannot be used because of an adverse brain reaction to these substances (12). A separate insulated wire runs from each contact to the proximal end of the electrode, where it inserts into a connector that can be plugged into a cable that connects to the amplifiers of an EEG recording machine.

Subdural and Epidural Electrodes

Subdural and epidural electrodes usually share a common design, irrespective of manufacturer (see Figs. 20.2 and 20.3). They consist of a flexible Silastic matrix, generally less than 0.6 mm thick, with embedded electrode contacts. As with depth electrodes, a separate insulated wire runs from each contact to a connector plug at the end of the electrode. The contacts are made of stainless steel or platinum, the latter producing less artifact in the MRI, and the exposed metal usually has a 2- to 3-mm diameter. Commercial manufacturers usually space the electrode contacts at 5- to 10-mm intervals, though any pattern can be fabricated. Strip electrodes usually have one or two rows of contacts arranged in a straight line, with between four and eight contacts per line. Grid electrodes come in a variety of sizes, and commonly range between four-by-four arrays and eight-by-eight arrays. Subdural strips and grids can be trimmed by the surgeon in the operating room to irregular shapes as needed to accommodate the craniotomy. Subdural strips can be removed at the bedside; an injection of intravenous narcotic prior to removal eases the brief discomfort sometimes experienced by patients. Subdural grid electrodes must be removed in the operating room because of the craniotomy, and the therapeutic surgical procedure is usually performed at the same time.

Another type of epidural electrode is the epidural peg electrode, which is a single contact attached to the skull through a twist drill hole (2). Epidural peg electrodes can be scattered over the skull to sample from different lobes of the brain. Because they are subject to limited spatial sampling, they are more useful for negative information—that is, demonstrating lack of involvement of underlying cortex—than for localizing an epileptogenic zone.

Foramen Ovale Electrodes

These electrodes, which are similar to depth electrodes, are commercially manufactured. They typically contain four to six contacts and have a flexible construction. In contrast to other electrode types, foramen ovale electrodes are inserted under fluoroscopic guidance in the radiology suite or the operating room under local anesthesia, and can be removed at the bedside (27,68,69).

Electrode Insertion

Depth, subdural, and epidural electrodes are inserted under general anesthesia in the operating room. If intraoperative electrocorticography is to be performed, then anesthesia should be restricted to nitrous oxide and narcotics, though propofol can be used briefly at the start of the procedure because it has a short half-life. If intraoperative electrocorticography is not planned, then any anesthetic agent can be used. Depth electrodes are inserted through a twist drill hole or burr hole, and subdural strip electrodes are placed through a burr hole. Subdural grid electrodes typically require a craniotomy, the extent of which depends on the size of the electrode. Depth electrodes are placed with either stereotactic frames or a frameless stereotactic technique, and subdural electrodes are placed freehand. Electrode location is tailored to the clinical picture, and can be modified in the operating room by using acute intraoperative electrocorticography to help define areas of interest for chronic electrode placement. The operative procedure generally takes 2–5 hours depending on the number and type of electrodes placed and whether electrocorticography is done. MRI obtained after implantation of electrodes verifies their location (Fig. 20.4).

Postoperative Course

Patients usually spend the first 24 hours after electrode implantation in the intensive care unit, and may then be transferred to specialized epilepsy units or remain in the intensive care unit for continuous video-EEG monitoring. There is no theoretical limit to how long intracranial electrodes may remain in the brain; the duration of monitoring depends on clinical needs and typically ranges between 1 and 3 weeks.

EEG Acquisition and Playback

The methods used to record and review the intracranial EEG are generally identical to those used for scalp EEG, with a few minor exceptions. The same amplifiers are used for scalp and intracranial EEG. Signals are usually digitized by commercial equipment at a rate of 200 Hz, which allows for adequate display of virtually all clinically relevant EEG signals. Some commercial equipment permits higher sampling rates; these are necessary to record signals greater than 100 Hz. The number of channels required depends on the number of electrode contacts used and the cortical regions that need to be sampled. Most commercial equipment is sufficiently flexible to permit simultaneous recording from at least 128 channels, though fewer channels are usually adequate. The same filter settings are used for depth EEG as scalp EEG (low filter, 1 Hz; high filter, 70 Hz), though high-frequency cutoff limitations do not necessarily apply. Indeed, very-high-frequency activity, up to 500 Hz, has been recorded in the intracranial EEG with depth electrodes using appropriate sampling rates (2,20). Because signal amplitudes are considerably higher, typically three- to eightfold, in the depth EEG than the scalp EEG, amplifier gains must be adjusted accordingly.

The intracranial EEG can be reviewed on a computer screen or on EEG paper; the method depends on the preference of the electroencephalographer. It is often helpful to view an extended period of time when examining a seizure. This is most easily accomplished with paper review, because 1 or more minutes can be laid out for simultaneous review. In addition, low-amplitude beta frequencies are sometimes more difficult to see on a computer screen than in a large paper format. Computer review, however, allows greater flexibility when reviewing data and, in many circumstances, is adequate for clinical purposes. EEG data are most efficiently stored in a digital format on a computer medium such as a compact disk.

Intracranial EEG montages are designed using the same principles as are employed in scalp EEG, although the specifics vary depending on the number of electrodes used and their location. Referential or bipolar montages can be created, and there are often advantages to reviewing data in more than one montage because of in-phase cancellation or active reference contacts. EEG channels are generally best displayed in a logical framework, with lin-

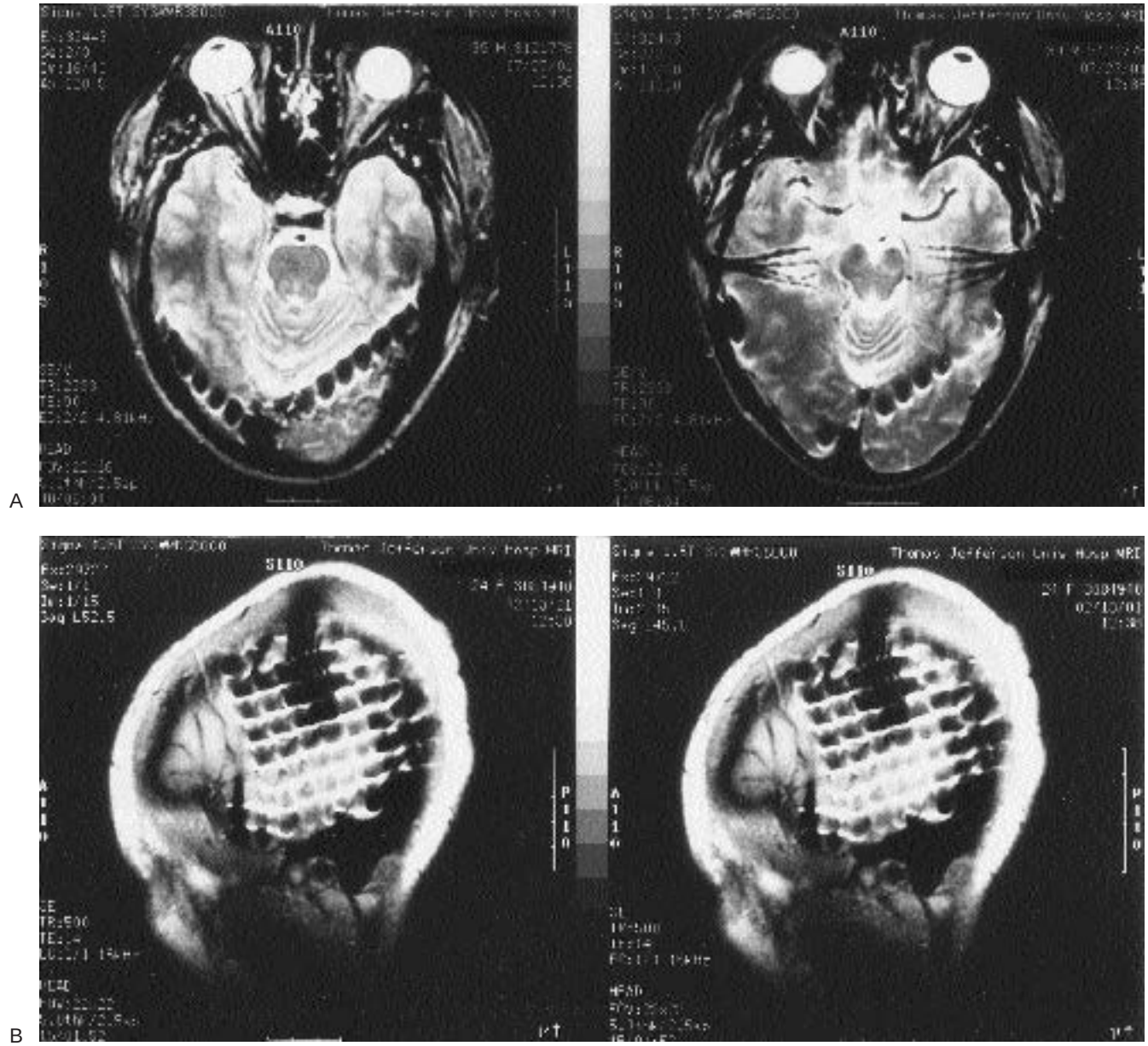

FIG. 20.4. A: MRI axial section showing depth and subdural electrodes. The depth electrodes are seen entering the lateral temporal cortex and crossing to the mesial cortex. Subdural electrodes are shown running posteriorly. **B:** MRI sagittal view showing subdural grid electrode contacts overlying the left hemisphere.

ear sequences (e.g., anterior to posterior, superior to inferior) and channels grouped by lobar location. For example, deep temporal lobe contacts may be grouped together in a series of channels, followed then by grouping lateral neocortical temporal contacts in the next series of channels, and so forth. This is shown in the EEG illustrations below. If a referential montage is used, either an extracranial or intracranial contact can be used. It is important to choose a reference contact that has as little artifact as possible and is uninvolved in the discharge of interest. Interpretation of intracranial EEG is often made difficult by the large number of channels needed to display information from all contacts. It is not uncommon to collect 64–128 channels of data, which must then be simultaneously reviewed.

ELECTRODE LOCATION

The majority of refractory patients who come for surgical evaluation have mesial temporal lobe epilepsy (18), which is characterized by seizures originating in the hippocampus or, less often, the amygdala. Depth electrodes are ideally suited to study patients with this condition because they directly record the EEG from limbic structures. In contrast, subdural, epidural, and foramen ovale electrodes are placed at a distance from the hippocampus and amygdala, which limits their sensitivity (this problem is further discussed later in this chapter). Temporal lobe depth electrodes are most often inserted via a lateral approach from the middle temporal gyrus to the desired mesial temporal targets, which include the amygdala, hippocampus, and parahippocampal gyrus. This is a relatively avascular route, which minimizes the risk of producing an intracerebral hematoma. Adequate sampling of mesial temporal structures requires placement of between three and six electrodes when a lateral approach is used. An alternative strategy, used less often, targets the hippocampus from a posterior approach through the occipital lobe. This technique permits placement of multiple contacts within mesial temporal structures with one electrode, though two electrodes are usually placed to ensure adequate sampling. The posterior approach puts the electrode through more brain tissue than the lateral approach, and objections have been raised because this method skewers the hippocampus, theoretically posing greater risk. In practice, however, no clinically significant problems have been reported using the posterior approach. Depth electrodes are generally placed in both mesial temporal lobes because of the possibility of bilateral independent seizure onsets, and to measure the interhemispheric propagation time (35). Unfortunately, temporal lobe neocortex is not well sampled by depth electrodes in either approach, so a combination of temporal lobe subdural strips and depth electrodes is employed to allow for detection of either limbic or extralimbic temporal lobe seizure origin (3,8,42,52,56).

Subdural electrodes are best suited to record from other regions of the brain outside mesial temporal limbic structures, although depth electrodes were used in past years to sample the other lobes of the brain. Advances in subdural electrode technology and increases in the number of recording channels in EEG monitoring equipment have largely rendered the use of extratemporal depth electrodes unnecessary in most cases. Subdural electrodes offer superior sampling of virtually all other neocortical regions at lower risk. Consequently, depth electrodes are now used sparingly outside the temporal lobe in most institutions, and are reserved for situations in which technical considerations prevent adequate sampling with subdural electrodes; the exception is the orbitofrontal cortex, for which some neurophysiologists still use depth electrodes. Finally, depth electrodes have been used in some patients with epilepsy and movement disorders to record from subcortical nuclei, such as the thalamus and basal ganglia (66).

RISKS AND COMPLICATIONS

Intracranial electrodes have a relatively low chance of producing a permanent serious complication. Literature reports suggest that chronic intracranial EEG recording has a serious morbidity and mortality ranging between 1% and 4%, and the low end of that range seems most applicable in recent years (43,59,65,71). Technical advances in electrode fabrication and modern neurosurgical techniques have made intracranial electrode implantation reasonably safe, and there appears to be no safety advantage of one electrode type over another; morbidity and mortality rates appear similar. Even foramen ovale electrodes, introduced as a theoretically safer method, appear to pose risks that do not differ in magnitude from those associated with subdural or depth electrodes. Acute intraoperative recording with subdural or epidural electrodes has virtually no added risk other than that imposed by the added time needed for general anesthesia. If depth electrodes are used for acute intraoperative recording, the main risk consists of hemorrhage, with incidence similar to that when depth electrodes are placed for chronic recording. However, the surgeon has a better capability of treating an acute hemorrhagic complication that occurs during an acute intraoperative procedure, because he or she has already performed the craniotomy and the patient is anesthetized.

Hemorrhage—mainly intracerebral hematoma with depth electrodes, subdural hematoma with subdural electrodes, and epidural hemorrhage with epidural electrodes—is the most feared complication. The incidence of life-threatening hemorrhage has been reduced by using preoperative angiography

to define vascular anatomy, directly visualizing cortex through use of a craniectomy rather than a bur hole for insertion, and using relatively avascular routes of electrode insertion in the case of depth electrode placement. In the authors' experience, major hemorrhages requiring therapy are rare, occurring in less than 0.3% of patients. The chance of hemorrhage can be reduced by preoperative evaluation of coagulation and clotting parameters, and counseling patients to avoid drugs that inhibit platelet function in the week before surgery. Because each puncture of the brain poses risk of hemorrhage, limiting the number of depth electrodes to the necessary minimum also reduces risk.

Another major risk is infection, though this is quite infrequent. In addition to the ordinary perioperative risks of any neurosurgical procedure, there is an ongoing risk of developing infection while the electrodes reside in the brain. The wire leading from the intracerebral contacts to the jack box provides a route for organisms to gain entry to the brain and meninges. The risk of infection is minimized by use of a technique whereby the wire is tunneled under scalp tissue for several centimeters before exiting the scalp through a separate stab wound. Tissues can then form a reasonably tight seal around the wire to block infection. Administering antibiotics during the perioperative period also helps prevent infection. Infections usually cause symptoms of meningitis, with fever, headache, photophobia, and stiff neck, and have always cleared with antibiotic use in the author's experience. The vast majority of patients with meningeal symptoms have a chemical meningitis rather than a bacterial infection, but examination and culture of cerebrospinal fluid is needed to clarify the diagnosis. In these circumstances, it is sensible to treat with broad-spectrum antibiotics until cerebrospinal fluid culture results are known. In our experience, infections readily respond to treatment. Antibiotic therapy should treat ordinarily benign skin organisms that may be inadvertently introduced during or after surgery. Although we have not observed brain abscesses following depth electrode placement, these are possible.

Infections sometimes pose a dilemma. Intracranial electrodes are foreign bodies that provide a direct link between the brain and the outside world of pathogenic organisms. Ordinarily, the best course of action when infection occurs is to promptly remove the foreign body and initiate antibiotic therapy. Even if a suboptimal number of seizures have been recorded, this is usually the wisest course of action. However, if seizures have not yet occurred, premature removal of the depth electrodes means that electrodes will need to be reinserted in the future, which exposes the patient to additional risks. If insufficient data have been recorded to make a diagnosis, the authors have elected to leave intracranial electrodes in place, prescribe antibiotics, and aggressively taper medication to record some seizures. The electrodes are removed once enough data are obtained to make a diagnosis; ideally, this is accomplished within a few days, and should be done at once, irrespective of the EEG findings, should any deterioration occur.

The other major risk pertains to subdural grid electrodes. On rare occasions, particularly with older, thicker electrode designs, brain swelling and edema could occur beneath the grid electrode. Herniation has been reported, usually in the first few days after electrode placement, though the incidence of this complication is well under 1% with modern electrodes. Because of this potential complication, careful neurological assessments are required, and emergent grid removal might be necessary.

Histopathological examination of resected tissue usually reveals evidence of the needle track, with reactive gliosis and inflammatory cells, in patients who have had depth electrodes inserted. Mild inflammation is also occasionally seen in tissue that lay beneath subdural electrodes. Because surgery is performed shortly after the electrodes are removed, this probably reflects a temporary alteration resulting from surgical trauma. These pathological findings are believed to be clinically insignificant. Although there is a theoretical risk of electrodes causing permanent brain injury, there is no published evidence suggesting permanent cognitive injury from depth electrodes except in the setting of hemorrhage. The electrodes are believed to be sufficiently small in diameter so that significant interruption of brain function is not seen. Because electrodes are fabricated from biologically inert materials, no toxic tissue reactions occur.

On balance, the decision to use an invasive EEG technique must be made weighing the anticipated benefits against the risks. There are two expected benefits: (i) to gain sufficient knowledge to perform a therapeutic procedure that otherwise could not be done, or could not be done nearly as well or as safely; or (ii) to avoid doing a procedure that would not help—for example, learning that seizures are multifocal and that surgery should not be performed. Although the use of intracranial electrodes carries some risk, it is small, and the benefits to be gained substantially outweigh those risks in carefully chosen patients.

EEG DATA

As detailed above, the intracranial EEG must be cautiously interpreted. When sampling a limited area of brain, one risks recording from cortex that is irrelevant or only marginally relevant to the epileptic process. The electrodes might be in the wrong place, perhaps even in the wrong hemisphere, and all data could be misleading. Only potentials that are near the electrode contacts are detected, and these potentials might consist of propagated activity that has spread from a primary epileptogenic zone. The significance of

abnormal interictal paroxysmal and nonparoxysmal discharges is not fully understood. How to interpret seizures is also a subject of debate, and how different seizure types should be weighed is not certain.

Most chronic intracranial EEG recording sessions aim to record and evaluate interictal and ictal data (see Table 20.1). The interictal abnormalities may be epileptiform or nonepileptiform. The ictal onset zone, where seizures begin, should be delineated. The remainder of this section reviews interictal and ictal EEG findings recorded with intracranial electrodes.

Interictal EEG

Normal Findings

All of the EEG rhythms seen in the scalp EEG can be seen in the intracranial EEG. Provided electrodes are placed over the appropriate lobe of the cortical area, any rhythm can be detected. For example, one can record the alpha rhythm, beta activity, mu rhythm, sleep spindles, and any other activity. These are illustrated in Figures 20.5 through 20.9.

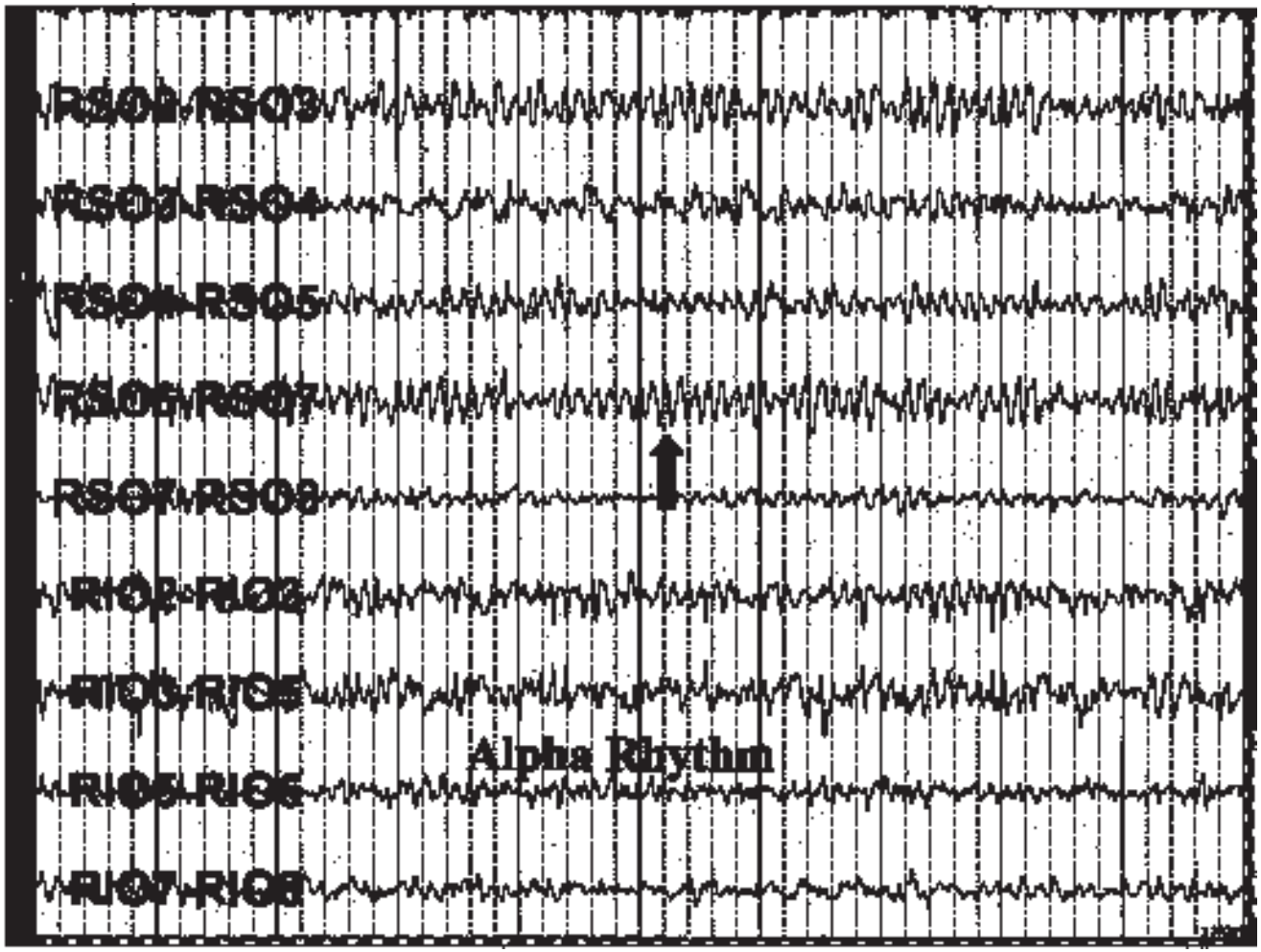

FIG. 20.5. Subdural recording showing the alpha rhythm (*arrow*) in the right occipital lobe.

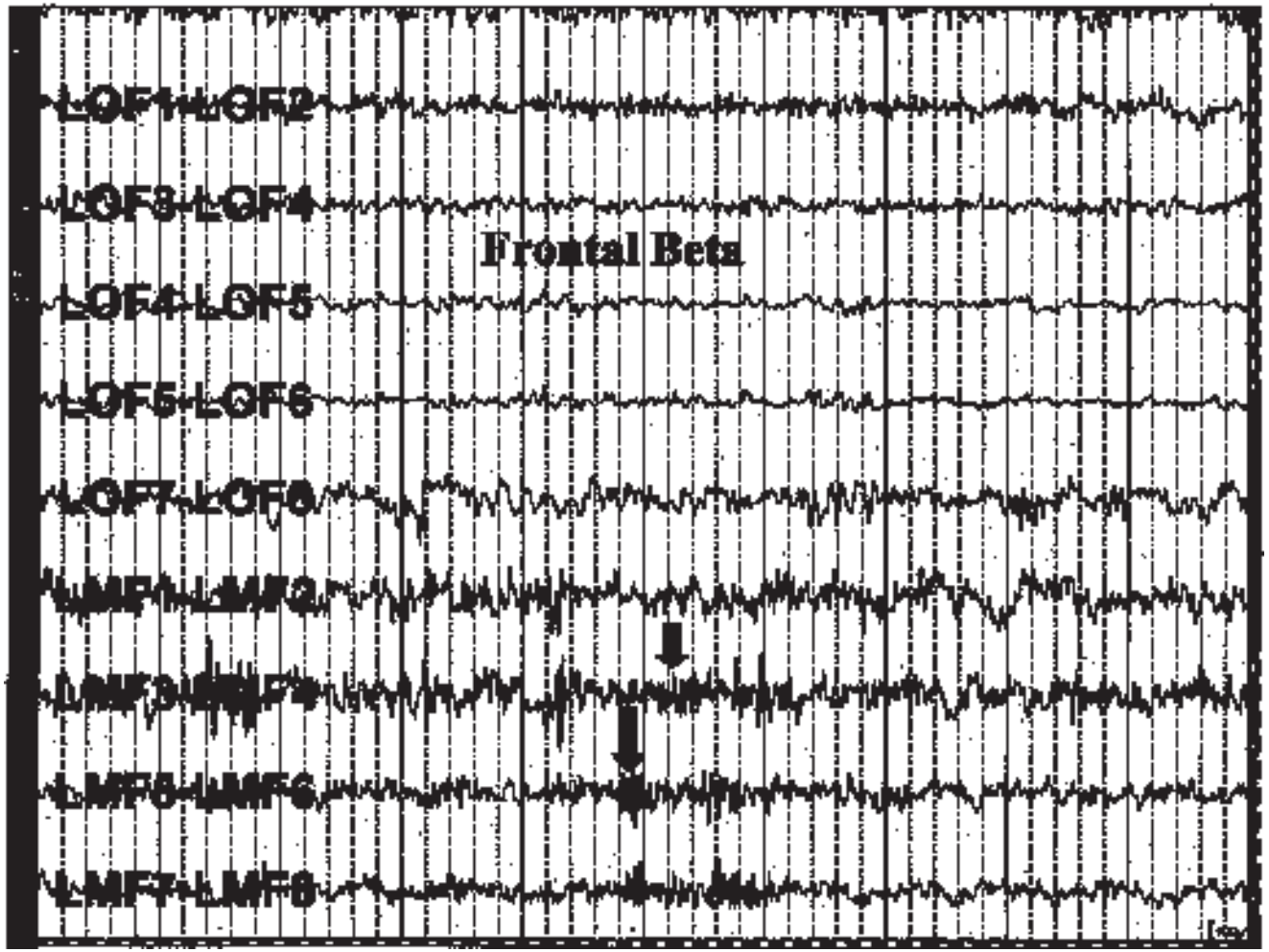

FIG. 20.6. Subdural recording showing normal frontal beta activity, most prominent in the mesial frontal cortex (LMF contacts) (*arrows*). Less beta activity is present in the orbitofrontal cortex (LOF contacts). Note the high frequency of the beta rhythm and its inherent sharpness.

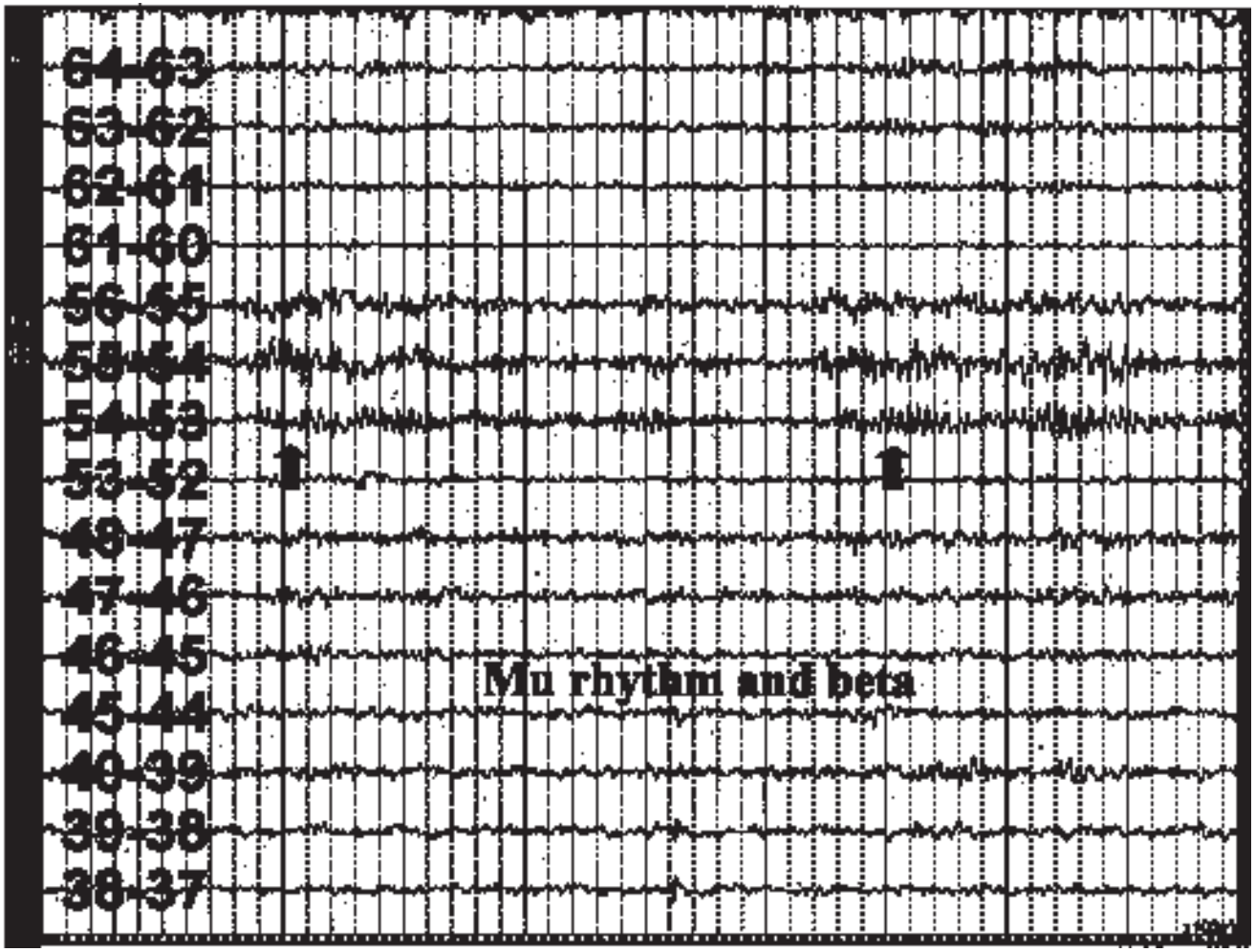

FIG. 20.7. Subdural grid recording showing mu rhythm (*arrows*) and beta activity in the frontal lobe.

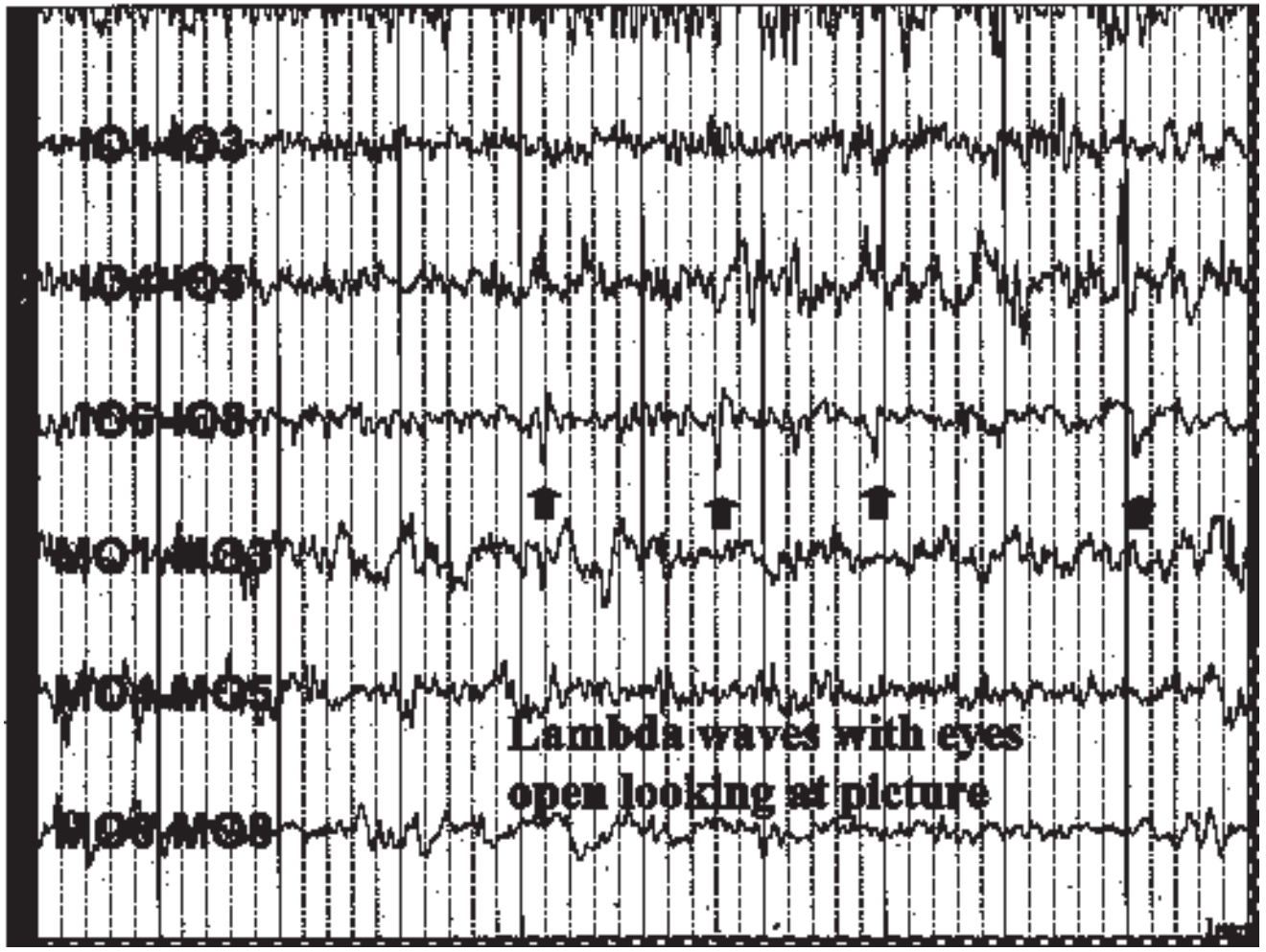

FIG. 20.8. Subdural recording showing lambda waves (*arrows*) while visually scanning a picture. These should not be mistaken for pathological sharp waves, and are abolished by looking at a blank sheet or towel.

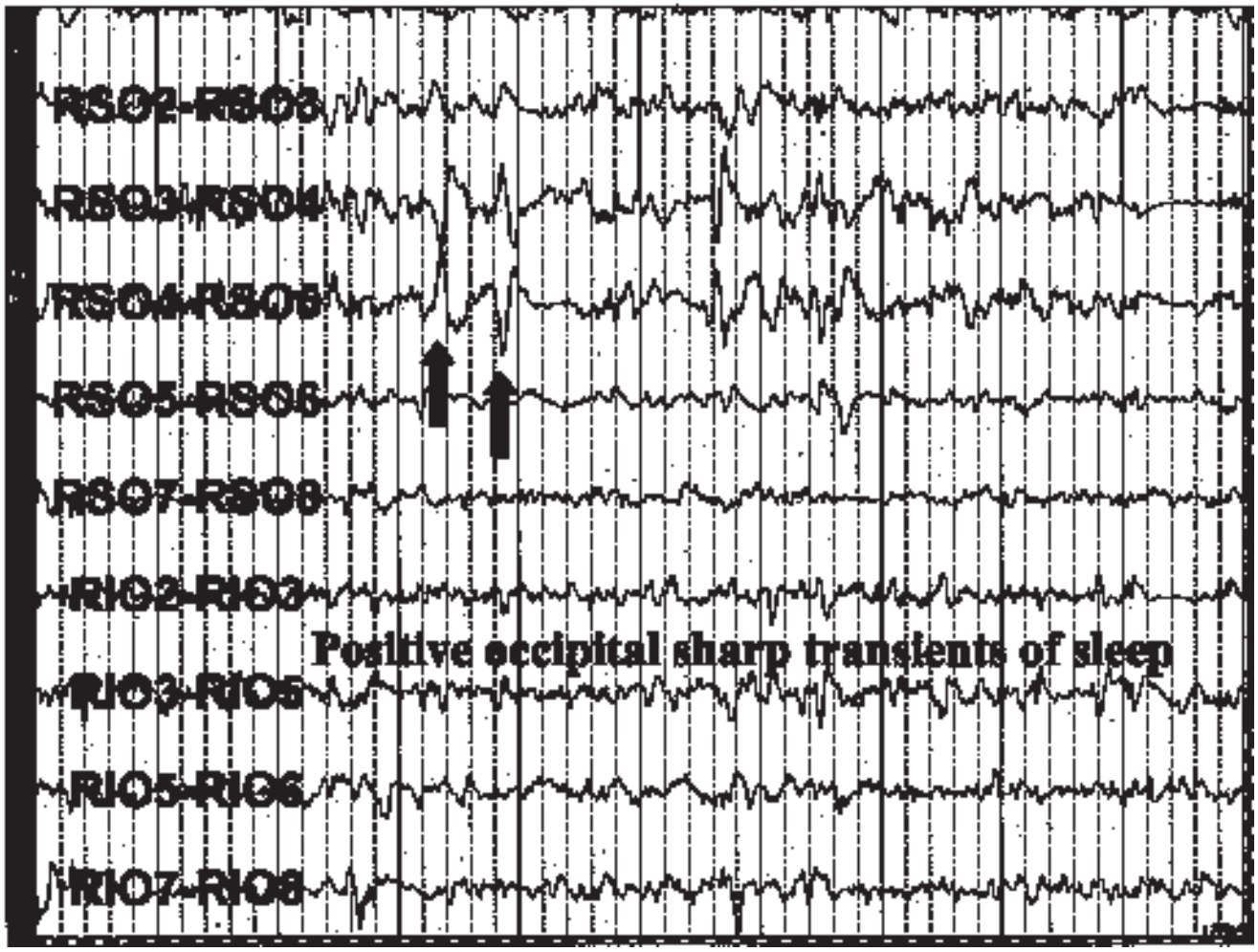

FIG. 20.9. Subdural recording showing positive occipital sharp transients of sleep (POSTS) (*arrows*). Note the varying magnitude of negative and positive components.

Nonepileptiform Abnormalities

The interictal EEG shows a number of focal nonepileptiform abnormalities (Table 20.3) (see also Chapter 17). It is worth reemphasizing that the faster frequencies are not attenuated by scalp and skull, so the electroencephalographer must avoid overinterpreting the EEG. Many normal rhythms, such as normal beta activity, rhythmic temporal theta activity of drowsiness, wicket rhythms, the mu rhythm, positive sharp transients of sleep, and even the alpha rhythm may look quite spiky in the intracranial EEG. These should not be misinterpreted as pathological spikes or sharp waves.

Focal disturbances in the EEG background correlate with the presence of either hippocampal atrophy or neocortical gliosis (11). The following types of nonepileptiform interictal abnormalities have been described:

1. *Focal slowing:* Focal slow waves may appear in the delta- or theta-frequency bands in one or more cortical regions (Fig. 20.10). Because many kinds of artifact can masquerade as focal slowing, diagnosing focal slowing requires comparison of the frequencies in the suspect area with rhythms in homologous contralateral cortex, with rhythms from surrounding cortex in the same lobe, and with an EEG recorded from the same region in other individuals. Transient slowing of frequencies from electrode placement, perhaps related to temporary edema, may be of no clinical consequence, and artifactual sources such as venous pulsation must be excluded as causes (1). Focal slowing may indicate that a structural lesion is present, and but it is reliable only when other abnormalities are present in the same area, as described below. Although focal slowing may indicate the presence of a structural lesion, it does not suggest that the lesion is epileptogenic, and seizures may emanate from a different region of the brain.
2. *Focal attenuation of alpha or beta frequencies:* A localized attenuation of fast frequencies suggests underlying cortical gliosis (see Fig. 20.10). When seen in combination with focal slowing of background frequencies, focal loss of faster frequencies strongly suggests the presence of an underlying structural lesion, such as gliosis or tumor.
3. *Focal attenuation of normal sleep rhythms:* Normal sleep rhythms seen in the scalp EEG are also seen in the depth EEG. During slow-wave sleep, sleep spindles can appear in the frontal, parietal, and temporal cortex. Spindles may even appear in the hippocampus. A focal attenuation of sleep spindles suggests that a lesion is present, such as gliosis.
4. *Focal burst-suppression:* A focal burst-suppression pattern may appear the depth EEG, usually in sleep, suggesting the presence of gliosis (Fig. 20.11).
5. *Lack of full beta induction with pharmacological activation:* Intravenous injection of thiopental or diazepam increases the amount and amplitude of beta activity in the scalp and depth EEG (16). Lack of or reduction in beta induction in one region suggests the presence of gliosis or tumor. Similarly, development of a focal burst-suppression pattern after thiopental injection suggests gliosis (54).

TABLE 20.3. *Interictal EEG abnormalities*

Nonepileptiform
Focal slow waves
Focal loss of fast frequencies
Focal loss of normal sleep rhythms
Focal burst-suppression
Focal attenuation of response to pharmacological activation
Epileptiform
Spikes, sharp waves
Focal or regional
Negative or positive
Synchronous or asynchronous
Acute or chronic recording

Epileptiform Abnormalities

Interictal spikes look somewhat different in the depth EEG than in the scalp EEG (Chapter 17) because of the lack of filtering by scalp and skull. They are shorter in duration and higher in amplitude, may be either positive or negative, and more often are polyphasic (Figs. 20.12 through 20.15). Some intracranial spikes have a highly restricted field and might appear in a single electrode contact. Other spikes may be quite widespread, involving part or all of a single lobe or more than one lobe in a hemisphere (see Fig. 20.12), or be generalized and synchronous in both hemispheres. Dipoles are more often evident in the intracranial EEG, and both positive and negative phase reversals might be seen along the course of a multicontact depth electrode or in a chain of subdural contacts. However, the usual cautions apply when interpreting spikes. Potential fields must make anatomical and physiological sense. Because spikes are sharper in the intracranial EEG, caution should be exercised when interpreting sharp waves. These may represent distant, temporally spread potentials that have propagated from a distant site or simply be normal sharply contoured activity. One should exercise great caution in interpreting sharp waves in the intracranial EEG as indicative of immediately underlying pathology.

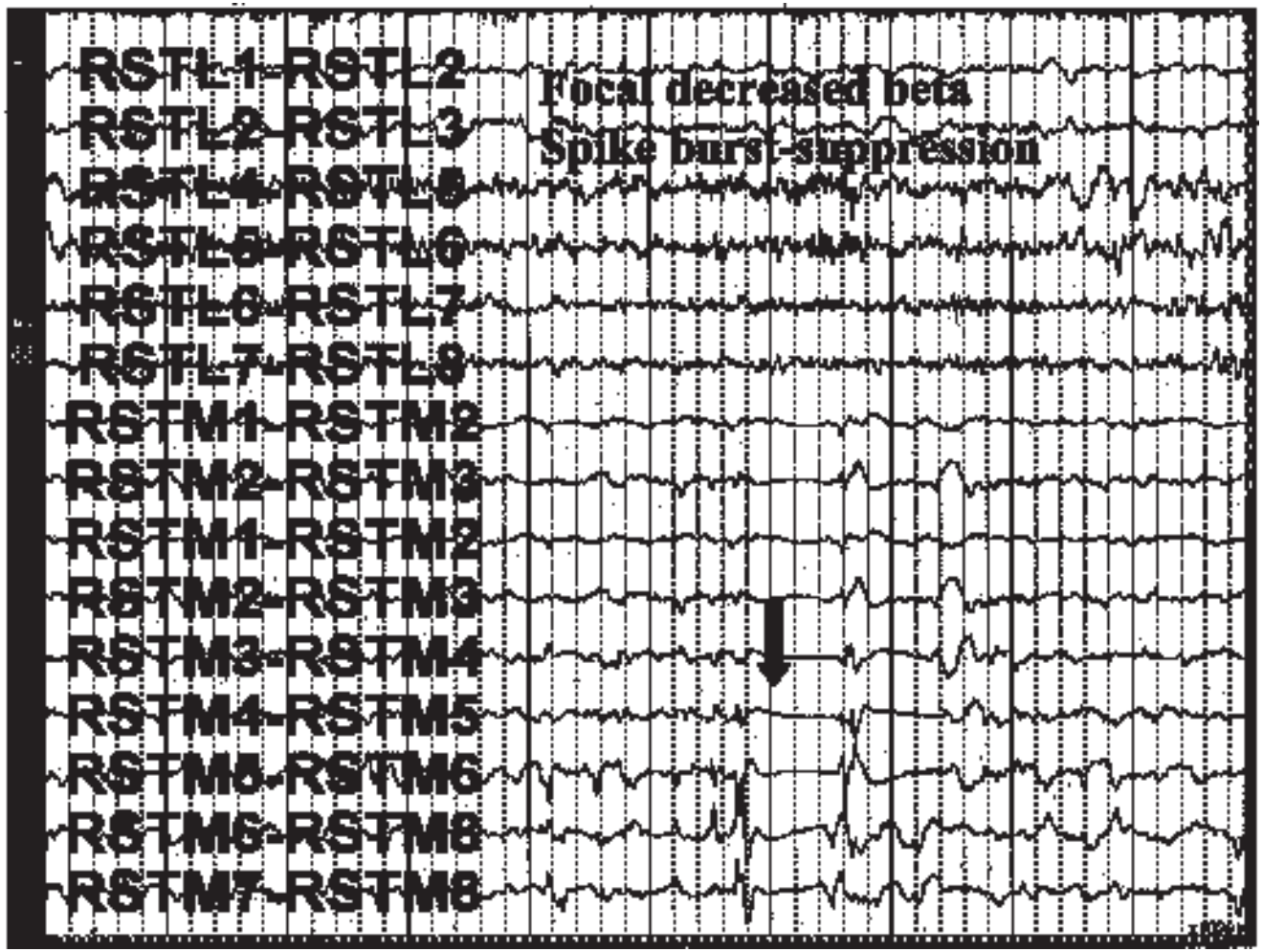

FIG. 20.10. EEG showing focal increase in theta and delta activity, and diminution of beta activity in basomedial right temporal lobe (*RSTM*) compared with basolateral right temporal lobe subdural contacts. In addition, focal spike burst-suppression is seen in the basomedial contacts (*arrow*).

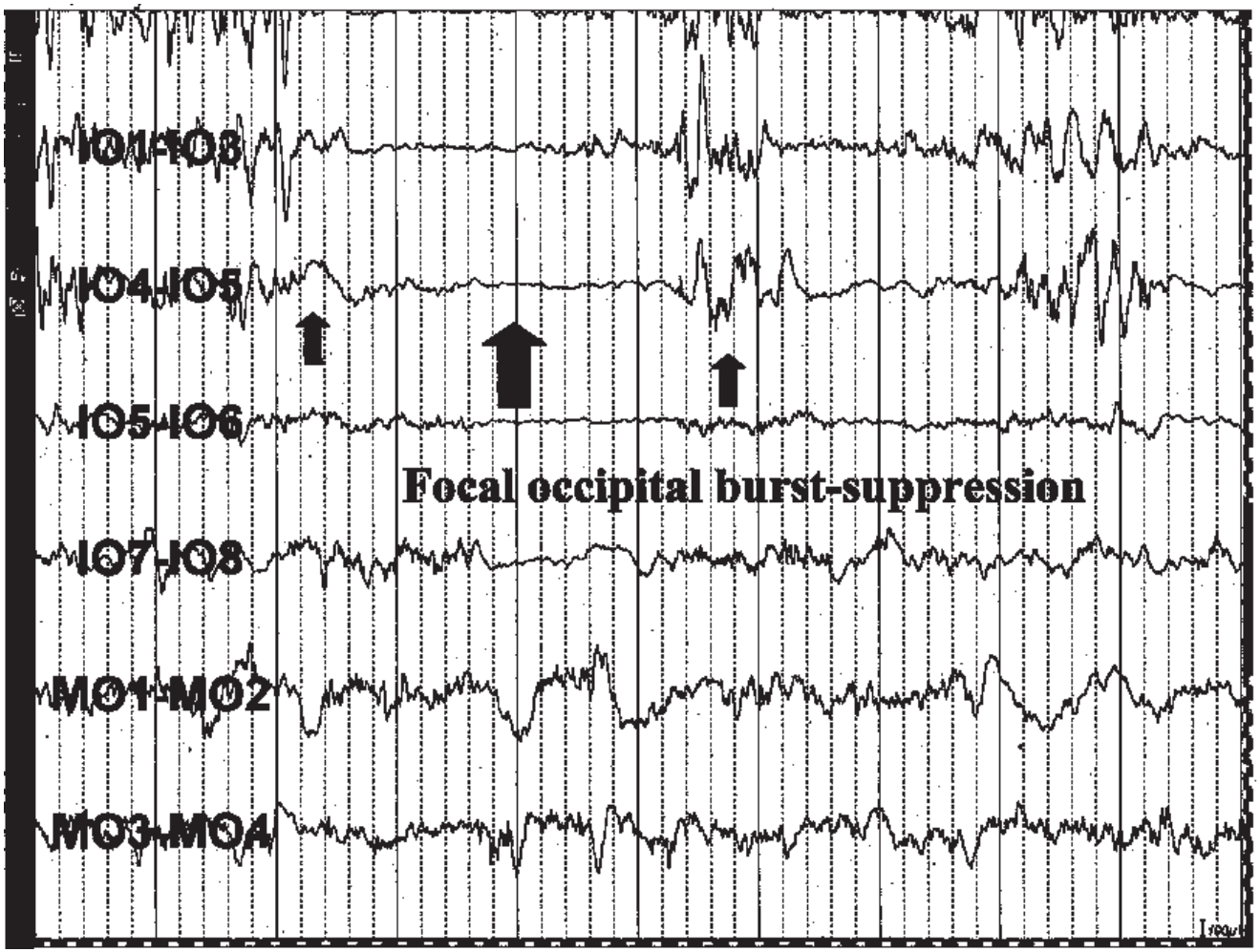

FIG. 20.11. EEG recording showing focal burst-suppression (arrows) in the inferior occipital subdural strip electrode (IO) but not the middle occipital subdural strip electrode (MO) during sleep.

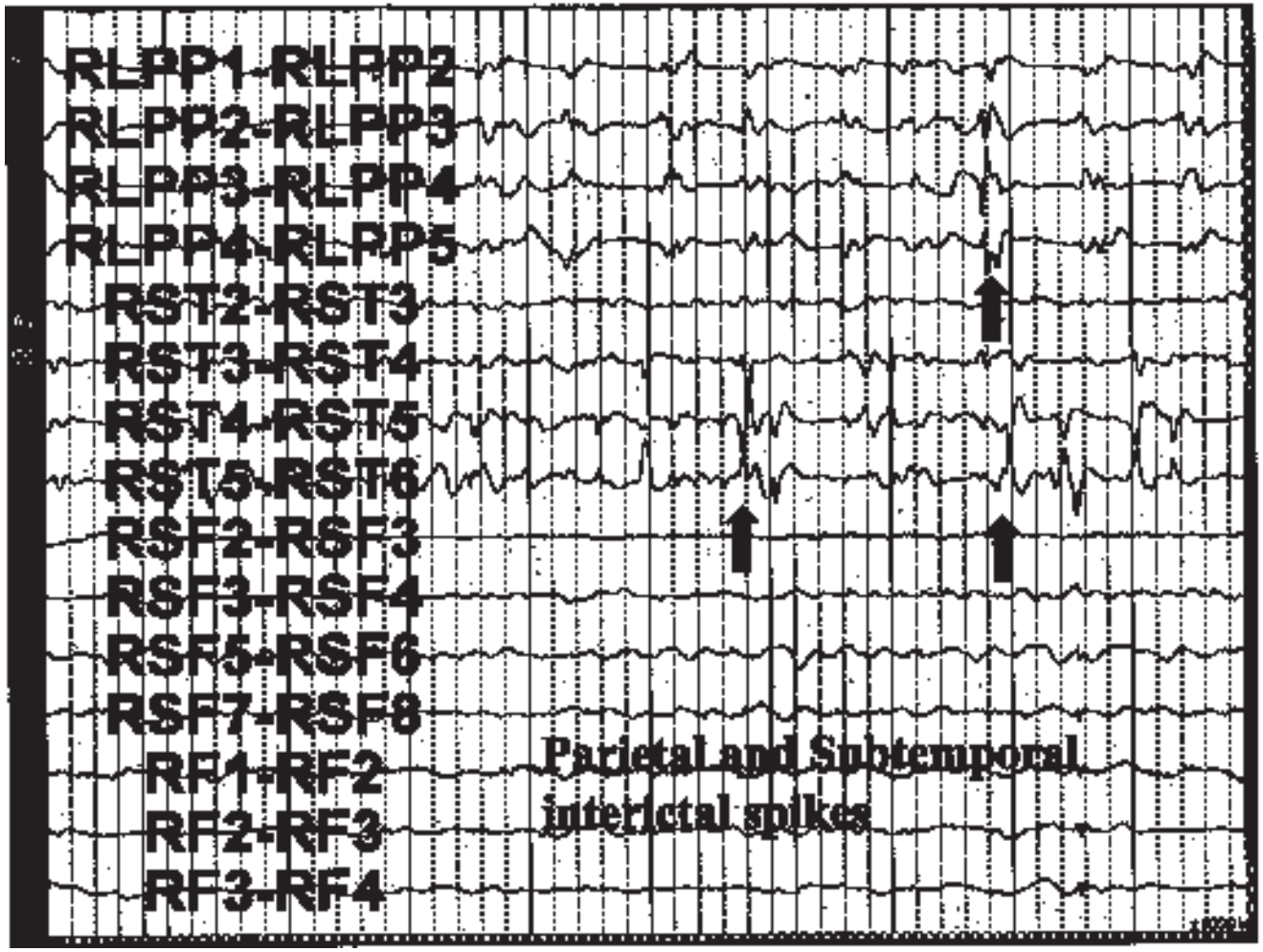

FIG. 20.12. EEG recording showing independent interictal spikes (*arrow*) in the right parietal (*RLPP*) and right temporal subdural (*RST*) electrodes. No spikes are seen in the right frontal lobe electrodes (*RSF, RF*).

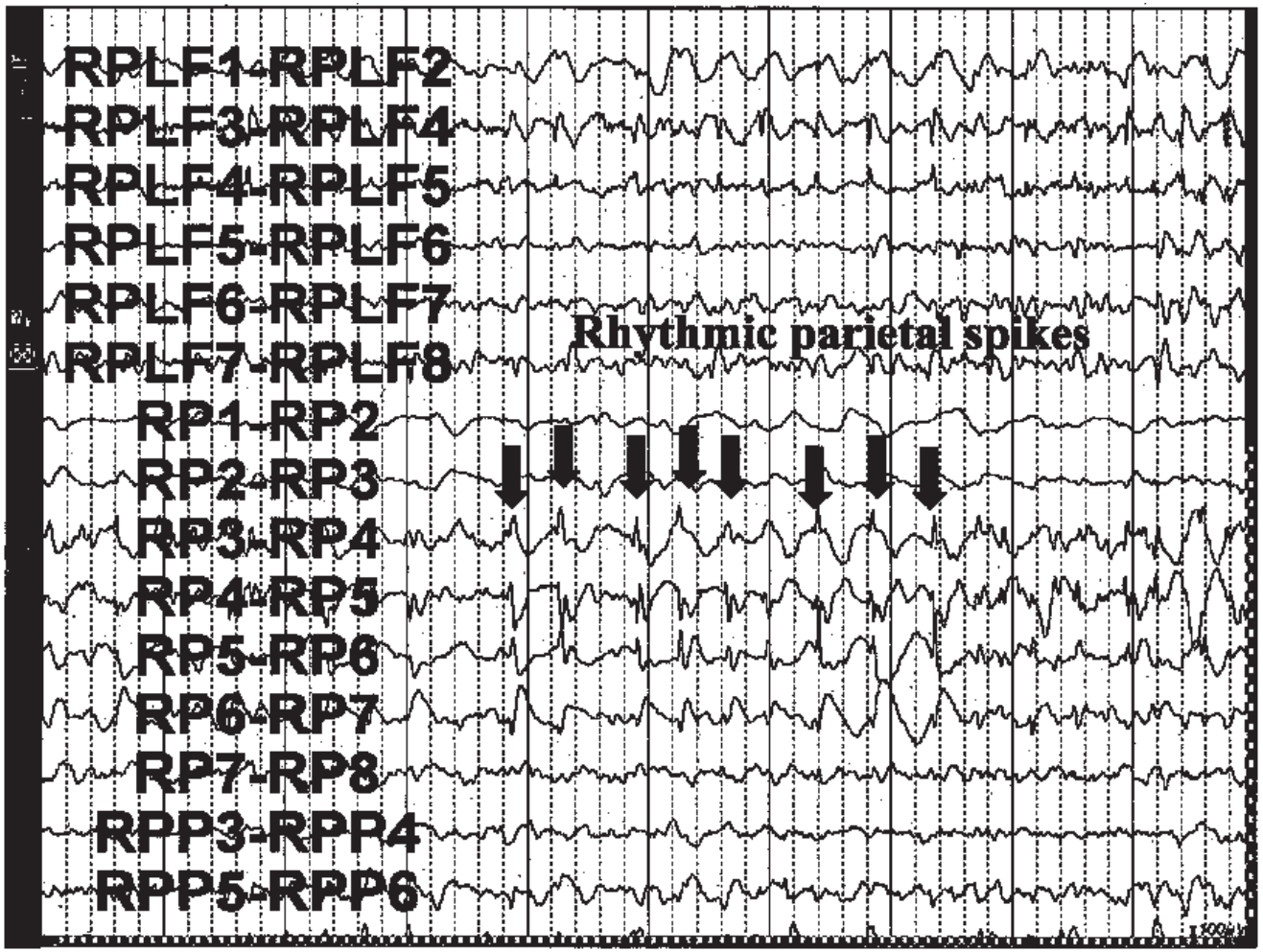

FIG. 20.13. EEG recording showing rhythmic spiking in the right parietal subdural contacts (*arrows*).

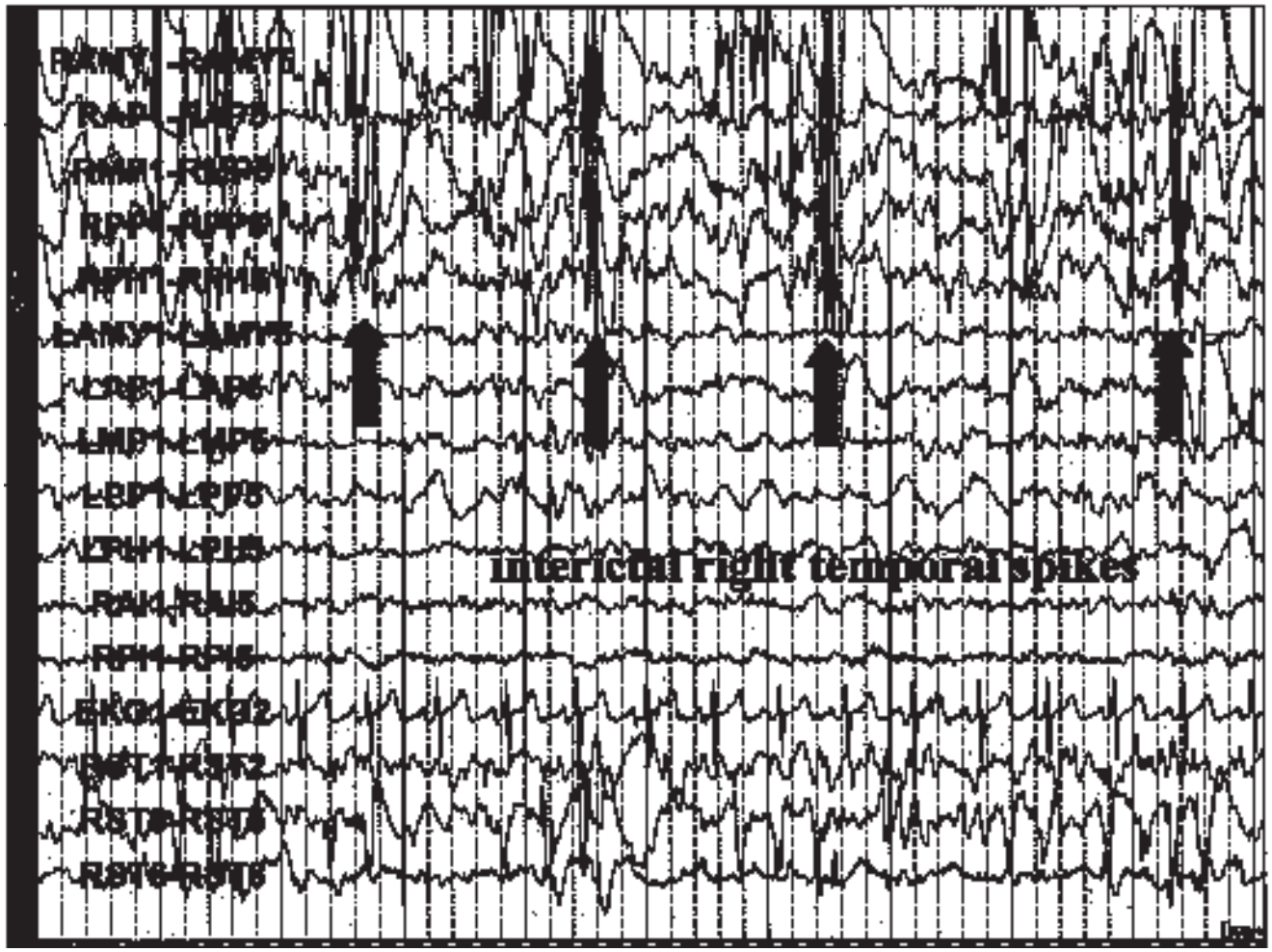

FIG. 20.14. EEG recording showing frequent interictal spikes and polyspikes (*arrows*) in the right mesial depth electrode contacts (*RAMY, RAP, RMP, RPP, RPH*) and occasional low-amplitude spikes in the subtemporal subdural strip electrode (*RST*). No spikes are present in the left mesial temporal depth electrodes (*LAMY, LAP, LMP, LPP, LPH*).

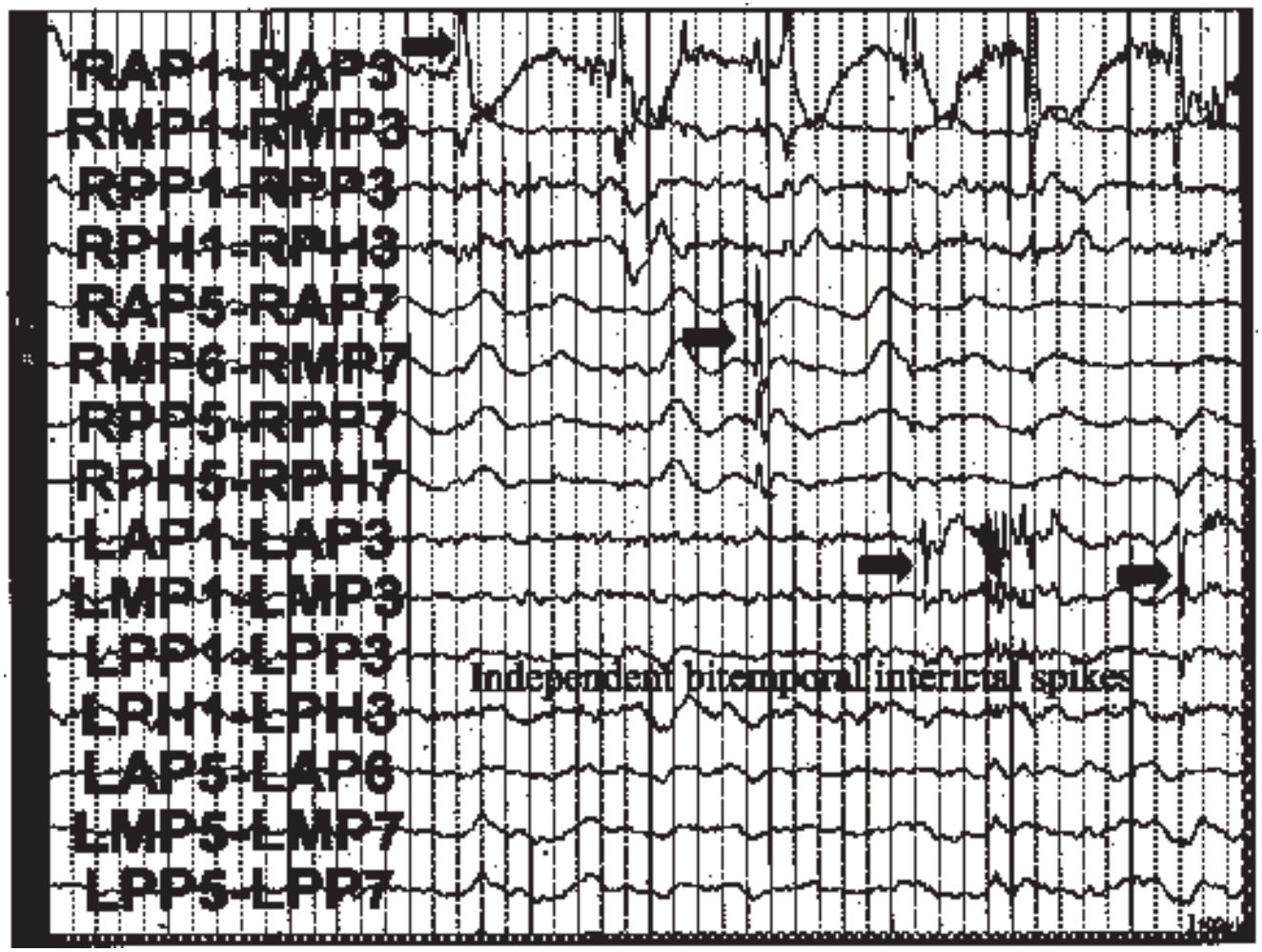

FIG. 20.15. Interictal EEG showing independent asynchronous interictal spikes in right (*R*) mesial and neocortical temporal contacts and left (*L*) mesial temporal depth electrode contacts (*arrows*).

In temporal lobe epilepsy, all patients have interictal spikes on intracranial EEG recording (see Fig. 20.14). Spikes commonly appear bilaterally and independently in the hippocampus, amygdala, and parahippocampal gyrus, and in temporal lobe neocortex (see Fig. 20.15). Negative spikes recorded in the hippocampus are usually not detected by sphenoidal or scalp electrodes (38,55,58). Scalp, nasopharyngeal, and sphenoidal electrodes record from basal temporal neocortex, not from the hippocampus. When a negative spike is seen in the surface EEG, hippocampal electrodes may show no activity, or may show a simultaneous negative or positive component. In the amygdala, a characteristic broad, triangular positive spike is often seen; this is not common in the hippocampus (58). Hippocampal spikes are nearly always asynchronous in mesial temporal lobe epilepsy. The occurrence of synchronous hippocampal spikes is associated with a poor prognosis after temporal lobectomy and suggests a strong possibility of a distant focus (37). In mesial temporal lobe epilepsy, multifocal spikes occur within the hippocampus and amygdala; independent spikes are commonly observed in the amygdala, anterior hippocampus, and posterior hippocampus, along with other widespread "regional" spikes that involve all mesial temporal limbic structures in one hemisphere. In addition, it is common to see interictal spikes occurring independently in other lobes of the brain in patients with temporal lobe epilepsy, especially in the orbitofrontal and cingulate cortex.

Interictal spikes nearly always occur in patients with frontal, parietal, and occipital epilepsies as well (see Figs. 20.12 and 20.13). Both positive and negative spikes and polyspikes can be seen, and their distribution varies from one patient to the next. Multifocal patterns are common, and, even though a structural epileptogenic lesion may be present in one lobe, interictal spikes can be widespread in one or both hemispheres. Interictal spikes are commonly activated by slow-wave sleep and have a reduced rate of occurrence in REM sleep and wakefulness.

Because spikes recorded with intracranial EEG may emanate from a minuscule amount of cortex, a general consensus is lacking with regard to their clinical relevance. It is unclear which types of spike signify the presence of pathological tissue that should be excised. For example, many investigators believe that pseudoperiodic lateralized epileptiform discharge (PLED)-like spikes and spike burst-suppression correlate strongly with the presence of underlying pathological cortex and an epileptogenic zone than do other types of spikes, but few empirical data exist to support this notion. The medical literature does not lend credence to any one interpretation (4,19,39,46,61–63). Fiol and colleagues (19) noted more spikes in the postexcision electrocorticogram in temporal lobectomy patients with recurrent seizures than in those whose seizures stopped. In contrast, Tran et al. (61) and Schwartz et al. (46) found no relation between presence of residual spikes and surgical success. However, no investigators have categorized spikes in a way that might distinguish between different types of discharges (PLED-like, isolated rare spikes, etc.). Lieb et al. (36,37) suggested that some characteristics of hippocampal spikes predict outcome. Spikes with greater autonomy, that is, with less dependence on sleep state and less interspike interval variability, more often indicated the epileptogenic zone than spikes that were less autonomous. The frequency with which spikes occur is a poor predictor of the site of seizure origin or surgical outcome. Lange et al. (33) noted alterations in the spatial organization of limbic spikes shortly before seizures begin, but no interictal spike patterns are yet proven to reliably identify when seizures might occur or their source of origin.

Consequently, most authorities are reluctant to rely on interictal spikes alone for planning surgery. For example, multifocal spikes may be present in patients with well-localized mesial temporal lobe epilepsy who respond to surgery, and interictal spikes may not be present in a location from which seizures arise (26). Hence interictal spikes are probably most useful when considered in conjunction with ictal EEG findings. If most interictal spikes arise from the same area as seizures and other interictal nonepileptiform disturbances, this is *probably* a favorable prognostic sign.

Ictal EEG: Seizures

In the epilepsy surgery patient, intracranial electrodes are mainly placed to record seizures and determine where they begin for purposes of mapping the epileptogenic brain area for resection. Seizures observed with intracranial EEG differ considerably from those recorded with scalp electrodes. A seizure typically only appears in the scalp EEG after it has spread considerably. A larger volume of cortex has been recruited into the seizure, and distant areas, perhaps even in the contralateral hemisphere, may show ictal discharges. Because of lack of filtering by scalp and skull and absence of spatial averaging, discharges with restricted spatial extent, limited voltage, and higher frequencies can be seen, though they were unapparent with scalp electrodes. In

TABLE 20.4. *Seizure characteristics*

Frequency at start of seizure
Location of seizure onset: focal, regional, multilobar, nonlocalized
Propagation routes (pattern and location of spread of ictal discharges)
Latency of spread to other lobes within hemisphere of onset
Latency of spread to contralateral hemisphere
Consistency of localization of seizure onset
Pattern of seizure termination
Location of postictal suppression

many patients, intracranial electrodes show focal seizure onset when extracranial electrodes have not done so. The cortex from which seizures originate often (though not always) harbors pathological changes when examined under the microscope, and excision of this region often results in seizure relief. However, a localized seizure onset in the intracranial EEG does not guarantee a successful surgical result, and a lack of consistently localized seizure onset does not preclude a satisfactory surgical outcome (26,47).

Seizures exhibit diverse features, so much so that one seizure may differ from the next within any particular person (Table 20.4; Figs. 20.16 through 20.25) (1,15,16,24,38,53,58). The electrical pattern usually provides a clear

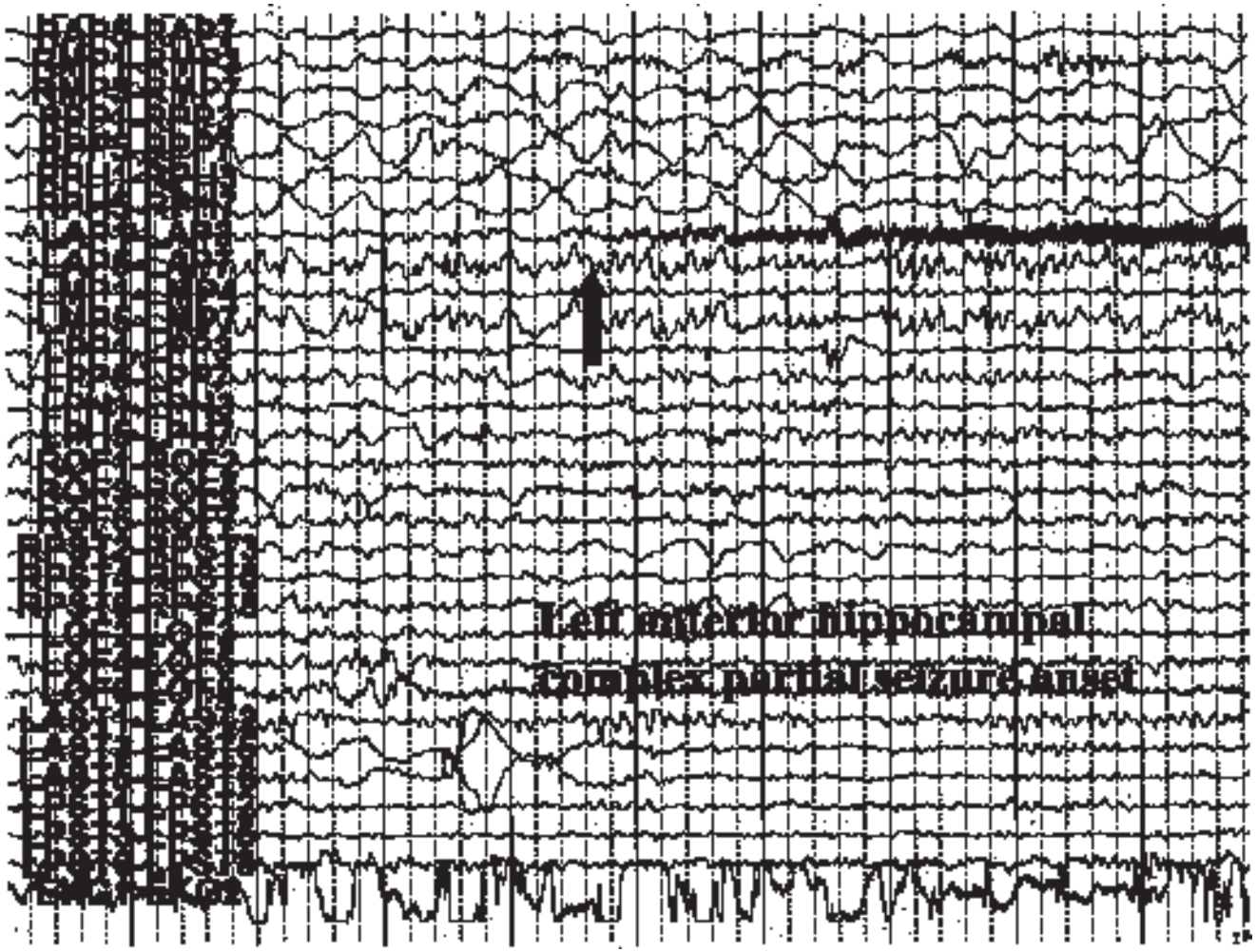

FIG. 20.16. EEG showing focal complex partial seizure onset (*arrow*) in the left anterior hippocampal depth electrode (*LAP*). Note how focal the onset appears, with no involvement of adjacent depth electrode contacts in the middle and posterior hippocampus (*LMP, LPP*) or parahippocampal gyrus (*LPH*), or of left temporal subdural strip electrodes (*LAST, LPST*). Right-sided contacts (all beginning with *R*) are similarly uninvolved.

A

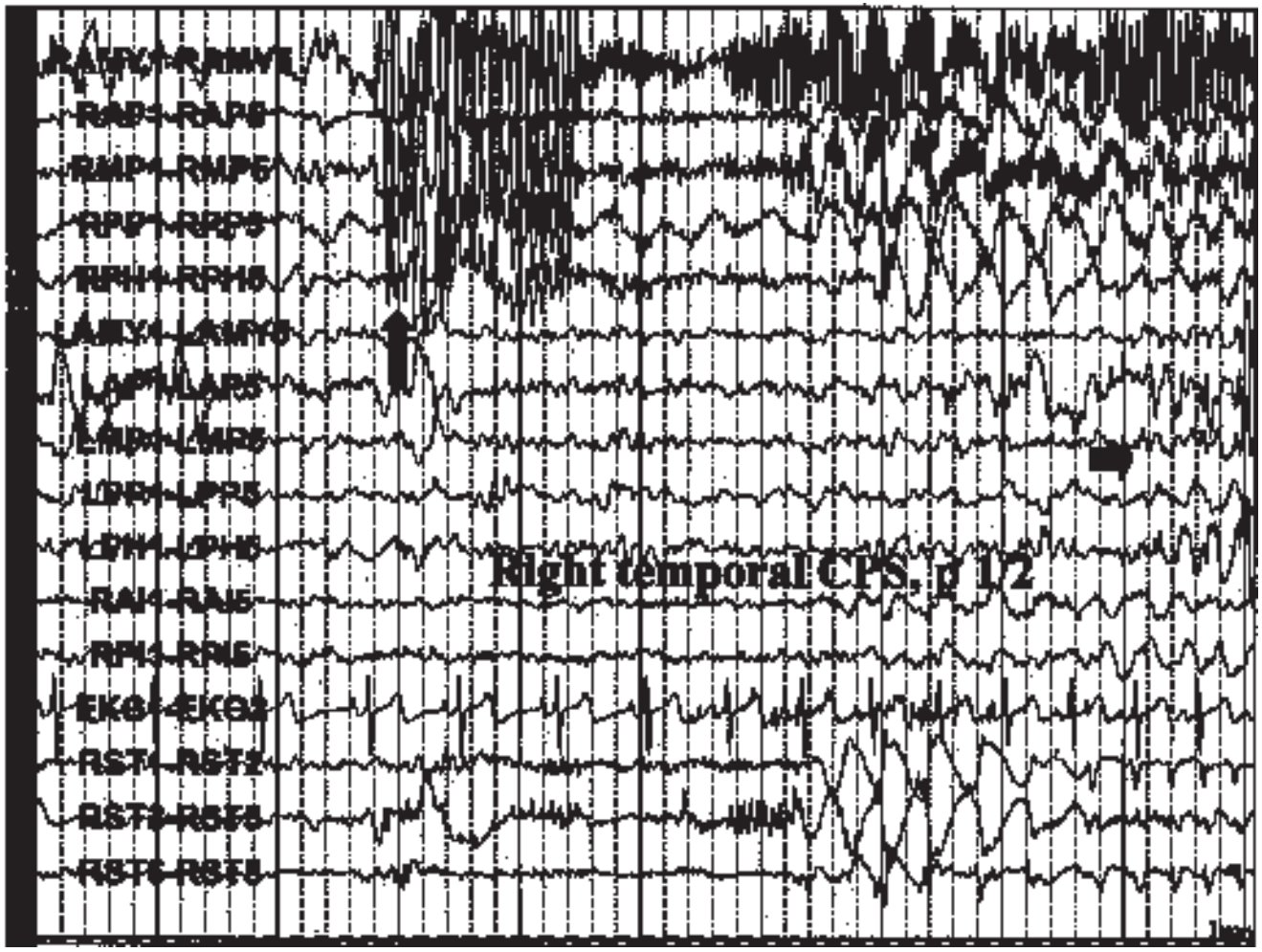

FIG. 20.17. A: Regional limbic complex seizure onset in the right temporal lobe (*vertical arrow*) with high-amplitude fast activity in the amygdala, hippocampus, and parahippocampal gyrus (*RAMY, RAP, RMP, RPP, RPH*) contacts. The subdural contacts beneath the right temporal lobe (*RST*) show the seizure onset nicely as well. The seizure spreads to the left temporal lobe (*horizontal arrow*, right side of figure) approximately 6 seconds after onset, with irregular theta- and alpha-frequency activity. Note the tachycardia that develops in the early seconds of the seizure. *(Figure continues.)*

B

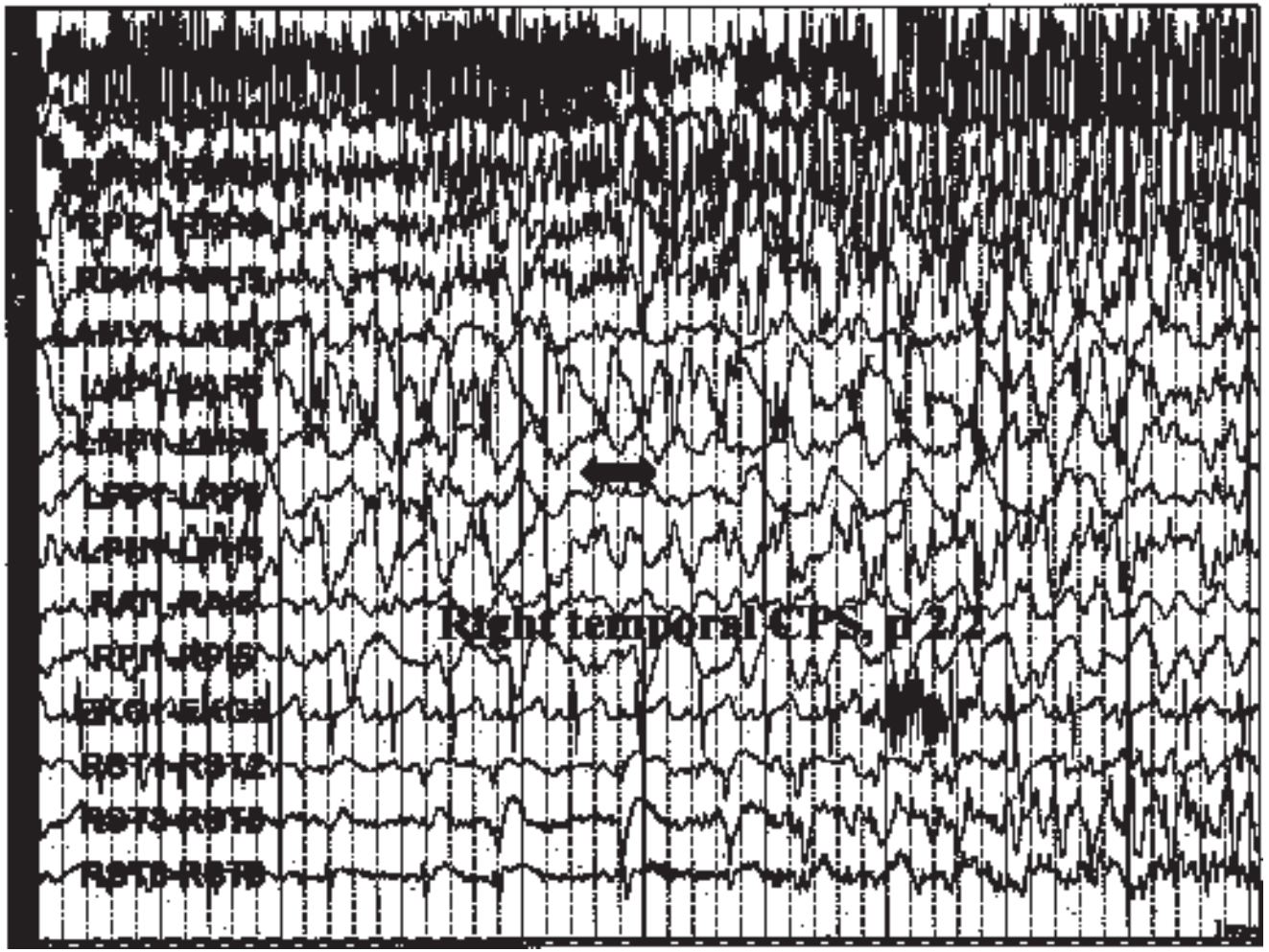

FIG. 20.17. *Continued.* **B:** On the second page of the complex partial seizure recording, note that the right and left temporal lobes are seizing independently with different ictal discharge frequencies. The *arrow* highlights the slow discharge frequency in the left temporal contacts.

A

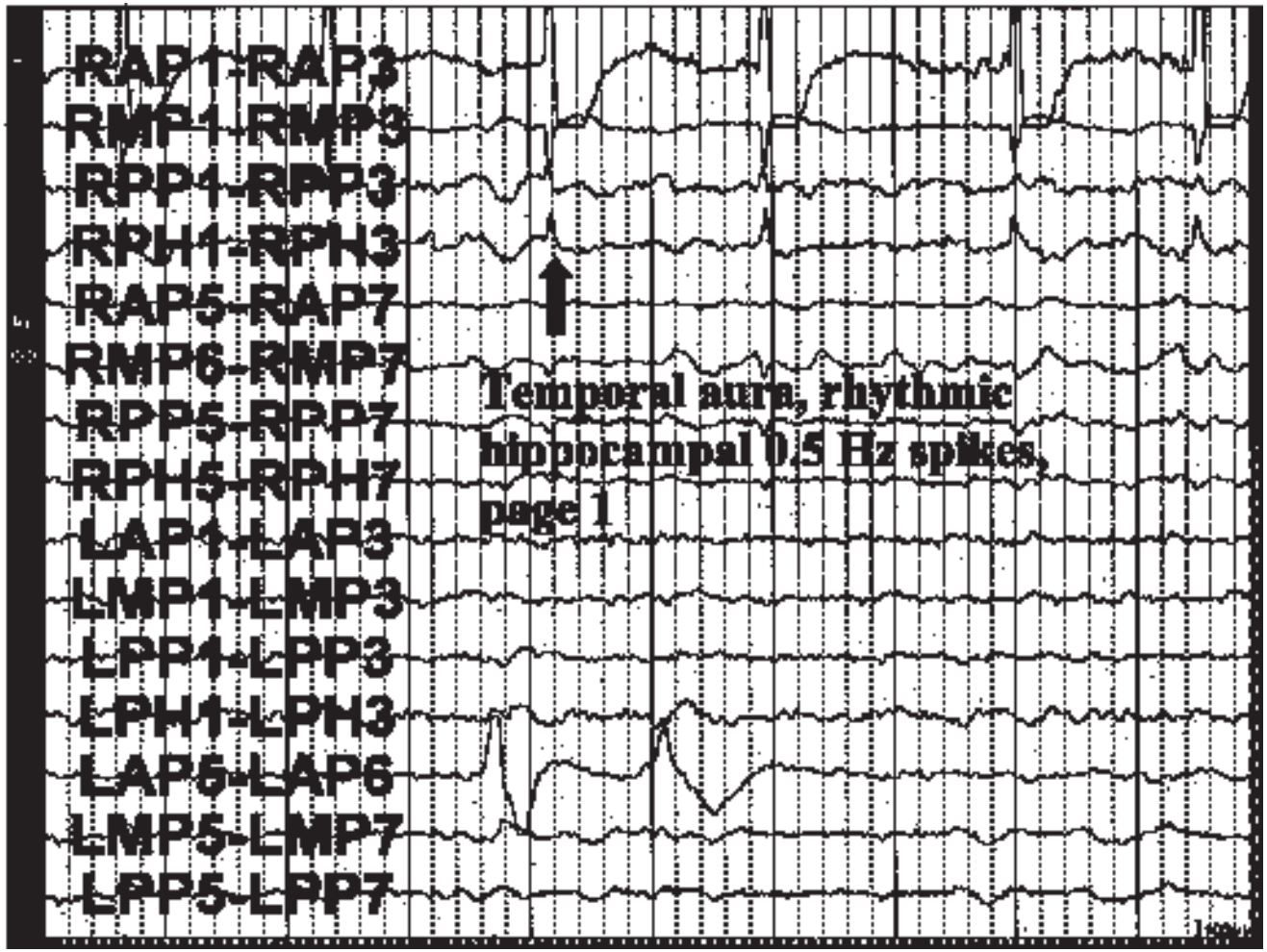

FIG. 20.18. A: EEG showing the beginning of an aura (simple partial seizure) in the right mesial temporal lobe with regional spikes (*arrow*) recurring at a rate of approximately 0.5 Hz. *RAP, RMP, RPP, RPH*, right anterior pes, middle pes, posterior pes hippocampus, and parahippocampal gyrus, respectively. Only the deep contacts of the depth electrode (1–3) are involved in the ictal discharge; the lateral superficial contacts (5–7) are uninvolved. The left-sided electrodes show no ictal activity. The rhythmic spiking was not present prior to the onset of symptoms, and can be considered an ictal pattern in this circumstance because it accompanies a behavioral change and progresses to more obvious ictal activity. *(Figure continues.)*

B

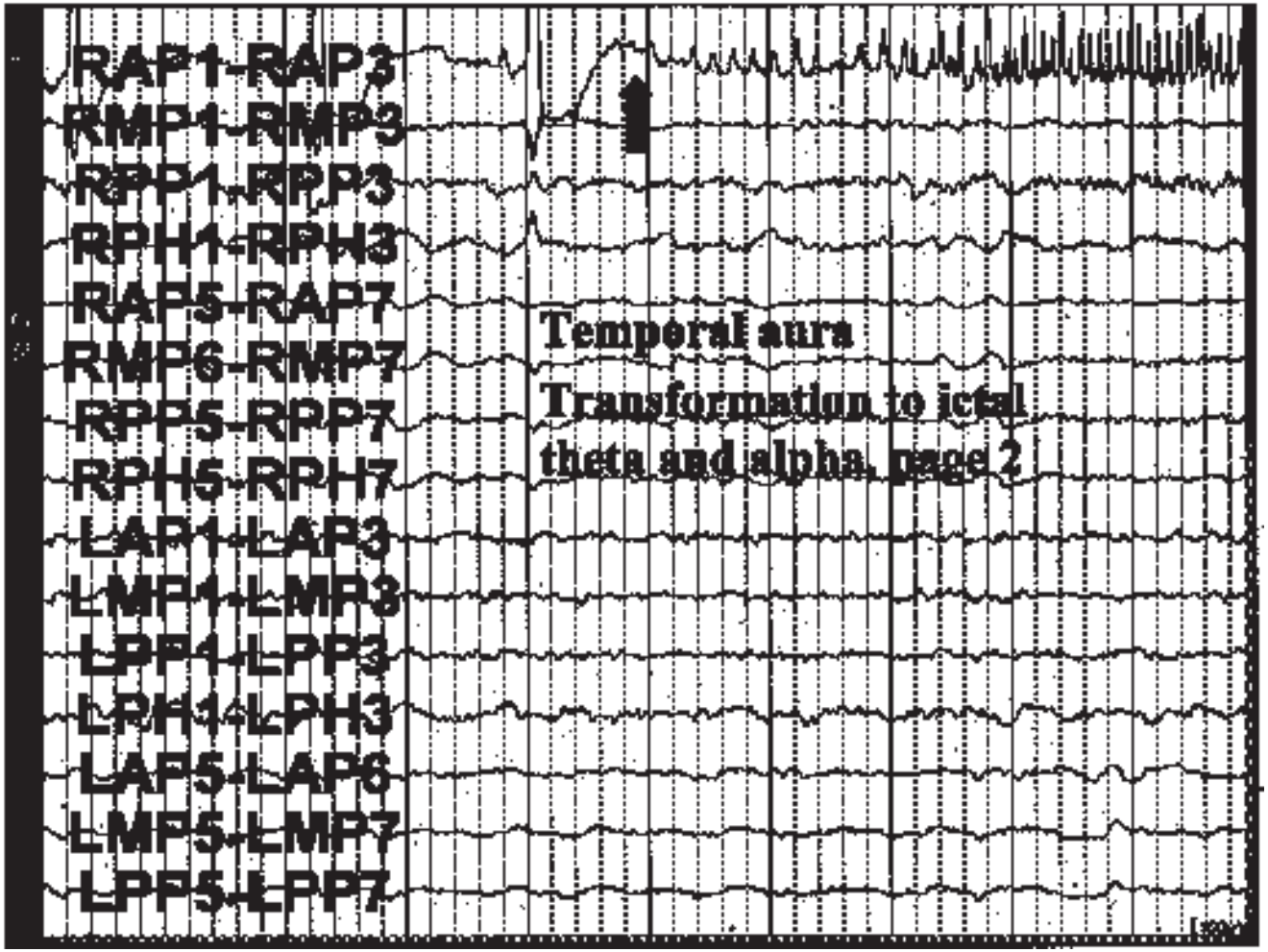

FIG. 20.18. *Continued.* **B:** This second page of the seizure recording shows the transformation from rhythmic spiking to rhythmic theta and alpha activity as the seizure progresses.

A

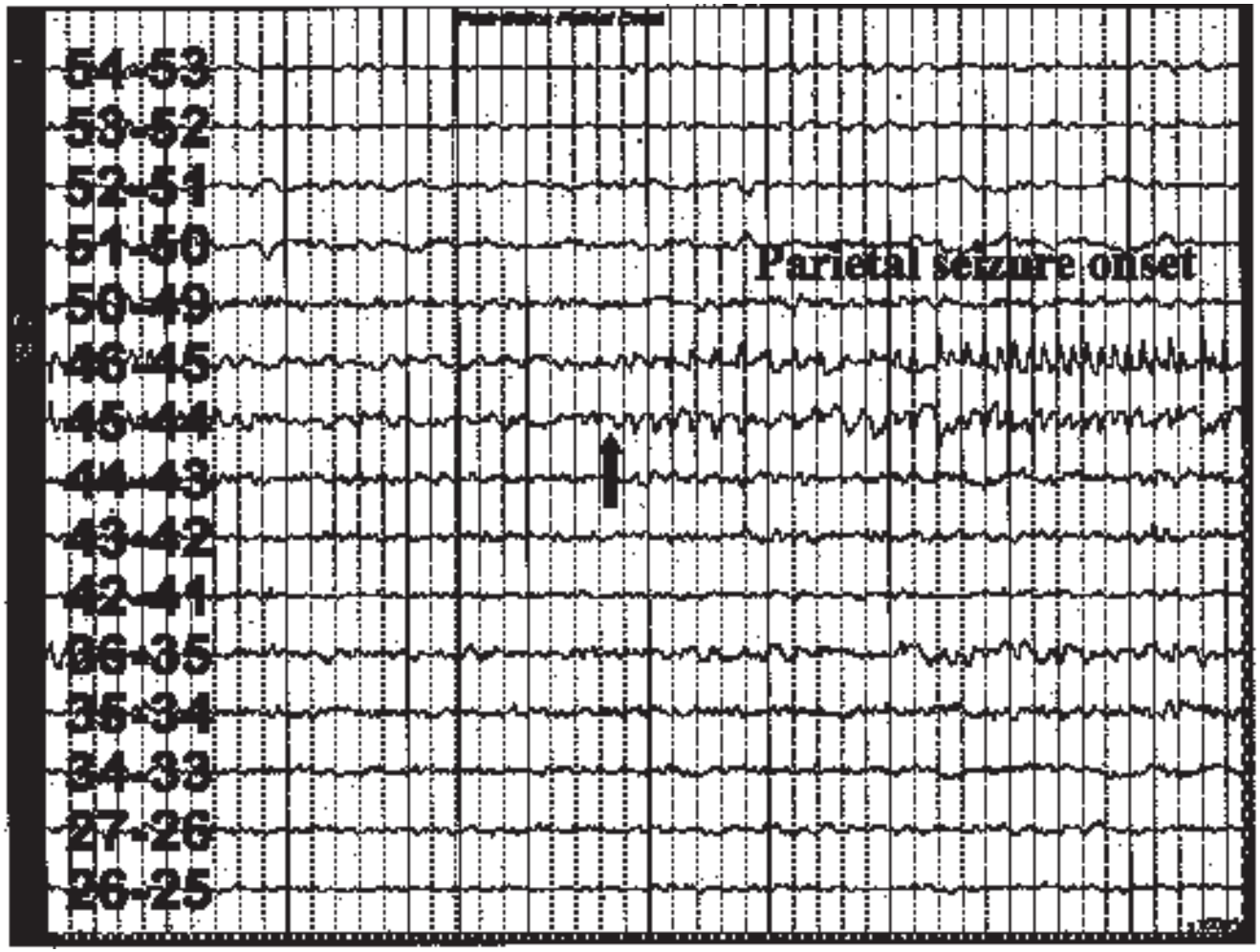

FIG. 20.19. A: EEG showing a parietal seizure beginning in a subdural grid with rhythmic theta-frequency activity (5–6 Hz) (*arrow*) that progressively increases in frequency to 9 Hz. *(Figure continues.)*

B

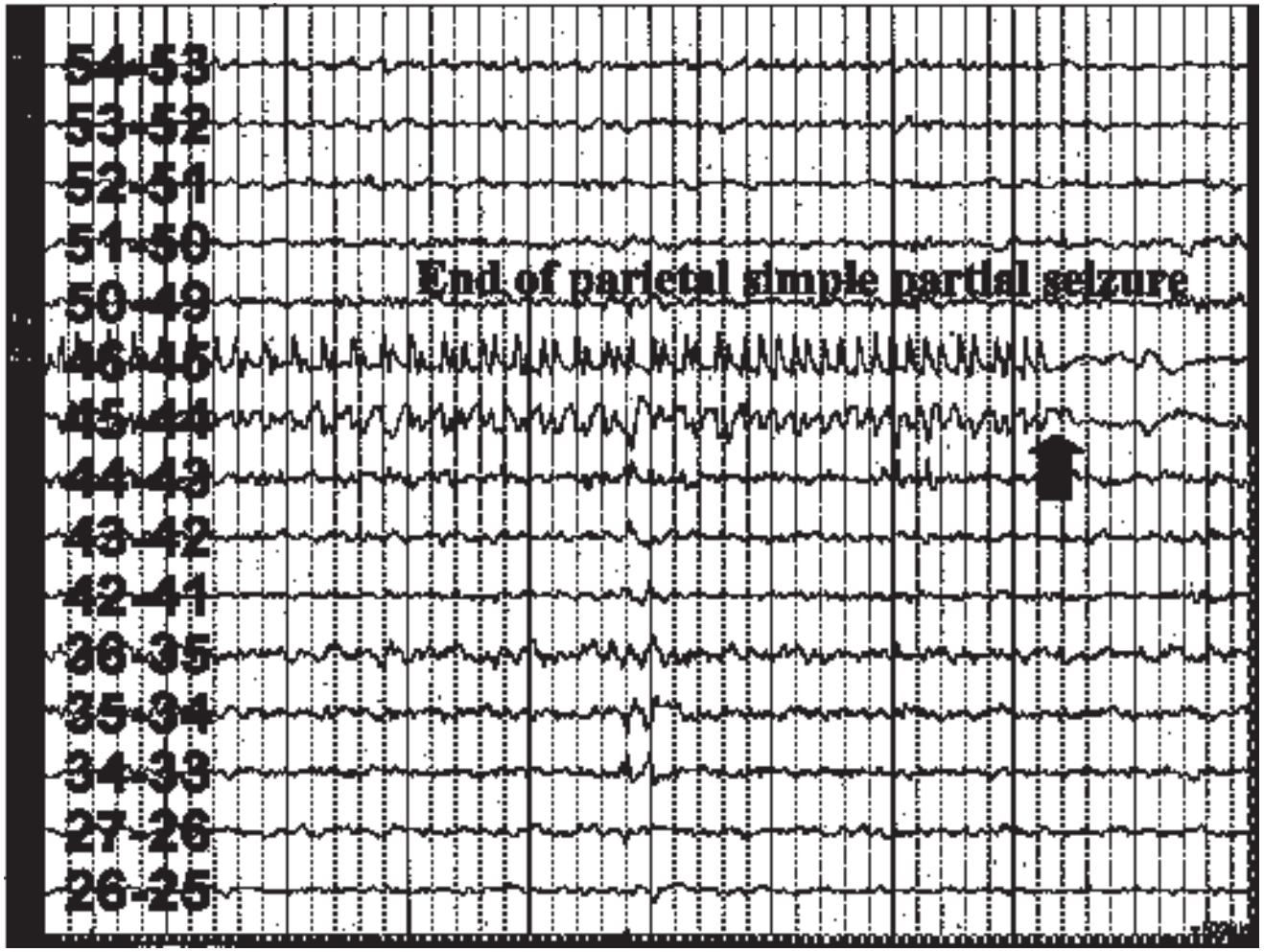

FIG. 20.19. *Continued.* **B:** Second and final 10-second page of the parietal seizure recording shows a slowing and then an increase in ictal frequency prior to seizure termination (*arrow*).

A

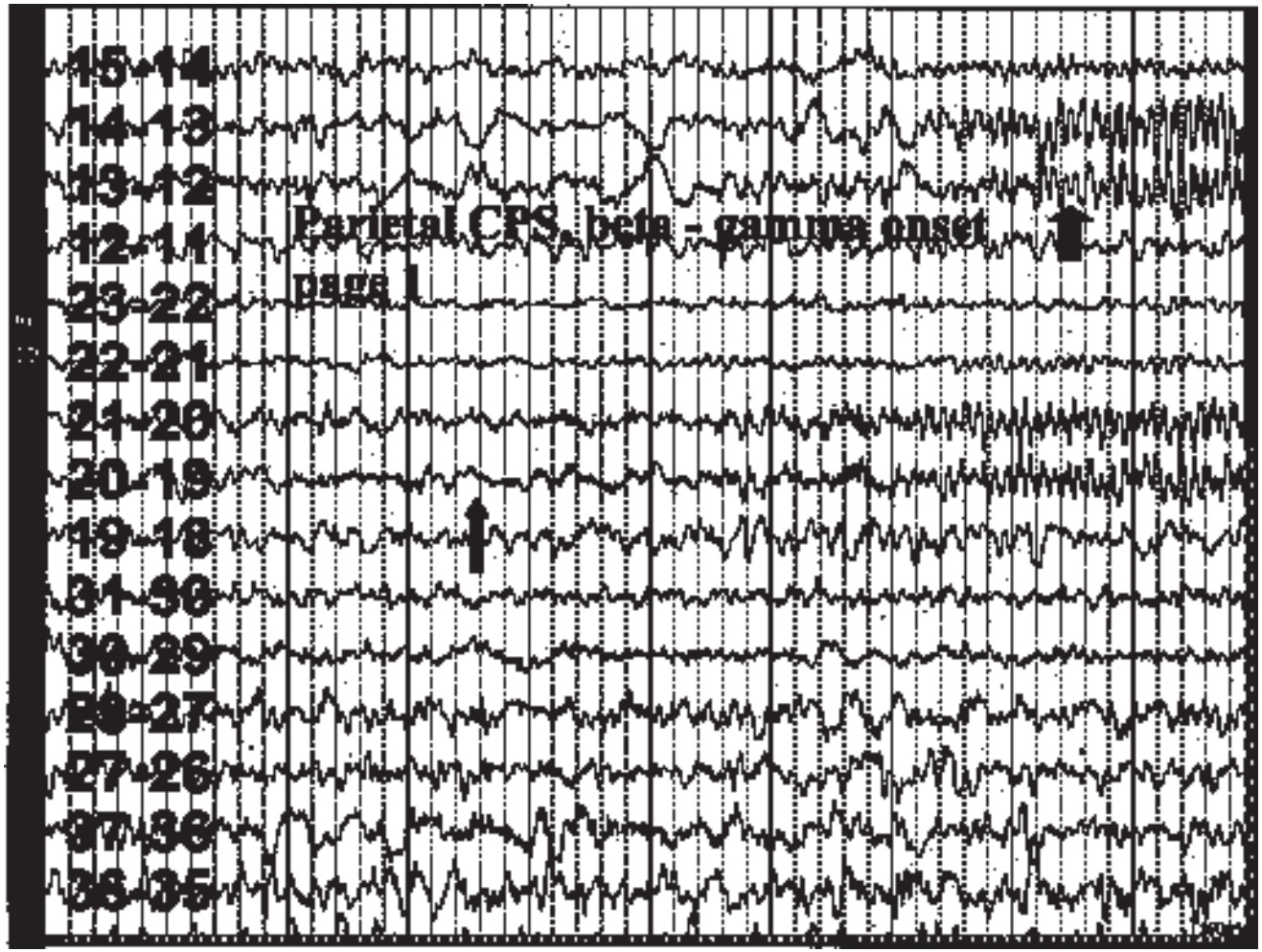

FIG. 20.20. A: This parietal complex partial seizure begins focally with low-amplitude gamma-frequency activity (*thin arrow* on left) in the subdural grid. The seizure slowly spreads through the parietal lobe as it evolves in amplitude and frequency. The pattern, a progressive increase in amplitude and simultaneous decrease in frequency (*thick arrow* on right), is characteristic of many seizures. *(Figure continues.)*

B

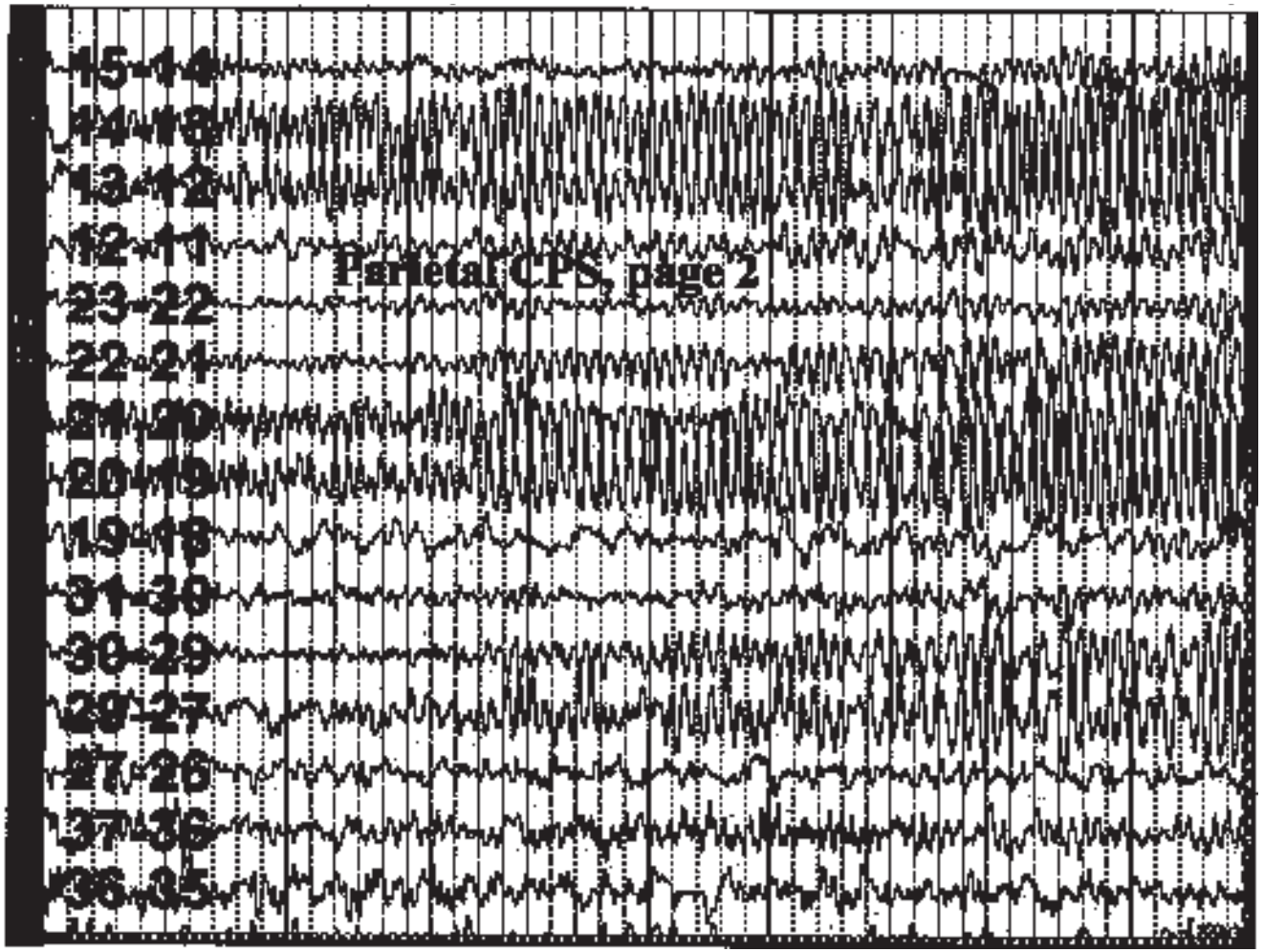

FIG. 20.20. *Continued.* **B:** In the next 10-second epoch during the parietal seizure, note the continuing evolution of amplitude and frequency and the spread of the discharge. *(Figure continues.)*

C

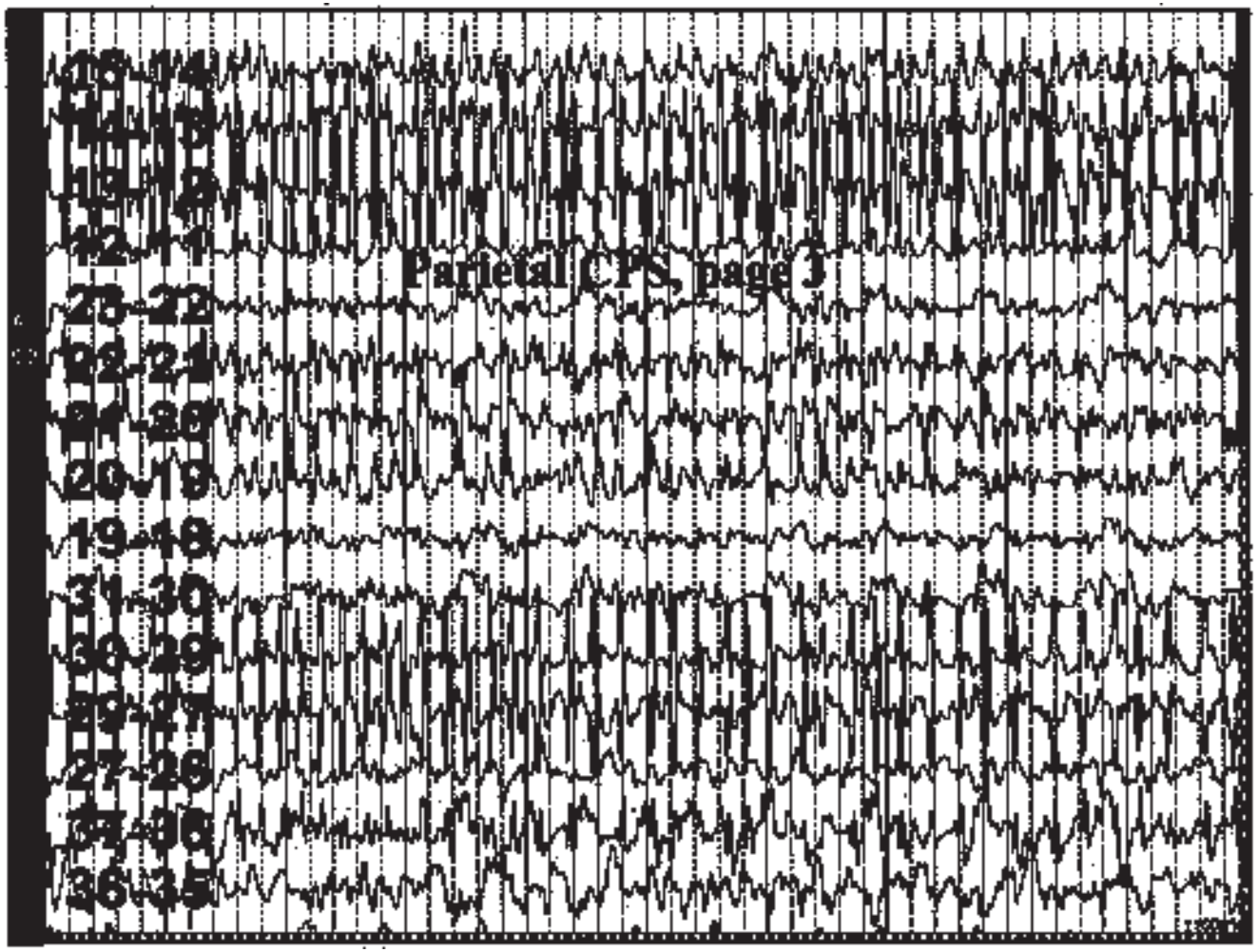

FIG. 20.20. *Continued.* **C:** The seizure continues, changing in electrographic character with less sinusoidal activity and more spike-like activity. *(Figure continues.)*

D

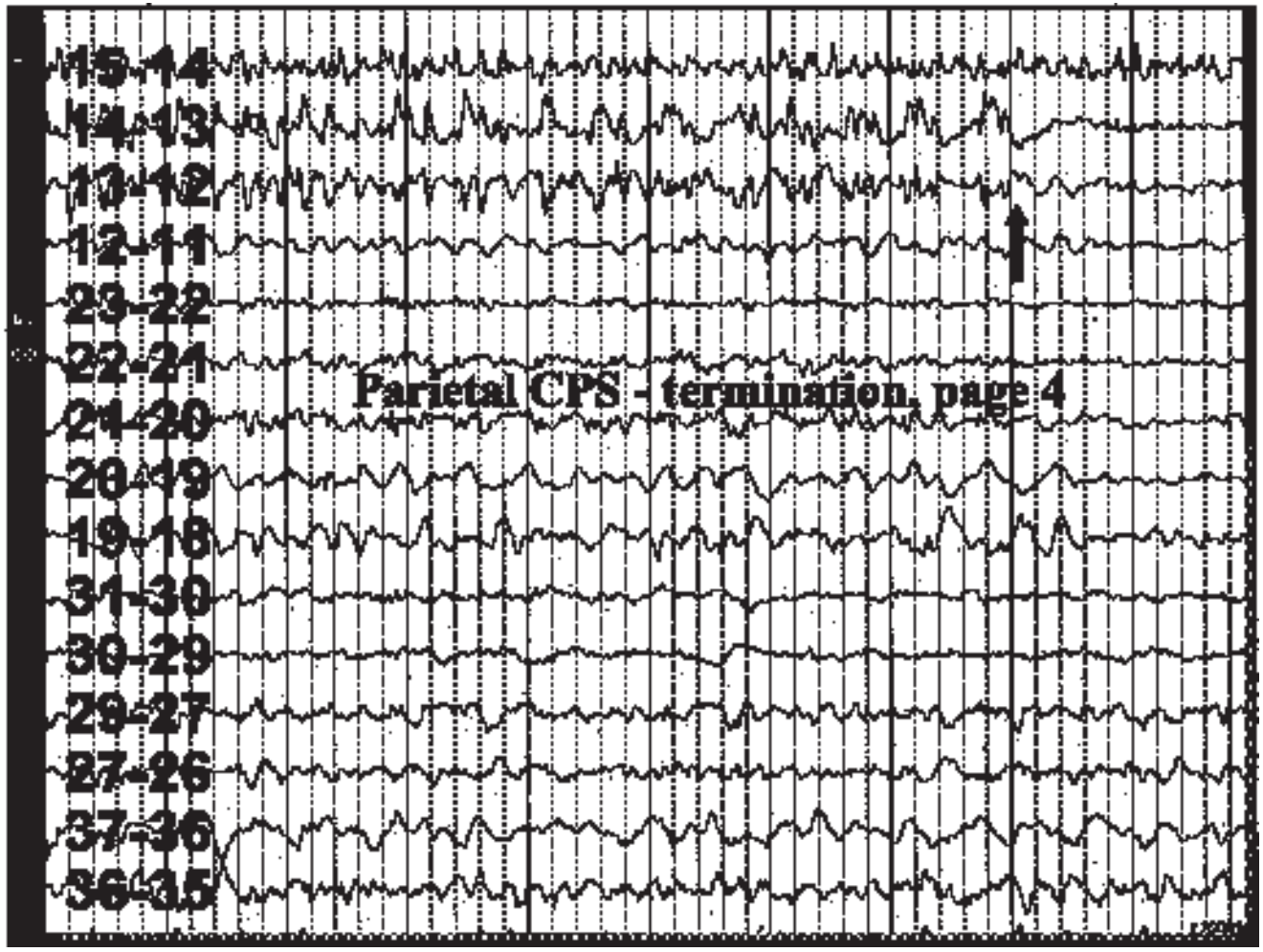

FIG. 20.20. *Continued.* **D:** The seizure gradually slows in frequency of the ictal discharge, and the amplitudes diminish as well. The seizure ends abruptly (*arrow*), terminating focally in contact 13 of the subdural grid.

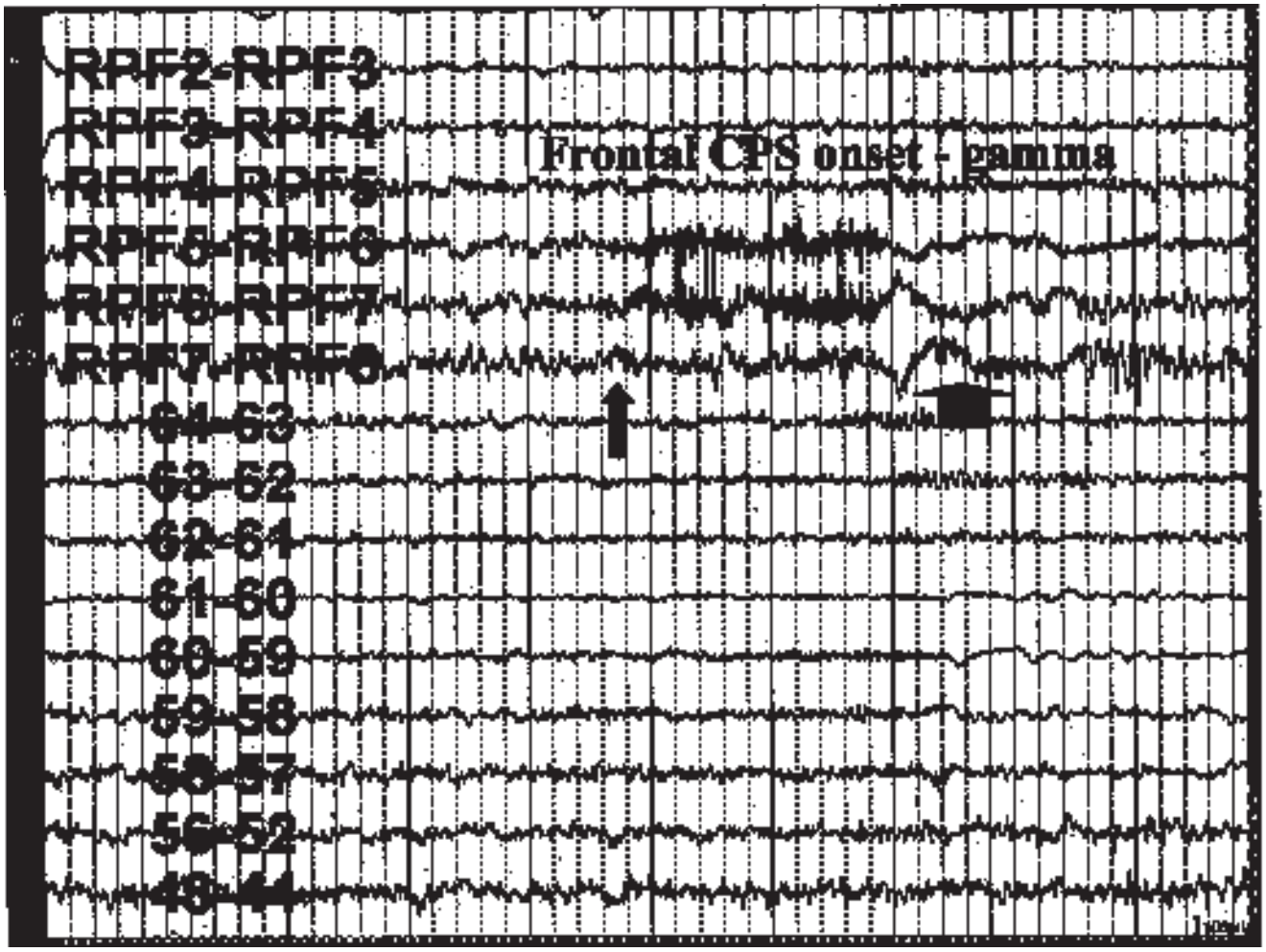

FIG. 20.21. This frontal complex partial seizure begins focally in the right posterior frontal subdural strip electrode (*RPF*) with high-amplitude gamma activity (*left arrow*), with some attenuation of amplitude several seconds after seizure onset (*thick arrow* on right).

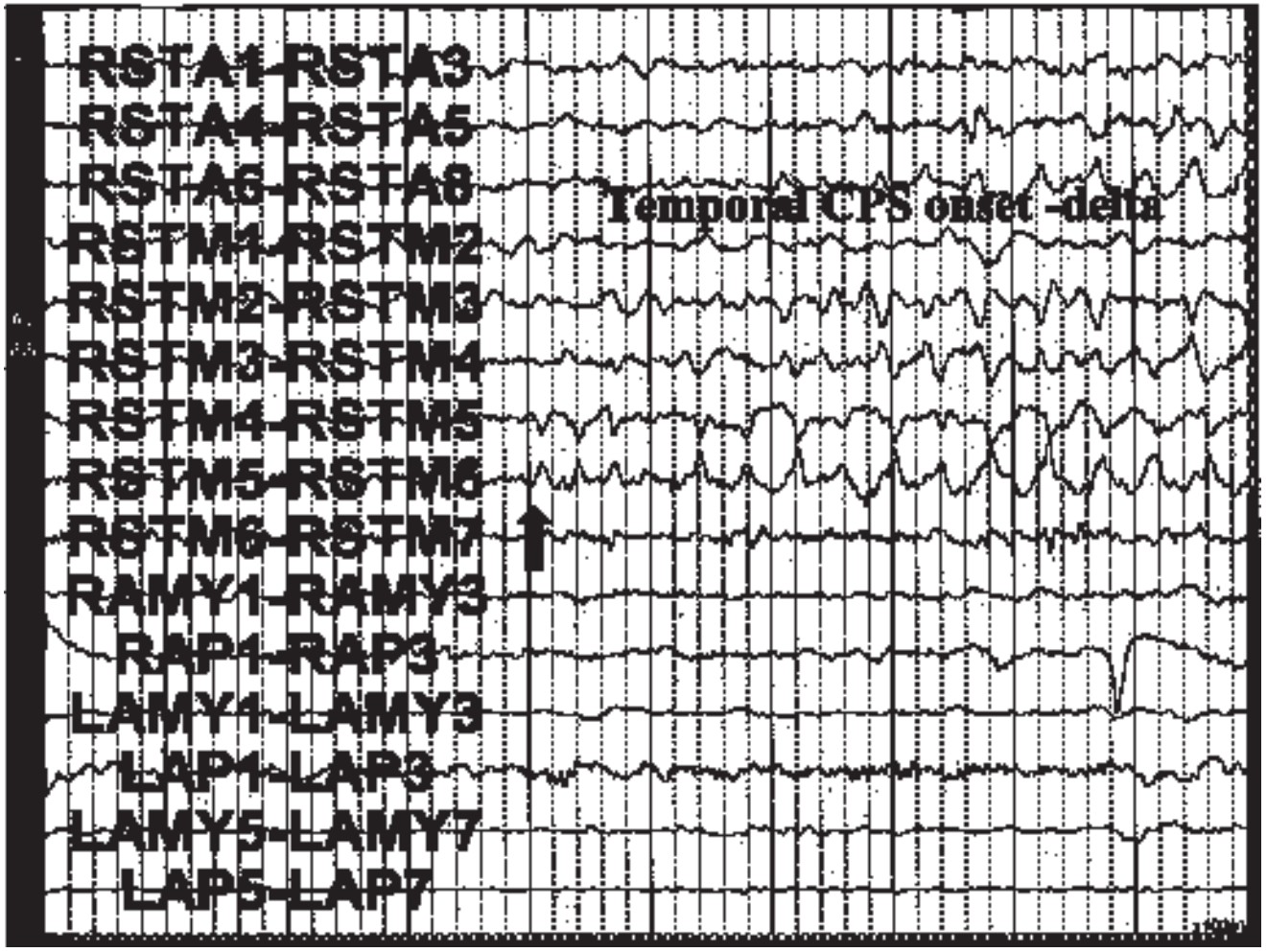

FIG. 20.22. This neocortical temporal lobe seizure begins with focal delta activity (*arrow*) in the middle subtemporal subdural strip contact 5 (*RSTM*), with semirhythmic delta-frequency activity. It spreads to other contacts in the same strip and the adjacent anterior temporal strip (*RSTA*) over the next few seconds. There is no spread to left-sided temporal lobe electrode contacts (beginning with *L*).

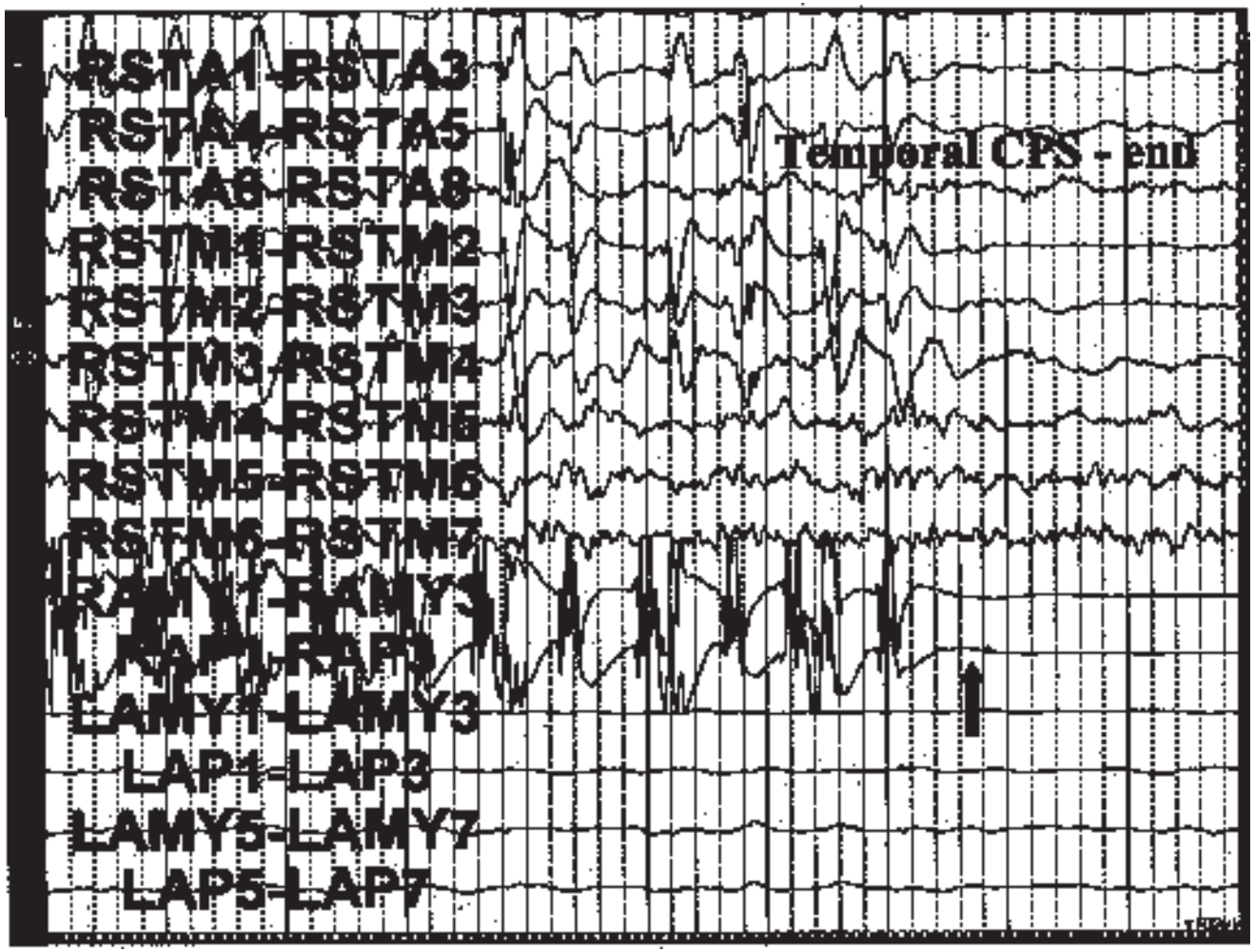

FIG. 20.23. Termination (arrow) of a temporal lobe complex partial seizure with focal suppression of activity in the right amygdala and hippocampus (*RAMY, RAP*) contacts. Other right temporal subdural contacts (*RSTA, RSTM*) show prominent slow waves but not the degree of suppression present in limbic structures. Left-sided temporal lobe depth electrode contacts (beginning with *L*) also register marked attenuation of background activity. This suppression usually lasts for 10 seconds to several minutes.

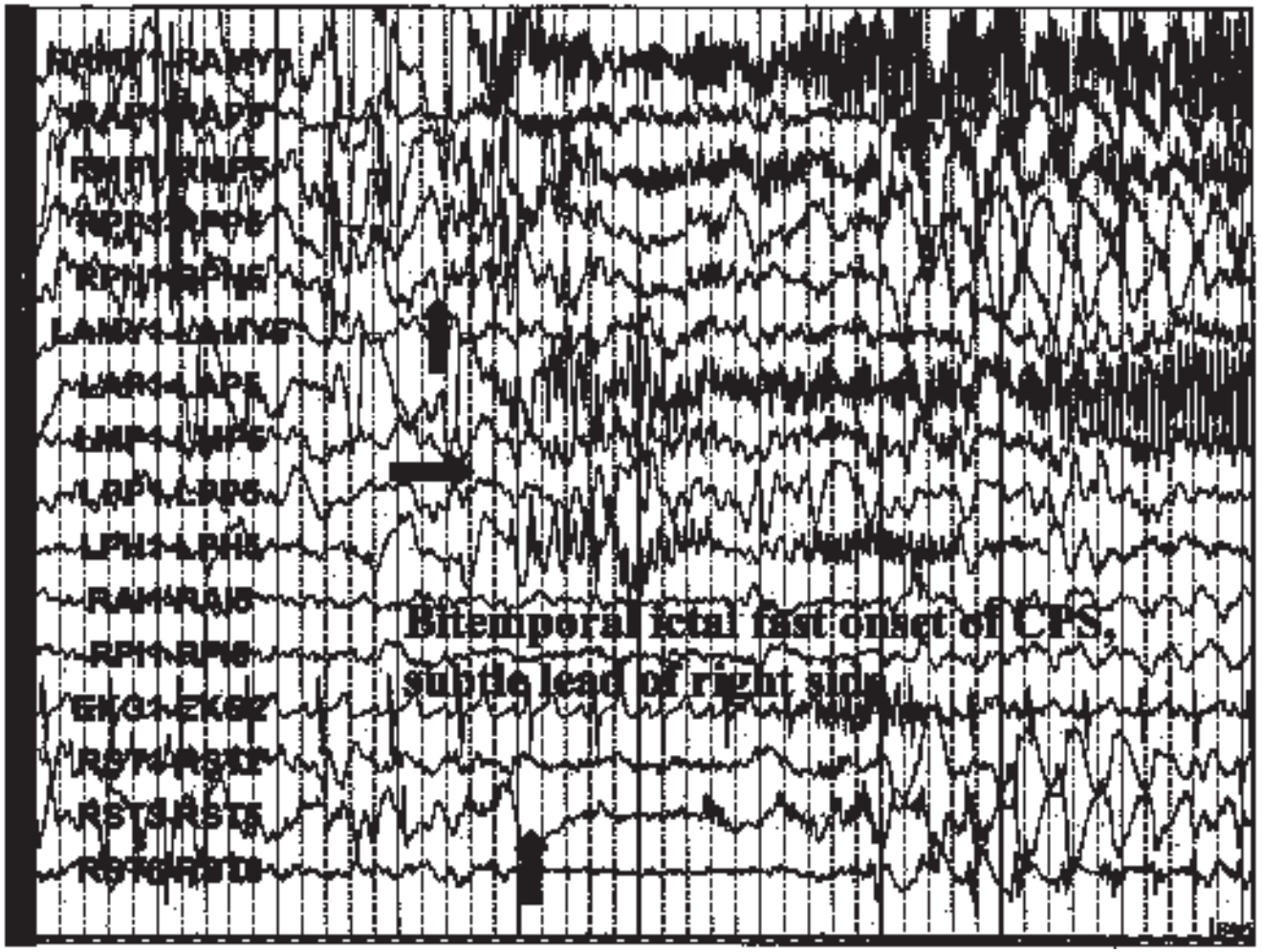

FIG. 20.24. EEG showing nearly synchronous complex partial seizure onset in both temporal lobes. The right temporal lobe depth electrodes show the earliest activity (*upper vertical arrow*), but ictal fast activity appears within 1 second in the left temporal lobe depth electrode contacts (*horizontal arrow*). The right temporal subdural strip contacts show seizure onset slightly later (*bottom arrow*) than the right-sided depth electrodes. This patient had some seizures with a 6- to 9-second interhemispheric propagation delay, and others with rapid spread as shown here. A right temporal lobectomy was performed. Although much reduced in frequency, the seizures have continued.

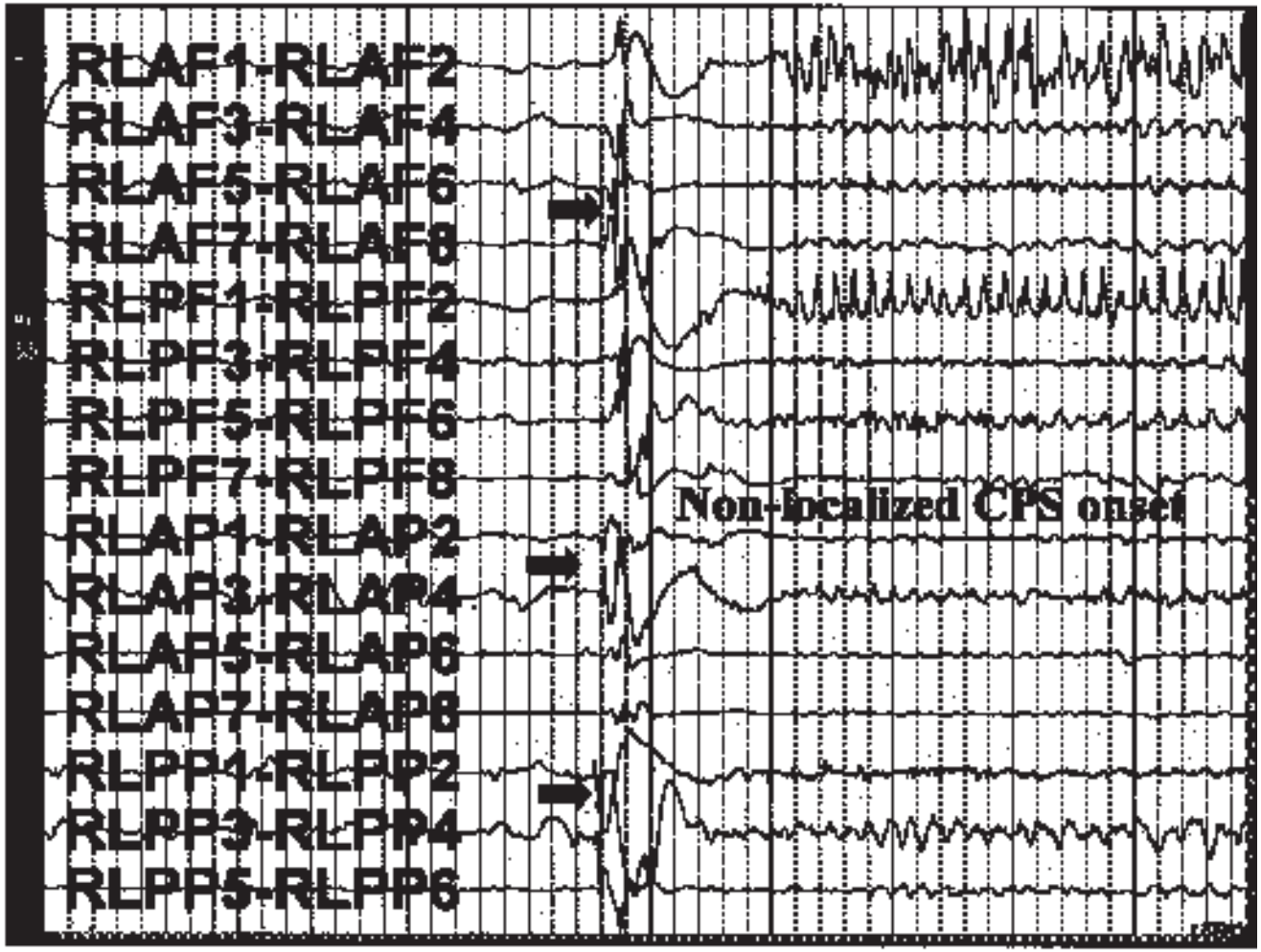

FIG. 20.25. Multilobar nonlocalized complex partial seizure onset in a patient with Rasmussen's encephalitis. Nearly simultaneous seizure onset is seen in the right frontal (*RLAF, RLPF*) and parietal (*RLAP, RLPP*) lobes (*arrows*). Although this seizure appears to start perhaps 20 milliseconds earlier than elsewhere in the posterior parietal subdural strip electrode (*RLPP*), other seizures appeared slightly earlier in the other strips. There was no clear predominant site of earliest seizure onset.

sign that the seizure is partial and not generalized. Partial seizures may begin at any frequency (delta, theta, alpha, beta, or gamma), sometimes preceded by an increase or decrease in the interictal spike rate, whereas generalized seizures begin with a generalized spike-and-wave, polyspike-and-wave, sharp-wave, slow-wave, or diffuse desynchronization pattern (see Figs. 20.16 through 20.22). Nearly all data are derived from patients with partial seizures, because intracranial electrode implantation is appropriately restricted to patients who are potential surgical candidates. The typical EEG pattern is one of varying ictal frequency that evolves during the course of the seizure (see Figs. 20.17 through 20.20), subtle or prominent lateralized amplitude maxima during different portions of the seizure, and postictal slowing or suppression of background frequencies (see Figs. 20.19*B*, 20.20*D*, and 20.23). At times, the beginning or the end of the seizure is not clearly delineated. Subtle changes may develop in the EEG over several seconds or more, and the precise moment of seizure onset or offset cannot be established. Sometimes, seizures appear to start and then stop 5–30 seconds later, only to resume a few seconds later in the same region or elsewhere.

Hippocampal seizures can begin in many ways (see Figs. 20.16 through 20.18) (20,32,40,41,45,48,49,53,60). They often commence with a burst of spikes followed by paroxysmal alpha- or beta-frequency activity of either high or low amplitude. It has been suggested that mesial temporal lobe seizures more often begin with 10- to 16-Hz frequencies, whereas neocortical seizures combine slower (4–10 Hz) and faster (40–50 Hz) frequencies (48). However, seizures of any type arising in any location can begin with any frequency; low-frequency onsets are seen in the hippocampus, and neocortical seizures can begin with frequencies up to 200 Hz (20). It is uncertain whether the frequency of the initial ictal discharge correlates with underlying pathology (48,49,60).

Neocortical seizures usually start with a low-voltage, high-frequency discharge, which may be accompanied by a focal or more widespread electrodecremental response (see Figs. 20.19 through 20.22) (32,40). There is sometimes a localized increase in power at frequencies above 40 Hz hidden within a more broadly distributed electrodecremental response; this localized area may indicate the site of seizure origin (20). However, many neocortical seizures start with slower frequency discharges or focal repetitive spiking that may or may not be well localized. The surface EEG pattern in neocortical seizures, similar to that of hippocampal seizures, reflects propagation and buildup of the ictal discharge rather than seizure onset (40).

Many partial seizures have an obvious focal onset in the intracranial EEG, but this is not a constant feature (see Figs. 20.24 and 20.25). Some partial seizures spread so rapidly that conventional EEG recording methods cannot reliably detect the localized ictal onset. In these cases, the earliest observed ictal changes may appear in more than one lobe of the brain, or in both hemispheres. Seizures recorded from the hippocampus may begin focally in just the anterior hippocampus, or regionally within the entire hippocampus and amygdala (13,16,21,22,35,48,53,58). Seizures that start in the neocortex display varying spatial extent at onset. They may begin in a restricted area of cortex and spread slowly or rapidly, or appear at once in more than one lobe of the brain.

Seizures commonly spread to other regions of the brain, and the extent of propagation determines the clinical behavior exhibited during a seizure. Some seizures remain confined to the cortex in which they begin and produce no symptoms (57). Other seizures may propagate within a single lobe or hemisphere; with unilateral spread, consciousness is generally preserved. When seizures propagate to the contralateral hemisphere, consciousness is nearly always impaired; the rare exception consists of mesial frontal or parietal seizures that remain restricted to the mesial cortex. Secondary generalization occurs as a consequence not only of widespread activation of cortex in both hemispheres and substantial subcortical activation, in both the diencephalon and midbrain.

Intracranial electrodes may be used to study propagation patterns, which relate to prognosis (51). Seizures can be assessed visually or with computer analysis (23,35). Most mesial temporal lobe seizures first propagate to ipsilateral temporal or orbitofrontal cortex, and thence to the contralateral hemisphere, presumably via the corpus callosum. Other propagation patterns occur; for example, some hippocampal seizures spread to the other hemisphere via the hippocampal commissure. Long interhemispheric propagation times predict a better prognosis after anterior temporal lobectomy, whereas short interhemispheric propagation times, particularly those less than 5 seconds, are associated with postoperative seizure recurrence (10, 34,35). Some seizures spread explosively throughout both hemispheres and cannot be localized. The patterns with which seizures stop are of interest, but there is no agreement as to whether they correlate with prognosis after surgery (7,50).

Depth electrodes have a particular advantage when recording hippocampal seizures. They are positioned to detect seizure onset earlier than other electrode types (see Fig. 20.16). Hippocampal electrodes detect seizure onset 30 seconds earlier on average than subdural electrodes in patients with mesial temporal lobe epilepsy (8,56). Because some seizures propagate rapidly throughout both hemispheres once they leave the hippocampus,

using depth electrodes offers a major advantage. Several investigators have reported that, because of rapid seizure spread, depth electrodes were needed to identify that seizures began in one hippocampus; had only subdural electrodes been used, localization would not have been possible (5,8,40,56). In several patients, spread of ictal activity from one hippocampus to the contralateral temporal lobe neocortex led to the conclusion that seizure onset would have been incorrectly localized by subdural electrodes (8,56,58). It should be emphasized that subdural and depth electrodes usually lead to the same diagnosis in patients with mesial temporal lobe epilepsy (see Fig. 20.17*A*). Nonetheless, because of the potential for inaccurate localization, the literature supports investigating patients suspected of having temporal lobe epilepsy with both depth and subdural electrodes to maximize the chances of making a correct diagnosis.

When planning to study patients with neocortical epilepsy, whether from the temporal lobe or elsewhere, subdural electrodes offer more comprehensive and versatile recording characteristics. Depth electrodes are not well suited to neocortical seizures. Because of limited sampling, they are more likely to detect propagated ictal discharges. Subdural electrodes also are better suited to electrical stimulation, a task sometimes required prior to epilepsy surgery.

INTRACRANIAL EEG INTERPRETATION

Intracranial EEG recording has been demonstrated to be worthwhile in two ways. First, intracranial EEG reveals epileptogenic cortex that is not apparent by any other testing, permitting surgery that otherwise could not be offered. Second, information gleaned during an intracranial EEG recording session can make it clear that an operation should be avoided, thereby sparing some patients unnecessary resection of brain tissue.

How is the intracranial EEG used to make a surgical decision? In the optimal surgical candidate, the intracranial EEG shows seizures that consistently arise in one location and concordant interictal EEG disturbances. If seizures cannot be localized or are multifocal, then surgery might be inadvisable. However, an ambiguous intracranial EEG evaluation sometimes still leads to a good surgical result. For example, some patients with bitemporal seizures stop having seizures after temporal lobectomy, and excising a structural lesion appears to be the major factor that predicts success (9,10,26,47).

Much must be learned to more effectively employ the intracranial EEG. How many and what types of seizures should be recorded? How should the different aspects of the interictal and ictal EEG be weighed to make the best clinical decision? Most epileptologists try to record at least several typical seizures, but clinical practice varies, and practical considerations (limited monitoring time) may prevent the gathering of all desired data. As discussed above, the interictal abnormalities are even more problematic. Human intuition and insight have triumphed in spite of these deficiencies, but the deficiencies still need remedy.

To assess the usefulness of a technique, one must also assess its yield. Unfortunately, the yield of intracranial EEG is difficult to determine. This depends largely on patient selection, which itself relies on referral patterns, physician judgment and experience, and the availability and sophistication of noninvasive testing methods. Because noninvasive methods provide sufficient information to offer surgery without intracranial electrodes in most individuals (10,17), intracranial EEG is used only in complicated patients with reduced chances of a successful outcome. Despite these biases, most intracranial EEG evaluations lead to a therapeutic procedure, although success rates are somewhat lower than in patients offered surgery on the basis of noninvasive testing alone (10).

A remaining challenge is to integrate intracranial EEG data with other clinical information. Interictal and ictal EEG findings must be interpreted in light of functional deficits (alteration of metabolism, blood flow, cognitive changes), structural lesions, and the clinical symptoms. The intracranial EEG does not proffer better information than noninvasive methods, it merely offers additional information that can be put to better use.

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Chapter 21

Intraoperative Electrocorticography

Gian-Emilio Chatrian

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Electrocorticography (ECoG), the method of recording electrical potentials directly from the cerebral cortex, was pioneered in humans by Hans Berger, who endeavored to validate the cerebral origin of the scalp electroencephalogram (EEG) by demonstrating that this activity could also be recorded over skull defects (25) as well as with a needle inserted through the cortex and underlying white matter in a patient with a distant brain tumor (26). Subsequent studies confirmed Berger's findings and found that brain tumors caused alterations of electrocerebral activity that contributed to their localization (3,23,96,269,271,320). During the 1940s and 1950s, direct brain recordings became established primarily as aids in the diagnosis and surgery of chronic, medically intractable partial (focal, localization-related) (60) epilepsies (6,124,142,143,148,160,210,234,314).

However, the preeminence of intraoperative ECoG in localizing epileptogenic brain tissue and guiding its removal was soon challenged by increas-

ing sophistication of preoperative electrophysiological studies using noninvasive as well as variously invasive electrodes (20,248,294,297,332). The introduction of prolonged video-EEG monitoring (172) with computer-assisted seizure detection (120) allowed detailed analysis of spontaneous electrographic and clinical seizure patterns only rarely apparent in intraoperative recordings. In most centers, invasive recordings of ictal events and mapping of functionally important cortex by electrical stimulation (151) became the cornerstone of the preoperative examination of most patients suffering from medically intractable partial epilepsies. Neuropsychological (225,261) and intracarotid amobarbital testing (153) complemented these studies. During the 1990s, rapid progress in structural and functional neuroimaging, especially high-resolution magnetic resonance imaging (MRI) (41,131), added a new dimension to the localization of partial epilepsies by revealing previously elusive structural lesions associated with local epileptogenesis. This progress diminished the need for both invasive preoperative studies and the intraoperative ECoG. This chapter reappraises traditional technical and interpretive principles of intraoperative ECoG and highlights controversial aspects and promising developments of this method in the context of current diverse approaches to the surgical treatment of chronic, medically intractable epilepsies.

TECHNIQUE

Electrodes

ECoG electrodes (7) must be capable of detecting the electrical activity of cerebral cortex exposed by the craniotomy as well as that of remote cortical and subcortical areas within the hemisphere undergoing surgery. Until recently, electrode-holder assemblies, or "ECoG sets," have been used (Fig. 21.1); these sets typically incorporate insulated, malleable silver wires whose distal ends terminate with a carbon ball (266) that makes contact with the exposed cortex. The proximal ends of the wires are connected by coiled springs to thin stainless steel rods, which are mounted on the universal ball joints of a holder clamped to the bone edge of the craniotomy. A cable from these joints leads to the inputs of the recording system. The surgeon applies the ECoG electrodes on the exposed cortex, which provides flexibility of electrode placement, ease of identification of individual electrode locations, and clear observation and photography of the operative field, where sites of special interest are marked by small lettered or numbered tags (7). However, these electrodes are limited in number, difficult to align in straight arrays at strictly equal distances as required by mapping studies, and unsuitable for surveying inferior and medial hemispheric surfaces.

An alternative technique that is most often used today utilizes variously shaped assemblies of 4–64 or more small platinum–iridium or stainless steel disk electrodes embedded usually 10 or 15 mm apart in soft, flexible, clear silicone plastic (Silastic) sheets (337). These "strips" or "grids" can be laid over the exposed cortex or introduced from the edges of the craniotomy over or under lateral, inferior, and medial cortical regions, and can be directly stimulated. Grids containing large numbers of equally spaced electrodes are ideally suited for detailed computer-aided mapping of epileptiform discharges and evoked potentials. However, they limit surgical manipulation as well as visual appreciation of the relationships of individual electrodes to the underlying gyri, especially when they are weighted down with cotton strips imbued with saline solution to assure good electrode contacts. Thus, during cortical resections, it is sometimes necessary practice to use both holder-supported electrodes to record from the exposed cortex and strip and grid electrodes to explore more remote cortical areas (307,308). During some surgeries, single- or multicontact "depth" needle electrodes are also introduced into otherwise inaccessible brain regions (75,108,123,148,160,239,298).

Reference leads used for intraoperative brain recordings include two interconnected electrodes on both sides of the neck (307,308), an EEG electrode over the spinous process of the C7 vertebra (108) or on the bone flap distant from the active area (229), or an alligator clip attached to a muscle near the edge of the craniotomy. Grounding of the patient is commonly provided by a metal clamp attached to the post of the electrode holder or the bone edge of the craniotomy. ECoG electrode sets require cleaning and appropriate sterilization after each surgery to prevent transmission of agents highly resistant to decontamination, whereas commercial plastic-embedded and some depth electrodes are disposable.

Instrumentation and Physical Arrangement

ECoGs are now generally recorded with digital instruments, and the electrical activity is displayed on screen, paper, or both. Ideally, both the EEG instrument and the clinical neurophysiologist should be located in a gallery adjacent to but separate from the operating room (142). A large glass window and an intercom system enable the clinical neurophysiologist to view the operating field and to communicate with the neurosurgeon. Photographs of the operating field can be taken through a tilted mirror. A recording system bandpass of 0.5–70 Hz (−3 dB) ensures appreciation of both epileptiform

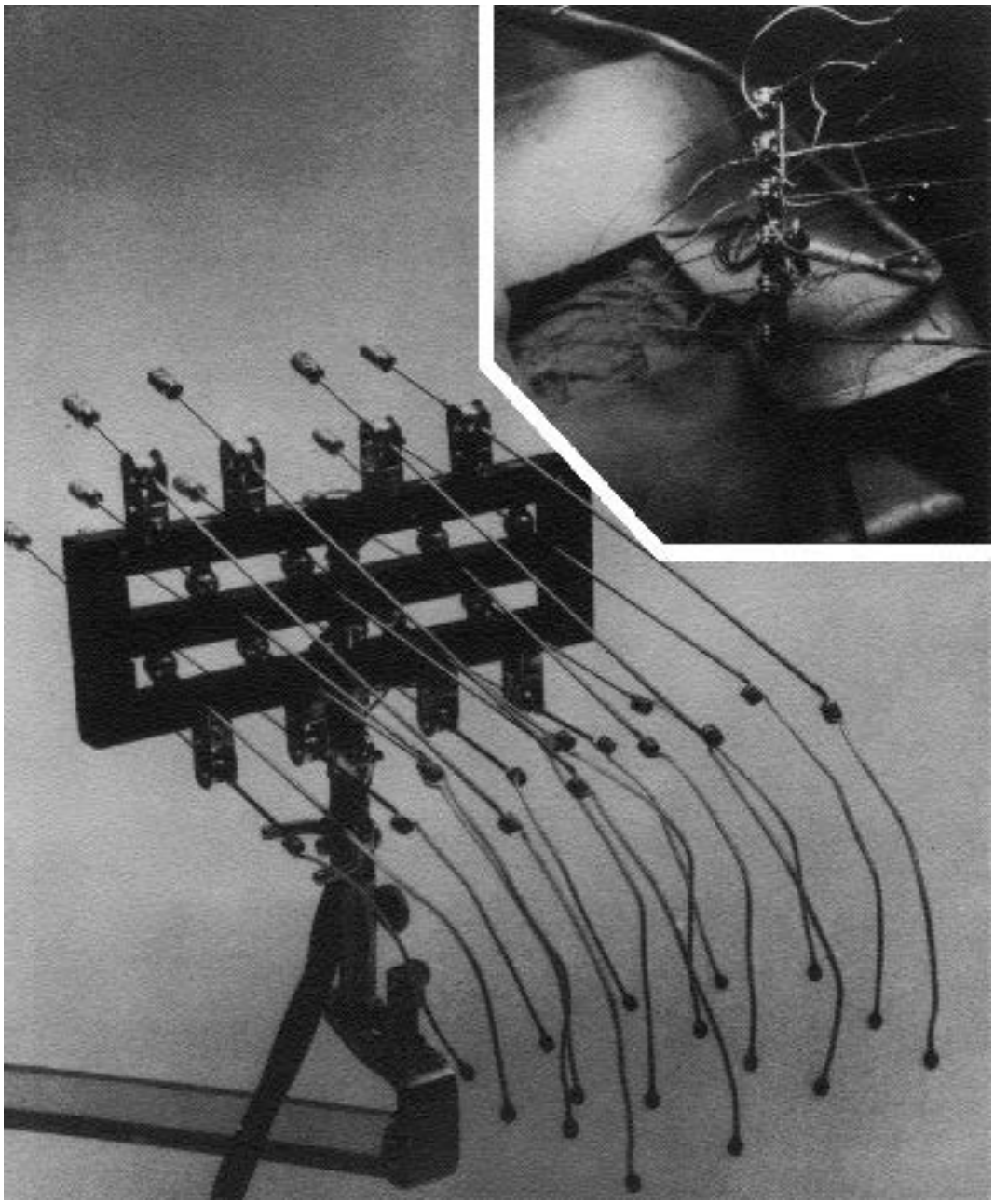

FIG. 21.1. Sixteen-electrode ECoG set used at the University of Miami and at the National Institute of Neurological and Communicative Disorders and Stroke, modified from an original design of the Montreal Neurological Institute. **Inset:** ECoG set in place, with holder clamped to the bone edge of the craniotomy and electrodes in contact with the exposed cortex. (From Ajmone-Marsan C. Chronic intracranial recording and electrocorticography. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a comprehensive textbook*, Vol 2. New York: Lippincott–Raven, 1997:1877–1890, with permission.)

discharges and background activities. During electrical stimulation, a low-frequency cutoff of 1.6 or even 5.0 Hz (−3 dB) helps diminish the duration of amplifier blocking following discontinuation of the stimulus. Because activities recorded directly from the cortical surface are about 2–60 times larger than those detected on the scalp (1), instrumental sensitivities of 10–50 μV per millimeter are most commonly used.

The use of digital recording devices make it possible to survey simultaneously as many as 64–128 brain sites, thus eliminating the need for several successive electrode placements and recordings, while providing detailed topographic assessment of interictal epileptiform discharges, other ECoG patterns, and evoked potentials. These systems also provide the opportunity to supplement the visual appraisal of the ECoG with computer analyses that in the future may increase the localizing power of this method. In addition, developments in the field of neuroimaging have made it possible to generate three-dimensional anatomical maps on which various functional images, such as those from functional MRI, positron emission tomography, single-photon emission computed tomography, magnetoencephalography, EEG, evoked potentials, and the ECoG can be superimposed (165). Frameless stereotactic systems interactively guided by these multimodal images promise to improve the precision of epilepsy surgery (222).

Methods

Preresection ECoGs must survey, in a systematic order, cortical regions within and outside the area of exposure and, whenever appropriate, pertinent subcortical structures. In patients undergoing temporal lobectomy, recordings should include thorough exploration of the infratemporal cortex, hippocampus and parahippocampal gyrus, uncus, and amygdala in addition to the orbital frontal and suprasylvian cortices (307). The hippocampus and amygdala can be surveyed via needle electrodes introduced either manually or stereotactically before resection (32,75,108,123,148,149,160,193,220,231, 239,298). Alternatively or additionally, strip or other electrodes can be applied over the ventricular surface of the hippocampus following incision of the lateral temporal cortex or anterolateral temporal lobectomy (32,148,156,193, 204,214,239,308). This last approach entails at least partial resection of the amygdala, which precludes the assessment of this structure. Acute deafferentation also may alter hippocampal and parahippocampal functions.

Postresection ECoGs should examine the cortices surrounding the ablation as well as more distant regions. After anteromedial temporal lobectomy, these should include, whenever possible, the remnants of the hippocampus and parahippocampal gyrus, the insula, and neighboring extratemporal cortices. When resection is carried out in stages, at least 10 minutes of technically adequate recording should be obtained following each resection. Total duration of intraoperative ECoG, excluding functional mapping, is generally 1 hour or longer.

Bipolar ECoG recordings are hampered by errors inherent in comparing the voltages of spikes detected by closely and often unequally spaced electrode pairs; difficulties in distinguishing low-voltage records caused by equipotentiality of adjacent electrodes from truly diminished activity related to other causes (7); the long time required to demonstrate instrumental phase reversals between electrode arrays at right angles to each other (108); and inability to readily demonstrate genuine, as opposed to instrumental phase, reversals (32,187,193,239,308). Provided an appropriate reference is chosen, referential montages are unhindered by these difficulties and permit rapid and reliable visual comparison of amplitudes and other features of spikes appearing in multiple channels. In addition, because the voltages of cortical potentials are large compared to those detected by reference electrodes commonly used in ECoG, the activity of the reference is not or is minimally apparent, and generally poses no interpretive problem. Thus displaying ECoGs in the form of referential montages expedites intraoperative interpretation and improves its accuracy. Current computer-based digital recorders offer the advantage that the ECoG, typically obtained referentially, can be displayed in the form of referential, bipolar, or mixed montages depending on circumstances and individual preferences.

Electrical Stimulation

Localized electrical stimulation of the brain is performed during surgery to elicit "afterdischarges" (see "Increased Susceptibility of Epileptic Tissue to Electrical Stimulation: The Afterdischarge" below) (Fig. 21.2), reproduce clinical manifestations of the patients' customary seizures, and map the functions of exposed cortices. In general, the stimulus is applied between two stainless steel ball electrodes that terminate a pencil-shaped probe held by the surgeon (7). Stimulus parameters and technique vary among centers (215), but most commonly individual stimulations consist of a train of diphasic pulses 0.3–1 millisecond in duration delivered at 60 or 50 Hz over 3–5 seconds via electrodes with an exposed surface of about 4 mm^2 and a separation of 5 mm (215). Strategies intended to minimize the chances of thermal (162) or electrolytic (242) damage to tissues that may not be included in the resection have been described (4,108), and a special stimulus paradigm has been suggested to overcome the problems posed by direct cortical stimulation in children, especially infants (150).

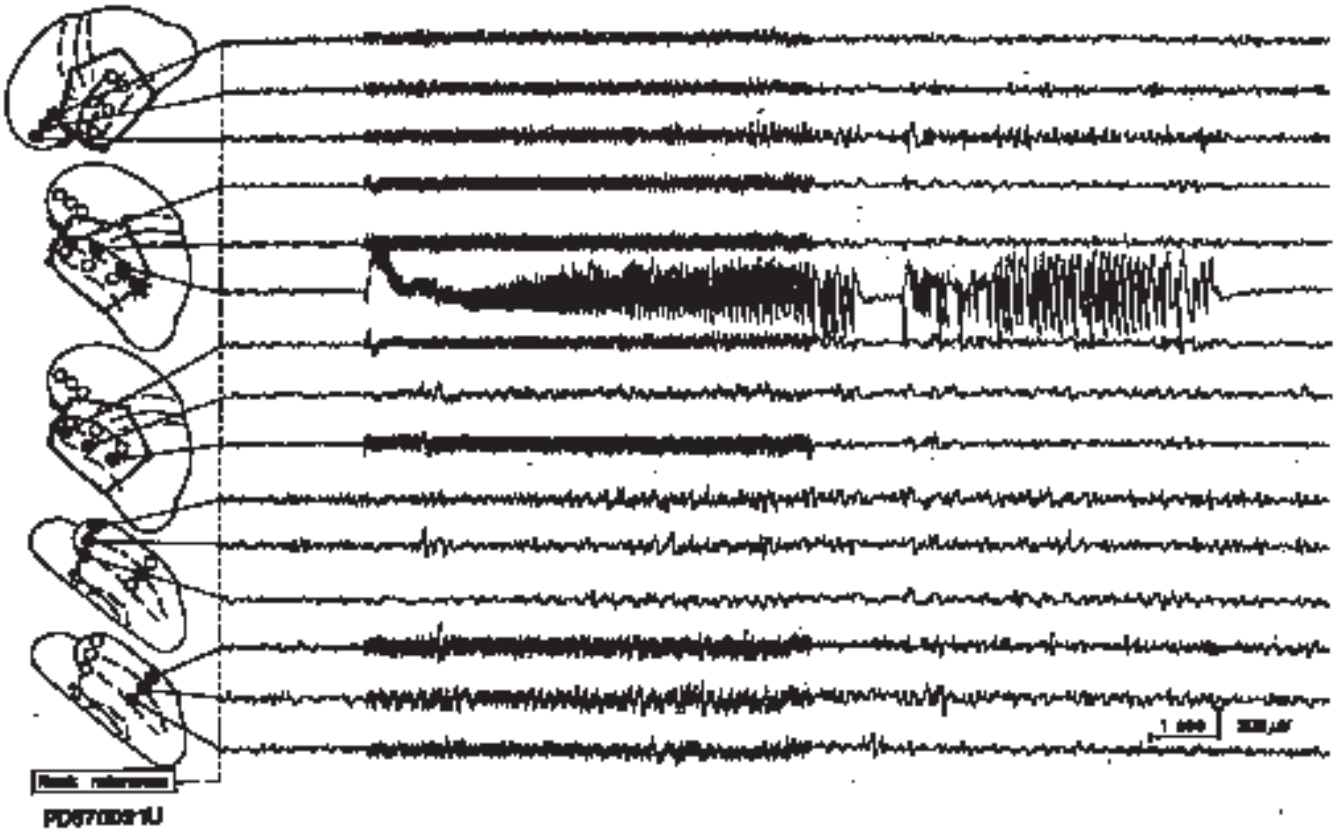

FIG. 21.2. Brief, localized afterdischarge (channel 6) unaccompanied by clinical changes is elicited by electrical stimulation of the posterior portion of the left superior temporal gyrus (rectangular diphasic pulses, 0.3 milliseconds, 60 Hz, 4 mA, 6.5 seconds) in a patient with medial temporal lobe seizures. (From Chatrian GE, Quesney LF. Intraoperative electrocorticography. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a comprehensive textbook*, Vol 2. New York: Lippincott–Raven, 1997:1749–1765, with permission.)

As distinct from stimulation of discrete cortical areas at intensities designed to elicit afterdischarges and reproduce clinical manifestations of the patient's attacks, repetitive electrical excitation at intensities subliminal for afterdischarge is widely used at present to map cortical functions under ECoG control. These stimulations are intended to identify in waking patients motor and sensory cortices often not clearly recognized by visual inspection, and to map regions involved in speech and memory functions that vary remarkably among subjects (218). Delineation of these areas makes it possible to exclude them from resection, thus decreasing the likelihood of functional deficits (218). EEG monitoring allows exclusions of trials in which an afterdischarge is detected. Careful mapping of the earliest cortical components of somatosensory evoked potentials to electrical stimulation of the median or posterior tibial nerves allows localization of motor and sensory cortices during surgery but may be time consuming and is sometimes difficult to interpret. Identification of the central sulcus by this method is most useful in patients undergoing epilepsy surgery under general anesthesia (182,336) and in children (125).

ECOG PATTERNS

The intraoperative ECoG has peculiarities that distinguish it from the scalp EEG. In the absence of gross structural pathology, the same normal rhythms that characterize scalp recordings can be detected from the cortical surface. However, these potentials usually are much larger in amplitude and more sharply demarcated on the cortex than on the scalp (1,7,108,143). Alpha activity predominates over occipital and parietal cortices, and beta activity and, less frequently, a mu rhythm are prominently represented over the central areas. In the temporal region, the alpha rhythm is less abundant, less regular, and variously intermixed with potentials in the theta and delta ranges (7). Because higher frequencies are attenuated to a greater extent than slower frequencies in the transmission of cortical potentials to the scalp (236), most rhythms tend to have a sharper appearance in ECoG than in scalp recordings, and, in general, the ECoG contains more prominent and abundant beta potentials than the scalp EEG (7). The presence of sharp-appearing alpha and mu rhythms over the central cortex (52,147), of occasional sharp potentials over the temporal areas (263), and of prominent beta waves induced by antiepileptic medications sometimes makes it difficult even for experienced interpreters to distinguish individual components of these activities from spike discharges (56).

Among the abnormal patterns recorded in the ECoG, spikes often have larger amplitudes (as much as 0.5–1 mV or more) and shorter durations (as little as 10–20 milliseconds) than in scalp recordings (7). Directly recorded spikes also tend to be more abundant in ECoGs than in scalp EEGs and to involve multiple, often noncontiguous cortical areas, a finding generally not clearly apparent in ordinary extracranial recordings (56,307). Special difficulties may be posed by the interpretation of areas of low-amplitude activity, which may due to equipotentiality of electrodes linked in bipolar derivations, the shunting effect of pooling of saline solution, or structural pathology in the underlying cortex (7). Similarly, in the absence of visually apparent structural alterations, it may be difficult to determine whether areas of arrhythmic delta activity apparent in preresection recordings are related to surgical trauma, such as is caused by division of adhesions, or to preexisting pathology (5,229). Less ambiguous is the finding in postresection ECoGs of similar alterations at and close to the margins of the resection (7). In contrast, a burst-suppression pattern occasionally observed at or near the margins of the excision (71,130) is sometimes difficult to distinguish from bursts of multiple spikes.

Spontaneous seizures are generally not recorded during relatively short-lasting intraoperative ECoGs except when surgery is performed on patients with localized cortical dysplasias (228), or in status epilepticus or by chance. Thus the ECoG examination of patients undergoing epilepsy surgery relies almost exclusively on the detection of interictal spikes.

Because ECoG recordings require instant, unhesitant interpretation that may influence the conduct of surgery, they must be interpreted by a trained and experienced clinical neurophysiologist (5) working in intimate collaboration with a neurosurgeon familiar with the implications of electrophysiological findings.

ACTIVATION AND SUPPRESSION OF ECoG SPIKES

In some patients the ECoG recorded during surgery disappointingly shows no (324) or rare spikes insufficient to define the spiking area. Attempts to elicit or enhance spiking in the intraoperative ECoG include the withdrawal of antiepileptic drugs prior to surgery and the use of physiological as well as pharmacological "activation" procedures. Pharmacological "suppression" of interictal spiking is also used by some to differentiate between primary and secondary spikes.

Withdrawal of Antiepileptic Drugs

In some centers, the patients' antiepileptic medications are discontinued or substantially diminished over a period preceding surgery. However, drug withdrawal is not associated with significant short-term increase of interictal spiking except after the manifestation of clinical seizures (122). Following withdrawal seizures, spikes tend to be more widespread and may even occur contralateral to the side of seizure onset (121). Also, withdrawal seizures may be particularly severe and are sometimes associated with life-threatening complications (283). Because of these drawbacks, several centers prefer to keep antiepileptic medications unchanged in the immediate preoperative period (218).

Physiological and Pharmacological Effects

ECoG spiking can be elicited or enhanced during surgery by activation techniques routinely used in scalp EEG studies, such as hyperventilation and drowsiness or sleep. However, activation of spikes has been achieved more commonly by the administration of pharmacological agents.

Effects of Pentylenetetrazol and Bemegride

In early studies, localized intracortical (14,314) or intravenous (126,148, 314) injection of pentylenetetrazol, a convulsant drug, was used with the

intent of promoting ictal discharges in presumably epileptogenic cortex. Because of limited localizing reliability of topical application, and difficulty in preventing the occurrence of generalized seizures with systemic administration (7,108,314), the use of this drug in intraoperative ECoG was abandoned. Another intravenously injected convulsant, bemegride (184,329), had similar shortcomings and fate.

Effects of General Anesthetics, Local Anesthetics, and Opioid Analgesics

General anesthetics, including thiopental, methohexital, etomidate, and propofol, have complex, dose-related effects on the ECoG (40,167).

Methohexital, an ultra-short-acting barbiturate, has been most widely used as an activating agent. Before resection, injection of a 25- to 100-mg bolus of this drug enhanced interictal ECoG spikes in 87% of patients (338) but also promoted expansion of the spiking area in 30% of patients and appearance of new spikes, partly or entirely outside the subsequent resection line, in 43% (92). In other instances, as time elapsed after the injection, the spikes again became restricted to the area involved before activation (Fig. 21.3). Methohexital injection after resection also caused the appearance of new areas of spiking at the margins of the excision or at a distance from it in 35% of patients (92). Additional alterations caused by this drug included induction of slow-wave activity (135,338) (Fig. 21.3) and reduction of beta potentials in the spiking area (135). The expansion of the spiking area under the influence of this, as well as other, agents can be deceptive. Even more

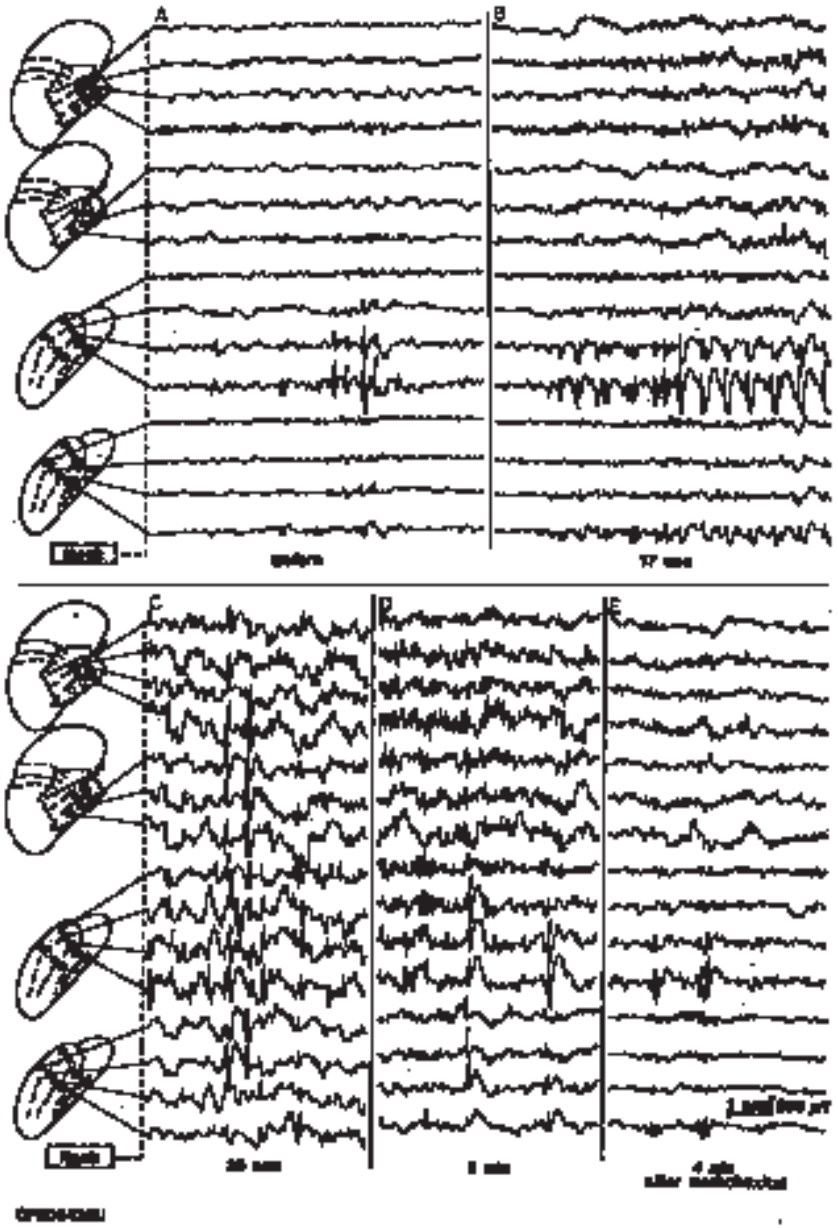

FIG. 21.3. A 23-year-old man experienced episodes of feeling weightless followed by loss of awareness and complex automatisms. **A:** Before activation, intraoperative preresection ECoG shows brief bursts of spike-and-slow-wave activity over the right inferomedial cortex with a maximum on the uncus. **B–E:** After rapid intravenous injection of 100 mg of methohexital, the recording successively demonstrates repetitive spike-and-slow-wave activity of higher voltage at the same location as in **A (B)**; spikes and delta waves occurring diffusely or multifocally throughout the temporal cortex **(C)**; spike-and-slow-wave activity again confined to the anterior infratemporal surface **(D)**; and spikes restricted to the areas involved before activation **(E)**. Beta activity was especially prominent in **D**. The patient fell asleep, and no ictal manifestations accompanied these ECoG changes. His hippocampus showed minor anterior herniation and slight nonspecific sclerosis. (From Chatrian GE, Quesney LF. Intraoperative electrocorticography. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a comprehensive textbook*, Vol 2. New York: Lippincott–Raven, 1997:1749–1765, with permission.)

vexing is the unresolved issue of the significance of those spikes that appear during activation in noncontiguous locations previously free of epileptiform activity. No established criteria allow us to distinguish drug-induced spikes that reveal the existence of epileptogenic tissue to be excised from spikes representing spurious drug effects that can be safely neglected (56,92). Because of these interpretive ambiguities, activation with methohexital or other anesthetic agents is discouraged.

General anesthetic agents such as methohexital may influence epileptiform activity not only when injected as a bolus in small doses to activate interictal spiking but also when used in relatively stable concentrations to produce anesthesia during surgery (97). Various alterations of interictal spiking are also produced by volatile anesthetics, including halothane (108), etomidate (224), enflurane (81,95), and combinations of enflurane and nitrous oxide (138). In contrast, isoflurane (89) and nitrous oxide (134) in commonly used concentrations were found not to alter significantly ECoG spiking.

Other drugs commonly used during surgery that may have epileptogenic effects include intravenously injected local anesthetics such as lidocaine (64) and opioid analgesics such as fentanyl (303) and ultra-short-acting alfentanil (40) and remifentanil (88). These medications enhance interictal spikes and may precipitate electrographic and, sometimes, clinical seizures, mostly in medial temporal structures of patients with temporal lobe epilepsy. However, the combined administration of isoflurane and fentanyl reduces the area and the mean frequency of interictal ECoG spiking (138).

Because many anesthetic drugs variously alter interictal spiking, whenever intraoperative ECoG is to be performed under general anesthesia in children, uncooperative adults, and individuals undergoing special procedures such as corpus callosotomy or medial frontal resections (119,221, 253), the anesthetic agent to be used should be carefully chosen. In some centers, combined short-lasting propofol anesthesia and local anesthetic field block has proved satisfactory in providing comfort to patients undergoing craniotomy while awake (215,274), without substantially altering interictal epileptiform activity (132).

Large doses of intravenously injected anesthetics have been used to suppress rather than activate interictal spiking in the ECoG. The "methohexital sodium suppression test" (198,199) is based on the contention that, because the spikes that characterize primary, autonomous epileptogenic zones are extraordinarily resistant to anesthesia, they tend to persist following methohexital injection even at doses that suppress the background ECoG, and tend to reappear first after the injection. In contrast, secondary, dependent spiking (see "Surgery of Dual Pathology" below), which is more vulnerable to anesthesia, would tend to be obliterated earlier, together with the background ECoG, and to reappear later after the injection. The proponents of this test reported using it successfully during chronic as well as acute ECoGs (135,198,199,280). Further investigation of this method is needed.

TRADITIONAL GOALS AND LIMITATIONS OF INTRAOPERATIVE ECoG

Prior to the introduction of preoperative video-EEG monitoring of spontaneous ictal patterns with noninvasive and variously invasive electrodes and the advent of highly informative structural and functional neuroimaging techniques, ECoG was performed intraoperatively in many centers following clinical and scalp EEG studies that had identified an epileptogenic process within the hemisphere targeted for surgery and established at least its broad location. In this context, intraoperative ECoG was intended to aid in (a) localizing the epileptogenic zone, (b) establishing the limits of the resection, and (c) assessing the completeness of the excision.

Localization of the Epileptogenic Zone

Traditionally, localizing the epileptogenic zone by intraoperative ECoG relied on the identification of an area of brain that (a) displayed interictal spikes,[1] (b) showed greater susceptibility than other regions to repetitive electrical stimulation, and (c) gave rise to the initial or all manifestations of the patient's habitual seizures when electrically stimulated.

Because no seizures are generally recorded during intraoperative ECoG, the utility of this method depends on the correctness of two assumptions: (i) that interictal spikes are reliable markers of the site of origin of the patient's seizures, and (ii) that they provide dependable information on the extent of epileptogenic tissue that must be removed to control the seizures.

Interictal Spikes as Markers of Local Epileptogenicity

Following the demonstration that spikes occurred interictally over limited areas of the scalp and brain of patients suffering from partial seizures

[1]For the sake of brevity, interictal epileptiform discharges (i.e., spikes, sharp waves, and their variants) are referred to in this chapter as "interictal spikes" without implying that they are functionally identical, and the full extent of neural tissue displaying spikes is designated the "interictal spiking area." This term is a better descriptor than its frequently used equivalent, the "irritative area."

(140,233), the notion that a close topographic and functional relationship existed between interictal events and ictal discharges became gradually established, although limitations of this concept were recognized (141–143,314), and dissenting opinions were voiced (195). This conjecture found strong support in elegant studies of penicillin-induced epileptic foci in animals. These investigations defined the nature of the cellular events associated with the cortically detected interictal spike (192) and documented the direct transition from interictal into ictal activity within the same neuronal aggregate (250) and even the same neuron (191). However, in patients afflicted by chronic partial epilepsies, the epileptogenic process often by far exceeds in complexity the epileptic focus produced by topical application of convulsants to a discrete cortical area in animals with otherwise normal brains. A manifestation of this complexity is that it is exceedingly difficult to distinguish interictal spikes generated by epileptogenic tissue at the site of recording from spikes neuronally propagated (or volume conducted) from a remote epileptogenic trigger (108,109,143,148,180) and to determine whether or not a secondary epileptogenic zone is capable of independent seizure generation (see "Surgery of Dual Pathology" below). In addition, studies utilizing depth, subdural, and epidural electrodes (20, 180,211,301,326) have demonstrated that, in individuals afflicted with these disorders, seizures sometimes arise outside the ECoG-identified interictal spiking area.

Increased Susceptibility of Epileptic Tissue to Electrical Stimulation: The Afterdischarge

Repetitive electrical stimulation of the brain of sufficient intensity elicits an "afterdischarge" (2,265). Afterdischarges consist of self-sustained rhythmic activity of variable form and frequency, including rhythmic oscillations of alpha or theta frequency and rhythmically repeating spikes, sharp waves, and multiple spikes often evolving into each other (4) (see Fig. 21.2). These electrically elicited seizures vary widely in duration from less than 1 second to 90 seconds or longer (4). They may remain restricted to the area stimulated or spread to wider cortical regions, to subcortical structures, and, sometimes, to distant or contralateral cortices (4,143). Afterdischarges are frequently followed by localized postictal voltage depression, which lasts several seconds and is in turn succeeded by slow activity of variable duration, often most marked at the site of stimulation (4).

Early investigators speculated that human epileptogenic tissues might display increased susceptibility to electrical stimulation in the form of afterdischarges of lower threshold, longer duration, or both, compared to nonepileptogenic tissue. They hypothesized that these findings might have special localizing value when associated with prominent, spontaneous interictal spiking or with the initial manifestations of the patients' habitual seizures (142,234,314,317). However, their observations and those of other researchers did not confirm these conjectures (4,108,143,174,181,218,234, 314,317,318). Afterdischarge thresholds also proved unhelpful in determining the presence and location of structural lesions (75), and stimulations of the brain via depth electrodes demonstrated lack of consistent relations between these thresholds and sites of spontaneous ictal onset (29).

Reproduction of Manifestations of the Patients' Habitual Seizures

Penfield and his associates (84,108,145,149,231,232,234,235,252,259) made extensive use of localized electrical stimulation of the brain to reproduce in waking patients undergoing surgery the initial, or all, manifestations of their habitual seizures. The utility of this technique was based on the assumptions that (a) the initial manifestations of partial seizures (i.e., the "aura"), indicated the site of the brain from which the seizures developed, and (b) the reproduction of these manifestations by electrical stimulation of a restricted area of the brain confirmed this localization.

Attempts to reproduce intraoperatively or extraoperatively the initial symptoms and signs of partial seizures by electrically stimulating various brain structures via cortical or depth electrodes provided evidence that these phenomena often did not reflect an ictal discharge arising at the site of stimulation but resulted from spread of the seizure at a distance from this location (20,75,127,145,180,314,329). One study (94) reported that stimulation of numerous frontal and temporal sites evoked in 85% of patients a broad range of clinical phenomena most of which also occurred during the patient's spontaneous attacks. However, similar responses occurred in the presence of an afterdischarge restricted to the site of stimulation or demonstrating only incipient spread from this location, or even the absence of afterdischarge. In addition, the same auras could be elicited from multiple and, sometimes, bilateral sites. These authors concluded that the electrically elicited initial manifestations of the patient's habitual seizures lacked localizing and even lateralizing value, and at best indicated the most likely lobar origin of the patient's spontaneous attacks. Clinical manifestations occurring later during spread of the afterdischarge presumably reflected the involvement of cerebral areas other than that stimulated (94).

Determination of the Limits of Resection

Careful observations have determined that the interictal spiking area defined by intraoperative ECoG often substantially exceeds the extent of brain the excision of which is necessary and sufficient to achieve control of the patient's seizures (254). Removal of the entire interictal spiking area is unnecessary and would increase the likelihood of postoperative neurological deficits (56,72,178,254). That the extent of the "surgically relevant epileptogenic area" (56) remains elusive even when the interictal spiking area has been clearly delineated is not surprising. It is likely that subtle gradations in epileptogenicity exist within the epileptogenic zone, ranging from a maximum (the ictal onset area) to a minimum (the periphery of the interictal spiking area.) Thus it would be unreasonable to expect visual analysis to detect an electrophysiologically sharp demarcation between tissues with sufficiently high epileptogenicity to mandate removal and tissues with sufficiently low epileptogenicity to warrant preservation (56). The frequent finding of multiple spiking areas, especially in the ECoGs of patients with medically intractable temporal lobe seizures (308), is an additional factor of complexity.

Whether or not ECoG recording aids in assessing the completeness of resection and predicting its effectiveness is best determined in the context of each individual operative procedure.

ECOG IN RESECTIVE SURGERIES

Surgery of Medial Temporal Lobe Epilepsy

The majority (about 70%) of patients undergoing surgery for chronic, medically intractable temporal lobe seizures suffer from "medial temporal lobe epilepsy" ("amygdalohippocampal," "mesiobasal limbic," or "rhinencephalic" epilepsy) (60). The electrographic and clinical features of this syndrome; its relations to early risk factors, MRI findings, and neuropsychological profile; and its frequently poor response to medical treatment have been studied in detail (74,76,98,330).

Depth recordings have long established that, in most patients with chronic, medically intractable temporal lobe epilepsy, seizures generally arise at one or multiple sites within a system of closely interconnected structures that include the hippocampus, amygdala, entorhinal cortex (uncus), and parahippocampal gyrus, and may variably propagate to the ipsilateral temporal or frontal neocortex and contralateral hippocampus (8,13,20,55, 62,72,84,111–113,163,177,243,284,290,291,296,310,319,327).

In the majority of patients, a close relationship exists between the medial temporal origin of the seizures and the histological demonstration of "medial temporal sclerosis." This pathology typically consists of a distinct lesion, "hippocampal sclerosis," that is characterized by marked (50% or greater) neuronal loss and gliosis most prominent in the CA1 and CA4 regions (16,80,188) and mossy fiber synaptic reorganization (299). High-resolution MRI reveals hippocampal atrophy and increased T2 signal in over 90% of patients with this pathology (28,42,139,169,170,300). A minority of patients with medial temporal sclerosis display mild, nonspecific hippocampal gliosis without neuronal loss. Variable degrees of sclerosis are also often observed in the amygdala, entorhinal cortex (uncus), and parahippocampal gyrus (48,112). Less frequent lesions include small benign structural lesions such as hamartomas, angiomas, low-grade gliomas, and cysts encroaching on the amygdalohippocampal region (78,190).

At present, surgeries for medically intractable medial temporal lobe epilepsy mostly consist of (a) anteromedial temporal lobectomies designed to remove medial temporal structures and anterior portions of temporal neocortex, and (b) selective removals of medial temporal structures. Anteromedial temporal lobectomy can be anatomically standardized (77,79,210) or individually tailored to ECoG spiking and functional mapping (214).

Temporal Lobe Resection

Preresection ECoG Findings

Intraoperative ECoG findings described in patients undergoing temporal lobe resection reflect the marked prevalence of medial temporal sclerosis among these individuals. However, most surgical series also include some patients with other medial temporal lesions, neocortical temporal lesions (see "Surgery of Neocortical Epilepsies" below), or no demonstrable pathology (see "Surgery of Cryptogenic [Nonlesional] Epilepsies" below).

In a remarkable early study, Jasper et al. (148) reported that the ECoGs of 93% of patients undergoing surgery for chronic, medically intractable temporal lobe seizures showed interictal spikes that involved most commonly the temporal tip, the uncus, the anterior portion of the hippocampus, the parahippocampal and fusiform gyri, and, occasionally, the insula. Subsequent investigators substantially confirmed these findings (6,8,31,32,50,54, 56,66,75,103,123,156,160,193,196,239,247,256,298,307,309,316).

Preresection spikes vary in extent all the way from individual restricted to widespread, often multiple areas (123,160,193,247,298,307) (Figs. 21.4,

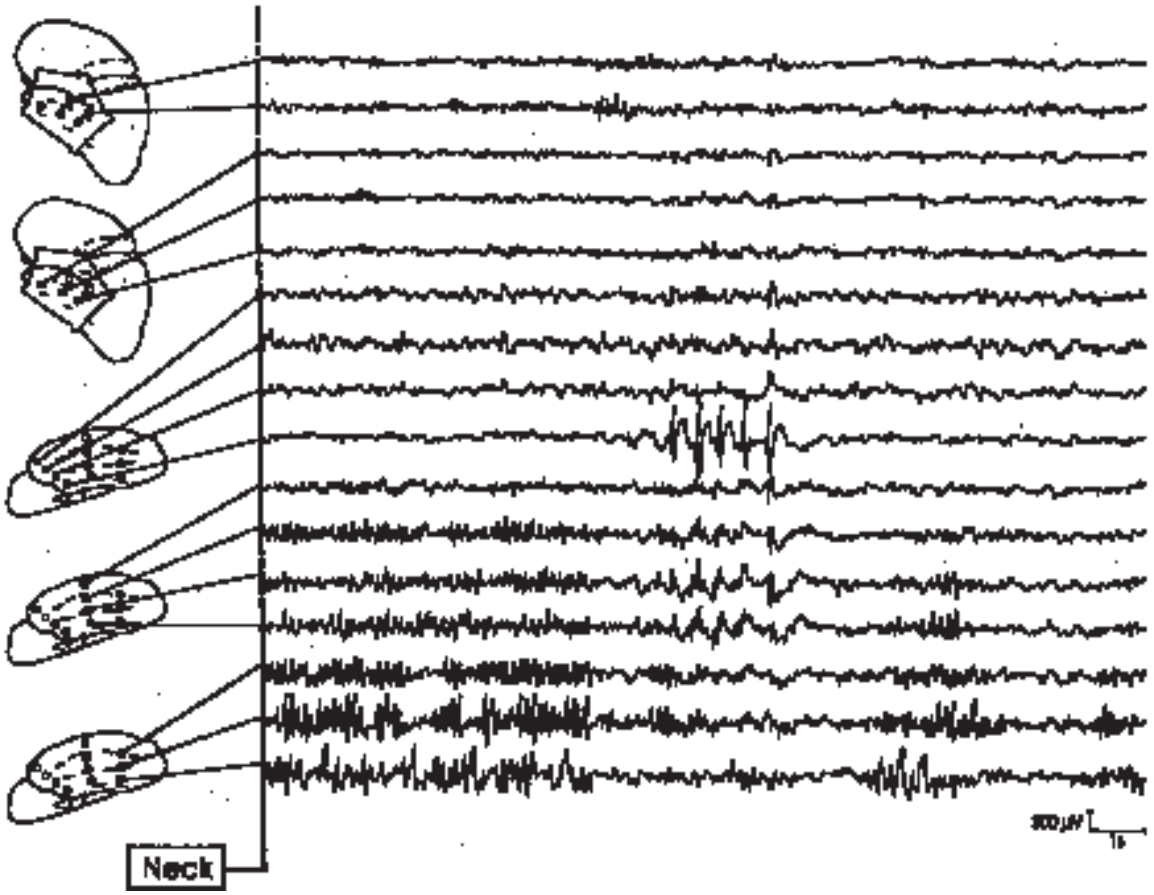

FIG. 21.4. Intraoperative preresection ECoG of a 24-year-old woman with attacks of stomachache, looking to the right, blinking, lip smacking, facial twitching, and impaired awareness. Bursts of spike-and-slow-wave activity occur over the left uncus with minor involvement of adjacent areas. (From Tsai ML, Chatrian GE, Pauri F, et al. Electrocorticography in patients with medically intractable temporal lobe seizures: I. Quantification of epileptiform discharges prior to resective surgery. *Electroencephalogr Clin Neurophysiol* 1993; 87:10–24, with permission.)

21.5, and 21.6*A*). In one series, 81% of all spikes recorded before exposing the hippocampus involved the infratemporal surface, 18% the lateral temporal, and 1% the orbital frontal regions (307). In this group of patients as a whole, the spikes were distributed in an orderly pattern, with the uncus/anterior parahippocampal gyrus and the inferomedial surface of the temporal tip displaying the highest and the lateral temporal and posterior infratemporal cortices showing the lowest propensity for the generation of spikes. Individual patients variously departed from this pattern (307).

In most subjects, electrodes introduced at surgery into the hippocampus through a lateral temporal incision (32) or laid over the ventricular surface of the hippocampus following anterolateral temporal lobectomy (307) demonstrate spikes that occur over the hippocampus and the parahippocampal gyrus apparently simultaneously but with opposite polarities. Commonly, the main component of these discharges is positive on the hippocampus and negative on the parahippocampal gyrus (32,239,307) (Fig. 21.6*B*). However, more complex temporal and polarity relationships between these structures are also frequently evident, suggesting that spikes can be generated at different locations and cortical depths within the hippocampus, the parahippocampal gyrus, or both (307). Hippocampal-parahippocampal spikes are the single most common finding in patients undergoing temporal lobectomy for medial temporal

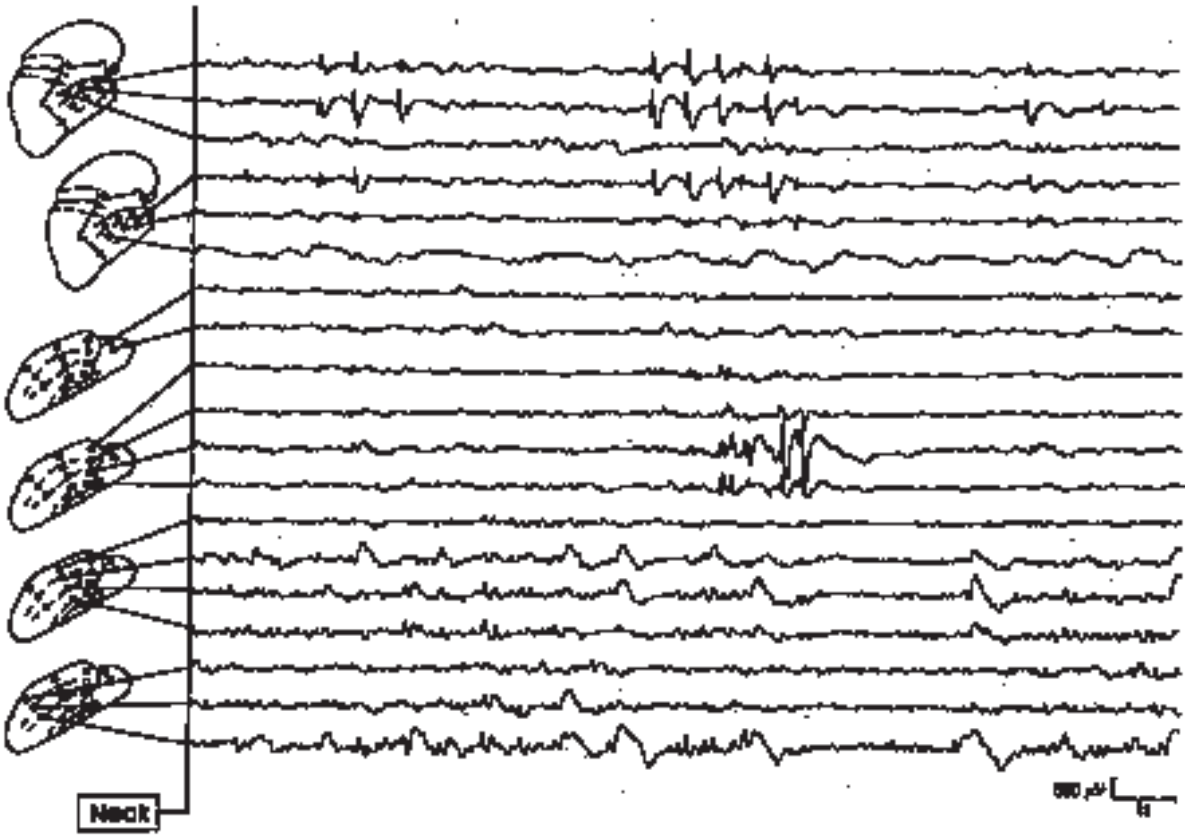

FIG. 21.5. A 31-year-old man had episodes of sour taste, swallowing, chewing, blinking, automatisms of the hands, and unresponsiveness followed by confusion and agitation. Intraoperative preresection ECoG displays spike-and-slow-wave activity that involves the lateral surface and the anterior portion of the inferomedial surface of the right hemisphere independently. (From Tsai ML, Chatrian GE, Pauri F, et al. Electrocorticography in patients with medically intractable temporal lobe seizures: I. Quantification of epileptiform discharges prior to resective surgery. *Electroencephalogr Clin Neurophysiol* 1993;87:10–24, with permission.)

lobe epilepsy. However, electrodes implanted intraoperatively into the amygdala also commonly detect spikes (324). Because these medial temporal discharges frequently fail to appear in recordings from the lateral temporal surface, direct recordings from inferomedial temporal lobe structures are essential to demonstrate them (54,56,307).

In some individuals undergoing temporal lobectomy (as well as other surgeries), no spikes are detected in any location during intraoperative ECoG, however thorough. This negative result is a major drawback if ECoG guides surgery. In a study of selected patients with chronic, medically intractable temporal lobe epilepsy who had undergone both preoperative chronic depth electrode recordings and intraoperative ECoGs (324), those individuals who displayed spikes during the operation had shown spikes in the same regions preoperatively. However, those patients whose ECoGs failed to show any spiking at surgery had also demonstrated spikes in medial or medial and lateral temporal lobe locations preoperatively (324). This discrepancy strongly contradicts the notion that temporal lobe structures free of interictal epileptiform activity during surgery can be assumed to be functionally intact and should be exempted from resection (158,204).

Preresection Spikes as Indicators of Pathology and Guides to Type of Resection. There is widespread agreement that no dependable relationships exist between the presence or absence as well as the rate, form, location, and polarity of interictal spikes in neocortical and medial temporal structures and the presence or absence and nature of pathology in or outside medial

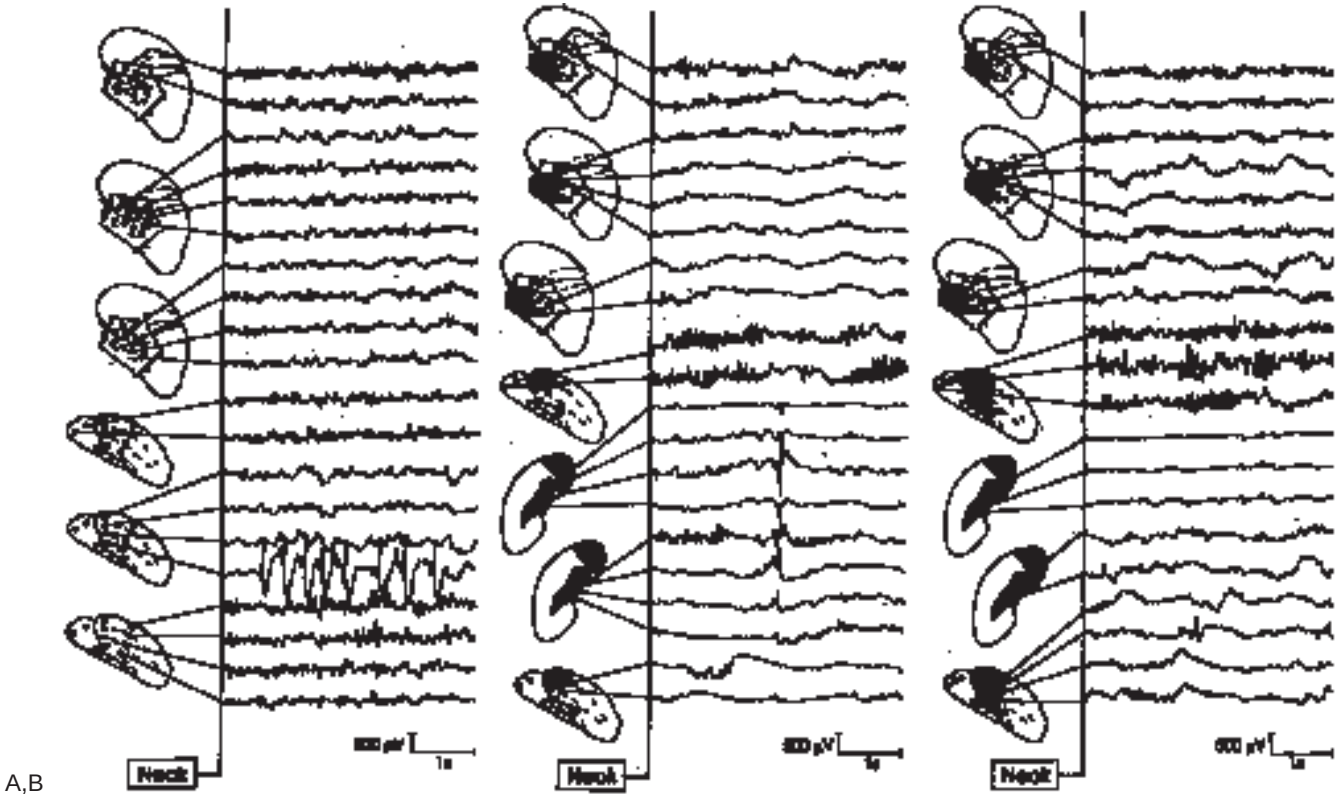

FIG. 21.6. A 33-year-old man had episodes of feeling strange, automatisms of the hands, loss of awareness, and occasional tonic–clonic generalization. **A:** Intraoperative preresection ECoG shows spike-and-slow-wave activity on the anterior hippocampus. **B:** After anterolateral resection, spikes occur simultaneously and with opposite polarities on the hippocampus (channels 11–14) and parahippocampal gyrus (channels 15–18). **C:** Following final ablation, including 2.5 cm of parahippocampal gyrus and hippocampus, infrequent discharges are detected posterior to the inferomedial margin of the excision. (From Tsai ML, Chatrian GE, Temkin N, et al. Electrocorticography in patients with medically intractable temporal lobe seizures: II. Quantification of epileptiform discharges following successive stages of resective surgery. *Electroencephalogr Clin Neurophysiol* 1993;87:25–37, with permission.)

temporal lobe structures (20,32,45,54,75,193,196,197,204,246,308,324). Discrepancies have even been reported between site(s) of seizure onset in neocortical and medial temporal areas and location of pathology (216). It follows that intraoperative ECoG provides no guidance in choosing between temporal lobectomy and amygdalohippocampectomy (32,239).

Preresection Spikes as Guides in Determining the Limits of Resection. Over the past five decades, numerous authors have variously expressed the belief that, in patients suffering from chronic, medically intractable temporal lobe epilepsies of various etiologies, the topography of intraoperative preresection spikes provided guidance in determining the extent

of resection (6,24,27,123,148,152,217,234,237,241,251,298,315). Other investigators disagreed with this view (9,61,72,79,282,288,302,318), and some successfully performed "anatomically standardized" temporal lobectomies without ECoG monitoring or consideration of ECoG findings (77,79).

Recognizing that removal of all spiking tissues would be unnecessarily extensive and could cause unacceptable deficits (56,72,75,178,256), those surgeons who perform "ECoG-guided" temporal lobe resections generally exempt from resection one or more of the following:

1. Spiking cortices involved in speech, memory, motor, and sensory functions demonstrated by intraoperative mapping (214)
2. Other cortices located outside anatomically safe boundaries, such as the insula (6,252,275)
3. Posterior temporal extrahippocampal areas
4. Part of the hippocampus when concerns about possible postoperative memory deficits are raised by the preoperative evaluation
5. Cortex displaying comparatively low levels of epileptiform activity
5. Spiking tissues remote from the dominant spiking area

The extent of excision determined by these criteria variably, and sometimes substantially, differs from the limits of the ECoG-defined spiking area (54,56). The presence of spikes outside the limits of the planned resection, whether individually tailored or anatomically standardized, does not detract from the postoperative outcome (66,193) provided that the ablation includes the site(s) from which the seizures arise, those to which the seizures most immediately propagate, and adjacent tissue displaying the most frequent and prominent spiking. Visual assessment of spikes cannot dependably identify these sites, but there is hope that computer analysis of the intraoperative ECoG will facilitate this task in the future (9,31,70,136).

Preresection Spikes as Predictors of Postoperative Seizure Outcome. No measures of preresection spiking, including topography, voltage, rate, and range of rates, reliably distinguish seizure outcomes (30,31,45,86,157,193,306). Exceptions reported in the literature include maximal spike voltages over posterior temporal and extratemporal areas (31) and very low spike rates (30,31,86,157,193) significantly associated with adverse outcomes, and relatively high discharge rates (24 or more spikes per minute) associated with favorable results (31). A recent comprehensive quantitative study in our center did not confirm any of these relationships (54).

Postresection ECoG Findings

When temporal lobectomy is carried out in stages, following each excision, spikes subside, persist, or newly appear in cortex bordering or neighboring the excision, often varying remarkably in distribution from one ablation to the next (308). After the last of several resections, or after a single lobar resection, the ECoGs of a variable proportion of patients (22%–85%) still display interictal spikes (6,38,54,66,91,116,183,194,306,308) (Figs. 21.6*C* and 21.7*C*). Postresection spikes commonly involve multiple cortical areas bordering or neighboring the excision and extend variably into adjacent regions (308). With some exceptions, they are variably diminished in number compared to preresection recordings over the remnants of the hippocampus and parahippocampal gyrus, and other infratemporal cortices, whereas they show no consistent changes in lateral temporal regions (308). In addition, postresection spiking areas are frequently less numerous and less extensive, and attain smaller maximal voltages than did spiking regions before resection (308). Increased spiking is sometimes observed in locations adjacent to the areas most active before resection or at a distance from them (143).

Postresection Spikes as Predictors of Postoperative Seizure Outcome. Whether or not postresection ECoGs contain information of prognostic value has long been the subject of controversy. Early work suggested that persistent or novel spiking following resection was frequently associated with poor postoperative seizure control and warranted additional ablation within neurologically safe boundaries until a normal or clearly improved recording was obtained (143,148,234). Subsequent studies confirmed the existence of a relationship between presence or absence of ECoG spiking after temporal lobectomy and unfavorable or favorable seizure outcome, directly or indirectly advocating the excision of as much epileptogenic tissue as was compatible with avoidance of functional deficits (5,7,24,38,91,108,116,144,146,159,164,173,193,219,287,298,306,311). No such relationship was found by other investigators (32,45,53,66,68,72,77,107,123,193,256,273,282,305,309,339).

A few studies found that individual measures of postresection spiking were significantly related to postoperative seizure outcome. These included reports of statistically significant associations between low spike rates (five or fewer spikes per minute) and better seizure control (66), and between reductions of postresection spiking to less than 50% of preresection levels and adverse results (32,193). In a somewhat different vein, significant differences in outcome were reported between ECoGs demonstrating simultaneous compared to independent spiking areas and residual compared to increased postresection spiking (183). No such relations were demonstrated

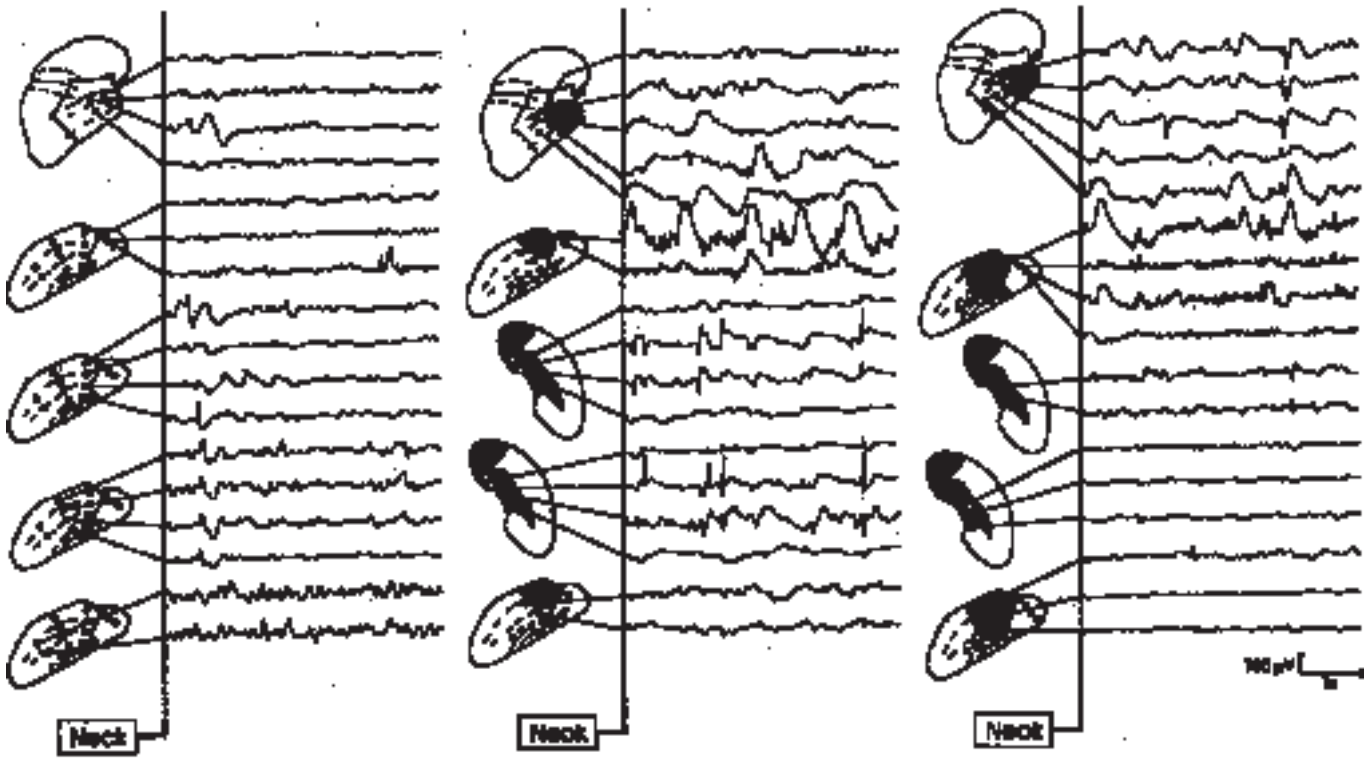

FIG. 21.7. A 20-year-old woman experienced attacks of feeling strange, hot flashes, orofacial automatisms, variably impaired responsiveness, and infrequent tonic–clonic generalization. **A:** ECoG preceding resection displays spike-and-slow-wave activity over the left uncus. **B:** After anterolateral resection, spikes are detected on the hippocampus and parahippocampal gyrus with variable temporal and polarity relationships, and rare lower voltage spikes occur on the right temporal surface posterior to the excision. **C:** Following medial extension of the resection, spikes are recorded posterior to the excision, especially over the lateral temporal areas, and rare low-voltage spikes are noted on the orbital frontal cortex and the residual hippocampus. (From Tsai ML, Chatrian GE, Temkin N, et al. Electrocorticography in patients with medically intractable temporal lobe seizures: II. Quantification of epileptiform discharges following successive stages of resective surgery. *Electroencephalogr Clin Neurophysiol* 1993;87:25–37, with permission.)

by other studies (91), including one by Schwartz et al. (273), who found no statistically significant associations between frequency and voltage of postresection spikes and seizure outcome in a fairly homogeneous group of patients with temporal lobe seizures and preoperatively diagnosed and histologically confirmed mesial temporal sclerosis.

Some investigations focused on the spikes detected postoperatively in individual areas of the temporal lobe. A recent comprehensive quantitative study in our center found no statistically significant relationships between postoperative seizure outcome and any of a number of measures of level (rate and voltage), or change in level, of interictal spiking recorded before and after tailored temporal lobectomy on the hippocampus; the parahippocampal gyrus; the anterior and posterior halves of either of these structures; other infratemporal, lateral temporal, and orbital frontal areas; and all these regions combined (54). A subsequent publication confirmed that the presence or absence of residual spikes in temporal neocortex and the parahippocampal gyrus was not predictive of seizure outcome (194). In contrast, those patients in whom hippocampal resection was pursued until a spike-free hippocampal recording was obtained ($N = 119$) had significantly more favorable results than did individuals in whom spiking persisted on the residual hippocampus, irrespective of the extent of resection ($N = 21$). The latter group included patients in whom hippocampal excision was limited because of concerns about postoperative memory function raised by preoperative intracarotid amobarbital and intraoperative mapping studies ($n = 7$), individuals with bilateral seizure onsets predominantly ipsilateral to the resection ($n = 2$), and individuals with contralateral mesial temporal MRI abnormalities ($n = 1$). The findings of this study were interpreted as strong evidence that ECoG monitoring predicted the extent of hippocampus that should be removed to achieve seizure-free outcome (194), although dissimilarities existed between the two groups compared.

Contradictory findings have been published on the prognostic significance of the frequency of postresection spikes on the insula (157,275). However, there is general agreement that persistent spikes on this cortex do not justify hazardous insulectomy (275).

That ECoG spiking following temporal lobectomy does not reliably predict seizure outcome is not surprising. Postresection spiking may indicate either persistent epileptogenicity resulting from incomplete removal, or inadequate disconnection, of epileptogenic tissue, or may represent new events, most likely caused by the trauma of excision (6,272). It is likely that both mechanisms play a role in the manifestation of spikes after resection, and distinguishing them is a difficult task.

Evolving Role of ECoG in Temporal Lobe Resections

The literature reviewed so far in this chapter suggests that, in patients with chronic, medically intractable medial temporal lobe epilepsy, the presence or absence, topography, and individual measures of interictal spiking detected in medial and lateral temporal locations before as well as after temporal lobectomy are of very limited assistance in the conduct of surgery. These features play no substantial role in establishing the site of onset of the patients' seizures; differentiating between primary and secondary spiking areas; determining the epileptogenic potency of the latter regions; choosing between anteromedial, lateral, and selective medial temporal resections; and predicting postoperative seizure outcome (56). These limitations and the progress of neuroimaging have reduced the dependence of resective temporal lobe surgery on ECoG recordings of interictal spikes, which is increasingly regarded as of primary academic interest. However, when functional mapping is required, ECoG monitoring is essential to determine afterdischarge thresholds and document the subliminal nature of the stimulus.

Reoperation after Unsuccessful Temporal Lobectomy

Failure of surgery following temporal lobectomy is most commonly due to incomplete removal of medial temporal structures. Reoperation with completion of this removal is often successful (106,238) but is usually performed without electrophysiological monitoring.

Selective Medial Temporal Resections and Stereotactic Lesions

Recognition that functional and structural pathologies of medial temporal structures play a central role in medial temporal lobe epilepsy (21,47,73,80,82,83,104,114,220,326) has inspired a number of selective medial temporal surgeries. These were designed to resect or destroy stereotactically the hippocampus, the amygdala, or both in selected individuals with seizures of established medial temporal lobe onset (36,37,55,85,118,158,161,204,212,220,230,258,328,333). Remarkably, all these procedures achieved similar good seizure outcomes, suggesting that medial temporal lobe seizures primarily result from concurrent epileptogenesis of closely interconnected medial temporal lobe structures, including the hippocampus and amygdala.

Following resective amygdalohippocampectomy, ECoG-detected interictal spikes (212) increase markedly in frequency, with intervening periods of low voltage or slow activity most evident over the anterior temporal cortex (50,212,323) (Figs. 21.8 and 21.9.) In some patients, a burst-suppression pat-

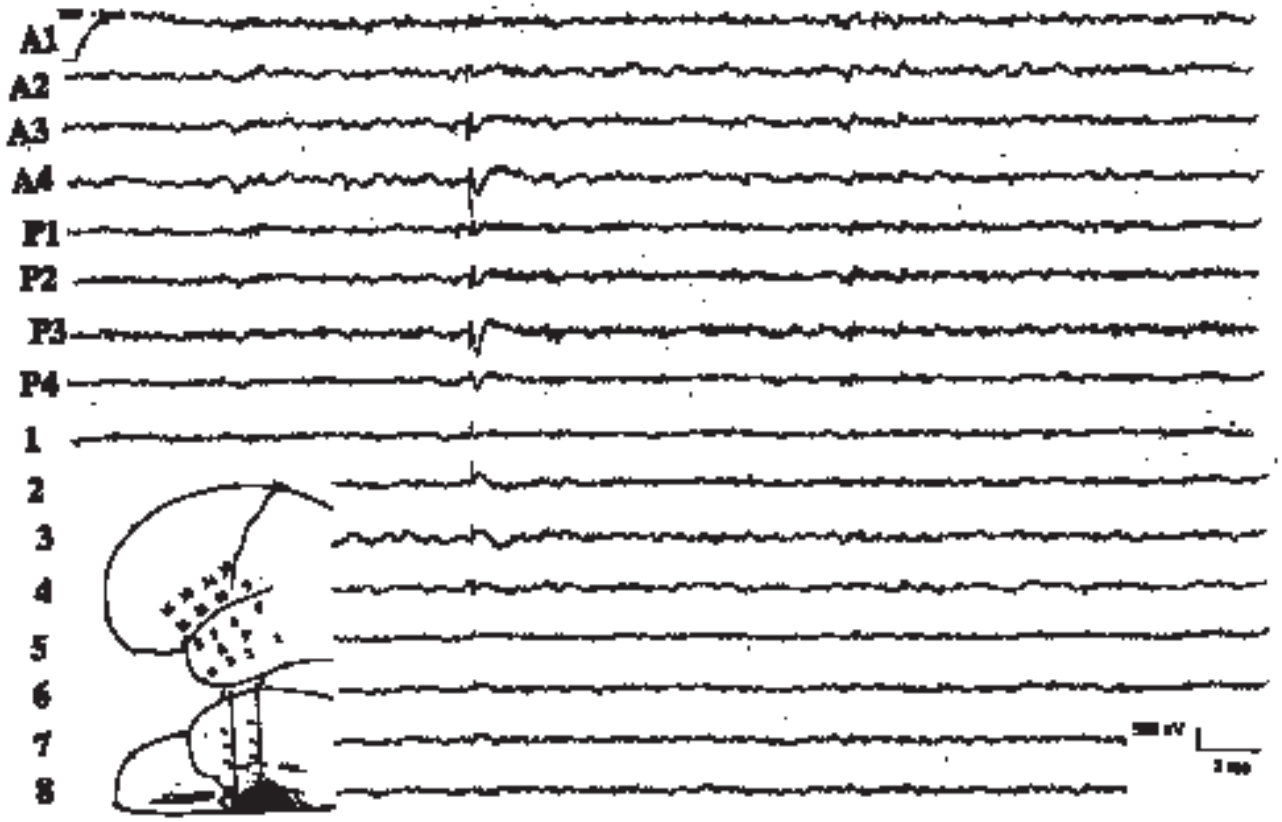

FIG. 21.8. A 36-year-old-man with temporal lobe seizures showed left temporal spikes in his EEG, and MRI demonstrated left amygdalar and hippocampal atrophy. Intraoperative preresection ECoG displays infrequent spikes involving most prominently the left inferior temporal gyrus, the amygdala, and the hippocampus, apparently simultaneously. A1-A4 and P1-P4 are progressively deeper contacts along anterior and posterior depth electrodes inserted manually through the midtemporal gyrus and aimed at the amygdala and the anterior hippocampus, respectively. (From Cendes F, Dubeau F, Olivier A, et al. Increased neocortical spiking and surgical outcome after selective amygdalo-hippocampectomy. *Epilepsy Res* 1993;16:195–206, with permission.)

tern becomes apparent in a similar distribution (323) that ma y be difficult to differentiate from epileptic acti vity. This exacerbation of interictal spiking subsides in fe w days, as indicated b y postoperative scalp EEGs (212), and does not presage unf avorable seizure outcome. In contrast to transcor tical amygdalohippocampectomies that entail excision of the entorhinal cortex surrounding the amygdala (the uncus), stereotactic amygdalohippocampectomies substantially sparing this cortex are followed by unchanged or decreased spiking in the acute ECoG (36,37,230). Because the entorhinal cor tex (the uncus) projects extensively to cortical association areas (112), acute widespread cortical deafferentation incident to ab lation of the entorhinal cor tex may play a

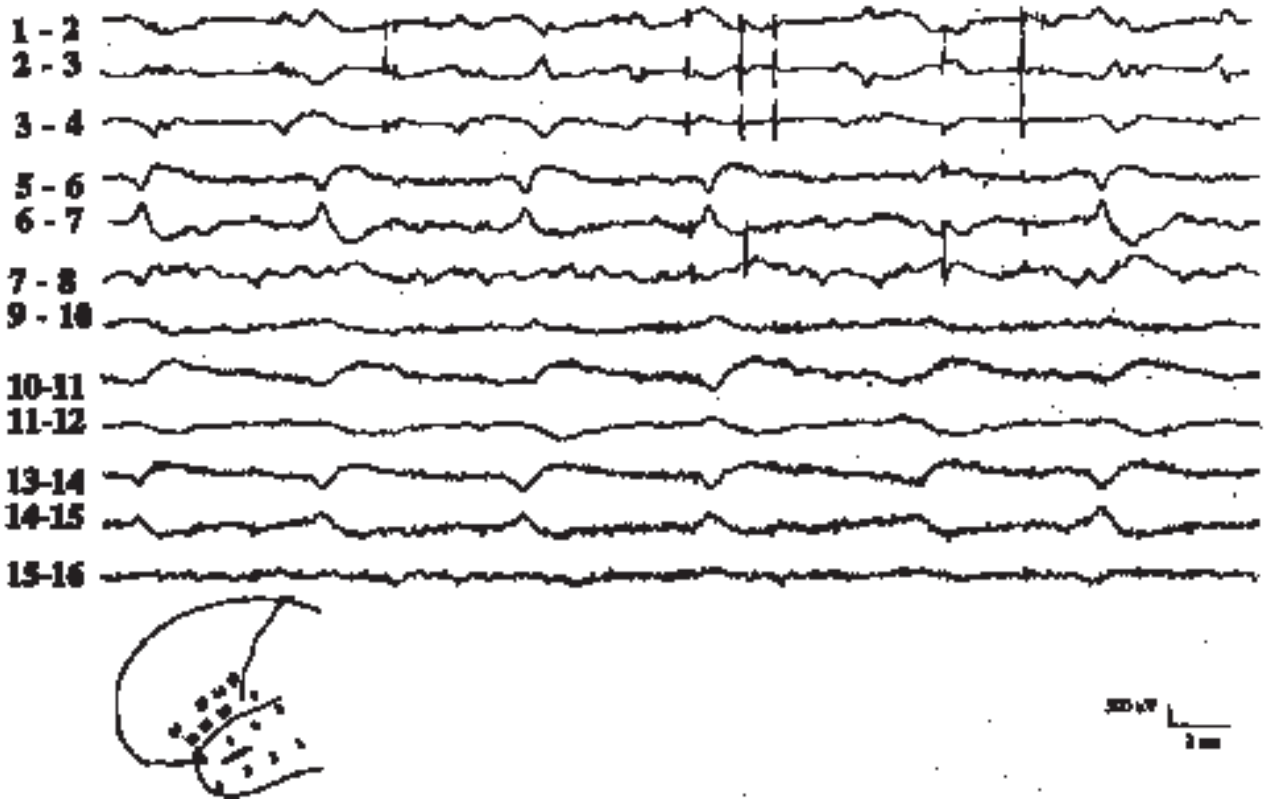

FIG. 21.9. Same patient as in Figure 21.8. After transcortical amygdalohippocampectomy, the ECoG shows frequent spikes over the lateral temporal cortex, with intervening periods of voltage depression and slow waves. (From Cendes F, Dubeau F, Olivier A, et al. Increased neocortical spiking and surgical outcome after selective amygdalo-hippocampectomy. *Epilepsy Res* 1993;16:195–206, with permission.)

major role in the dramatic but transient increase of cortical spiking that follows immediately after amygdalohippocampal resection (230).

In some of the preceding studies, the hippocampus, the amygdala, or both were spared from resection when their intraoperative recordings were free of spikes (158,204). The belief that lack of interictal spiking during a brief intraoperative recording guarantees the functional integrity of any brain area is contrary to basic interpretive EEG criteria and is impugned by the observation that no spikes were detected intraoperatively in some patients whose earlier preoperative recordings had demonstrated spikes in medial or medial and lateral temporal lobe structures (324) (see "Preresection ECoG Findings" under "Temporal Lobectomy" above). Also, favorable seizure control was achieved by the reoperation of individuals whose seizures had not been relieved by an earlier resection that spared mostly spike-free medial temporal structures (106).

Surgery of Neocortical Epilepsies

Lobar Origin of Neocortical Epilepsies and Factors Hindering Localization

Partial epilepsies symptomatic of structural lesions other than medial temporal sclerosis (and other less frequent medial temporal lesions) are grouped under the term *neocortical* epilepsies (60). The most common lesions include slow-growing tumors, localized cortical dysplasias, vascular malformations, encephalomalacia from previous stroke, and posttraumatic scars.

A major feature of seizures arising in the neocortex is that, because of extensive connecting pathways, they tend to spread rapidly to other areas within and outside the lobe in which they originate. Clinical manifestations of spread to other regions often predominate and tend to obscure the manifestations of the initial localized discharge, thus providing inadequate or even deceptive localizing information. This is evident in neocortical temporal lobe epilepsy, in which ictal activity developing from the temporal neocortex spreads rapidly to medial temporal areas, thus often making it exceedingly difficult to differentiate clinically between seizures of lateral and of medial temporal onset (334). Similarly, seizure spread from functionally distinct areas of the lateral, orbital, or medial frontal lobe surfaces (19) to other regions of the same and adjacent lobes causes clinical manifestations that often provide no precise or even misleading localization (334,335). Major clinical features of seizures originating in the parietal and occipital cortices also reflect spread to other lobes.

Localization of seizure onset and extent of the epileptogenic zone by extracranial as well as intracranial EEG recordings is often difficult, especially in patients undergoing surgery for frontal lobe epilepsy. Biophysical and physiological factors concur to prevent the detection or to hinder the recognition of restricted interictal as well as ictal neocortical discharges while favoring the manifestation of extensive lobar, multilobar, or even widespread discharges. Spikes generated in discrete areas of the depths of cortical sulci often are not detected even by overlying subdural electrodes (109,143,245), and discharges occurring in medial or inferior hemispheric surfaces or in the insula often fail to appear in recordings from the lateral surface while giving rise to secondary widespread discharges. Seizures and interictal spikes rapidly propagating from small cortical sites to other areas of the same and other lobes frequently mimic large spiking areas (245,246). Depth recordings are limited by poor spatial resolution of depth electrodes at the cortical level (129,245,246). The inadequacies of direct cortical recordings were evident in a series of patients with frontal lobe epilepsy only 15% of whom displayed unilateral focal or regional frontal lobe spiking, whereas 32% had lobar and 25% multilobar spikes (244). In harmony with these findings, 75% of patients who underwent frontal lobe resections demonstrated spikes outside the limits of the excision (32) (Fig. 21.10). Despite these limitations, some statistically significant associations have been reported between postoperative seizure outcome and the presence or absence of spikes or individual measures of preresection (193) or postresection (38,193,222,249,268, 321) ECoG spiking.

Lesionectomy for Epileptogenic Slow-Growing Tumors, Vascular Malformations, Encephalomalacia, and Posttraumatic Scars

The relationship between a lesion demonstrated by neuroimaging and the epileptogenic zone varies depending on the pathological substrate. Neocortical lesions such as slow-growing tumors (most commonly low-grade astrocytomas, oligodendrogliomas, gangliogliomas, and dysembryoplastic neuroepithelial tumors), vascular malformations, encephalomalacia from previous stroke, and posttraumatic scars are not intrinsically epileptogenic but often cause interictal spiking whether limited to adjacent tissues or more widespread (15,110,234). Removal of the lesion while sparing "potentially epileptogenic" bordering tissues, or "strict lesionectomy," has given variable results, with seizure-free outcomes being reported in 30%–75% of patients (44,205,289). Resection of potentially epileptogenic adjacent tissues while sparing the lesion has proved unsuccessful (93). In contrast, up to 80%–90% of patients are rendered seizure free or nearly seizure free by excision of both the lesion and a generous margin of potentially epileptogenic bordering tissue, or "extended lesionectomy" (15,27,38,67,101,152,237,251,341). Even partial resection of the lesion met with appreciable success provided all potentially epileptogenic cortex had also been removed (34,100,216).

In principle, intraoperative ECoG appears to be better suited than other methods to identify the potential epileptogenicity of neural tissues bordering the lesion. However, the frequently broad distribution of ECoG spiking may invite unnecessarily large excisions (99,154,295,305). Thus some centers have chosen other approaches to the determination of the margins of the resection that are based on visual inspection, MRI signal abnormalities, histopathological analysis of frozen sections, or combinations of these methods (101). Functional mapping by electrical stimulation may be needed as well to exempt indispensable cortical areas from resection.

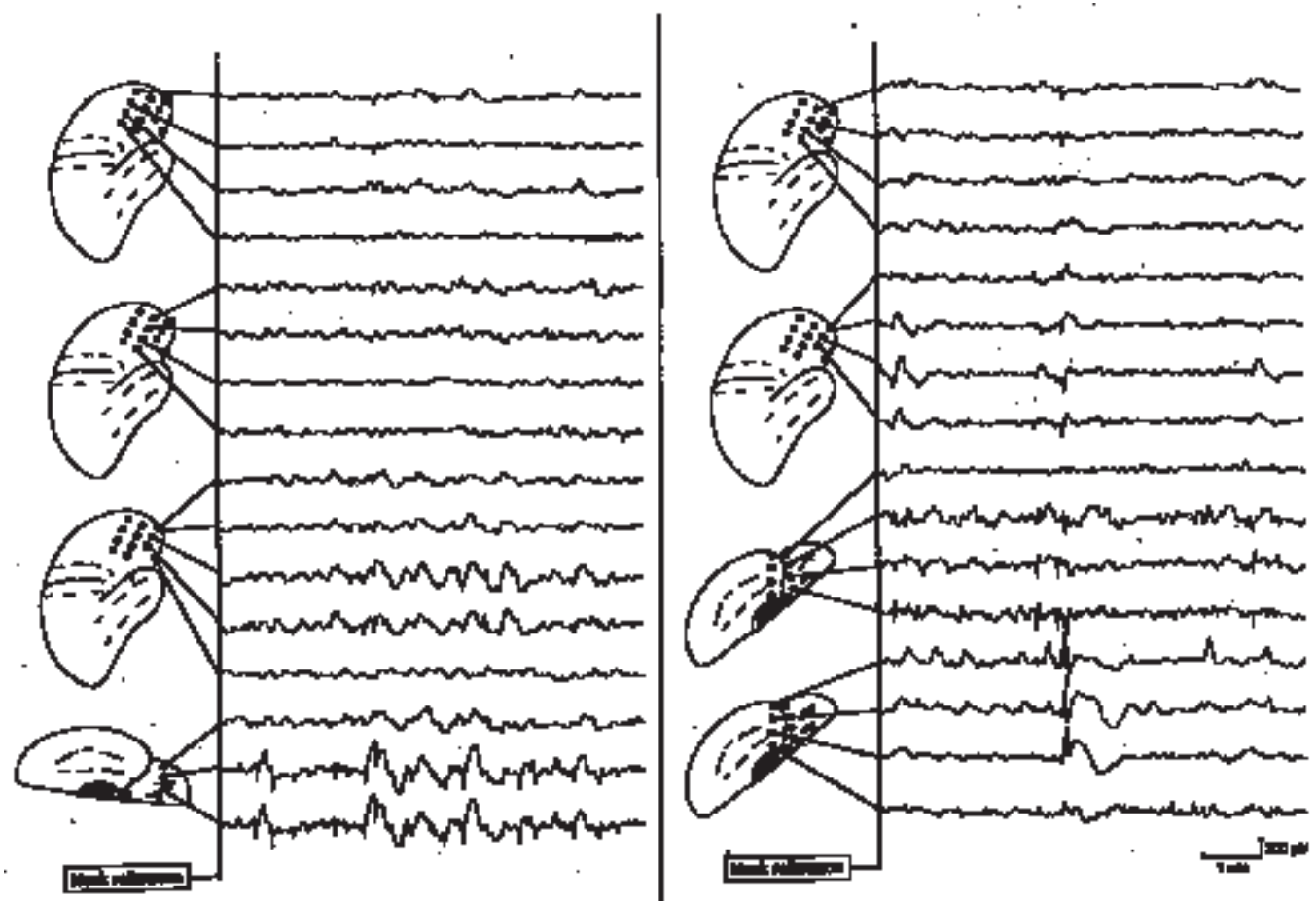

FIG. 21.10. A 31-year-old-man had seizures characterized by body numbness and tingling, a queasy feeling in the stomach, frightened expression and vocalizations, flailing movements of the arms and legs, and infrequent minor automatisms, followed by prompt recovery of responsiveness and denial of having lost consciousness. Occasionally, seizures were followed by tonic–clonic generalization. Intraoperative ECoG shows frequent spikes and sharp waves over the right orbital frontal and inferior frontal cortices, with complex polarity and temporal relationships, and spike-and-slow-wave activity occurring independently over the right infratemporal surface. Two years after surgery, the patient was seizure free. (From Chatrian GE, Quesney LF. Intraoperative electrocorticography. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a comprehensive textbook*, Vol 2. New York: Lippincott–Raven, 1997:1749–1765, with permission.)

Surgery of Localized Cortical Dysplasias

Cortical developmental malformations identified by high-resolution MRI are increasingly recognized as causes of medically intractable neocortical epilepsy. Subdural electrodes overlying these lesions frequently detect seizures, interictal spikes, delta waves, and decreased thiopental-induced beta activity (59,223). The manifestation of seizures that consist of bursts of repetitive spikes mostly restricted to the dysplastic lesion attests to intense intrinsic epileptogenicity that distinguishes dysplastic cortex from most other cerebral lesions (69,228,262) (Fig. 21.11). Sporadic spikes have a more widespread distribution (69,228,262). Remarkably, in a group of patients with frontal lobe epilepsy, seizure activity had 94% sensitivity to and 75% specificity for localized cortical dysplasias, whereas sporadic spikes showed no significant association with type of pathology (87). The detection of intrinsic localized seizures allows the ECoG to complement the MRI delimitation of these lesions, thus contributing to ensure the completeness of resection (222). Abolition of ECoG-detected seizures is significantly associated with favorable seizure outcome, whereas persistent sporadic spikes show no such relationship (87). The use of the ECoG in the resection of localized cortical dysplasias is a promising development that deserves further study.

Surgery of Dual Pathology

In a substantial proportion of patients in whom resection of indolent tumors, arteriovenous malformations, or localized cortical dysplasias involving lateral temporal, posterior temporal (93), or occipital (227) cortices fails to achieve seizure relief, acute and chronic depth recordings demonstrate interictal spikes in the ipsilateral hippocampus (49,93,267,340) and seizures that mostly arise in medial temporal structures, including the hippocampus (189). The finding of this "dual pathophysiology" is mirrored by the intraoperative demonstration of interictal spikes that widely involve the temporal neocortex in patients with epileptogenic tumors confined to the medial temporal structures (128,197). These observations suggest that intense, protracted firing of neocortical epileptic neurons can incite the development of interictal as well as ictal discharges in previously normal, anatomically remote but synap-

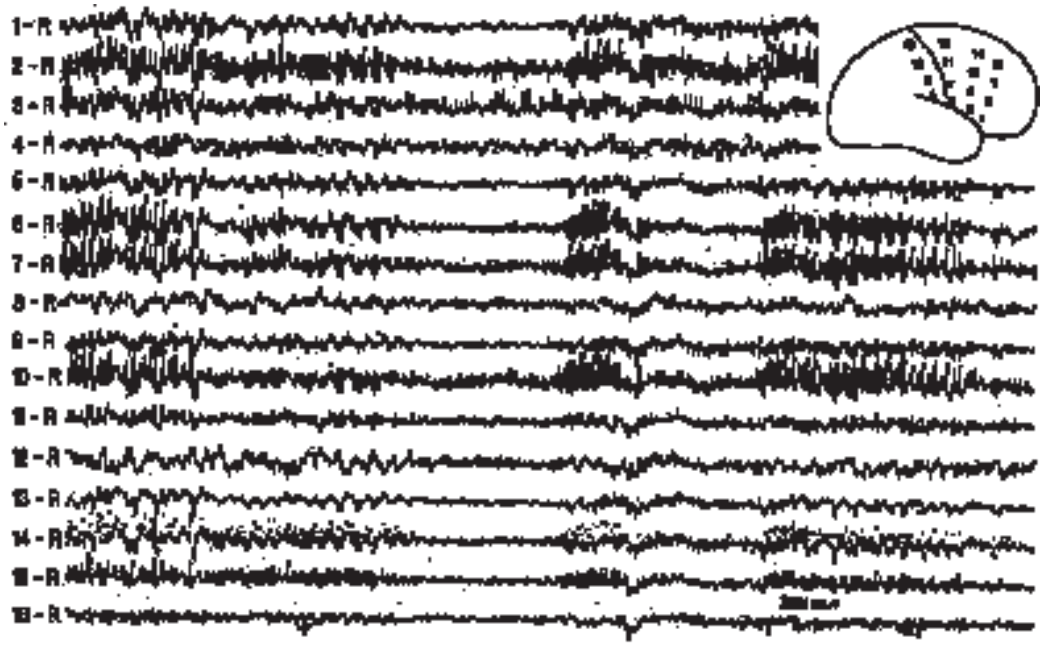

FIG. 21.11. A 7-year-old girl had a right frontocentral cortical dysplasia demonstrated by MRI. Her intraoperative ECoG showed numerous seizures consisting of bursts of high-amplitude spikes over the right frontocentral cortex as in this figure. (From Palmini A, Gambardella A, Andermann F, et al. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol* 1995;37:476–487, with permission.)

tically connected medial temporal neurons, and that the reverse can also be true. An analogy has been recognized by some between these findings and those characterizing the animal model of secondary epileptogenesis by kindling (39,115,133,313). That interictal spikes can be secondarily elicited in humans at a distance from an epileptogenic zone has long been known (108,143). However, despite suggestive evidence (200,203), it has not been adequately demonstrated that secondary spiking areas can become independently epileptogenic in humans as in animals, that is, capable of spontaneously generating seizures after removal of the primary epileptogenic zone (179). Unfortunately, visual analysis of interictal ECoG spikes occurring independently in distant areas of the temporal lobe can neither differentiate between primary and secondary discharges nor determine the epileptogenic potency of the neural tissues generating them.

Many patients with cortical neuronal migration disorders and porencephalic cysts and a few individuals with slow-growing tumors and vascular malformations also show various degrees of hippocampal neuronal loss and sclerosis (16,51,102,175,289) or MRI-defined hippocampal atrophy (43, 49)—evidence of "dual pathology." In some centers, awareness of the frequency of dual functional and structural pathologies has influenced the surgical approach to extrahippocampal epileptogenic lesions, which currently consists of complete removal of both the extrahippocampal lesion and medial temporal structures to the extent that it is functionally possible. There is no agreement on whether electrophysiological monitoring is useful (51, 164,176,216,340) or unnecessary (43,99) during these resections.

Surgery of Cryptogenic (Nonlesional) Epilepsies

Localization-related epilepsies without a lesion demonstrated by current neuroimaging methods are referred to as "cryptogenic" or, less appropriately, "nonlesional" epilepsies (60). Microdysgenesis and microscopic gray matter heterotopias are frequent findings in resected specimens, suggesting that developmental alterations more discrete and diffuse than those characterizing (lesional) neocortical epilepsies may be the substrate of some cryptogenic epilepsies (171). Such pathology could account for the poor seizure control (15%–30% seizure-free outcome) achieved by localized resections for cryptogenic, as opposed to lesional, epilepsies (46,270,278).

The belief is widely held that most seizures of partial cryptogenic epilepsy arise in the neocortex. Thus several authors include them in the category of neocortical epilepsies, which they subdivide into lesional and nonlesional. However, recent observations suggest that a substantial number of seizures of cryptogenic temporal lobe epilepsy involve at the onset medial temporal structures or both medial temporal and neocortical (temporal or extratemporal) areas (216). The localization of cryptogenic (nonlesional) epilepsies requires careful preoperative studies of ictal patterns with intracranial electrodes. Whether the intraoperative ECoG can contribute additional useful information is unclear at present.

Resection of Large Hemispheric Lesions: Functional Hemispherectomy, Hemidecortication, and Multilobar Removals

Extensive resections such as hemispherectomy, hemidecortication, or multilobar removals are sometimes necessary to alleviate medically refractory seizures in patients displaying profound, lateralized neurological deficits caused by long-standing hemispheric lesions. These include sequelae of prenatal, perinatal, and postnatal insults; extensive cortical dysplasias; hemimegalencephaly; dysplastic gangliocytomas; tuberous sclerosis; Sturge-Weber syndrome; and chronic progressive Rasmussen's encephalitis (11,285). ECoG findings are best known in "functional hemispherectomy," which, unlike complete or "anatomical hemispherectomy," removes the temporal lobe and the central cortex, leaving in place disconnected, vascularized frontal and parieto-occipital cortices (255). Prominent multilobar spikes are commonly demonstrated in the ECoG before this procedure (281,286,322, 325). These discharges often persist or increase, and a burst-suppression pattern may develop over the isolated frontal and parieto-occipital cortices (281,286,322,325) without any relation to seizure outcome (281,312,322). Best seizure control is achieved by carrying out as complete a removal of obviously damaged cortex as can be safely done, irrespective of ECoG findings (257,312). However, in some patients with Rasmussen's encephalitis in whom a more limited resection had been planned preoperatively, the distribution of spiking may suggest the need for additional insulectomy or hemispherectomy (312). Also, the demonstration of spikes in contralateral parasagittal cortex by electrodes applied against the falx has been said to portend poor seizure outcome (312).

ECoG IN CORTICAL DISCONNECTION SURGERIES

Multiple Intracortical Subpial Transections

Morrell and his colleagues (202,207,279) have devised a procedure consisting of multiple intracortical subpial transections designed to selectively

interrupt horizontal intracortical connections while largely preserving vertical columnar organization and connections, and blood supply. This alteration of local cortical connectivity is intended to minimize the opportunities for neuronal synchronization and horizontal spread of excitation, thus diminishing epileptogenicity without impairing function. Multiple subpial transections are used, mostly in combination with resection of adjacent dispensable cortex, to relieve partial seizures caused by epileptogenic processes encroaching on nonresectable regions such as precentral, postcentral, Broca's, and Wernicke's areas (137,202,206,207,279). This operation offers an at least temporary alternative to hemispherectomy in conditions that include focal cortical dysplasias and heterotopias, chronic progressive Rasmussen's encephalitis, and epilepsia partialis continua (202,207,279). According to their proponents, transections are followed immediately by marked decrease in voltage of all ECoG activities, followed by recovery of background rhythms but not of spikes (202,207,279). ECoG recordings would be essential to determine the extent of cortex to be transected and to verify the effectiveness of the procedure. However, other investigators have described more variable effects of multiple subpial transections that ranged all the way from complete abolition to 200% increase of ECoG spiking, without demonstrable relation to either seizure outcome or completeness of transection (30,32).

Corpus Callosotomy

EEGs have been monitored during total or partial section of the corpus callosum (264) performed with the intent of mitigating medically intractable drop attacks associated with severe diffuse epileptogenic encephalopathies such as Lennox-Gastaut syndrome (12,35), as well as unilateral seizures with frequent generalization that commonly occur in Rasmussen's encephalitis (10,260,293) and other hemiplegic syndromes, including Sturge-Weber disease, hemimegalencephaly, and cerebral cortical dysgenesis. Evidence was published that increasing disruption of bilaterally synchronous epileptiform discharges occurs in the scalp EEG as callosal section progresses (105,186). Also, combined EEG and ECoG monitoring suggested that sections limited to the most anterior part of the corpus callosum were sufficient to interrupt the bilateral synchrony (185,240). However, synchrony often resumed and generalized seizures variably persisted or returned after callosotomy (35,105,186). Most authors agree that intraoperative loss of bilateral synchrony of epileptiform activity neither reliably determines the extent of corpus callosotomy to be performed (90) nor dependably predicts the success of this palliative surgery (292). Moreover, it is unclear whether ECoG recording offers appreciable advantages over surface EEGs in monitoring the effects of callosotomy (32).

ECoG IN THE SURGERY OF OTHER EPILEPTIC DISORDERS

Epilepsia Partialis Continua

Occasionally the electrophysiologist is called on to perform an ECoG during surgery for epilepsia partialis continua (166), a particular form of status epilepticus characterized by localized, virtually incessant clonic jerks sometimes associated with intermittent, spreading partial somatomotor seizures. Most commonly, this disorder occurs in patients with (a) a variety of acute or chronic unilateral lesions in or near the motor cortex; (b) more extensive, primarily cortical, unilateral or strongly lateralized inflammatory alterations such as those characterizing Rasmussen's chronic encephalitis; (c) certain systemic metabolic derangements unaccompanied by detectable structural lesions such as nonketotic hyperglycemia; and (d) no demonstrable etiology (18,33,260,276,286,304). In keeping with the variable nature and extent of pathological and scalp EEG alterations, when present (17,57,58,168,286, 304), ECoGs from the hemisphere contralateral to the jerking reveal in some patients spiking and sometimes seizures that may be confined to a small portion of the precentral gyrus or may involve multifocally larger cortical areas, and may or may not be temporally related to the muscular jerks (286,304). These events may be absent in scalp EEGs. In other individuals, no discharges can be demonstrated even by meticulously surveying the cortical surface in the presence of ongoing clonic activity (286,304). Lack of epileptiform activity in the ECoG, the EEG, or both is likely related to the small spatial extent of the cortical area producing the jerks (109,117); the possible location of the discharging neurons in the depths of sulci (109,304); the asynchronous firing of multiple, small groups of neurons within the area involved (304); or a combination of these factors. Results of recordings and electrical stimulations with stereotactically implanted electrodes (18,331) have discredited the alternative interpretation that the electrophysiological and clinical manifestations of epilepsia partialis continua may have a subcortical substrate (155,208).

Limited ECoG-guided corticectomies have succeeded in abolishing epilepsia partialis continua in a few patients, especially in the absence of widespread pathology (63,168). However, in most individuals, particularly

those suffering from Rasmussen's encephalitis, spikes persist in cortices spared by limited excisions, and clinical epileptic manifestations show no or little improvement (213,286,304). In these instances, multiple subpial resections with ECoG monitoring have provided at least temporary relief (208) before resorting to multilobar resections or hemispherectomy (213).

Landau-Kleffner Syndrome

The ECoG has contributed to the understanding of the mechanisms underlying the Landau-Kleffner syndrome, or acquired epileptic aphasia. This puzzling disorder characterizes children who have developed age-appropriate speech, lose speech capacity acutely or gradually, and typically manifest various types of epileptic seizures and behavioral deterioration. Although long-term prognosis for seizures is good, serious neuropsychological sequelae are reported in the majority of patients (277).

A peculiarity of most patients with Landau-Kleffner syndrome is that, during non–rapid-eye-movement sleep, their EEGs show virtually continuous bilateral and widespread spike-and-slow-wave activity most prominent over the temporal areas (22,65,277). Methohexital suppression and intracarotid amobarbital tests have demonstrated that the bilateral spike-and-slow-wave activity is dependent on discharges emanating from one hemisphere (201,209), and dipole mapping and magnetic source imaging studies have shown that they originate in the dorsal surface of the superior temporal gyrus (201,226). In a few selected individuals, intraoperative ECoGs have detected spikes that are confined to a small patch of cortex located within the sylvian fissure on or close to Heschl's gyrus, that is, in cortex involved in acoustic processing (201,226). ECoG-guided multiple subpial transections of the intrasylvian source and of surrounding tissues resulted in cessation of seizures, normalization of the EEG, and gradual recovery of speech in the majority of these patients (209) (Fig. 21.12). However, because no localized structural lesion is demonstrated in most cases and the seizure disorder tends to resolve with advancing age (22,277), there are no clear indications at present for the surgical treatment of patients with Landau-Kleffner syndrome.

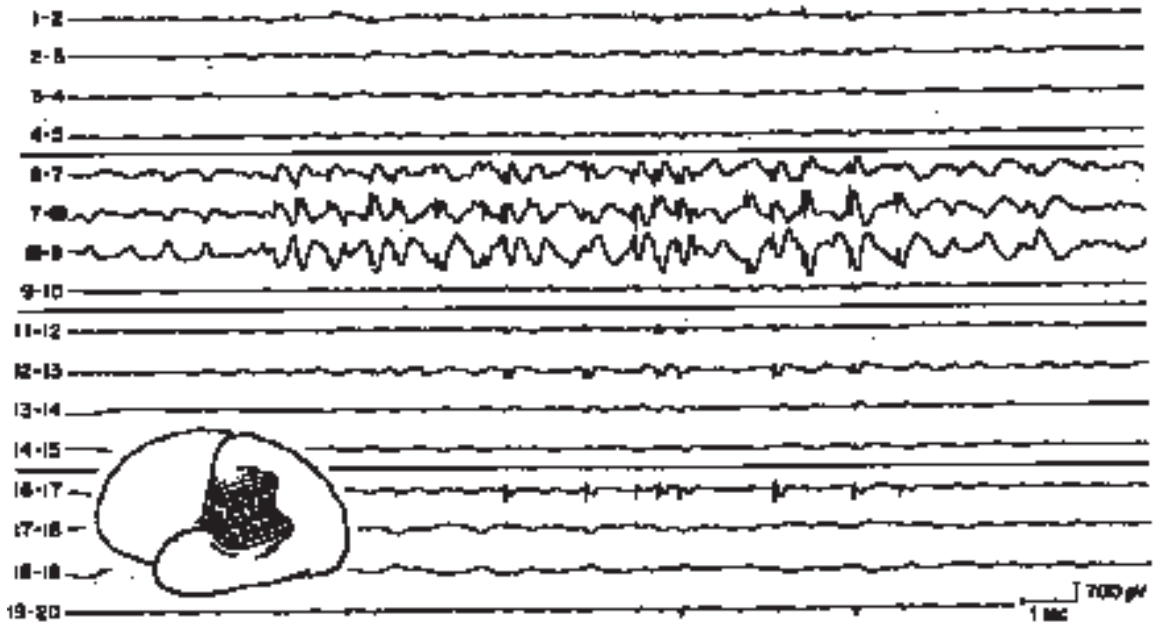

FIG. 21.12. Recordings from a subdural electrode plate inserted between the lips of the Sylvian fissure opened at surgery. Prominent spike-and-slow-wave activity is detected at electrode 8 and to a lesser extent electrode 7, located on the dorsal surface of the superior temporal gyrus immediately posterior to Heschl's gyrus. (From Morrell F. Electrophysiology of CSWS in Landau-Kleffner syndrome. In: Beaumanoir A, Bureau M, Deonna T, et al, eds. *Continuous spikes and waves during slow sleep: electrical status epilepticus during slow sleep*. London: John Libbey, 1995:77–90, with permission.)

CONCLUSIONS

Critical review of traditional principles of intraoperative ECoG reveals that this method has major limitations. Generally, localized interictal spikes directly recorded from the brain are not reliable markers of local epileptogenicity defined as the capacity for active, independent seizure generation. Afterdischarge thresholds and the reproduction of the initial, or all, manifestations of the patient's habitual seizures do not dependably identify the site of origin of the patient's spontaneous seizures. In addition, because interictal spikes often variably exceed the extent of tissue that must be removed to achieve seizure control, their distribution provides no reliable guidance in determining the margins of the resection.

In patients with chronic, medically intractable medial temporal lobe epilepsy, the presence or absence, topography, and individual measures of interictal spiking detected in medial and lateral temporal locations before as well as after temporal lobectomy generally are of little assistance in the conduct of surgery. These features play no substantial role in establishing the site of onset of the patients' seizures; differentiating between primary and secondary spiking areas; determining the epileptogenic potency of the latter regions; choosing between anteromedial, lateral, and selective medial temporal resections; and predicting postoperative seizure outcome. Recognition of these limitations and the progress of neuroimaging have decreased the dependence of resective temporal lobe surgery on intraoperative interictal ECoG (as well as preoperative invasive recordings). Direct recording of interictal spikes during temporal lobectomy is increasingly regarded as of primarily academic interest. However, whenever functional mapping of indispensable cortex is performed, ECoG monitoring is essential to determine afterdischarge thresholds and document the subliminal nature of the stimulus.

Transcortical amygdalohippocampectomy is commonly followed by marked, transient, clinically insignificant increase in interictal spiking in the temporal neocortex. Thus, ECoG monitoring during this surgery serves no practical purpose and may prove misleading.

In neocortical epilepsies symptomatic of lesions such as slow-growing tumors, vascular malformations, encephalomalacia, and posttraumatic scars, whether temporal or extratemporal, excision of the lesion and of a generous margin of potentially epileptogenic bordering tissue is commonly performed. Although, in principle, electrophysiological recordings appear to be eminently suited to identify potential epileptogenicity of surrounding tissues, the frequently extensive distribution of interictal ECoG discharges limits the use of this method in the surgery of these lesions.

Some patients who have undergone unsuccessful excision of epileptogenic lesions involving the lateral temporal, posterior temporal, and occipital cortices but sparing medial temporal structures manifest interictal spikes and seizures that mostly arise from ipsilateral medial temporal structures, especially the hippocampus. In a proportion of cases, medial temporal sclerosis and hippocampal atrophy are demonstrated. Such dual functional and structural pathologies are treated in most centers with resections of both the extrahippocampal lesion and medial temporal structures. However, there is no agreement on the need for ECoG during these surgeries.

There is no indication that ECoG is helpful in performing multilobar resections and functional hemispherectomies, and that direct recordings are more valuable than scalp EEGs in assessing the acute effects and long-term results of corpus callosotomy. Also, it is not clearly established that this method dependably monitors the effects of multiple intracortical subpial transections.

The utility of ECoG in the surgery of epilepsia partialis continua varies depending on factors that include the nature and extent of the underlying pathology. In a few cases, direct cortical recordings during surgery have contributed to clarification of the pathophysiology of Landau-Kleffner syndrome. However, there are no clear indications at present for the surgical treatment of this condition.

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Chapter 22

Automatic Detection and Analysis of Seizures and Spikes

Jean Gotman

Computer-Assisted Long-Term EEG Monitoring
Recording Seizures
Recording Interictal Activity
Recording Behavior
Postdetection Analysis
Analysis of Seizure Activity
Analysis of Interictal Activity
Conclusion
Acknowledgment
References

When evaluating epileptic patients, it is often important to obtain thorough documentation of ictal and interictal electroencephalographic (EEG) patterns, in conjunction with behavioral patterns if possible. This is critical to help in the differential diagnosis of epilepsy, to determine seizure type for adequate medical treatment, in various situations in the intensive care unit, and of course when considering surgical treatment. This information can be obtained with long-term monitoring, during which the EEG and the patient's behavior are observed and recorded continuously. Thus all spikes and seizures are recorded, the observer may interact with the patient during seizures, and electroclinical correlations may be performed fully. In order to properly characterize a complicated seizure problem that can involve multiple seizure types, or to measure the effect of antiepileptic medication, it may be necessary to monitor a patient for 1–3 weeks. The EEG may include scalp or intracranial electrodes, typically 32–64 channels. Continuous observation and recording of the EEG and of behavior over a period of several days or weeks is an immense and expensive task, requiring considerable personnel for observation and equipment for recording. If sufficient personnel are not available for constant observation and recording, the following questions arise: Should a complete recording be made on magnetic medium? Should this complete recording be reviewed (also a very time-consuming task), or should a selective review be performed? If a selective review is performed, how is the selection to be made? Or should the recording itself be selective, including only the events of interest?

It has become clear in the last several years that computers can be extremely helpful in making the procedure of long-term epilepsy monitoring less tedious and less expensive. They can also assist in the review and analysis of the EEGs of epileptic patients, and they are used for data archiv-

ing. In a more recent development, behavioral video recording can be performed with the assistance of computers as well. The first part of this chapter discusses how computer-based recordings, particularly automatic spike-and-seizure detection methods, can facilitate long-term epilepsy monitoring in the hospital and at home. The second part discusses how spikes and seizures can be further analyzed by computer methods.

COMPUTER-ASSISTED LONG-TERM EEG MONITORING

Whereas it was cumbersome to perform a continuous 24-hour recording on a paper-based machine, the present size of computer disks and the resolution of computer screens are such that it is simple to perfom a continuous 24-hour recording on a standard computer. A computer-based recording has the advantages over paper of a flexible review procedure, with immediate access to any part of the recording, and the availability of numerous methods of data manipulation and analysis.

Storing a recording on a computer makes use of its memory capacity, but its computing power also offers the opportunity of attempting to identify the events specific to epilepsy. In most 24-hour recordings, 95%–99% of the recording offers little information of value in the evaluation of the epileptic disorder. Computer analysis methods can help in marking the 1%–5% of the recording that is important, thus greatly facilitating review. The detection of *seizures* and of *interictal spikes* is discussed separately in this section.

Recording Seizures

What Is a Seizure?

In the context of epilepsy monitoring, it is necessary define what is meant by "seizure." We can define first a "behavioral seizure" as the behavioral manifestations of an epileptic seizure, as perceived by the patient, seen by an observer, or recorded on videotape. We can then define the "electrographic seizure" (or "EEG seizure") as an abnormal paroxysmal EEG pattern. In a large fraction of cases, behavioral and electrographic seizures can be observed simultaneously, which is why we have been able to identify the EEG changes specific to seizures. In many cases, however, there is dissociation between behavior and the EEG. Two types of dissociation are possible: a behavioral seizure in the absence of EEG evidence of a seizure, and an electrographic seizure without behavioral manifestations.

When a behavioral seizure is present in the absence of EEG changes, if we assume that the seizure is indeed epileptic (this chapter does not discuss the means of differentiating epileptic from nonepileptic seizures), then abnormal EEG activity is present *somewhere in the brain*. It is simply not available to the particular method of observation being used, that is, to the particular arrangement and location of electrodes. The discharge may, for instance, be limited to the mesial frontal regions, and the patient is being monitored with only scalp electrodes, or only intracerebral electrodes in the temporal lobes. In the context of epilepsy monitoring, it must be clear that such a seizure will be missed by observation, review, or computer analysis of the EEG alone.

An EEG seizure that is present in the absence of a behavioral seizure is commonly referred to as a "pure electrographic seizure" or "subclinical seizure." If the absence of an EEG discharge accompanying a behavioral seizure is a pitfall of the method of measurement (the discharge was present but not visible to the electrodes), the absence of a behavioral manifestation of an EEG seizure may be a pitfall of the method of observation. If a patient is lying in bed watching television, unresponsiveness, inability to speak or to understand, minor automatisms, or loss of muscle tone cannot be observed unless active questioning is performed. Even correct responses to many questions do not exclude clinical signs: Seizures involving only memory have been observed (63). In other words, the presence of clinical signs is a function of the method of questioning or observation, hence the importance of recording all seizures, with and without overt clinical signs, and observing them as precisely as possible. The importance of "subclinical" seizures has been discussed with respect to evaluation for epilepsy surgery (76). Automatic seizure detection and seizure warning systems can be helpful in this situation (see "Limitations and Future Developments" below).

Recording and Review Strategies to Obtain Seizures

All types of seizures, with or without clinical and EEG manifestations, should ideally be recorded. As indicated above, it is possible to perform a continuous recording on a computer disk for a period of 24 hours. This represents a large amount of EEG to be reviewed, but computer review on a high-resolution screen can be quite fast: 32 channels of EEG can be presented 10–20 times faster than real time, resulting in a review lasting 1–2 hours. Such a fast review can result in small seizures being missed, particularly when more than 12–16 channels are utilized (64). The 1–2 hours also

do not include the time required for the analysis of seizures or other potentially interesting events. Thus the full review of a 24-hour recording is quite time consuming and strenuous.

Alternative strategies have been developed by many institutions. These strategies consist mainly in a partial review, with an attempt to select the most relevant sections. The most important sections are of course those when a behavioral seizure was noted by the patient or an observer. In addition, randomly selected sections are often reviewed as well. This strategy entails the significant risk that seizures of which the patient is unaware and that are not observed will be almost systematically missed. This may be an acceptable compromise if the patient is under close observation, but could be quite dangerous otherwise.

Methods of Automatic Detection of Seizure Patterns

Some methods of seizure detection are based on behavioral manifestations of seizures; for example, mechanical sensors under a mattress can detect the strong rhythmic movements of generalized tonic–clonic seizures. The limitations of this kind of detection method are obvious—many seizures do not include such strong movements. This discussion instead concentrates on seizure detection methods based on EEG analysis. Because some seizures do not have EEG changes, EEG-based methods cannot be expected to detect them. There are also seizures that have mild or *nonspecific* changes, such as brief desynchronization or groups of theta or delta waves (1), making their differentiation from commonly seen patterns difficult. Thus there are also limitations to seizure detection by EEG, but these are not too restrictive because the vast majority of seizures have clear and relatively specific EEG changes.

The problem of seizure detection is inherently difficult because seizure activity can consist of a variety of morphologies. Unlike spikes, which have a relatively well-defined morphology, seizures can include patterns such as low-amplitude desynchronization, polyspike activity, rhythmic waves at a wide variety of frequencies and amplitudes, and spike-and-wave activity (6). In extracranial recordings, electromyographic (EMG) movement and eye blink artifacts often obscure seizures. From the point of view of pattern recognition, the problem is therefore complex.

Prior et al. (68) described the use of their cerebral function monitor to identify generalized tonic–clonic seizures; these could be recognized on the tracing as a large increase followed by a clear decrease in EEG amplitude (the postictal depression) and by large EMG activity. Such large seizures with major changes could also be identified in monkeys with experimental epilepsy by a characteristic pattern on slow paper tracings (56). Ives et al. (48) described a method in which 16 channels of EEG were added, bandpass filtered, and subjected to amplitude discrimination. This technique could detect large seizure discharges but was quite insensitive. Babb et al. (4) implemented an electronic circuit for the detection of seizures in recordings from intracerebral electrodes. A seizure was recognized when a rapid succession of large-amplitude spikes, lasting at least 5 seconds, was found. Murro et al. (61) described a method based on spectral parameters and discriminant analysis.

Gotman (23,24) presented a computer detection method that attempted to recognize a wide variety of seizure patterns. This method identified patterns that might represent seizure activity, marking them for later examination by traditional visual inspection. The method was therefore designed to be as sensitive as possible. False detections, as long as they were not extremely frequent, were not detrimental because all detections had to be visually reviewed. Observation of numerous seizures with this method led to the conclusion that most seizures, at some time during their development, would include activity that is *paroxysmal* compared to the background (the paroxysm could consist of increased amplitude or increased frequency); such activity would also be *rhythmic* (with frequencies varying from 3 to 20 cycles per second), and relatively *sustained* in duration (lasting several seconds).

Measurements of these characteristics were obtained by breaking down the EEG into half-waves and measuring, for every 2-second epoch, the average amplitude of the half-waves relative to that of the background (indicating whether an epoch was paroxysmal), the average duration of the half-waves (indicating frequency), and the coefficient of variation of half-wave duration (indicating the regularity of duration, or the rhythmicity). The background was constantly updated and included EEG sections recorded before and after the active epoch. Comparing the amplitude, frequency, and rhythmicity measurements of the background to those of the active epoch allowed the development of a decision tree for the detection of seizure activity. Detections may be triggered by rhythmic activity of moderate amplitude (Fig. 22.1) or by a sudden increase in frequency. It is not necessary to detect the *onset* of a seizure because the purpose of detection is to mark the recording. The interpreter will start at the mark and look for the onset.This method of seizure detection has been made available commercially and is in widespread use throughout the world. It has also been used to monitor experimental animals (60).

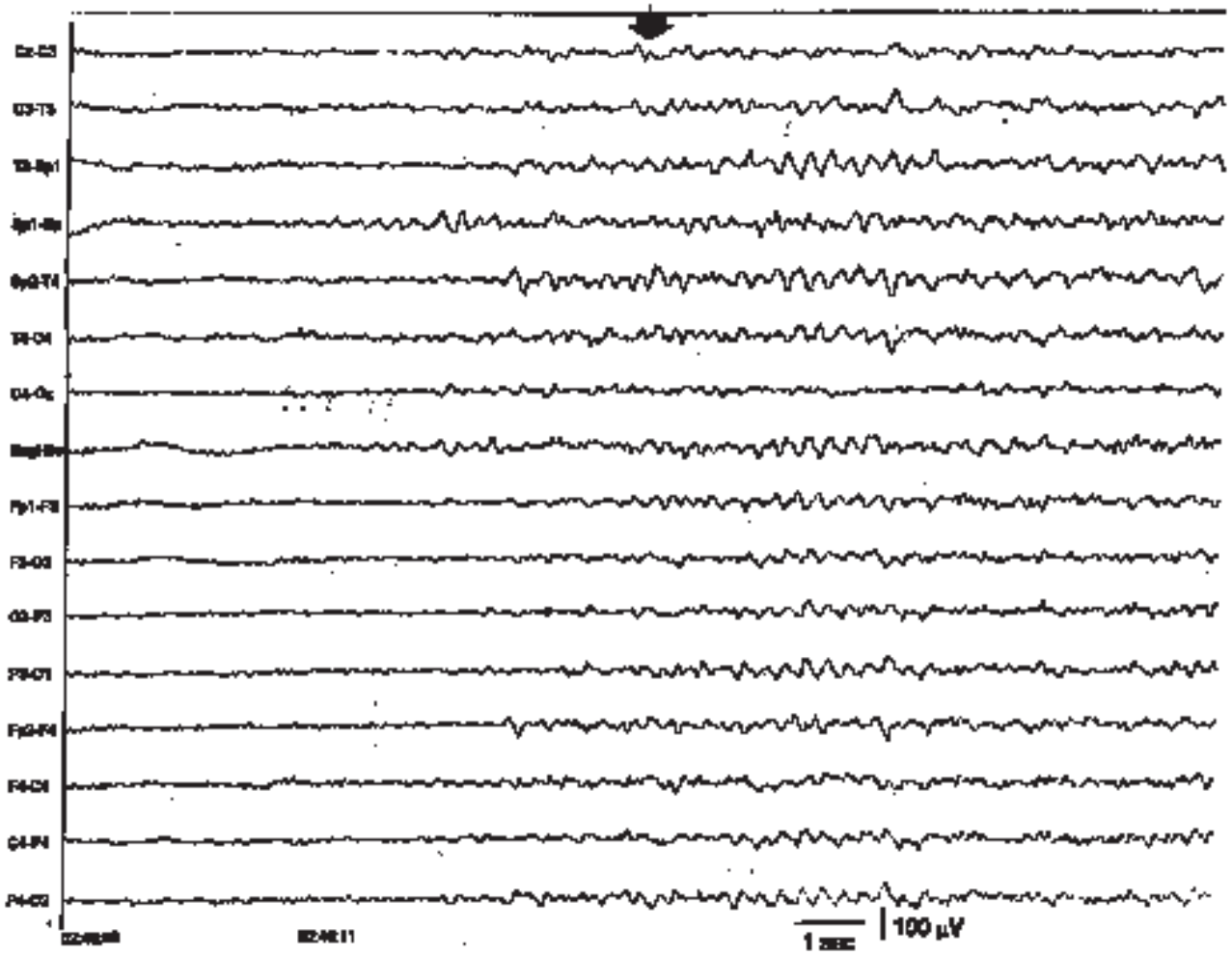


FIG. 22.1. Example of a seizure automatically detected because of a widespread rhythmic discharge (later followed by faster activity and generalized spike-and-wave activity, not shown). The *vertical arrow* marks the time of detection. Note that detection took place even though the rhythmic activity was not very prominent. The push button was not pressed by the patient or an observer.

Harding (43) presented a method specifically for intracerebral recordings, based on the detection of a repetitive spiking pattern, as well as possible flattening at seizure onset. This method was implemented on line and was subjected to an extensive evaluation (see " Clinical Validation of Seizure Detection Methods" below).

The detection of seizures in neonates is quite different from that in adults: discharges are often much slo wer (down to 0.5 Hz); seizure onset can be very gradual and seizures can last se veral minutes; and w aveforms of seizures and of interictal backg round show a high le vel of variability (see also Chapter 18). Liu et al. (55) presented a method for seizure detection in neonates based on the autocorrelation function for the detection of rhythmic slow patterns of an y morphology. Gotman et al. (31) also presented a method specifically for neonates, b ut based on a combination of spectral analysis and mimetic anal ysis, aimed at detecting a wide v ariety of slo w rhythms as well as irregular bursts of spikes (Fig. 22.2).

Recent developments in automatic detection ha ve emphasized that performance can be improved significantly by incorporating in detection algorithms a wide context. Rather than defining the event only locally (i.e., com-

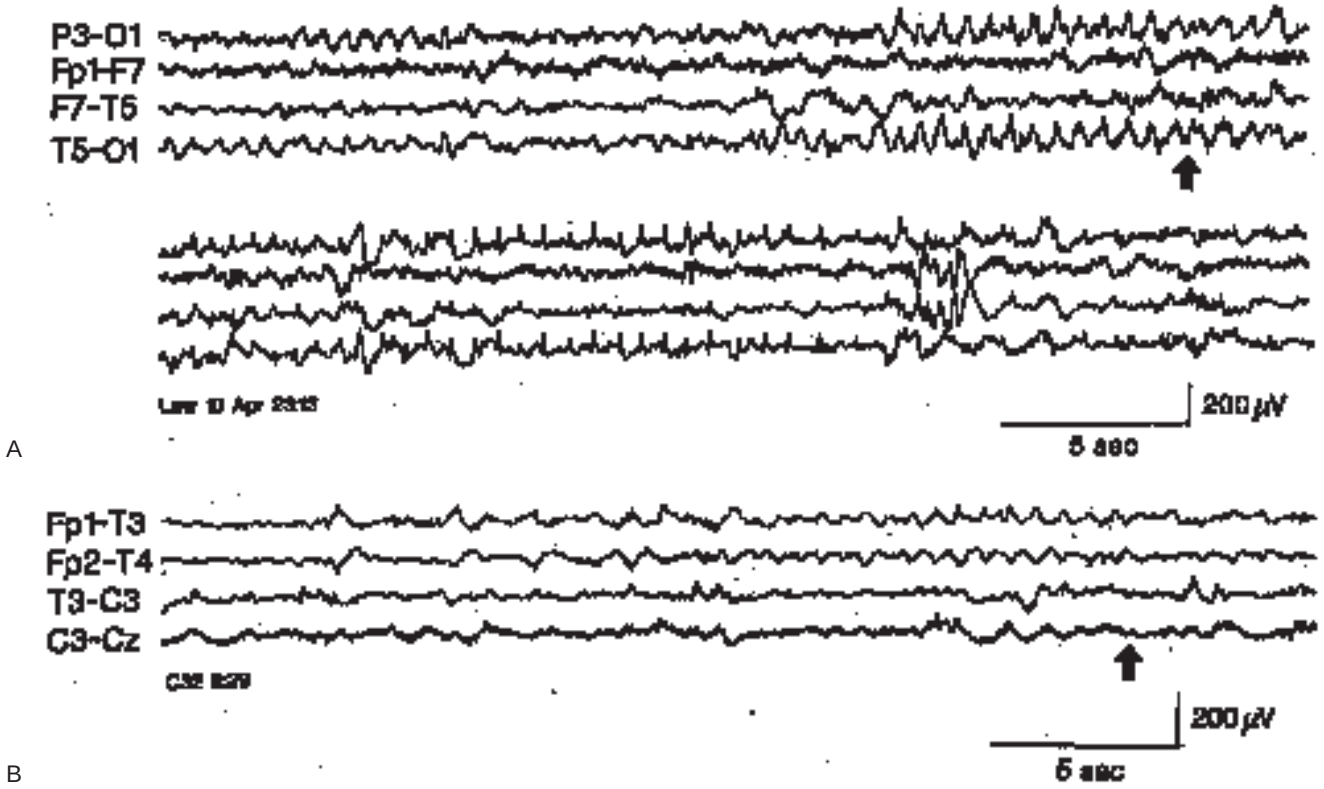


FIG. 22.2. Example of automatically detected seizures in a newborn infant. Only a subset of recorded channels is shown (channels not shown had no seizure activity). The discharges are very slow (note the time scale) and would not be detected by standard methods developed for adults. **A:** Seizure present only in one occipital electrode. **B:** Short seizure in the frontopolar regions. The *arrow* marks the time of detection. (From Gotman J, Flanagan D, Rosenblatt B, et al. Evaluation of an automatic seizure detection method for the newborn EEG. *Electroencephalogr Clin Neurophysiol* 1997;103:363–369, with permission.)

paring the characteristics of a 5-second epoch in one channel to the 30 seconds that precede it), it is important to include measurements of the spatial context (activity in other channels) and the temporal context (state of the subject: awake, stages of sleep, previously recorded events). Using this philosophy, it was possible to greatly reduce the number of false seizure detections by allowing the program to remember the patterns that caused frequent false detections in a particular subject (71). Klatchko et al. (51) presented a method for enhancing seizure detection by clustering in space and time elementary detections made on individual channels, thus obtaining a more global representation of seizures.

Artificial neural networks (ANNs) have found broad applications in many areas of pattern recognition, including seizure detection. Gabor et al. (19) and Webber et al. (77) presented methods of seizure detection based on ANNs, in which the ANN is trained by a large number of sample seizures. This class of method is very powerful because it is not necessary to obtain a formal description of the patterns to be detected; they simply have to be presented to the ANN in sufficiently large number. A large number of "non-seizure" patterns must also be presented, and the ANN learns to separate the two groups optimally. It is still necessary, however, to determine which features must be computed as representing a seizure on the EEG (mean frequency, rhythmicity, relative amplitude, etc.). If the features that really represent the characteristic aspects of seizures are not selected correctly, it will be impossible for the ANN to learn how to detect them. The ANN determines from its learning process which *combination* of features is characteristic of seizures.

Clinical Validation of Seizure Detection Methods

Evaluating the performance of automatic detection methods is difficult because results may depend as much on the selection of EEGs included in the evaluation set as on the detection method itself; for instance, a method may perform well if only very clear seizure patterns are included, but much less well with uncertain patterns, or with a recording having many artifacts. To give a fair impression of performance, what type of EEG should be included in the evaluation? The person selecting the EEG is often subjective, and this can bias strongly the results.

In evaluating the seizure detection method developed at the Montreal Neurological Institute, we made every effort to avoid bias in data selection (24). EEGs were recorded from 293 *consecutive* monitoring sessions from 49 patients. All EEGs were included, independently of EEG patterns and technical quality. Monitoring was performed in the absence of an EEG technologist; electrode problems and other technical difficulties were frequent but all EEGs were retained. Patients were over 10 years old, and the average recording duration was 18.1 hours, for a total of 5,303 hours of EEG.

In 241 of the 293 recordings (44 of 49 patients), scalp and sphenoidal electrodes were used; in the remaining 52 recordings (5 patients), intracerebral and epidural electrodes were used. Twenty-four percent of the 244 seizures were recorded by the push button alone (seizures were missed by the computer, but the patient or an observer pressed the button). In 35% of seizures, both the computer and the push button triggered the recording. In the remaining 41%, only the computer detected the seizures. Pauri et al. (64) performed an independent evaluation of the same method and came to very similar conclusions. In a third evaluation, Salinsky (73) concluded that the use of automatic seizure detection allowed clinicians to catch a large number of seizures missed by the patient and observers, and to reduce significantly the length of hospital stay. As in the above study, approximately 20% of seizures were not detected by the computer but were detected by the patient or an observer.

Thus it is clear that one cannot rely exclusively on human observation (the push button), nor can one rely exclusively on automatic detection. Using both considerably increases the yield of long-term monitoring. In addition, the average detection rates given above poorly reflect the reality of individual patients. Among the five patients with intracerebral electrodes, we had two cases that illustrated the extremes. In one patient 16 clinical seizures were recorded by the push button (with or without computer detection), with only 3 being detected by the computer alone. The computer operated continuously for 2 weeks and yielded little additional information. In another patient, however, 21 seizures were detected by the computer alone and 1 seizure by the computer and the push button. All were clinical seizures consisting of long but quiet automatisms, during which the patient stayed in bed and made no noise; such seizures went unnoticed because the patient was lying in bed, but they were very disruptive in his active life. In this case, the computer was particularly helpful.

We have not given details of false-positive detections. In the majority of cases, false detections are small enough in number not to be disruptive: false detections only cause the EEG to be marked unnecessarily, and can simply be discarded during visual inspection. Rates are usually around one to two false detections per hour of monitoring (24,64).

Harding (43) also performed a thorough evaluation of his method of seizure detection for intracerebral recordings by using large amount of *unselected* data: almost 1,600 hours from 40 patients. He obtained few false negatives and a very acceptable level of false positives. However, the results are difficult to compare directly to other methods because detection parameters were altered slightly in each patient according to results after the first seizure was recorded. Gabor (18) validated his seizure detection method on 4,500 hours of recording from 65 patients with scalp electrodes. He found that 92.8% of seizures were detected and the false alarm rate averaged 1.35 per hour. He also found that fast replay of the EEG to transform it in the audio range allowed the detection of almost all seizures (98.3%).

Gotman et al. (32) evaluated their newborn seizure detection method in a large set of data (from 55 newborns) obtained from three hospitals. Results showed seizure detection rates similar to those of adults (around 70%) and false detection rates of approximately 2 per hour. This study illustrated how it can be difficult to extrapolate results from one patient group to another: the performance varied considerably among the data sets of the three hospitals, reflecting the variability of recording conditions, technical quality, and types of pathology.

Limitations and Future Developments

Current seizure detection programs are not perfect and could use significant improvement. It would be extremely difficult, however, to detect all seizures because some seizures have almost no EEG accompaniment and the discharge morphology is often nonspecific (1). The suggestion is sometimes made that performance could be improved by fine tuning the detection program to each patient's seizure, after the first seizures are detected by the computer or by an observer. However, this would result in the introduction of an unacceptable bias in detection performance, toward seizures of the type recorded early in the monitoring session; in many cases the purpose of monitoring is to document all types of seizures and particularly to see if there are also seizures *different* from those recorded early. Tailoring the detection to a particular seizure type is only acceptable if one is interested in assessing the occurrence of that particular seizure type and is less concerned with other seizures.

The ways in which seizure detection can reduce the load of EEG interpretation during long-term monitoring were discussed above. Seizure detection could also be used to warn the patient or relatives that a seizure is starting. This would allow close clinical observation early in the seizure, and permit necessary precautions in some cases. It could also be useful to increase the applicability of ictal single-photon emission computed tomography (5). One can even conceive of rapid intervention, in the form of electrical stimulation or drug injection with an implanted device to abort the seizure. Unlike *seizure monitoring* as discussed above, this *seizure warning* application requires a very low rate of false alarms and detection very early in the seizure. This places very stringent requirements on the method. Promising results were obtained by the seizure warning system of Qu and Gotman (69,70), which used a first recorded seizure as a template to train the detection system (Fig. 22.3). Such a method can provide a warning only when a seizure similar to the template is taking place. It cannot warn of a new and different type of seizure, and is thus not useful for seizure monitoring. Osorio et al. (62) described a complex method based on time–frequency analysis for seizure warning. They reported perfect performance, although they did not indicate how quickly after the EEG onset the method was able to give a warning.

Recording Interictal Activity

The interictal activity that is specific to epilepsy consists mainly of spikes, sharp waves, and bursts of spike-and-wave activity. This paroxysmal activity occurs unpredictably and sometimes infrequently. In order to obtain a full documentation of the different types of abnormalities, the traditional short EEG recording may not be sufficient. Long-term monitoring may be required, including periods of the different stages of sleep, which most often activate and can modify interictal patterns (74). The reduction of antiepileptic medication, often done during long-term monitoring to precipitate seizures, also results, indirectly, in increased spiking: It has been shown that spikes are more frequent after seizures (28,36,40). It is clear that continuous day-and-night recording is an awkward method to document interictal activity; automatic detection methods can be very helpful.

Past Methods

Numerous publications, particularly in the 1970s and early 1980s, have dealt with automatic spike detection. The usual approach consisted of (a)

A

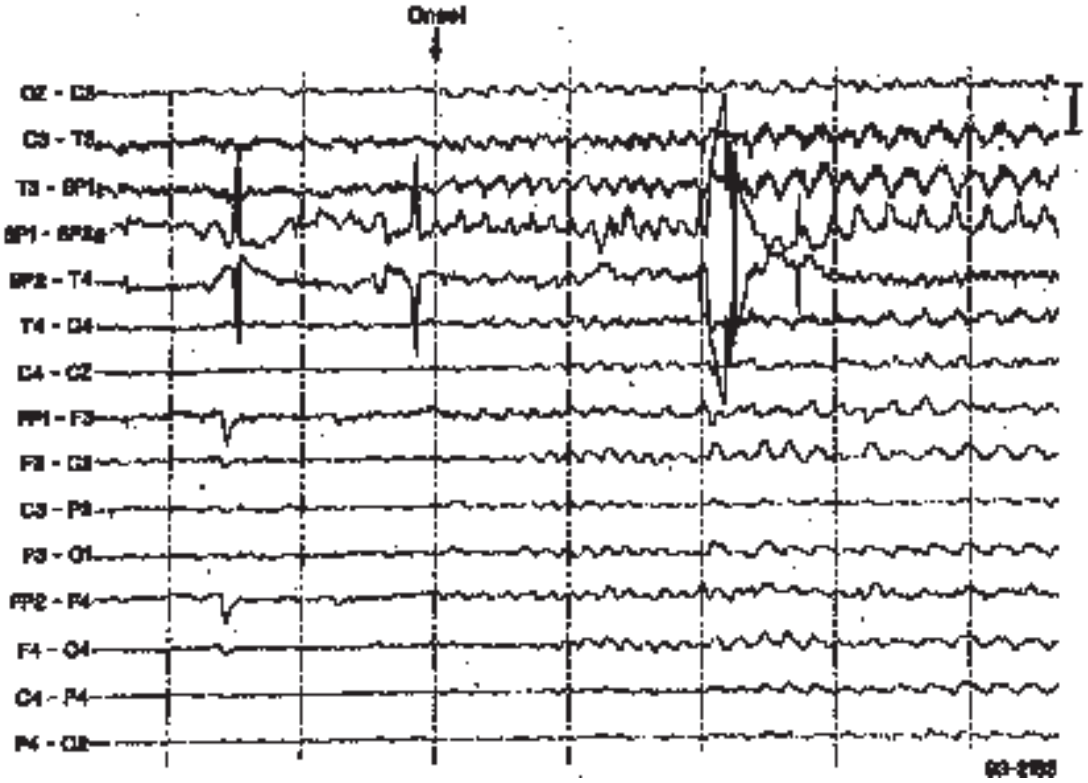
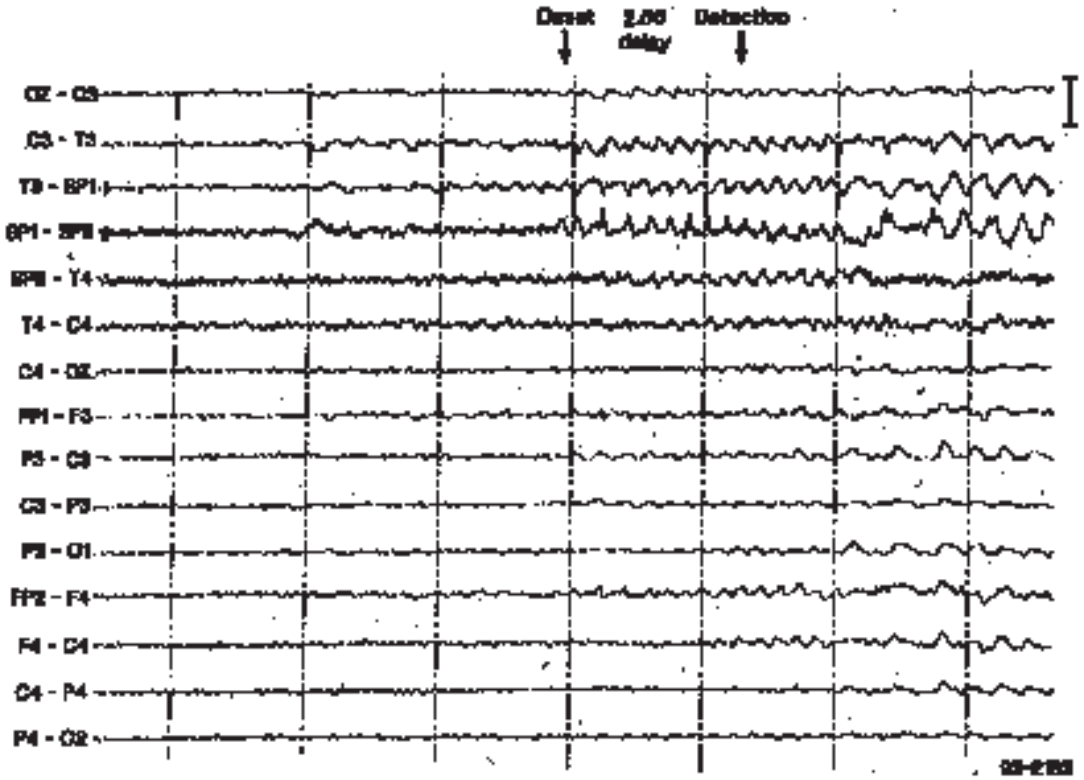


FIG. 22.3. Illustration of seizure warning method. **A:** Template seizure given to the program for training. *(Figure continues.)*

selecting EEG sections lasting 1 or 2 minutes that were free of artifacts and included a sufficient number of spikes, (b) devising a method for their detection, and (c) comparing results of automatic detection to what qualified electroencephalographers considered "true" spikes. Details of the various detection methods have been reviewed extensively (30) and are not repeated here. These methods relied generally on two approaches. In the first, the EEG is broken down into elementary waves and the method attempts to identify the waves having morphological characteristics normally associated with spikes (amplitude, duration, sharpness). In the second, the EEG is analyzed in order to find statistically improbable events of short duration.

For most methods, good performance was obtained, usually with 80%–90% of "true" spikes detected and a low rate of false-positive detection. Many publications ended with statements such as: "As computers become more powerful and less expensive, practical implementation will be simple." In fact, computers became more powerful and less expensive faster than expected but most methods did not reach practical implementation. The major reason is that the detection problem became much more complex when longer sections were analyzed; artifacts and normal transients had to be included, and they caused numerous false detections. In addition, there is little use for spike detection in 10-minute recordings when human inspection is perfect.



B

FIG. 22.3. *Continued.* **B:** Seizure occurring at a later time that was detected by the warning system 2.5 seconds after its onset. (From Qu H, Gotman J. A patient-specific algorithm for the detection of seizure onset in long-term EEG monitoring: possible use as a warning device. *IEEE Trans Biomed Eng* 1997;44:115–122, with permission.)

Difficulties of Detection

Spike recognition methods have relied on a definition of a spike adapted from Chatrian et al. (10), quoted in many publications: "a sharp transient, easily distinguishable from the background, having a duration of less than 70 ms for a spike and 70 to 200 ms for a sharp wave." This definition is extremely incomplete because it lacks features differentiating transients that have the same local morphology but that are not spikes, such as eye blinks, vertex sharp waves, isolated alpha or spindle waves, electrode artifacts, and movement artifacts. Such transients are common during long-term monitoring, when automatic spike detection is particularly useful. Figure 22.4 shows a typical example of results from a standard spike detection method: genuine spikes are mixed with false detections resulting from nonepileptiform transients.

Which characteristics allow a human interpreter to separate an epileptiform sharp wave from an eye blink, even though the waves themselves may have the same morphology and emerge from a similar background? These characteristics relate to the overall context in which the waves appear, where "context" covers much wider space and time than "background." When interpreting a wave having the morphology of a spike, the human observer takes into account what happens in other channels (spatial context),what happens in earlier and later parts of the recording (temporal context), and

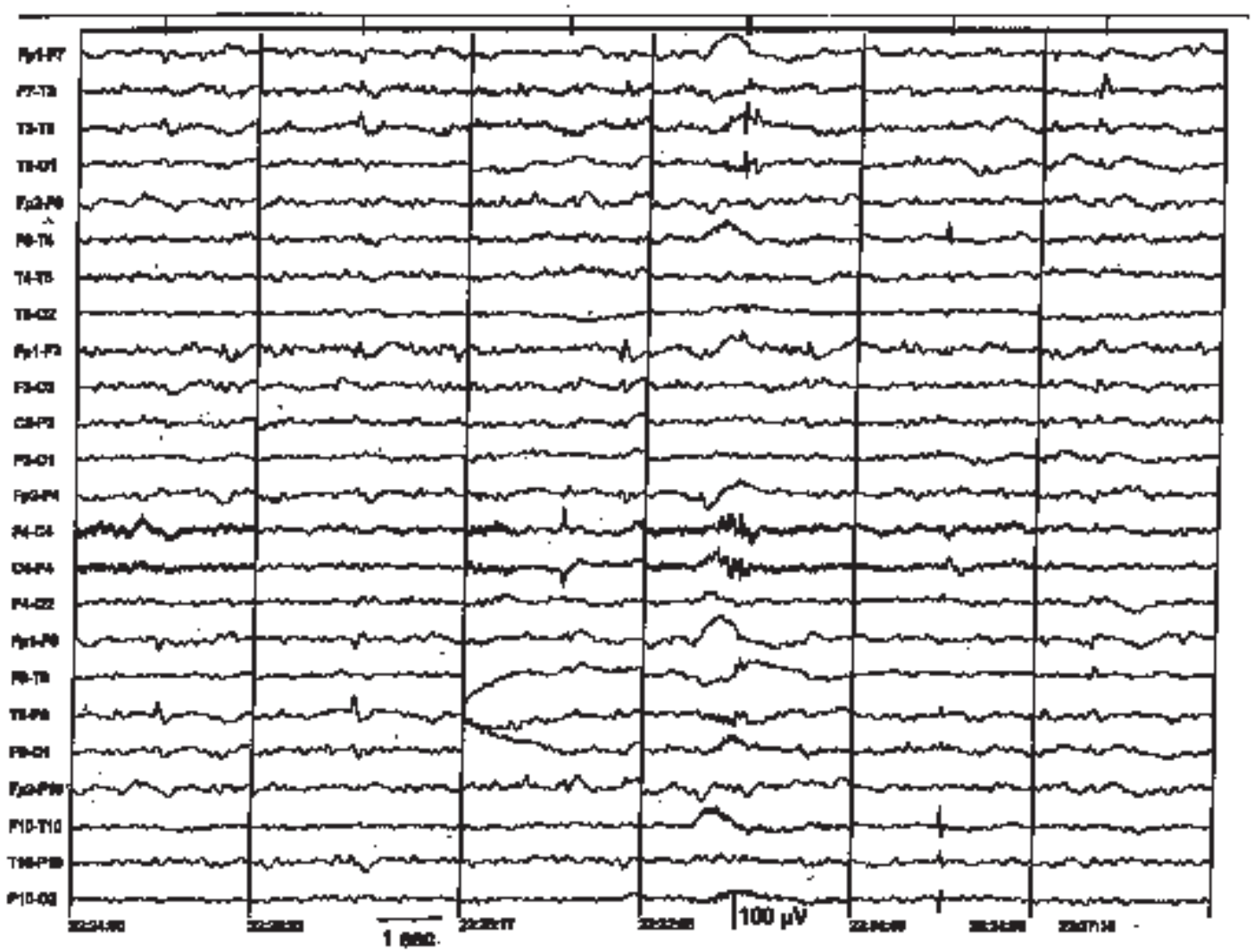


FIG. 22.4. EEG sections marked because of automatic spike detection (method of Gotman et al. [33]). *Vertical lines* represent discontinuities. Sections shown here represent some of the automatically marked events during a 15-minute segment of a 24-hour monitoring session (see time at the beginning of each section, at bottom of page). The intervening EEG is not shown. The method is able to detect clear spikes (section 5) and genuine sharp waves that are not very prominent (sections 1, 2, and 6), mixed with nonepileptiform transients (sections 3 and 4). Even though there are false detections, the method provides valuable data reduction.

even non-EEG information such as the age or clinical state of the subject. Optimism about early detection methods originated in the failure to appreciate how much spike identification relies on this context. In addition, human interpreters have a low level of interrater agreement when asked to mark every spike in a recording (78,81). Although such marking is important in evaluating detection methods or in training detection systems, it is not a task that is normally performed by human interpreters, who look at a record globally and not at each waveform.

The problems discussed above do not affect the ability to detect most epileptiform spikes, but they result in a large number of false-positive detections. For this reason, it is possible to make practical use of an automatic spike detection method, as long as it is conceived as a method to detect a high proportion of the spikes along with a possibly large number of nonepileptiform transients, rather than as a method to detect *only* spikes. Such a practical implementation was made with the spike detection algorithms developed at the Montreal Neurological Institute (24,33). The method has been in use for many years and operates in many other institutions. It runs on line and marks the detected events on the recording; these are subsequently reviewed and the electroencephalographer decides which are true and which are false. Despite false-positive detections, the system allows marking of a large fraction of the spikes and can speed up EEG review considerably. It can be combined with automatic seizure detection and form a system for automatic extraction of epileptiform activity, ictal and interictal, during long-term monitoring. Such a system results in the marking of only 5%–10% of a 24-hour recording, including spikes, seizures, and false detections.

Pietilä et al. (65) presented a system including automatic segmentation of the EEG followed by feature extraction. In comparison to the system of Gotman, their system showed a higher sensitivity but a lower specificity. The system of Gotman was also validated by Hostetler et al. (44), who stated that "the computer system, while not as specific as an EEGer, can be as sensitive and can be a reliable screening editor for large amounts of monitoring data. On balance, it is more effective than an EEGer for this limited purpose." Spatt et al. (75) also confirmed the clinical utility of this method when used as a screening device.

New Approaches

ANNs, a new tool for seizure detection, are also used for spike detection. The process requires a large number of sample patterns for training, including spikes and nonspikes. This method was used by Gabor and Seyal (20), who obtained good performance but evaluated their method on a very small sample. Webber et al. (79), also using a relatively small data set for evaluation, compared the use of the raw EEG to that of preprocessed variables as the input to the ANN and concluded that the raw EEG was not optimal. ANNs have also been used for detecting bursts of spike-and-wave activity in experimental models of epilepsy (49). Wavelet analysis, a new method of signal processing, has also been used to detect spikes (12), but only very preliminary results have been published.

Another approach to improving detection performance is to make automatic methods operate more like humans, that is, to allow them to use information from a wide context, as discussed above. This is conceptually simple but difficult to implement because the context encompasses a large amount of information, and one must decide which part of that information is relevant to spike detection. It is this very selection that humans do so well. Glover et al. (22) described a context-based system aimed largely at reducing false spike detections by making use of *spatial* context: information from all EEG channels, as well as from EMG, electro-oculography, and electrocardiography channels, was used to assess whether a transient in a particular channel was likely to be epileptiform.

Gotman and Wang have proposed an approach in which a wide *temporal and spatial* context is used to decide on the nature of a sharp event (41,42). We labeled the method "state-dependent spike detection" because criteria for spike detection are rendered dependent on the state of the EEG. We defined five states in which spike detection should operate differently: active wakefulness, quiet wakefulness, desynchronized EEG, phasic EEG, and slow-wave EEG. In these different states, the events that cause false detections have to be handled by different means. In active wakefulness, for instance, one must be particularly aware of symmetrical frontal sharp waves that may be due to eye blinks, whereas there is no such concern in the phasic EEG state; in that state, sharp waves maximal at the vertex are a problem (Fig. 22.5). The method was evaluated in 20 patients, each having close to 2 hours of EEG recording covering all states; it showed a reduction in false detection of 65% and an increased sensitivity of 35%, compared to the original method.

Whether using neural nets or more traditional methods, it is unlikely that local wave morphology is sufficient to differentiate epileptiform transients from other transients. Some form of context sensitivity appears necessary.

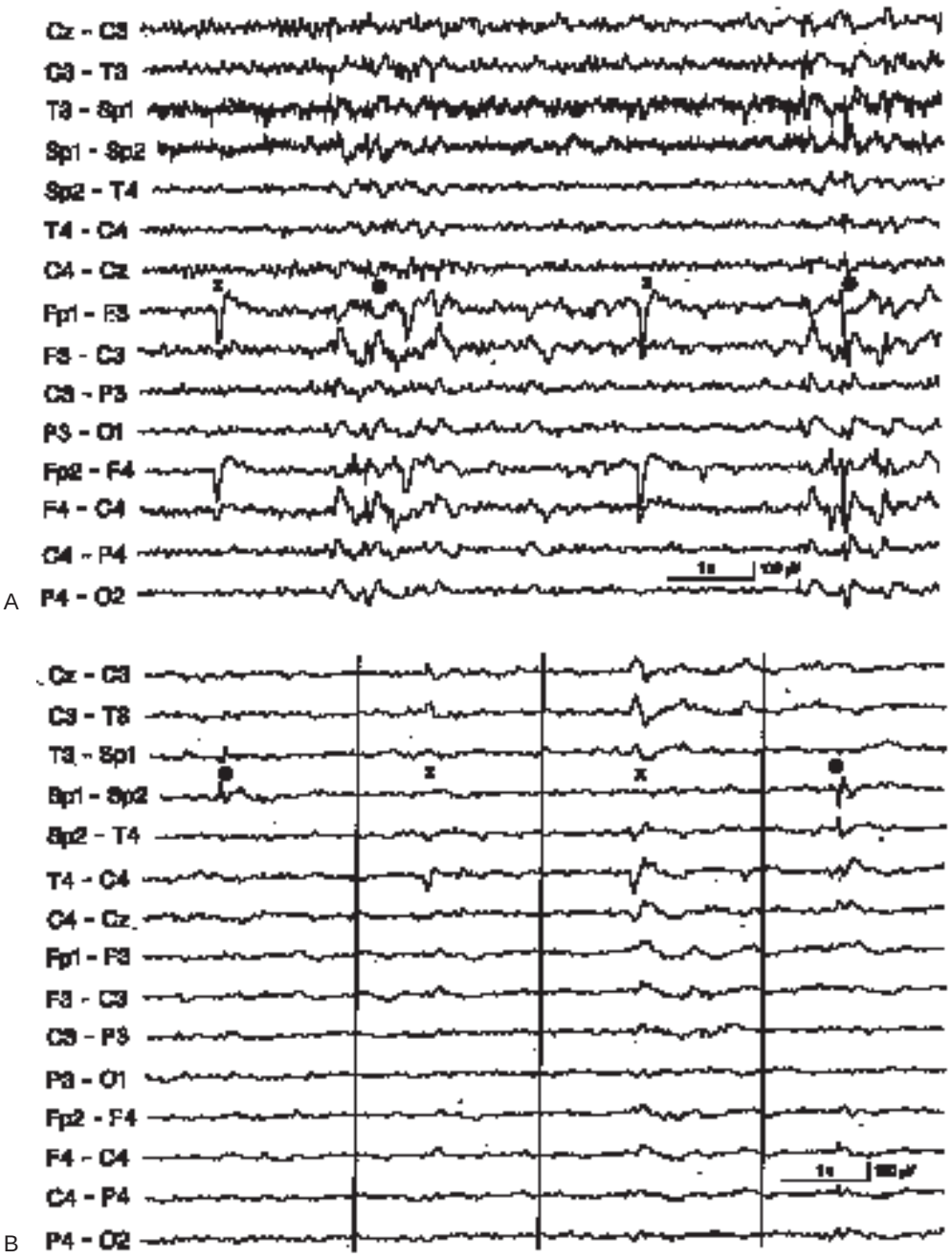


FIG. 22.5. Example of use of spatial and temporal context in spike detection. Nonepileptiform transients are selectively rejected (rejected events are marked with *x*). **A:** During active wakefulness, as determined by automatic state classification, waves having the morphology and distribution of eye blinks are eliminated. **B:** During phasic sleep, sharp waves having a maximum at the vertex are eliminated. (From Gotman J, Wang L-Y. State-dependent spike detection: concepts and preliminary results. *Electroencephalogr Clin Neurophysiol* 1991;79:11–19, with permission.)

Recording Behavior

The analysis of behavioral manifestations of seizures is obviously a critical element. It can be performed by an observer or by video recording, or often by both. Video recording is simple, most often making use of standard camera and videocassette recorder (VCR) technology. Recent developments in computer technology may, however, have a significant impact. One such development is of minor importance: some VCRs can be controlled by computers, so that the tedious task of finding the right time on the tape is facilitated by use of a direct command from the computer.

A second development will have a much greater impact: it is now possible to record a video image directly in the computer, rather than on videotape (72). This presents important advantages: one has immediate random access to any part of the recording; and behavior and EEG recordings can be replayed simultaneously at many speeds and archived together. However, one problem remains with practical implementation of this technology: The disk space required for storing a 24-hour video recording is still difficult to manage for most computers, even when using powerful image compression techniques (unless one is prepared to accept a lower image quality and a lower frame rate). It is almost certain that this situation will improve rapidly and that computer-based video recording will become standard. Until that time, the difficulty can be overcome by recording the digital video signal selectively, around the times at which the push button is pressed or automatic seizure detections take place.

POSTDETECTION ANALYSIS

The benefits derived from computers are found not only in detecting epileptiform events during long-term monitoring, but also in displaying, manipulating, and analyzing the EEG. Various methods have become standard in the review of digitally recorded EEGs. This section presents some analysis methods specific to epileptic activity.

Analysis of Seizure Activity

One can go beyond visual interpretation and analyze seizures in order to extract information of diagnostic or scientific interest. For instance, digital filtering makes it possible to remove most of the EMG artifact that obscures many seizures recorded from the scalp (34), as well as decrease the effect of electrode movement artifact (Fig. 22.6*A* and *B*). Spectral analysis of the signal contaminated by EMG artifact can sometimes help interpret the result of filtering (Fig. 22.6*C*). One has to be careful in interpreting the filtered signal, however, because there can sometimes be rhythmic low-frequency contraction of scalp muscles (34). The graphic representation of seizures and quantitative measurements of their features can improve EEG interpretation (2,9,11,37,38). It is also possible to develop measures that are able to compare multichannel seizure patterns as one entity. They break down seizures into sections having uniform patterns (low-amplitude fast activity, high-frequency spikes, spike-and-wave activity, etc.), and then determine the similarity between two seizures, taking into account the succession of patterns over multiple channels (80,82).

The ability to analyze the propagation pattern of seizures or the possible influence of one region over another has been the focus of attention of many investigators. The study of interactions between brain regions during seizures was pioneered by Brazier (8). She used the coherence function to measure the strength of interaction between seizure discharges in two locations, and the phase spectrum to measure time differences of a few milliseconds. Thus rapid propagation of seizures could theoretically be followed. The reliability of this method was improved by Gotman (26,27), who included in the measurement a range of frequencies rather than a single frequency. Its validity was established in experimental and human epilepsy, in cases where the location of the focus was known. This method allowed the study of interhemispheric interactions during widespread spike-and-wave activity (26,52) and during temporal lobe seizures (25,39,54). Figure 22.7*A* shows a small seizure recorded with intracerebral electrodes from the hippocampus and amygdala in one patient. The coherence and phase spectra in Figure 22.7*B* show that the discharge in the hippocampus leads that in the amygdala by 25 milliseconds. One should be cautious in interpreting this result; it does not prove that the discharge originates in the hippocampus and propagates to the amygdala. However, if one has to choose between amygdala and hippocampus as the most likely origin of the discharge, results favor the hippocampus.

There are other methods to measure interactions during seizures. The average amount of mutual information (AAMI) has a theoretical advantage over coherence because coherence can only detect *linear* (in the mathematical sense) relationships, whereas AAMI can also detect more complex relationships. However, coherence and AAMI most often give similar results. AAMI and other nonlinear methods have been described by Lopes da Silva and Mars (58). Fernandes de Lima et al. (15) compared a linear and a nonlinear regression coefficient in the study of interhemispheric interactions during hippocampal seizures in rats; they found that the nonlinear measure

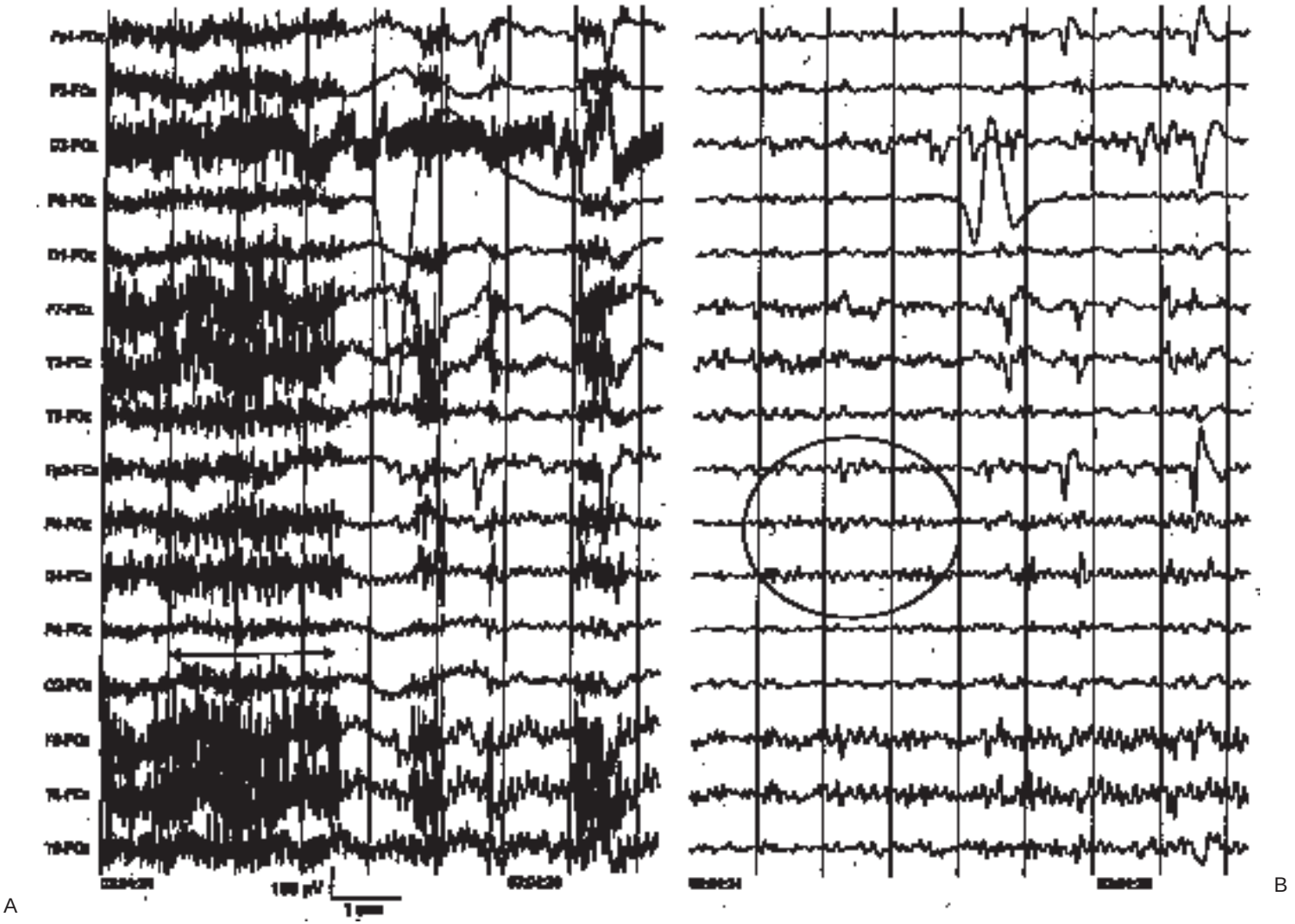


FIG. 22.6. Digital filtering of seizure. **A:** Section of a seizure recording in which one portion is completely obscured by EMG artifact and the following portion shows cerebral seizure activity in the right hemisphere. There is also a large electrode artifact at the P3 electrode. **B:** The same EEG section, but digitally filtered (low-pass finite impulse response filter at 15 Hz and high-pass infinite impulse response filter at 1.5 Hz). The high-pass 1.5-Hz filter reduces the impact of the electrode artifact. The low-pass filter at 15 Hz reveals that rhythmic activity was present under the EMG activity, particularly at C4 and P4; it is more difficult to assess whether cerebral rhythmic activity is also present in F8 and T4 because it appears that there could be some remnants of EMG activity.

(Figure continues.)

C

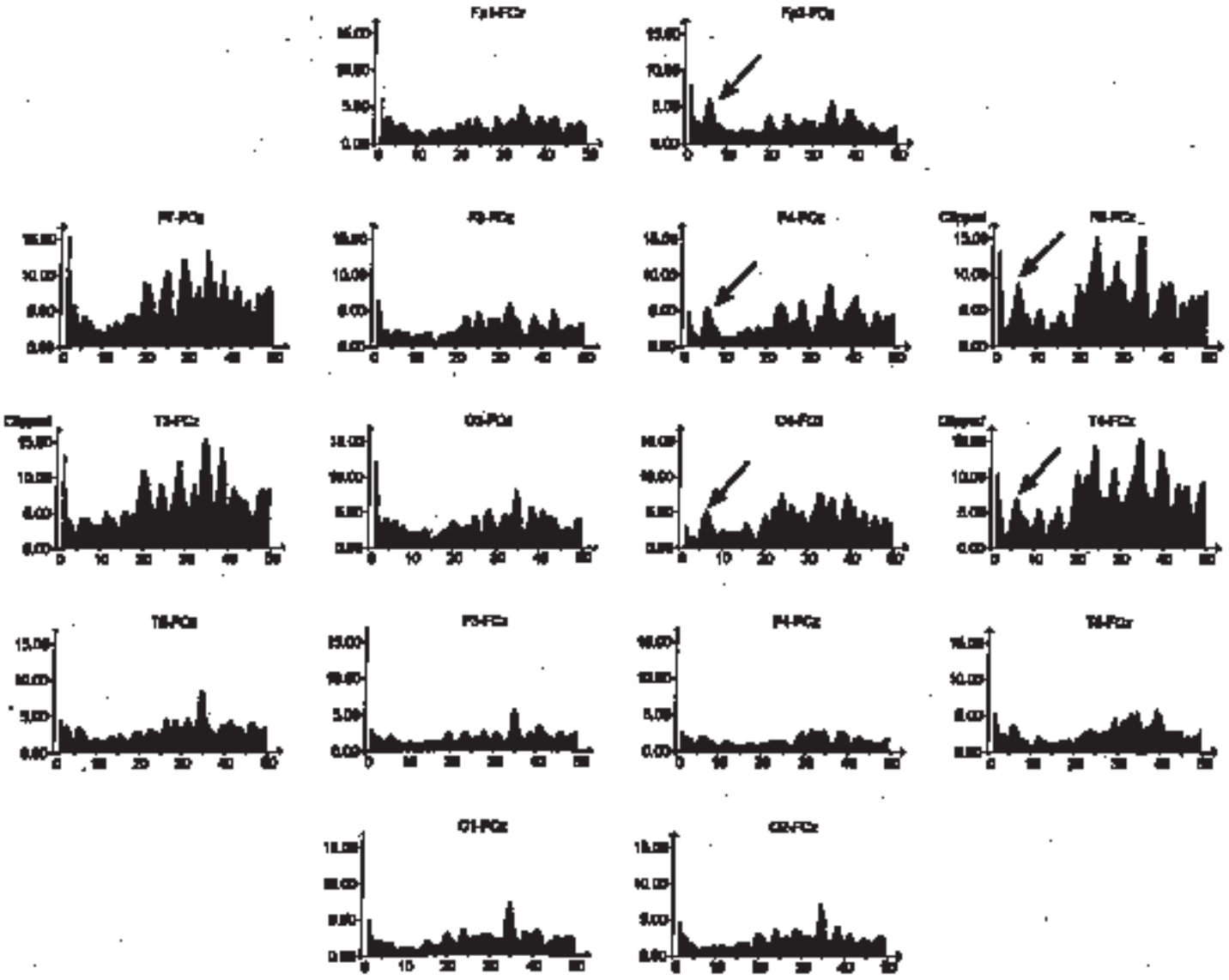


FIG. 22.6. *Continued.* **C:** Frequency spectra of the 2.5-second section marked in **A**. Many peaks are visible at high frequencies, as is always the case with EMG artifact. It is very rare, however, to see rhythmic activity of muscle origin at low frequencies. The peak at 6 Hz, marked by *arrows*, is present in the right hemisphere but not in the left. This is the same frequency as the activity seen after the EMG artifact stops. It therefore clearly represents activity of cerebral origin.

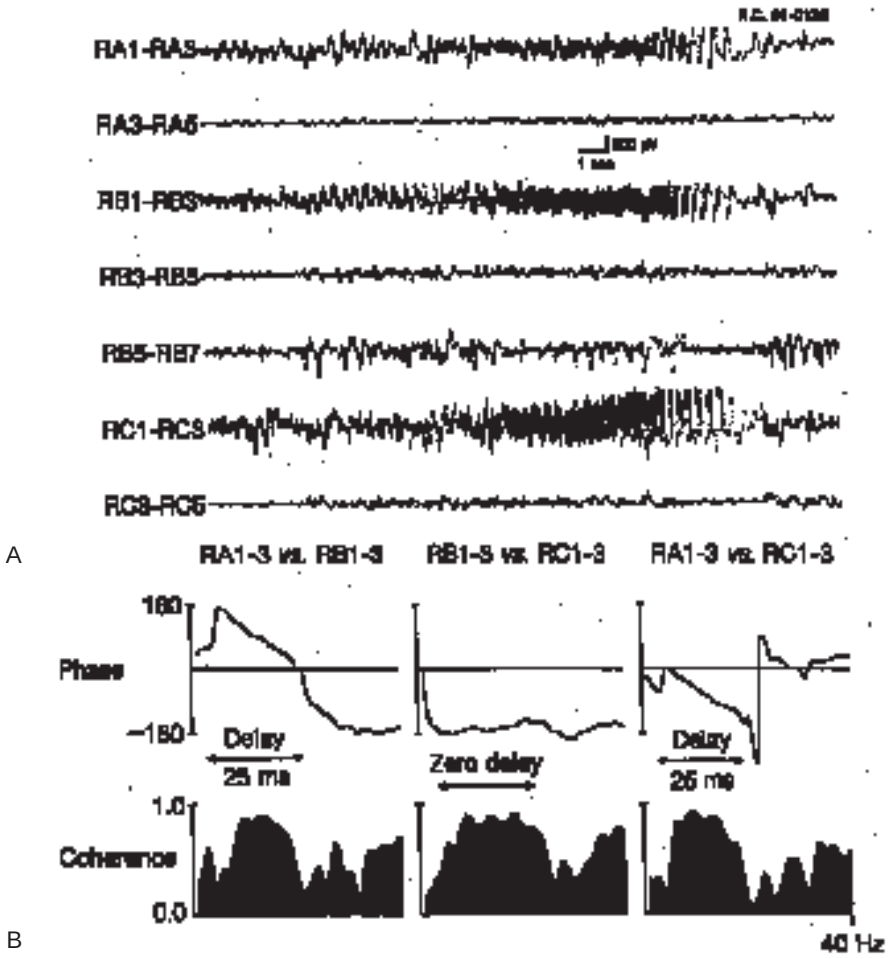


FIG. 22.7. Seizure propagation measured by coherence and phase. **A:** Short seizure localized to deep structures of the temporal lobe; electrodes are in the horizontal plane with contacts 5 mm apart, contact 1 being deepest; RA is aimed at the amygdala, RB at the anterior hippocampus, and RC at the middle hippocampus. **B:** Phase and coherence spectra between the three pairs of deepest channels; phase is linear over the frequency range where coherence is high (*horizontal arrow*); a time delay measurement is therefore possible, indicating a lead from RB1-3 to RA1-3 of 25 milliseconds, a lead from RC1-3 to RA1-3 also of 25 milliseconds, and no time difference between RB1-3 and RC1-3. The discharge in the hippocampus therefore leads the discharge in the amygdala, as was most often the case in seizures limited to mesial temporal structures. (From Gotman J, Levtova V. Amygdala-hippocampus relationships in temporal lobe seizures: a phase-coherence study. *Epilepsy Res* 1996;25:51–57, with permission.)

was more robust and could show interactions when the linear measure was at noise level. One important factor is not often discussed when comparing these methods: The size of the recording electrodes probably influences the type of relationship. Discharges from very small electrodes, which may record multiple-unit activity, are more likely to have nonlinear relationships than discharges from macroelectrodes, which record from large populations of neurons.

Another method of analysis of seizure propagation is that of the directed transfer function, indicating the direction of flow of information. It has been shown in a few seizures that, even when a discharge is widespread, the region in which the seizure originated appears to remain that from which the information flows (16,17). The relationship between the directed transfer function and the coherence/phase method described above has not been established.

Source analysis methods, usually based on dipole modeling, have been used extensively for interictal spikes, but a few studies have also shown their applicability to seizure analysis (3,7).

Concepts of nonlinear dynamics have been used in the study of seizures: Could seizures result from chaotic systems? Some of the complex issues related to the estimation of the correlation dimension, the most commonly used measure, are discussed by Pijn et al. (66) and Lopes da Silva (57). Iasemidis et al. (47) and Pijn et al. (67) showed that, during the seizure, the region of the epileptic focus most often corresponded to an area of low dimensionality. Iasemidis and Sackellares (46) and Iasemidis et al. (45) showed that the Lyapunov exponent (related to the dimensionality of the system) could gradually become synchronous in several channels prior to a seizure (a phenomenon they term *entrainment*). Elger and Lehnertz (13) also indicated that the dimensionality of the EEG may decrease several minutes prior to seizures. A similar finding was also obtained by Martinerie et al. (59), using a multichannel nonlinear measure. These studies raise the interesting possibility that seizures might be predictable.

Analysis of Interictal Activity

Automatic spike detection was described above mainly in the context of data reduction, but it also offers the benefit of quantification. It is possible to edit out the false spike detections interactively on the computer screen so that only valid detections remain. Quantification of spike activity during several days of monitoring has proven invaluable in the study of factors that might affect the rate and localization of spikes. It was found that the rate of focal spiking does not change (increase or decrease) before seizures (40,50).

In contrast, there is a large increase in spiking in the days that follow most secondarily generalized seizures and many partial seizures; surprisingly, spiking rates appear unaffected by changes in antiepileptic drug levels (36,40). The postictal increase in spiking and the absence of decrease in spiking with high antiepileptic drug levels were replicated in the kindling model of epilepsy (21,29,53). Thus quantification of spiking rates has established that spiking does *not* change (increasing before seizures, decreasing with high drug levels), as was intuitively believed.

Spikes were also quantified during the different stages of sleep in patients evaluated for epilepsy surgery with noninvasive recordings. Results indicate that spiking is more focal during rapid-eye-movement (REM) sleep than during slow-wave sleep. The localization obtained from REM sleep spiking correlates better with other tests of localization (e.g., seizure onset, radiological findings) than does the localization obtained during slow-wave sleep or wakefulness (74).

The question of whether spike activity propagates between brain regions has also been studied. Emerson et al. (14) used spike-triggered averaging to measure the propagation between temporal and frontopolar regions and concluded that it was possible to see relationships not visible by visual inspection. Spatiotemporal dipole modeling has also been used to see whether spikes could be represented by one or several dipoles, in an attempt to localize the source of spike activity. This is discussed extensively in Chapter 23.

CONCLUSION

Computers play an important role in assisting in the recording and analysis of the EEGs of epileptic patients. During long-term monitoring, computer assistance is almost indispensable for the detection of epileptic events. There is no single economical method that ensures the detection of all seizures and spikes in every patient: All available help must be used, including staff and patient reporting and computer detection. In some patients, one method will prove more useful than others, but this is not known in advance of the monitoring sessions.

We have seen that spike and seizure detection is not a simple task, as researchers in this area originally thought. The human who reads an EEG uses clues from a wide spatial and temporal context, clues that are difficult to encode in computer programs. Most methods analyze the EEG at a very local level (looking at 10–30 seconds of EEG at a time, often one channel at a time). It would therefore be naive to expect high reliability from such automatic methods. Nevertheless, they can be extremely useful if implemented in the context of human validation. Recent methods incorporate knowledge of a wider context, as does the state-dependent spike detection method mentioned above. This will in all likelihood result in much better performance, but it is very unlikely that we will reach a stage where human validation is not required.

The technological context in which automatic detection methods are implemented is changing rapidly. Detection programs can readily operate in real time in personal computers. Several computers may be connected via a local area network so that review of a recording can take place while the recording is in process. EEGs may be reviewed on several review stations in different locations within a hospital. Given the data reduction ability of detection programs, it is feasible to archive the EEGs from a 3-week monitoring session, including interictal and ictal epileptiform activity, on a single disk.

Finally, computer analysis of seizures and spikes may provide information that is not readily available from traditional visual examination. This is primarily due to the possibility of quantifying the EEG and of making mathematical analyses that can be related to brain function.

ACKNOWLEDGMENT

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Chapter 23

EEG Voltage Topography and Dipole Source Modeling of Epileptiform Potentials

John S. Ebersole

Principles of Dipole Source Modeling
EEG Voltage Topography in Temporal Lobe Epilepsy
Dipole Modeling in Temporal Lobe Epilepsy
Single-Dipole Modeling
Spatiotemporal Multiple-Dipole Modeling
Dipole Modeling of Temporal Lobe Seizures
Co-registering EEG Data with Magnetic Resonance Imaging and Realistic Head Models
Extended Source Models
References

The ultimate goal of electroencephalography (EEG) is to gain an understanding of brain activity at the time of the recording. Not only is it important to determine if the brain's function is abnormal, but often it is imperative to localize the abnormality. Localization by EEG is a time-honored skill that, for most of its 70-year history, has involved interpreting patterns of EEG traces. Chief among the techniques has been the use of bipolar montages and the identification of phase reversals in bipolar chains, which signify the crossing of a negative field maximum. This method is typically used to localize epileptiform spikes, and it is based on the assumption that the spike generator necessarily lay under the electrode recording maximum negativity. It has been demonstrated in Chapter 2 that this assumption is often not correct.

Although scalp EEG voltage fields of interictal spikes approximate those that would be produced by a dipole, as discussed in Chapters 1 and 2, cerebral sources of EEG are in reality sizable areas of cortex that often encompass 6–20 cm^2. Viewed at a distance, however, as with scalp electrodes, the summed activity of countless aligned pyramidal cells in such a cortical area produces a field that looks dipolar. A particularly useful aspect of this likeness is that there are mathematical techniques for approximating the location and orientation of dipoles in a volume conductor or, in our case, an EEG source within the brain.

PRINCIPLES OF DIPOLE SOURCE MODELING

In the mid-nineteenth century, Helmholtz (24) developed the electromagnetic principles of volume conduction. Nearly 100 years later, Wilson and Bayley (48) developed a method for calculating the voltage field that would appear on the surface of a spherical volume conductor from any given dipole source within it. For a source of specified location, orientation, and magnitude, there can be only one potential field distribution on the surface of the

conductor. This answer is called the *forward solution*, and it is unique. Our problem in EEG analysis is the opposite, however—namely trying to characterize an intracerebral source having measured the topography of a scalp potential. The answer to this problem is called the *inverse solution*, and, unfortunately for any given voltage field either on a theoretical spherical volume conductor or on a real head, there is no single answer, but rather multiple possibilities because fields from any number or combination of sources can sum linearly to produce the resultant surface field. This is the principle of *superposition*, and because of it attempts to identify source character (number, location, amplitude, and magnitude) always yield ambiguous results.

Certain assumptions are also usually made to make this inverse problem mathematically tractable and to apply these principles to EEG. The brain is usually modeled as a sphere of uniform conducting material (9), and concentric shells are added around this sphere to imitate the different conductivities of the skull and scalp (12,26,37,45). For ease of modeling, the source of the scalp EEG field is considered to be a theoretical point-like dipole. Although the real generators of EEG potentials are areas of cortex that extend over several square centimeters, the activity of such a region may be modeled effectively by a single dipole, because the field that would be produced by this "equivalent dipole" is very similar to that of a real source. In general, such an equivalent dipole source must reside close to the geometrical center of the actual generator area and have an orientation similar to the net orientation of this cortex. Usually, however, the equivalent dipole must be located deep to the generator cortex in order for it, as a point-like source, to simulate the field produced by an extended cortical region.

The instantaneous, single-dipole, inverse solution is the most common form of source model. This technique defines a single equivalent dipole source for the scalp voltage field at one moment in time (12,25,26,44,45). An iterative minimization technique with a directed search pattern is usually employed. Such dipole modeling programs calculate the forward solution for a given source location/orientation and compare this to the measured voltage field. A difference measure is obtained, and the program repeats the calculations for another source location/orientation multiple times until the one having the minimal difference with respect to the measured field is identified. This is the best equivalent dipole solution for the scalp voltage field at that point in time. Regardless of the complexity or number of real cerebral generators underlying the scalp field, the single-dipole model finds the best single-source explanation.

For some EEG potentials, the voltage field maxima rise and fall as the potential evolves, but the maxima do not move or change shape substantially. Single-dipole models are appropriate for such voltage fields that are spatially stable over time. Repeated dipole solutions over the time course of this type of potential are consistent and vary only in magnitude, not substantially in position or orientation. Such dipole models are consistent with either a single cerebral source or several nearby synchronously activated sources with no propagation of activity (Fig. 23.1).

When the maxima of EEG voltage fields substantially move in location or change shape during the course of the potential, the single-dipole model is inappropriate. The temporal evolution of a changing voltage field can be described, however, by a series of sequential single dipoles (14,19). This "moving dipole" model may usefully reflect characteristics of a propagating source, as commonly seen with spikes or seizures, if the propagation is simple and unidirectional and terminates before the original source repolarizes (Fig. 23.2). Moving dipole models that spiral in a loop or make sudden turns in direction or position are usually the result of fields created by the superposition of several sources with temporally overlapping activity. One-dipole solutions in these instances can be misleading. Moving dipole trajectories should therefore be interpreted with caution. If several cortical areas are active simultaneously, a different technique is needed to identify each of them.

Spatiotemporal dipole modeling is a technique that takes into consideration an overlap of activity from multiple generators (38–40,42). Dipoles are fixed in location and orientation, but they can vary over time in strength and polarity. This technique attempts to determine the fewest number of equivalent sources that can explain the EEG field over time. Not only are the dipole positions given, but the assumed and necessary activity of each dipole over time is estimated in the form of a source potential. This is akin to what an intracerebral electrode would record from the source (see Fig. 23.2).

When dealing with more than a single equivalent dipole, there is no unique solution to the inverse problem. Modeling strategies must be used to constrain the solutions to those that are most realistic. Strategies based on sequential temporal activation of generators or those based on a priori knowledge of the orientation of likely cortical sources are the ones most commonly used. Implicit in the temporal strategy is the idea that early latencies of an EEG potential are more likely to be the result of a single source than are later latencies. Accordingly, one should first model the early evolution of the voltage field with a single dipole, rather than that at the potential peak. Additional dipoles are used for any residual field left unexplained by preceding dipoles. If the initial dipole explains, both in spatial and temporal terms, the entire voltage field evolution, the cortical generator is simple in

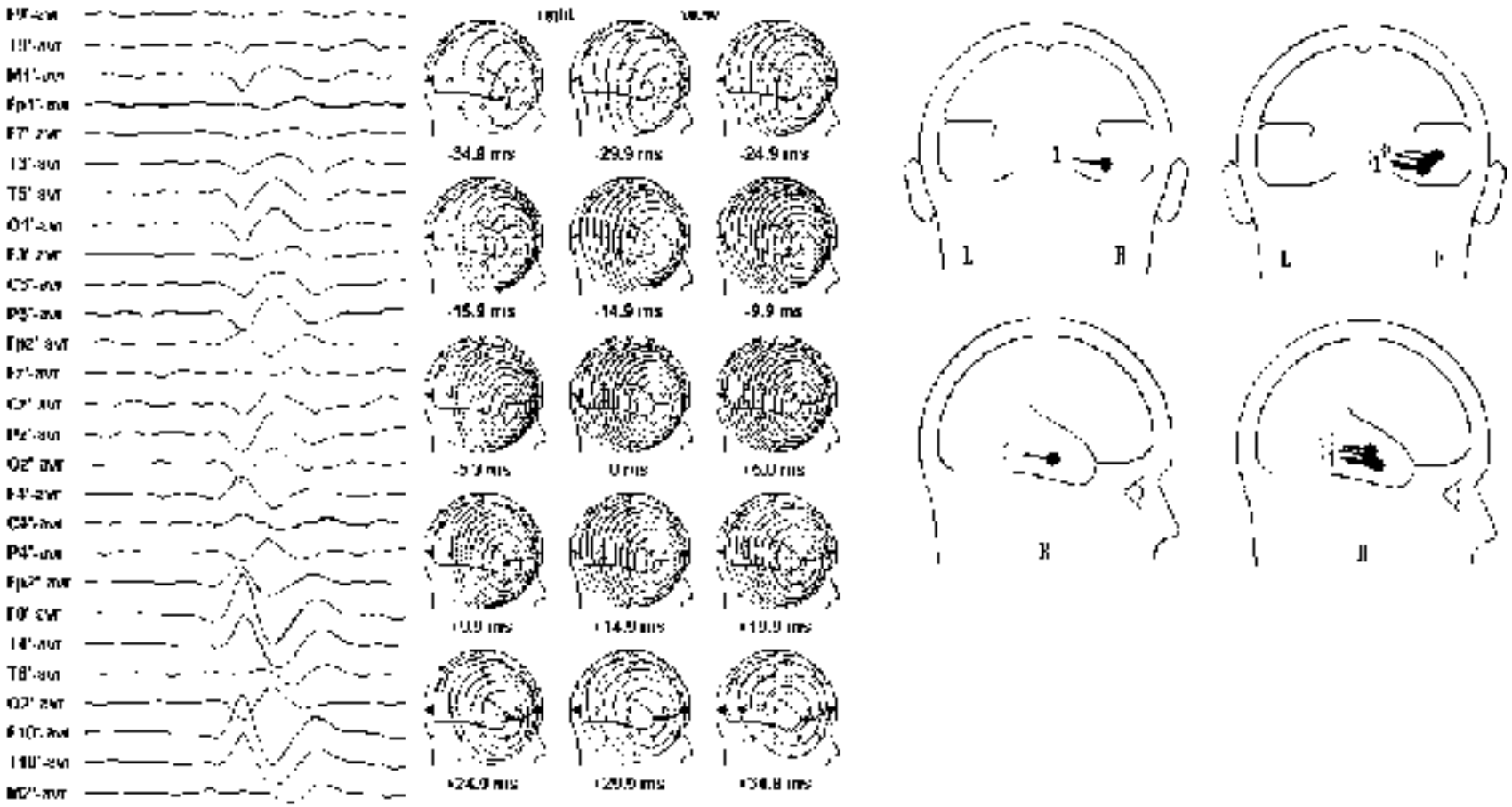

FIG. 23.1. Left: EEG traces (common average reference) of a right, type 2 temporal spike. Cursor denotes 0-millisecond latency. **Middle:** Sequential voltage topography of the spike. Note stable shape of the voltage fields over 70 milliseconds. **Right:** Instantaneous single-dipole model of the spike (at cursor) and moving dipole model of the spike over its duration. Note that voltage field stability and the tight cluster of similar dipoles in a moving model suggest a simple source well modeled by a single, instantaneous dipole. Horizontal, radial orientation is consistent with a lateral temporal cortex source. (From Ebersole J. Noninvasive localization of epileptogenic foci by EEG source modeling. *Epilepsia* 1999;41[Suppl 1]:24–33, with permission.)

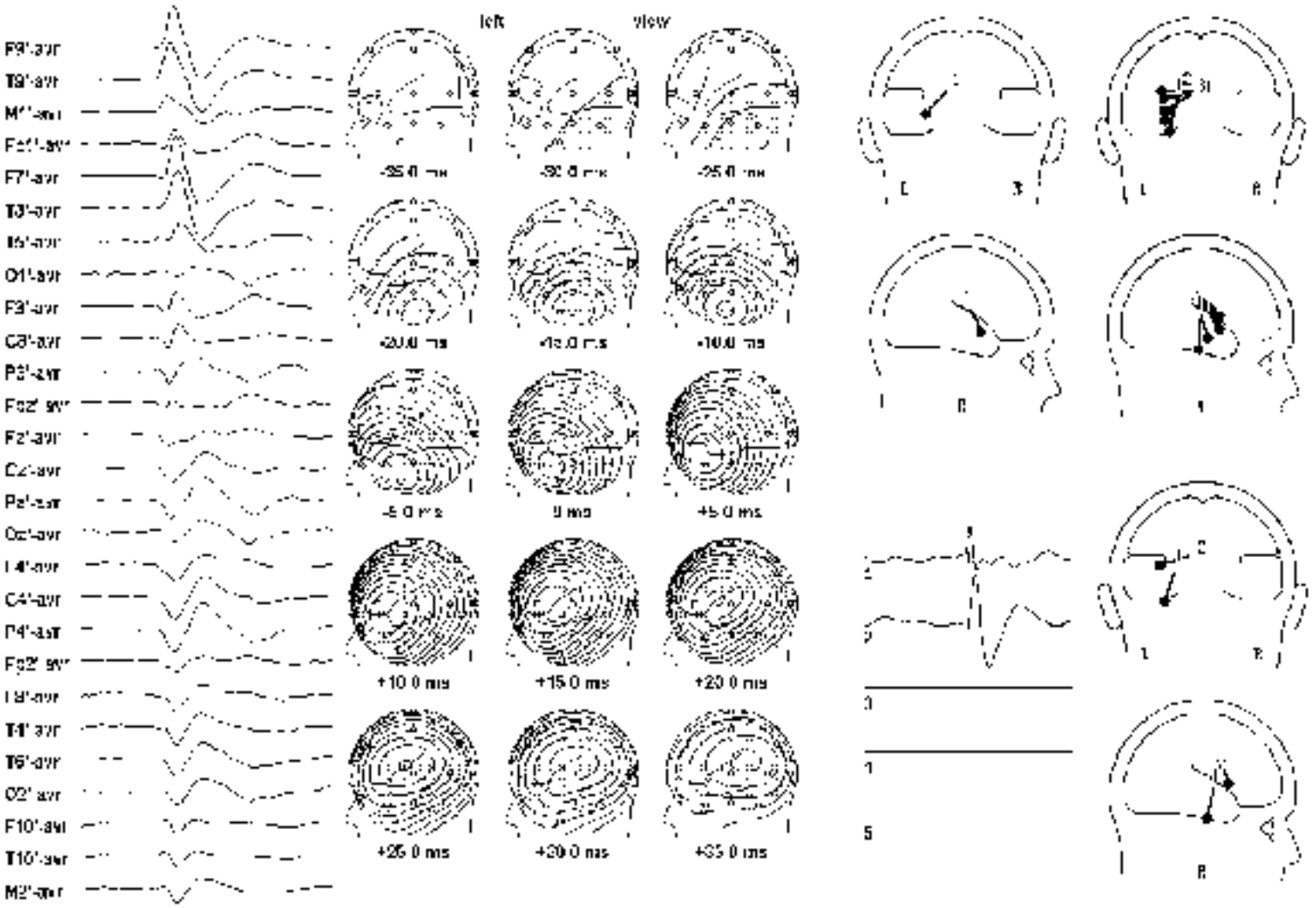

FIG. 23.2. Left: EEG traces (common average reference) of a left, type 1 temporal spike. Cursor denotes 0-millisecond latency. **Middle:** Sequential voltage topography of the spike. Note progressive change in shape of the voltage fields over 70 milliseconds, in particular movement of maxima. **Top right:** Instantaneous single-dipole model of the spike (at cursor) and moving dipole model of spike propagation. **Bottom right:** Spatiotemporal, two-dipole model of the spike. Note that spike field evolution can be explained with as few as two fixed dipoles, if the activity of dipole 1 precedes that of dipole 2. Vertical, tangential orientation of the earliest moving dipole and earlier spatiotemporal dipole is consistent with temporal base source. Later dipoles suggest spike propagation to the lateral temporal cortex. (From Ebersole J. Noninvasive localization of epileptogenic foci by EEG source modeling. *Epilepsia* 1999;41[Suppl 1]:24–33, with permission.)

character. Commonly, however, two or three dipoles may be needed to explain a temporally and spatially changing voltage field, such as that of a propagating spike.

Proper interpretation of equivalent dipoles requires an appreciation for the weaknesses in source modeling assumptions and for the complexity of real cortical source geometry and physiology. Dipole models seldom reflect precisely the location of actual cortical generators. Dipole localization techniques are least accurate in depth determinations because the actual size of the cerebral source is quite variable and always much larger than a point dipole. Activation of a large area of cortex, as is common with epileptic spikes, produces a broad scalp voltage field that will be modeled by a dipole that is deeper than the actual source.

Dipole orientation is often more useful than is dipole location/depth in determining which area of cortex in a given lobe is the likely generator of a scalp field. Because cortical sources of scalp-recordable EEG are large in area, both sides of sulci are commonly active. The tangential fields of opposite polarity generated from opposing sulcal walls tend to cancel one another, however. For this reason, activity in individual sulci tends to contribute less to scalp EEG fields than do gyral crowns. A reasonable simplification for interpreting dipole models of spontaneous potentials, such as epileptiform spikes, is to consider only the overall shape of the brain lobes and not the individual convolutions. Radial scalp EEG fields will come from gyri of convexity cortex, while tangential fields will most likely come from major fissures (interhemispheric and Sylvian) or from basal cortical surfaces (Fig. 23.3).

EEG VOLTAGE TOPOGRAPHY IN TEMPORAL LOBE EPILEPSY

Ebersole and Wade (14,20) first noted that the voltage topography of temporal spikes was not consistent, even among those with a similar frontotemporal negative field maximum. They showed that the corresponding positive field maximum varied in location from near the vertex to the contralateral temporal region. They called the former distribution, with vertex positivity, a type 1 spike field, and the latter pattern, with contralateral temporal positivity, a type 2 spike field (Figs. 23.4 and 23.5). Patients with predominantly type 1 spikes tended to have unilateral hippocampal atrophy, intracranial EEG seizures that began in mesial temporal structures, and an increased likelihood of seizure elimination following standard anteromedial temporal resection. Those patients with type 2 spikes were less likely to have hippocampal atrophy, commonly had seizures originating from non–mesial temporal structures on intracranial EEG, and were less likely to be surgical successes. Subsequent investigation demonstrated that a rigid categorization of spike topography into types 1 and 2 was overly simplistic (15). Although voltage fields may be stable for the duration of the spike, particularly in a type 2 pattern (see Fig. 23.1), voltage fields also commonly evolve, which usually signifies a propagating spike source (see Fig. 23.2). A type 1 pattern may evolve into a type 2 pattern and vice versa. Maxima locations may also shift without a change of spike type.

The location and in particular the orientation of the discharging cortical area determines the resultant spike voltage topography. Type 1 spikes, with an inferior temporal negative maximum and a vertex positive maximum, are generated

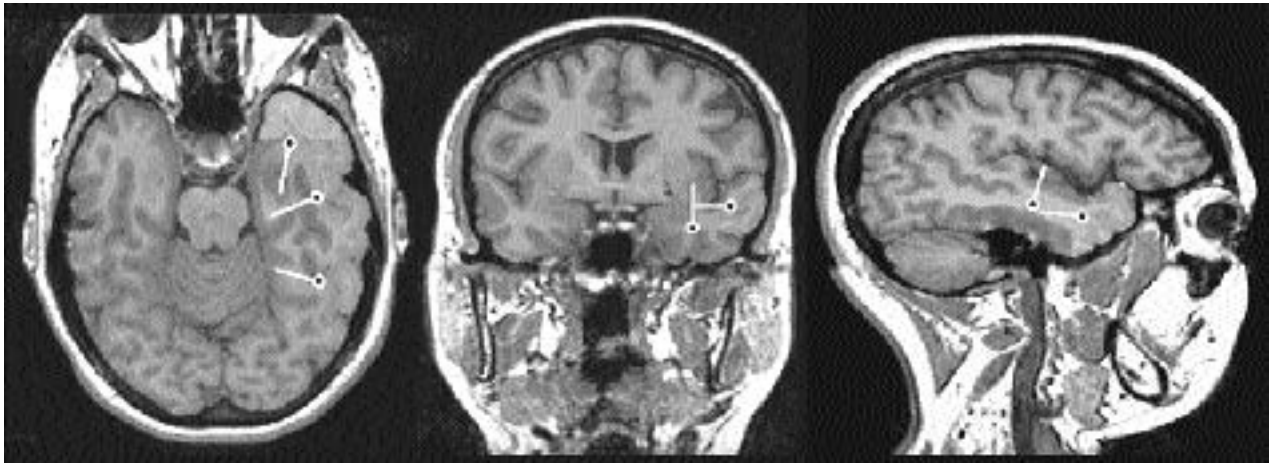

FIG. 23.3. Single dipoles of appropriate location and orientation can effectively model most temporal lobe surfaces. Vertical, tangential dipoles (*middle, right*) model the basal temporal cortex. Horizontal, tangential dipoles (*left, right*) model the temporal pole cortex. Horizontal, radial dipoles (*left, middle*) model the anterior and posterior lateral temporal cortex. (From Assaf BA, Ebersole JS. Continuous source imaging of scalp ictal rhythms in temporal lobe epilepsy. *Epilepsy* 1997;38:1114–1123, with permission.)

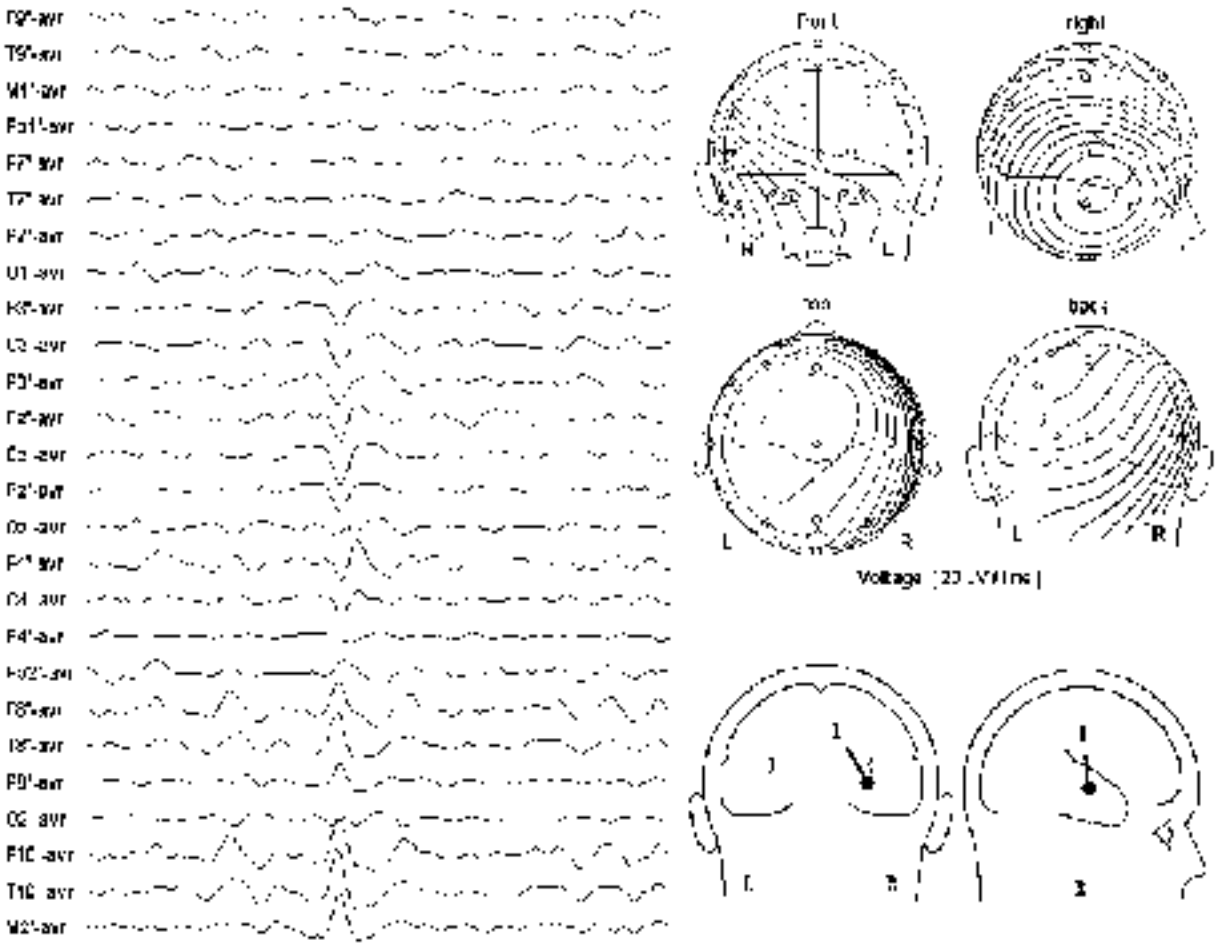

FIG. 23.4. Left: Right temporal type 1 spike. In this and subsequent figures, the EEG is depicted in a common average reference montage. **Top right:** Voltage topography of the spike at the cursor. In this and subsequent figures, the scalp voltage fields are illustrated by isopotential lines; the negative field is speckled. **Bottom right:** Single-dipole model of the spike field at the cursor and in the voltage map. Dot denotes location; vector denotes source orientation. Note the subtemporal negative field maximum and vertex positive field maximum, which are characteristic of type 1 spikes. The dipole model has an elevated orientation. Both the field and the dipole suggest a temporal basal cortex source. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000:353–364, with permission.)

principally by basal and inferolateral cortex. Only these areas of temporal lobe cortex have a net orientation that could produce such a field. The type 1 spike field does not directly reflect hippocampal or amygdalar activity. Spikes confined to these structures do not generate scalp-recordable voltage fields because of the small source area and curved source shape, which favor voltage cancellation. Rather, it is the common and preferred propagation of this epileptiform activity from mesial structures into the entorhinal, fusiform, and other basal cortex that results in a generator of sufficient area to produce scalp EEG potentials (16,18,34). In general, some degree of propagation commonly occurs before either spike or seizure potentials are recordable at the scalp. Because voltage fields are orthogonal to the net orientation of their source cortex, a temporal lobe base spike is seen as subtemporal negativity and vertex positivity.

Spikes that originate in basal temporal cortex may produce a similar voltage field. Alternatively, these spikes frequently propagate into temporal tip cortex by the time sufficient cortex is activated to produce a scalp EEG field. Temporal tip cortex has a net anterior-facing orientation. Accordingly, spike sources in this cortex result in a voltage field with a frontotemporal-to-frontopolar negative maximum and a posterior positive

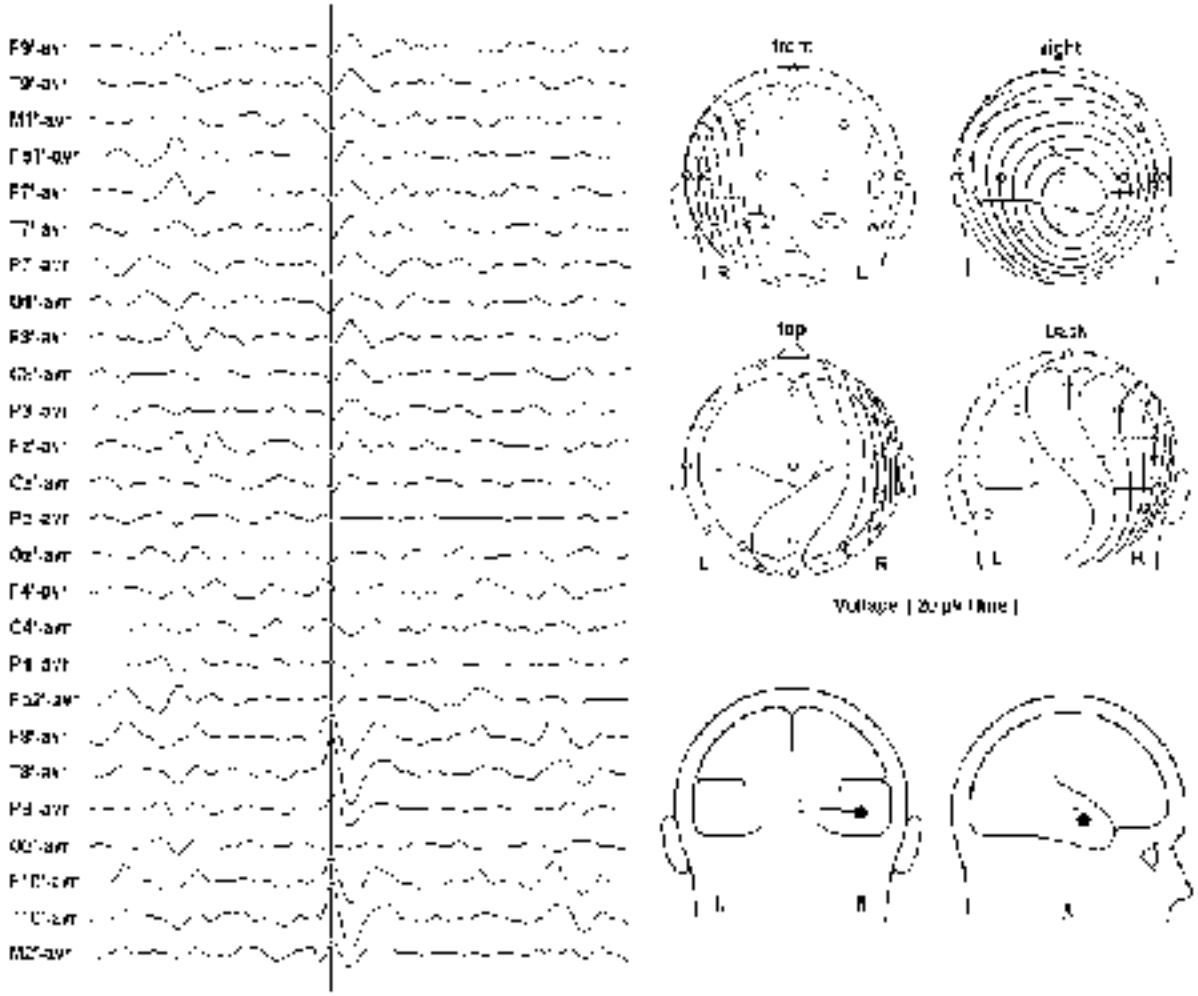

FIG. 23.5. Left: Right temporal type 2 spike. **Top right:** Voltage topography of the spike at the cursor. **Bottom right:** Single-dipole model of the spike field at the cursor and in the voltage map. Note the lateral temporal negative field maximum and contralateral positive field maximum, which are characteristic of type 2 spikes. The dipole model has a horizontal and radial orientation. Both the field and the dipole suggest a lateral temporal cortex source. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000: 353–364, with permission.)

maximum (16,47) (Fig. 23.6). That the source of such a field is temporal tip in origin rather than frontal pole can be appreciated by the negative and positive field voltage gradients, which are nearly equal, suggesting that the source lays near the zero isopotential line, which overlays the temporal lobe, rather than beneath the negative maximum over the frontal lobe.

Type 2 spikes are generated by lateral temporal cortex. These spikes commonly propagate in an anterior–posterior (AP) direction along the lateral convexity. The net vertical orientation of this temporal cortex results in a lateral negative maximum and a positive maximum over the contralateral temporal area. Occasionally lateral temporal spikes will propagate medially into the basal cortex, which causes the later portions of its voltage field to change. It is therefore always important to consider the evolution of each spike voltage field. Because propagation is common, one cannot conclude that the voltage field of the spike peak best represents the character of the spike source. This is only true if the contours of the voltage field do not change over the course of the spike potential. Otherwise, the voltage topography and dipole model of the earliest portion of the spike potential should be regarded as being most closely associated with the spike origin (15,16).

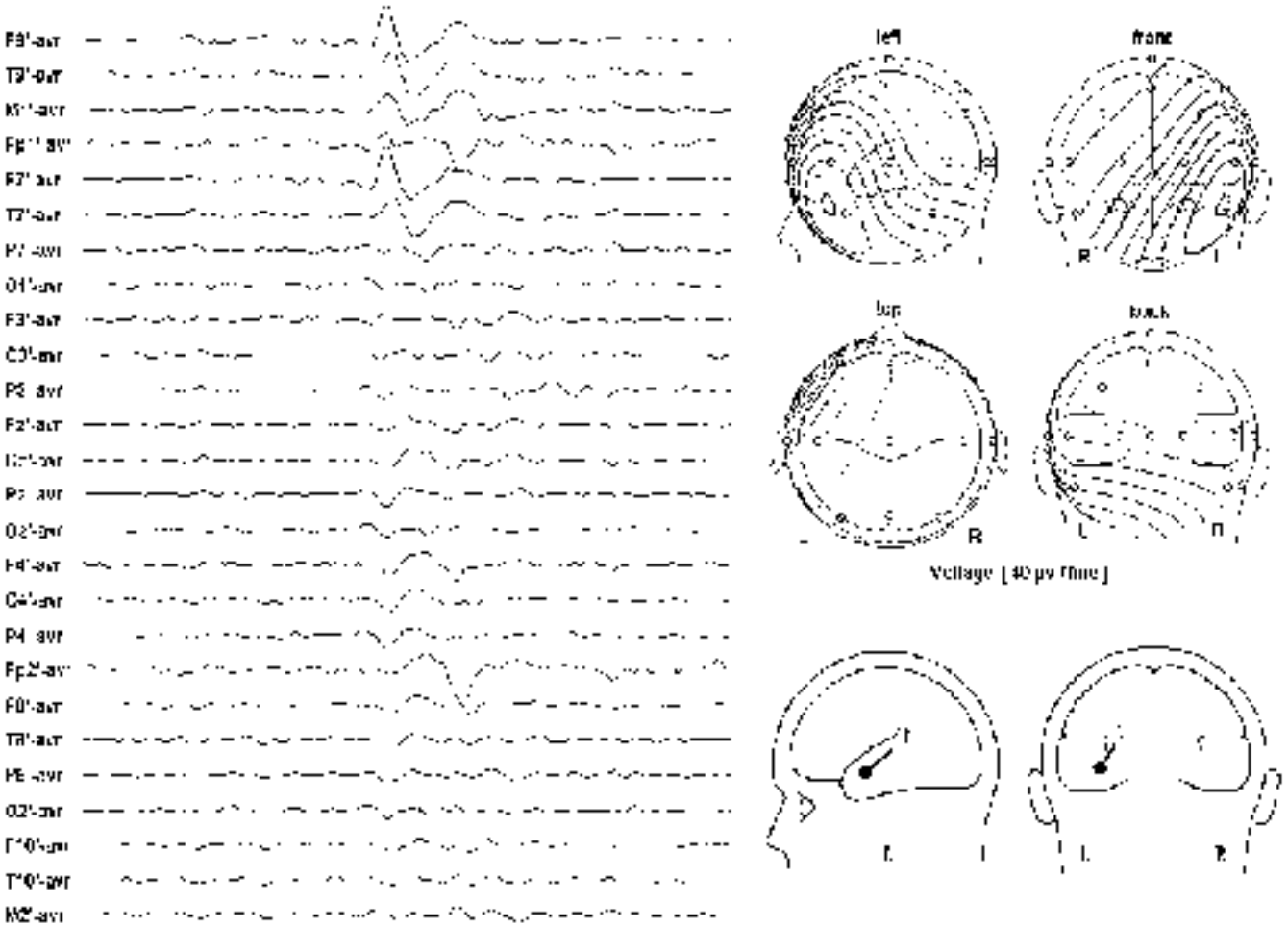

FIG. 23.6. Left: Left temporal tip spike. **Top right:** Voltage topography of the spike at the cursor. **Bottom right:** Single-dipole model of the spike field at the cursor and in the voltage map. Note the inferior frontotemporal negative field maximum and the contralateral posterior positive field maximum, which are characteristic of temporal tip spikes. The dipole model has mostly a horizontal and AP orientation. Both field and dipole suggest a temporal tip cortex source. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000:353–364, with permission.)

DIPOLE MODELING IN TEMPORAL LOBE EPILEPSY

Single-Dipole Modeling

When single, instantaneous dipole modeling was performed on type 1 versus type 2 spike voltage topography, only dipole orientation (elevation) was significantly different between the two (13,14,19). In a group of 24 patients with anterior temporal discharges, models of type 1 spikes had a mean dipole elevation of 42 degrees (SD 5.0), whereas models of type 2 spikes had a mean dipole elevation of only 2 degrees (SD 10.0). Thus equivalent dipoles for type 2 spikes tend to have an orientation that is radial to the lateral skull convexity (see Fig. 23.5), whereas type 1 spike dipoles have a vertical or oblique orientation (see Fig. 23.4).

For some spikes, repeated single-dipole solutions are very consistent during the course of the spike. Their voltage fields rise and fall in magnitude but change little in position or orientation (see Fig. 23.1). As noted before, a single-dipole model fits these data well and suggests a focal cerebral generator. For other spikes, sequential solutions over the spike time course show progressive drift in dipole location and rotation of vector orientation (see Fig. 23.2). Such behavior is consistent with spike propagation or asynchronous activation of different cortical areas (13,14,19). A single moving dipole model may be misleading in an attempt to explain a complex field, which may be a composite from several generators.

Spatiotemporal Multiple-Dipole Modeling

Several different patterns of multiple-dipole models have emerged when applying this technique to the spikes of patients with temporal lobe epilepsy (13–16). Spikes with type 1 voltage topography usually require two or more dipoles to be modeled adequately (see Fig. 23.2). One of these dipoles typically has an orientation that is vertical and tangential to the lateral skull convexity, whereas the other is horizontal and radial. The tangential dipole is usually deeper than the radial one. Type 1 spike topography is the result of the superposition of fields from both sources when their activity overlaps in time. Source analysis of type 1 spikes from different patients has shown tangential source activity leading, lagging, or being synchronous with radial source activity. The pattern of voltage field evolution for a particular spike is thus dependent on the temporal relationships of its various source components. Information about the direction of spike propagation is conveyed by the sequence in which dipole sources become active. Simultaneous intracranial and scalp EEG recordings have validated previous assumptions that the vertical tangential dipole models activity from the basal temporal lobe cortex and the horizontal radial dipole models activity from the lateral temporal cortex (18,34). Basal-to-lateral cortex propagation and vice versa, suggested by timing differences in dipole source components, have also been confirmed.

The majority of spikes with type 2 topography require only one horizontal radial dipole to be modeled (see Figs. 23.2 and 23.5). In approximately one-third of patients, however, two or more dipoles are needed. In these cases, the dipoles usually differ in azimuth orientation and AP position, yet continue to be predominantly radial. Differences in timing between these sources can suggest anterior-to-posterior or, less commonly, posterior-to-anterior propagation along the lateral temporal convexity.

More recently, a third major cortical source contributing to temporal spike fields has been identified by dipole modeling (17,21,46,47). Synchronous activity of anterior temporal tip cortex results in a field with a negative maximum recorded from frontopolar and frontotemporal electrodes because of its net forward-facing orientation. Dipoles modeling this activity are horizontal, but have a distinct AP direction (see Fig. 23.6). Occasionally, spikes have just this dipole solution, but usually the tip component is present in combination with other temporal source components in more complex spikes exhibiting propagation.

Spatiotemporal modeling strategies using anatomical constraints can also be useful. Unconstrained inverse solutions consider any position within the spherical head model and any orientation of dipole vector to be equally likely as a source. This is obviously not true biologically. Spikes arise from cortex that has limited and definable locations and orientations. Of the two, it is more useful to specify the orientation of possible equivalent sources. As noted previously, it is reasonable to consider for purposes of modeling only the orientations of major lobar surfaces. For the temporal lobes, these dipole orientations are horizontal radial for the lateral convexity cortex, vertical tangential for the basal cortex and superior temporal plane, and AP horizontal tangential for the temporal tip. One approach in using this strategy for the temporal lobes is to create a priori a multiple spatiotemporal dipole model of major lobar surfaces and note from the source potentials of this model to what extent each constituent dipole contributes to explaining the scalp EEG voltage fields over time (1,2,41,46). This technique can be used to review continuous EEG in so-called source montages. Spikes or seizures, along with background rhythms, are decomposed into the source potential contributions of a fixed number of dipoles. For an EEG transient to appear in a particular source channel, it must have a voltage field that is appropriate for the dipole whose source potential that channel is displaying (see Figs. 23.11 through 23.13).

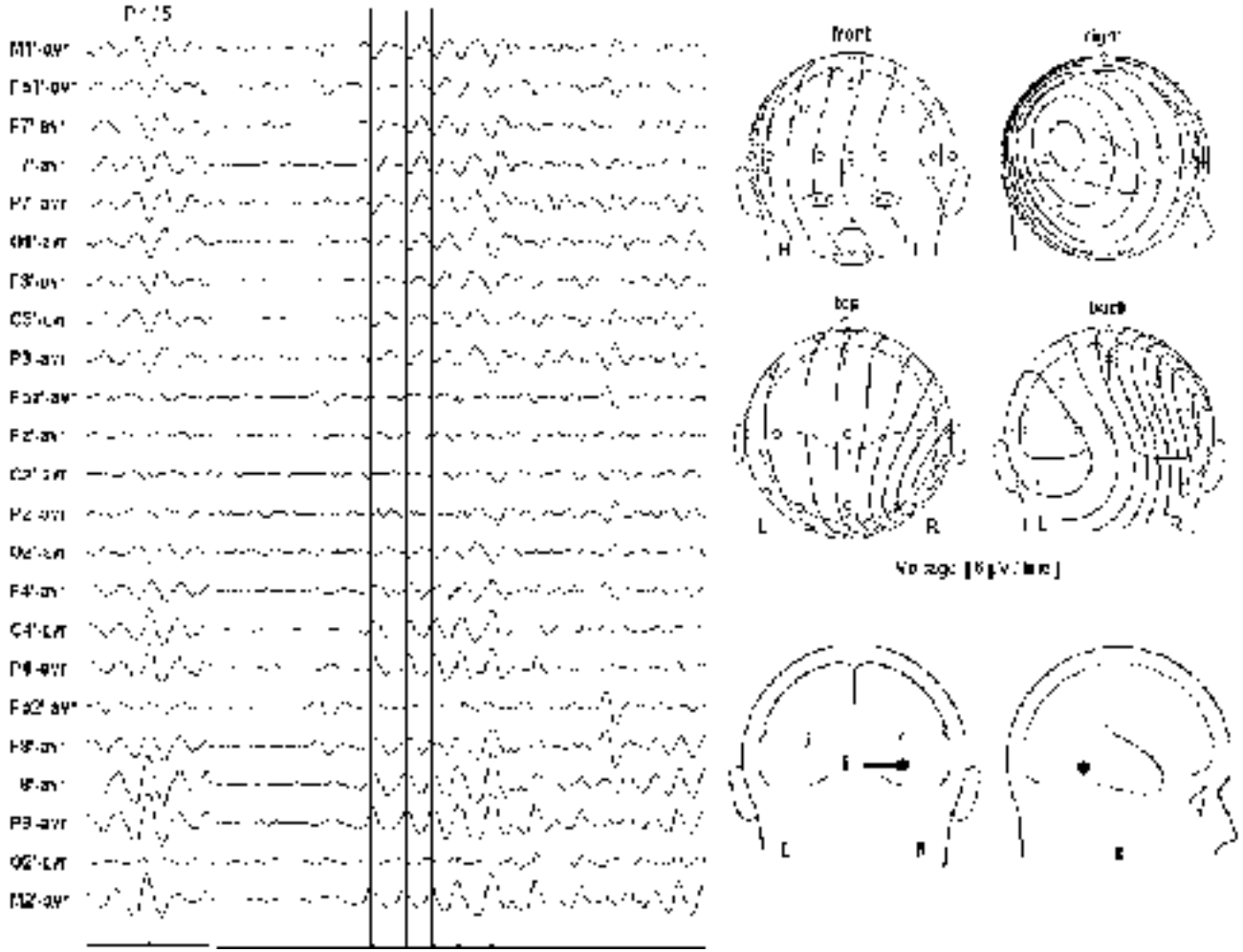

FIG. 23.7. Left: Right temporal type 2 seizure onset pattern. Cursors mark ictal potentials that were averaged to improve the signal-to-noise ratio. The averaged ictal waveform is at the far left. **Top right:** Voltage topography of the averaged ictal waveform at the cursor. **Bottom right:** Single-dipole model of the ictal field at the cursor and in the voltage map. Note the lateral, midposterior negative field maximum and the contralateral positive field maximum, which are characteristic of type 2 seizures. The dipole model has a horizontal and radial orientation. Both the field and the dipole suggest a lateral temporal cortex source. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000:353–364, with permission.)

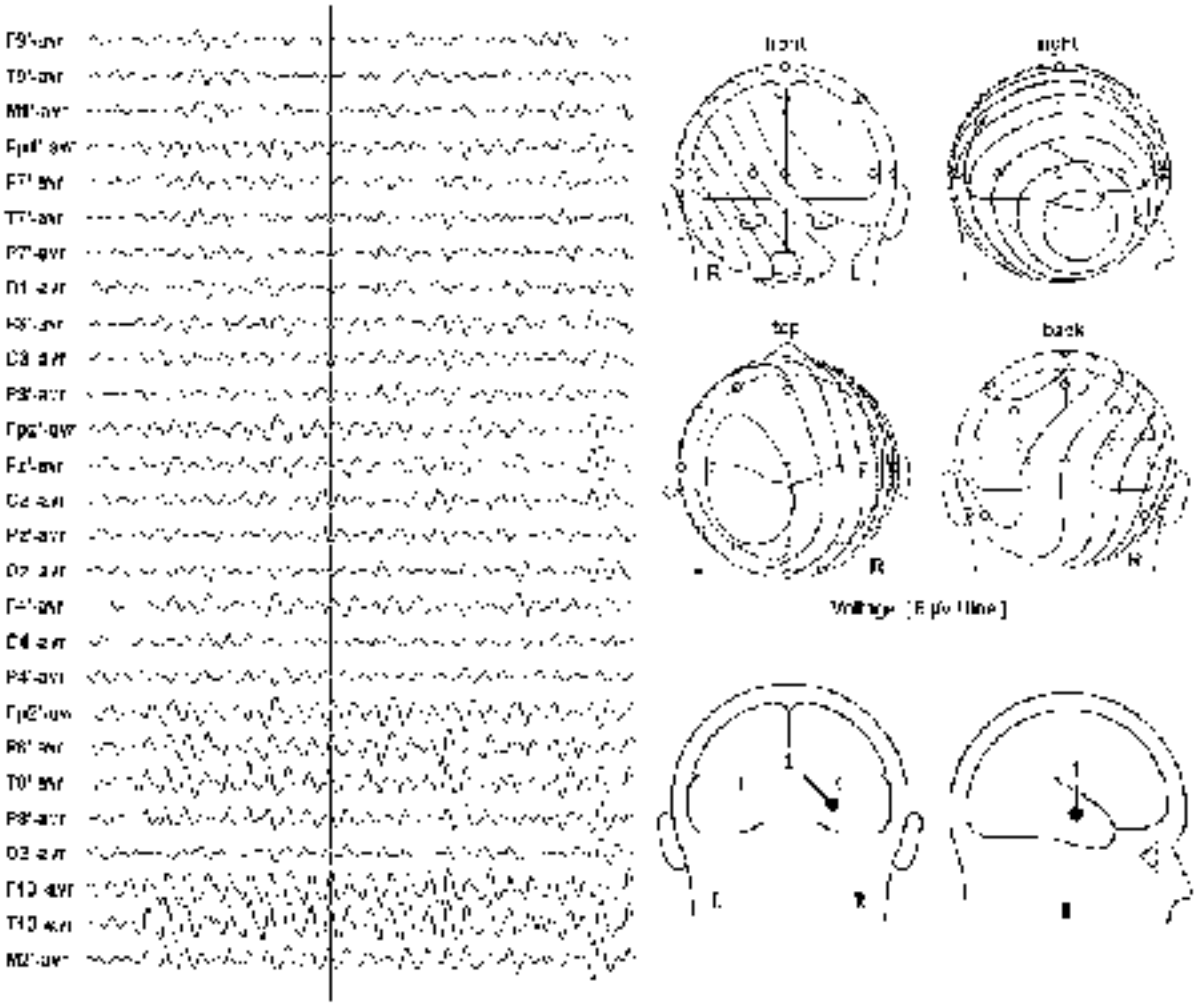

FIG. 23.8. Left: Right temporal type 1 seizure onset pattern. **Top right:** Voltage topography of the ictal waveform at the cursor. **Bottom right:** Single-dipole model of the ictal field at the cursor and in the voltage map. Note the anterior subtemporal field maximum and the vertex positive field maximum, which are characteristic of type 1 seizures. The dipole model has an elevated orientation. Both the field and the dipole suggest a temporal basal cortex source. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000:353–364, with permission.)

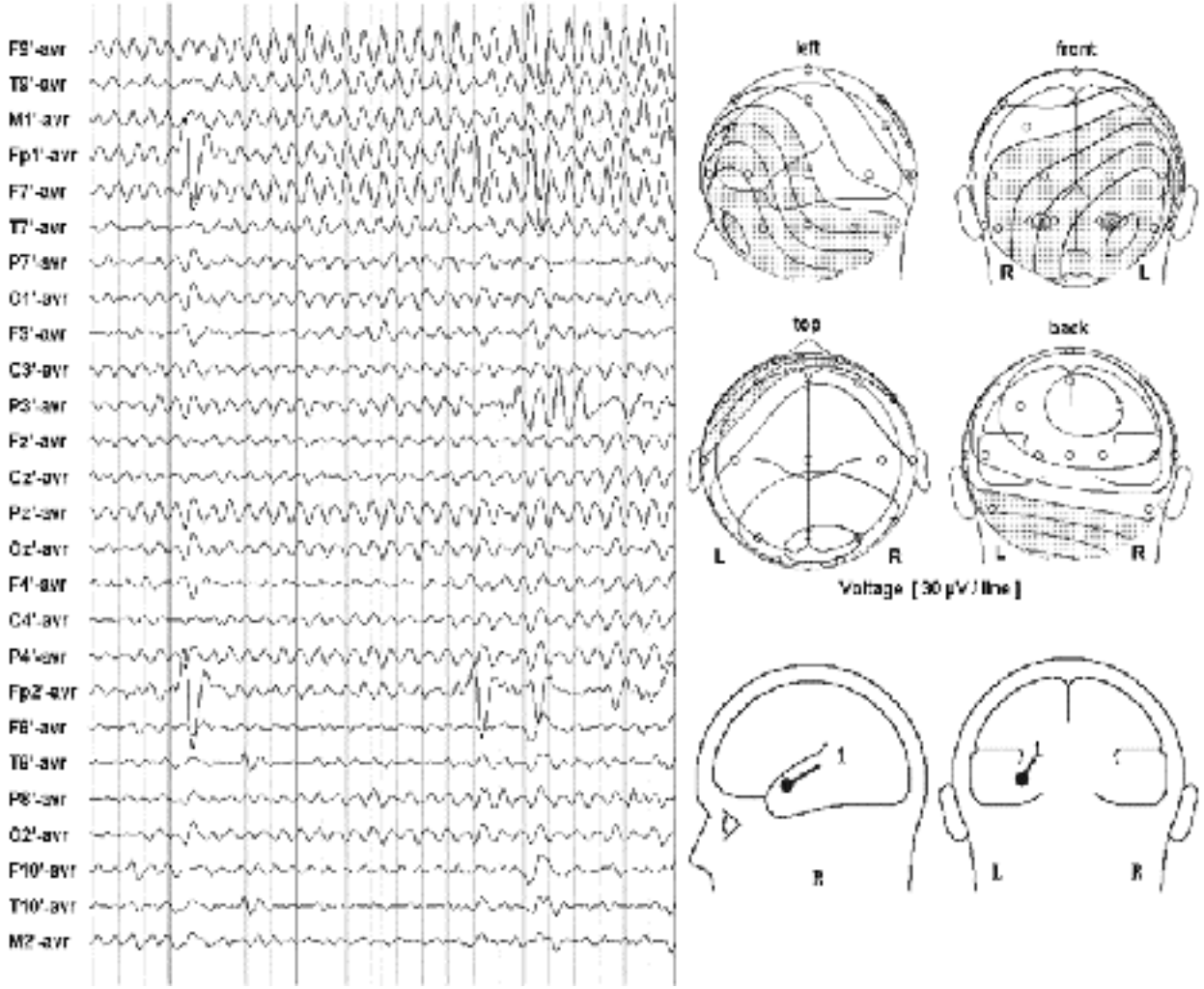

FIG. 23.9. Left: Left temporal tip seizure onset pattern. **Top right:** Voltage topography of the ictal waveform at the cursor. **Bottom right:** Single-dipole model of the ictal field at the cursor and in the voltage map. Note the inferior frontal negative field maximum and the posterior positive field maximum, which are characteristic of temporal tip seizures. The dipole model has mostly a horizontal and AP orientation. Both the field and the dipole suggest a temporal tip cortex source. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000:353–364, with permission.)

DIPOLE MODELING OF TEMPORAL LOBE SEIZURES

Dipole modeling can also be applied to seizure rhythms with some modifications in the protocol used for spik es (4–7,15,17). The earliest recognizable seizure potentials should be preferentiall y modeled because the y are more likely to reflect the seizure origin than are later rhythms, which usually evolve only after significant propagation. Because ictal-onset rhythms are typically of low amplitude and commonl y are confounded with mo vement and muscle artifact, averaging successive potentials may be necessary to increase the signal-to-noise ratio. The key is to average seizure waveforms with similar voltage topographies (Fig. 23.7); only these reflect the same source configuration. Ictal EEG voltage fields are usuall y spatially stable for onl y a few seconds, however. Tight bandpass filtering is also useful in ictal dipole modeling. Most temporal lobe seizure frequencies are less than 12 Hz. A high-frequency filter

of 13–20 Hz is therefore reasonable to reduce muscle artifact. Similarly, a low linear filter of 1–2 Hz will minimize low-frequency artifact secondary to movement of the patient or electrode leads.

The orientation of dipole models of ictal waveforms carries the same significance as those of spikes, in that it is most useful in identifying sublobar temporal lobe sources (1,2,4–7,15,17,46). Temporal lobe seizures modeled by dipoles with dominant horizontal radial, vertical tangential, or AP horizontal tangential orientations are most likely associated with lateral temporal, hippocampal/basal, or temporal tip seizures, respectively (Figs. 23.7 through 23.9). Additionally, many temporal lobe seizures are modeled best by dipoles having an anterior oblique orientation, that is, a combination of all three of the previous orientations (Fig. 23.10). In this case, the ictally active cortical region includes inferior, tip, and lateral temporal cortex. Multiple fixed dipole models also can be used to identify the contribution of various sublobar cortical

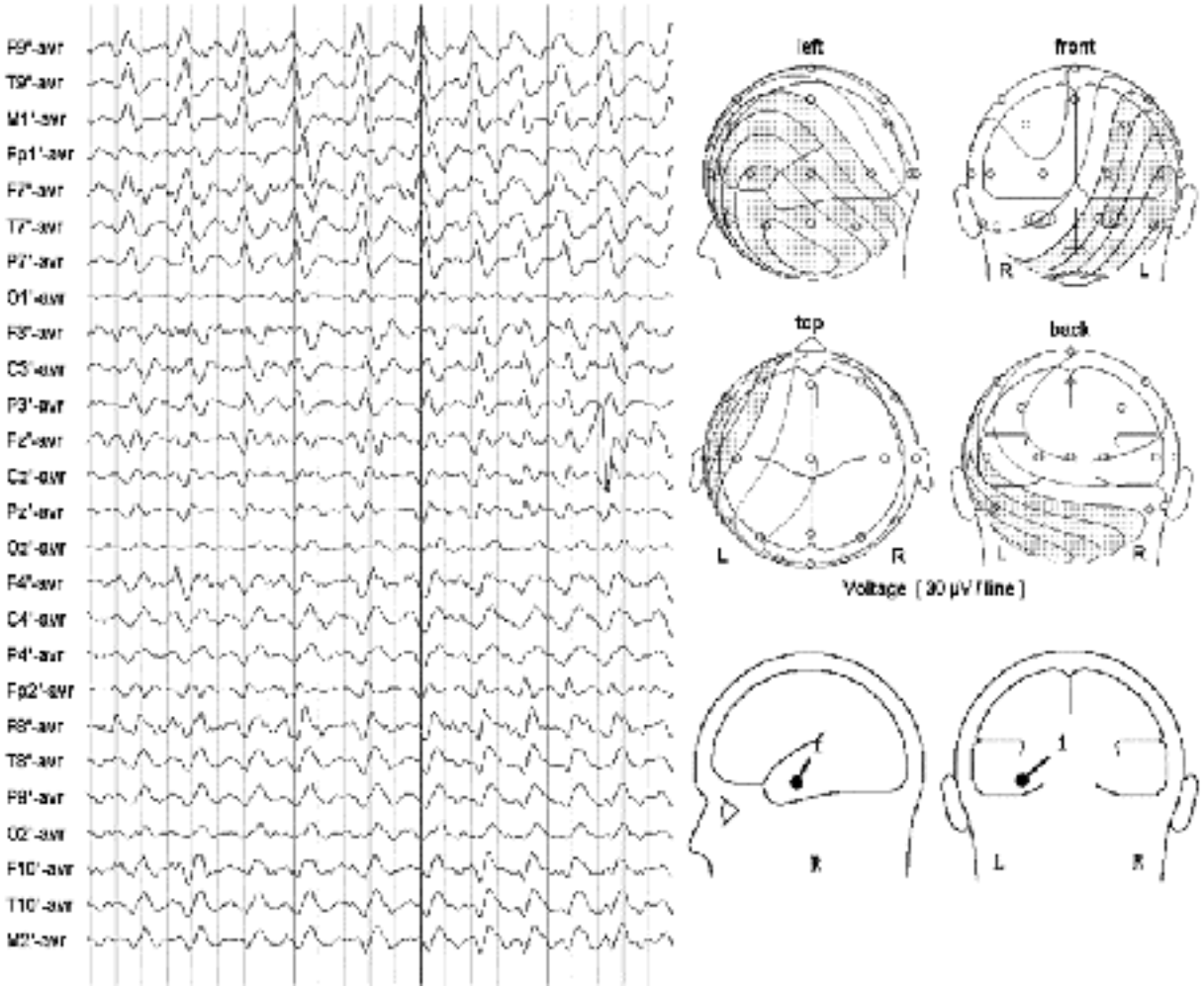

FIG. 23.10. Left: Left temporal, "oblique dipole" seizure onset pattern. **Top right:** Voltage topography of the ictal waveform at the cursor. **Bottom right:** Single-dipole model of the ictal field at the cursor and in the voltage map. Note the anterior subtemporal negative field maximum and the posterior vertex positive field maximum, which are characteristic of these temporal seizures. The dipole model has an anterior oblique orientation. Both the field and the dipole suggest a temporal source involving the anterior basal tip and inferolateral cortex. (From Ebersole JS. Sublobar localization of temporal epileptogenic foci by EEG source modeling. In: Williamson PD, Siegel AM, Roberts DW, et al, eds. *Neocortical epilepsies*. Philadelphia: Lippincott Williams & Wilkins, 2000:353–364, with permission.)

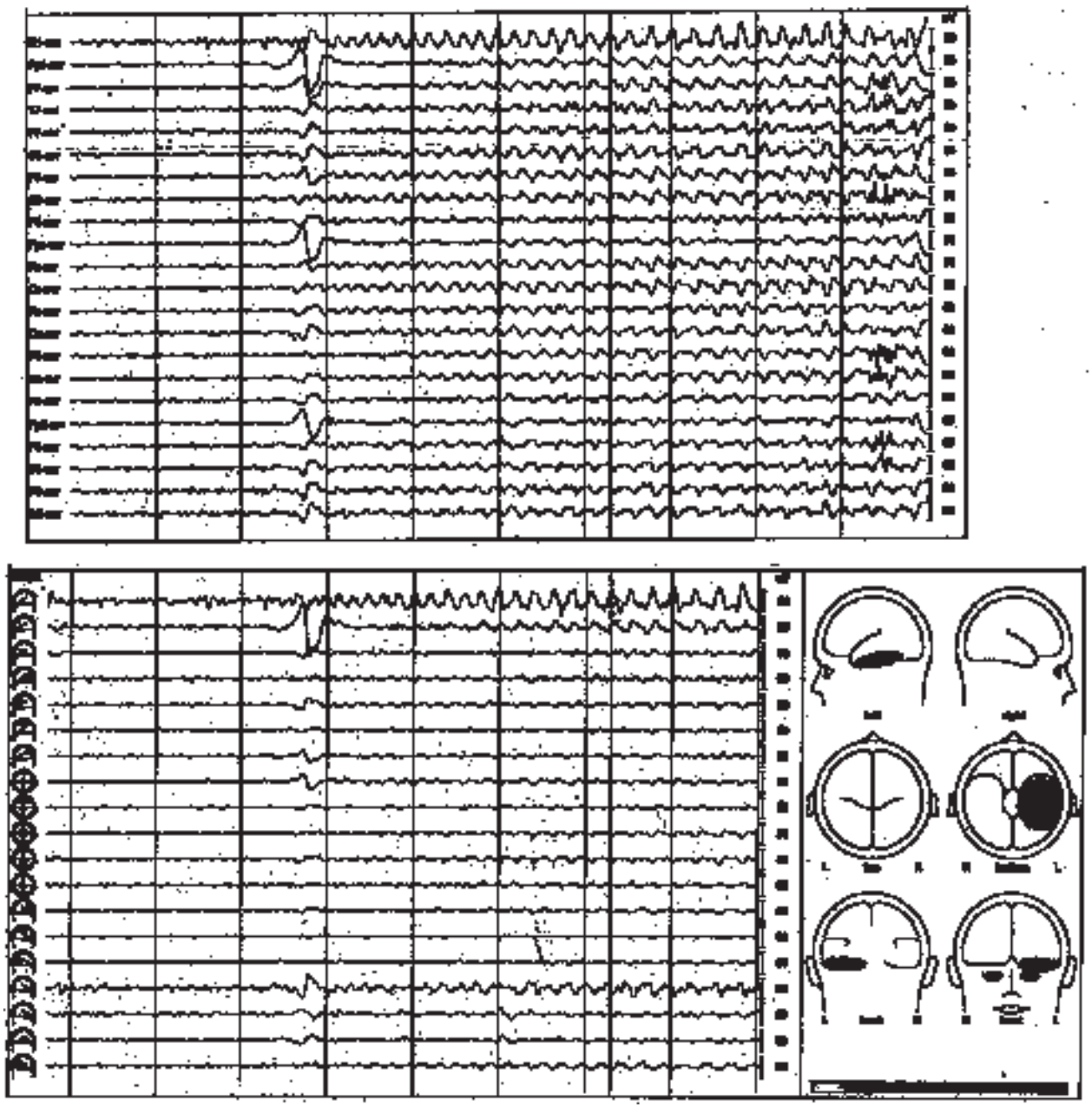

FIG. 23.11. Top: Traditional EEG depiction of a hippocampal-onset seizure, which produces an ictal rhythm with a widespread scalp distribution. **Bottom:** Same seizure displayed in a continuous source imaging montage (Focus 1.1), which decomposes the EEG into the activity of 19 dipolar sources modeling selected cortical surfaces, four of which are in each temporal lobe. The prominent left basal temporal source component (*top trace*) accounts for most of the ictal rhythm. The source image (*right*) displays the most active cortical region at the time of the cursor. In this and in Figures 23.12 and 23.13, the top EEG is displayed in a common average reference with 2- to 20-Hz bandpass filtering. Calibration markers: 60 μV, 1 second. (From Assaf BA, Ebersole JS. Continuous source imaging of scalp ictal rhythms in temporal lobe epilepsy. *Epilepsy* 1997;38: 1114–1123, with permission.)

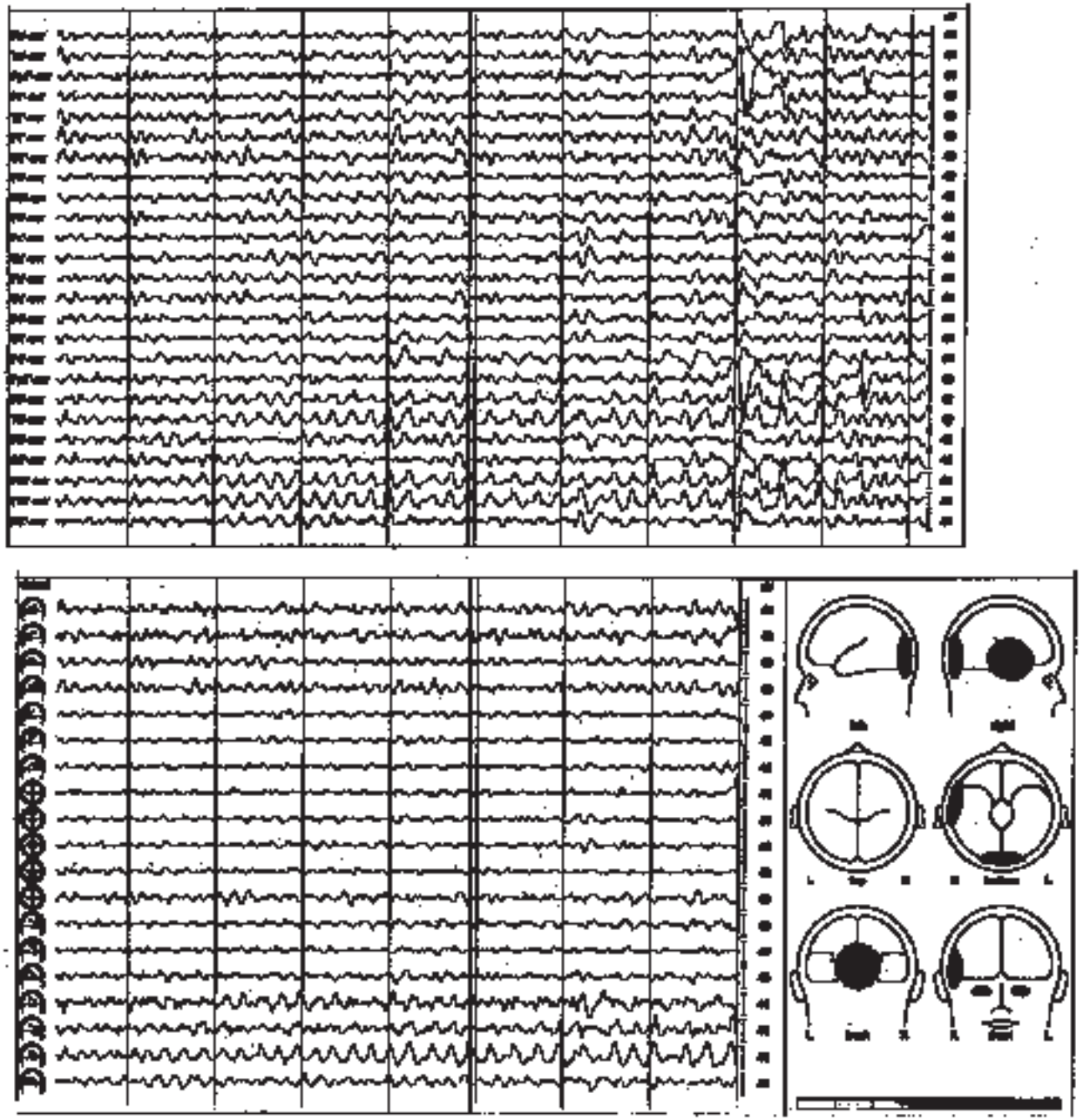

FIG. 23.12. Top: Scalp EEG of a right temporal seizure of lateral neocortical origin. **Bottom:** A prominent anterolateral temporal source component (next to last trace) is evident when the same seizure is displayed in the source imaging montage. **Right:** The most active cortical region at the time of the cursor. Calibration markers: 40 μV, 1 second. (From Assaf BA, Ebersole JS. Continuous source imaging of scalp ictal rhythms in temporal lobe epilepsy. *Epilepsy* 1997;38: 1114–1123, with permission.)

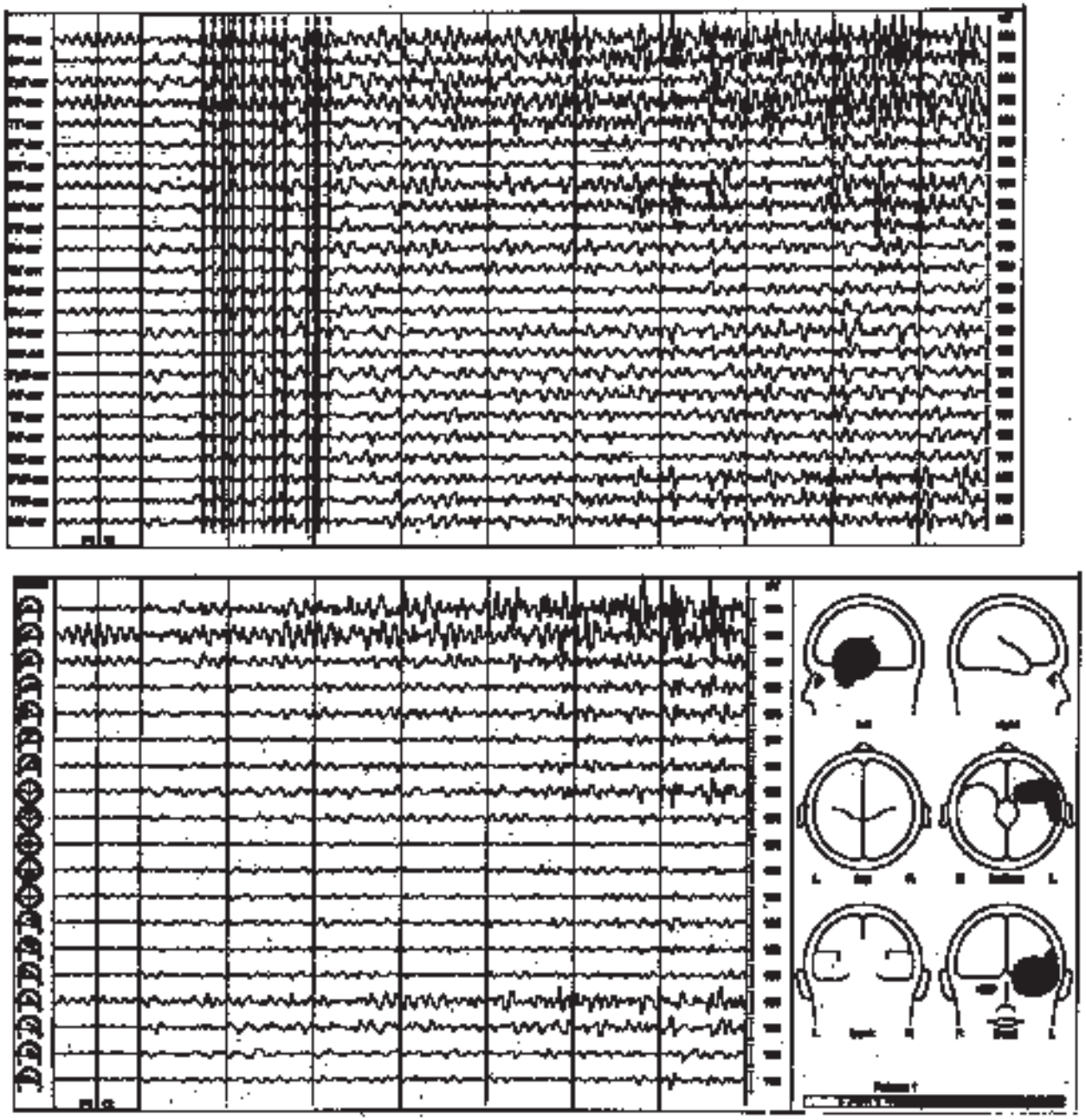

FIG. 23.13. Top: Scalp EEG of a left temporal seizure of entorhinal cortex origin. Cursors "1" mark the 12 waveforms of the ictal rhythm that were averaged to improve the signal-to-noise ratio. **Top Left:** Resultant averaged ictal EEG. **Bottom:** A prominent temporal tip source component is evident when the same seizure is displayed in the source imaging montage. This is better appreciated in the averaged ictal data shown at left. **Bottm Right:** The most active cortical region at the time of the cursor. Calibration markers: 150 μV, 1 second. (From Assaf BA, Ebersole JS. Continuous source imaging of scalp ictal rhythms in temporal lobe epilepsy. *Epilepsy* 1997;38:1114–1123, with permission.)

areas to seizure potentials (Figs. 23.11 through 23.13). This technique has been used to determine temporal lobe seizure origins and to predict surgical outcome following standard temporal lobectomy (1,2,17,41,46).

Ictal EEG dipole models have been correlated with intracranial EEG and surgical outcome (1,2,4–7,15,46). The results are similar to those found with spike dipole modeling. Patients with seizures modeled by horizontal radial dipoles, which suggest a lateral cortex origin, do less well following a standard anteromesial resection and should be considered candidates for invasive monitoring and possibly tailored temporal lobe resections. Patients whose seizures are modeled best by dipoles with a vertical, horizontal AP, or anterior oblique orientation have seizures originating probably in mesial structures: basil, entorhinal, or temporal tip cortex, respectively. All of these patients do well following surgery because these cortices are customarily removed in the standard temporal lobe resection.

Other laboratories have confirmed the utility of EEG dipole modeling in the evaluation of patients with focal epilepsy (3,27–31). There is a consensus that most spikes (and seizures) can be modeled usefully by equivalent dipoles and that activated regions of cortex, rather than mesial structures in the temporal lobe, are the sources. These investigators have also found that dipole orientation more clearly differentiates basomesial from lateral temporal epilepsy than does dipole location. Similarly, change in dipole orientation over time is a better marker of spike propagation than the trajectory of the dipole locus.

CO-REGISTERING EEG DATA WITH MAGNETIC RESONANCE IMAGING AND REALISTIC HEAD MODELS

With the advent of computed tomography and more recently magnetic resonance imaging (MRI), detailed anatomical information about an individual's head and brain are readily available. Only very recently, however, have these data been combined with EEG to provide "functional imaging" of the brain's electrical activity. One of the earliest EEG-related observations using three-dimensional (3-D) MRI reconstructions was the geometrical relationship between standard scalp electrode positions and the underlying brain. As illustrated in Figure 23.14, the standard international 10-20 temporal electrode chain passes across the superior aspect of the temporal lobe. Supplementary inferior temporal electrodes are necessary for properly recording the negative field of basal frontal, temporal, and occipital spikes/seizures. By digitizing the scalp electrode locations and certain head landmark fiducials, such as the nasion and preauricular points in 3-D space, the topography of the scalp EEG fields could be co-registered with and superimposed on a 3-D MRI reconstruction of the patient's head or brain. In similar fashion, calculated dipole models could be co-registered with the same 3-D brain image (16,23,40) (Fig. 23.15).

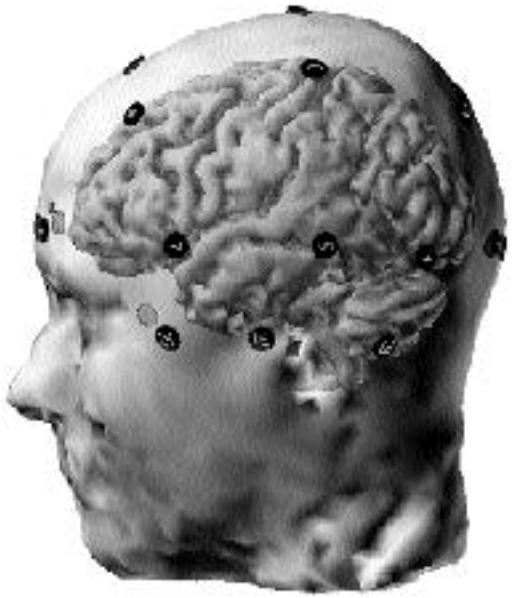

FIG. 23.14. Standard international 10-20 and supplementary subtemporal scalp electrode positions superimposed on transparent three-dimensional reconstructions of the head and brain. Note that the standard longitudinal temporal chain of electrodes passes over the superior aspect of the temporal lobe. Only subtemporal electrodes effectively record from the inferolateral and basal temporal cortex. (From Ebersole JS. Defining epileptogenic foci: past, present, and future. *J Clin Neurophysiol* 1997;14:470–483, with permission.)

It has been appreciated for some time that the spherical head model commonly used to calculate EEG dipoles was a convenient approximation, but an approximation nonetheless. Systematic errors in dipole location introduced by spherical head models have been identified (10,11,43). Roth and colleagues (35,36) first simulated and more recently studied real EEG sources in the temporal and frontal lobes to compare the effects of spherical versus realistic head models on dipole solutions. They noted location errors in the spherical models of 1–3 cm that were worse in the vertical or *Z* direction. Yvert et al. (49,50) and Fuchs et al. (21,22) simulated EEG dipoles sources throughout the brain and found that spherical head modeling errors were worse for basal regions and in the *Z* direction. These results were also confirmed using temporal lobe spike and seizure foci as the source and validating the true location of these foci with intracranial EEG (16). Segmented volumetric MRI data were used to calculate a realistic head model by the boundary element method (Fig. 23.16). Dipoles

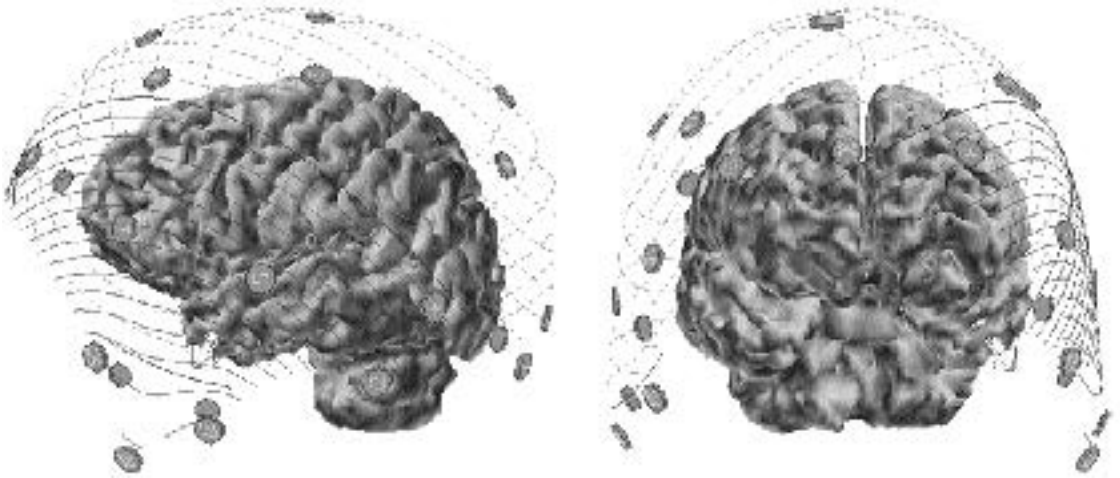

FIG. 23.15. Scalp voltage isopotential field lines of a left temporal spike and recording electrode positions are superimposed on a three-dimensional reconstruction of the patient's brain. Dipole model of the spike source is depicted as an *arrow* emerging from the temporal tip.

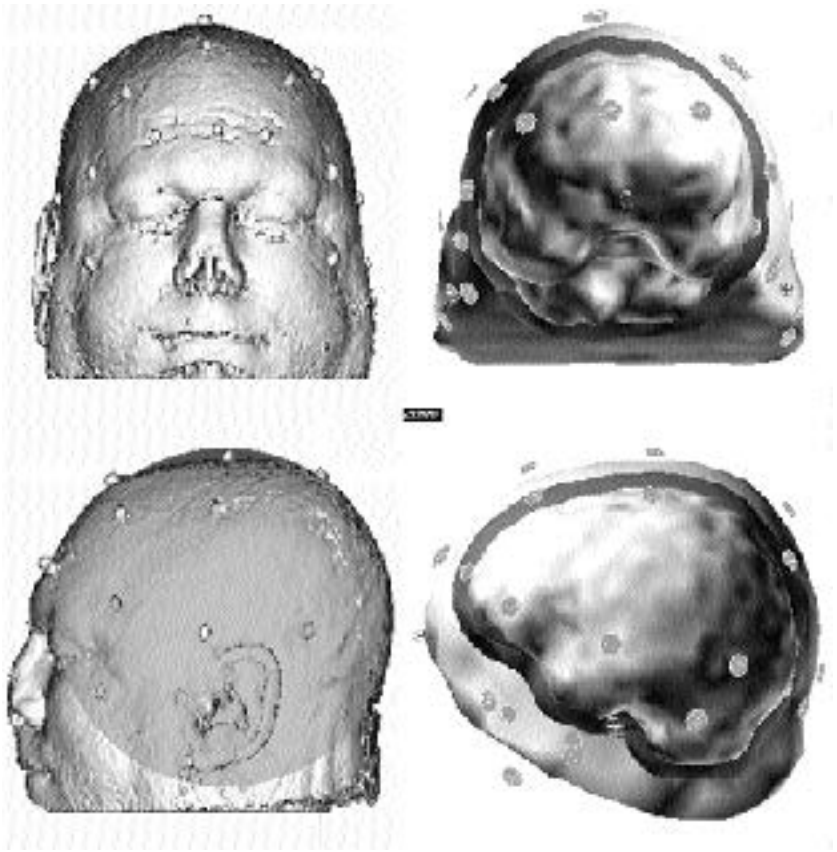

FIG. 23.16. Right: Realistic boundary element method (BEM) head model (inner and outer surfaces of skull and scalp) derived from three-dimensional MRI reconstructions. **Left:** *Shaded circle* on patient's head depicts the shape of typical spherical head models. Note divergence of the brain and skull base from this spherical shape. (From Ebersole JS. Defining epileptogenic foci: past, present, and future. *J Clin Neurophysiol* 1997;14:470–483, with permission.)

calculated with spherical head models were misplaced on average 2–3 cm upward from their true temporal lobe source (Figs. 23.17 and 23.18). In several patients, this gave the false impression that the spike/seizure sources were of frontal rather than temporal lobe origin. It would appear that realistic head models should be used whenever dipoles are co-registered with MRI for interpretation. This is particularly so for basal frontal, temporal, and occipital sources, where brain cortex and skull depart most from a spherical shape.

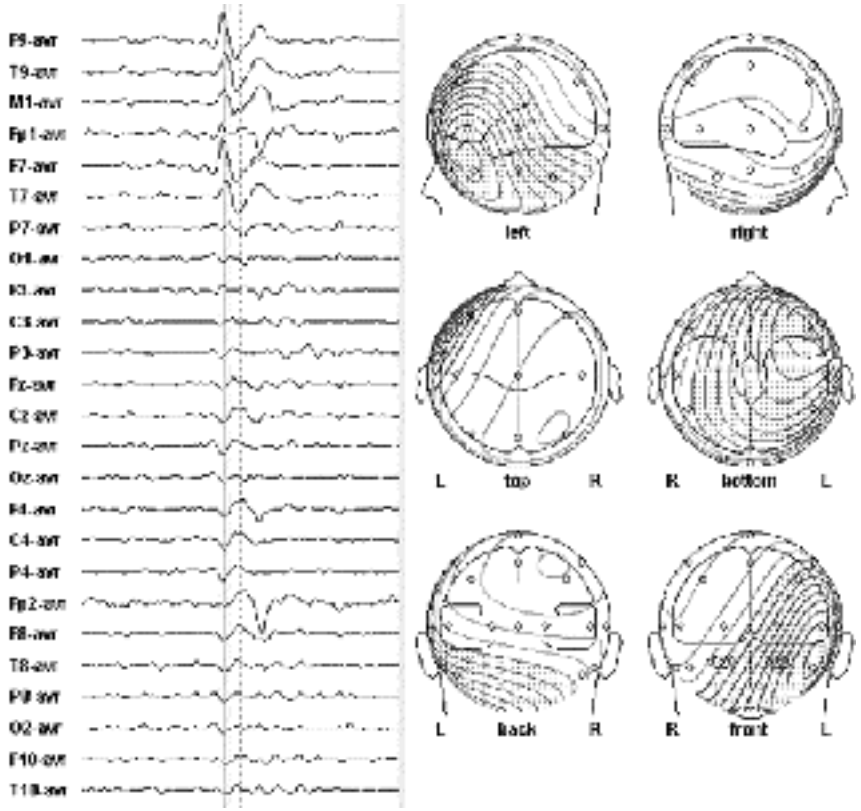

FIG. 23.17. Left: Common average reference EEG of a left anterior inferior temporal spike. **Right:** Voltage topography of the same spike at the cursor.

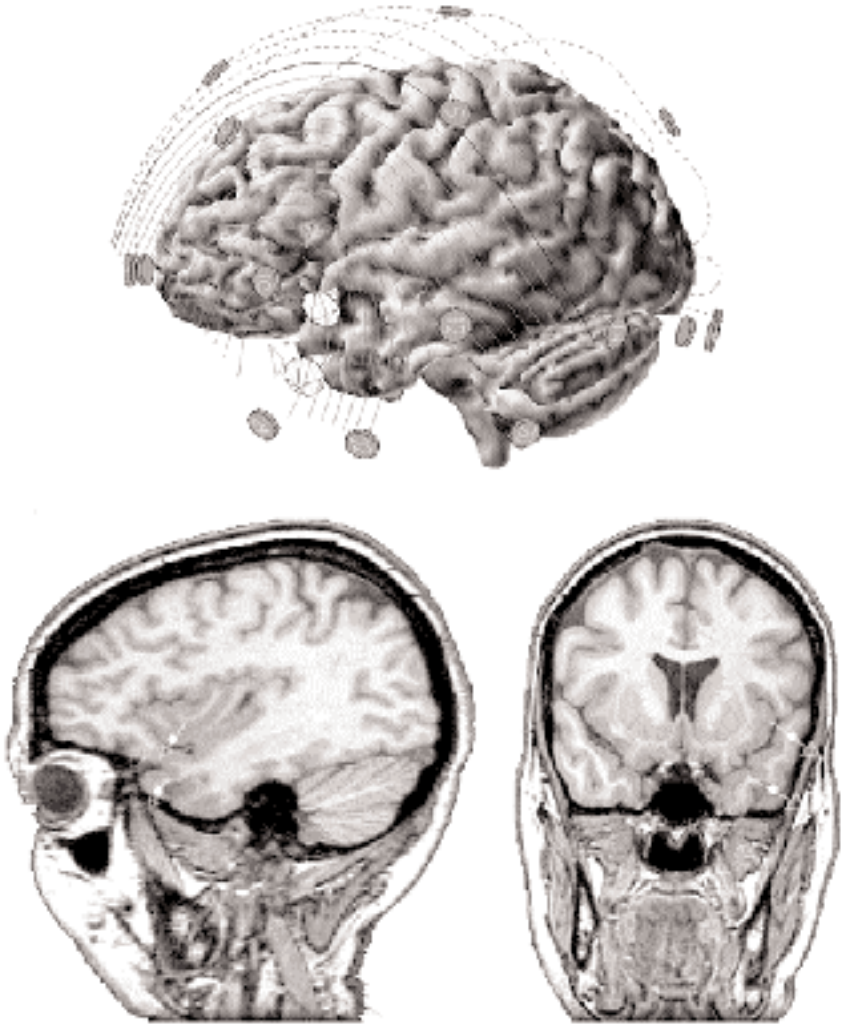

FIG. 23.18. Dipole models of the spike in Figure 23.17, calculated with spherical and realistic BEM head models, are co-registered with three-dimensional (*top*) and two-dimensional MRI sections of the patient's brain. The dipole model derived from a spherical head model is displaced approximately 2.5 cm above that obtained with a realistic head model. The actual spike source is the cortex surrounding the cystic lesion adjacent to the lower dipole.

EXTENDED SOURCE MODELS

Though very useful as a model of EEG sources, the dipole model is unrealistic. Actual brain sources of EEG potentials are extended areas of activated cortex. A number of "extended" or "distributed" models have been employed to simulate more accurately the character of cerebral epileptogenic sources (23,32,34). Some of these use brain anatomy as a powerful reconstruction parameter to restrict the search space to the cortical surface (23). Algorithms have been devised that can calculate discrete approximations of the current density distribution on a defined surface. This current source density estimate is an ill-posed problem, however, if many local sources are to be calculated from measurements at relatively few electrode locations. Regularization is necessary to proceed in these circumstances. This represents a compromise between the demands to explain the measured data and to meet certain source or boundary conditions. One such boundary condition is the minimum norm criterion, in which the source constellation of lowest electrical power is calculated. Variations include the L2 or L1 norms (23) or the minimum spatial Laplacian (34).

Although these methods can produce seductive images of "activated" cortex, much the same as functional MRI, considerable research is needed to validate the accuracy of the results.

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Chapter 24

Quantitative Electroencephalography

Marc R. Nuwer

Nomenclature
- Digital EEG
- Quantitative EEG
- Signal Analysis
- Topographic EEG Displays
- Statistical Analysis

Problems
- Artifacts
- "Different" Versus "Diseased"
- Contaminated References
- Alertness
- Medication Effects
- Statistical Problems
- Small Technical Changes
- Selection of Results

Clinical Settings
Conditions for Clinical Use
References

Quantitative methods for analyzing electroencephalograms (EEGs) provide new ways to view data that are different from traditional visual analysis. Sometimes these quantitative techniques can offer new and interesting, even clinically valuable, insights into the EEG. Many types of analysis have been proposed.

The rapid adoption of digital EEG techniques has opened the door for easy application of quantitative analysis. Once EEG data are stored in digital format, applications of various algorithms can become available as simple extensions of the reading process. Although quantitative techniques have been available for 50 years, for much of that time their use was hampered by difficulties accessing these technologies from traditional analog recordings. Digital analysis techniques, however, are accompanied by considerable difficulty in routine use. They still defy attempts to make them easy, user friendly, and free from sources of potential error.

Applications of quantified techniques are discussed in other chapters in this book. Over time, these various techniques imperceptibly will become a standard part of the field of EEG. Successful techniques will be separated from less successful earlier attempts at defining clinically useful analysis. At that point, we shall stop considering quantitative techniques separately from routine EEG. Currently, however, it is still useful to identify separately some of the techniques, inherent problems, and literature in this field. The reader is referred to Chapters 2, 3, 4, 22, 23, and 25 for further discussion.

NOMENCLATURE

A variety of terms are used in the field of quantitative analysis. The terms *digital EEG*, *paperless EEG*, and *quantitative EEG* (qEEG) as well

TABLE 24.1. *Nomenclature used to describe qEEG techniques*

Digital EEG
Quantitative EEG (qEEG)
Signal analysis
Automated event detection
Monitoring and trending
Source analysis
Frequency analysis
Topographic displays (“brain maps”)
Statistical analysis
Comparisons to normal values
Diagnostic discriminant analysis

From Nuwer MR. Assessment of digital EEG, quantitative EEG, and EEG brain mapping: report of the American Academy of Neurology and the American Clinical Neurophysiology Society. *Neurology* 1997;49:277–292, with permission.

as *EEG brain mapping* are used to describe certain aspects of these methods. Table 24.1 shows the organization of some of this nomenclature.

Digital EEG

Digital EEG refers to EEG recording on a digital medium, typically a small desktop computer. Recording and display are consistent with existing American Clinical Neurophysiology Society (ACNS; formerly the American Electroencephalographic Society) and International Federation of Clinical Neurophysiology (IFCN) standards for clinical EEG recordings (1–4,19,36,37). Displays are produced on a routine monitor screen, typically of average or larger screen size. Such digital recording allows for subsequent replay with changes and filters, display scales, reformatted montages, remote network access, and larger numbers of recording channels. These topics are reviewed in more detail in Chapters 3 and 4.

Quantitative EEG

Quantitative EEG is a general term for analysis of the EEG, generally with mathematical formulas or statistical comparisons. The EEG data are transformed in ways that highlight certain features that may be difficult to assess by visual inspection of the raw EEG. Numerical results, statistical tables, or transformed datagraphs are produced.

Signal Analysis

Signal analysis refers to techniques to transform the EEG into its frequency components, or to identify or localize possible epileptic spikes, or to determine trends in EEG features over time for monitoring. Several common types of signal analysis are used.

Automated event detection is the process of identifying specific segments of EEG that contain particular events of interest (see Chapter 22 for more detailed discussion). Most often these are epileptic spikes or seizures, which can be flagged during extended recordings. A common application is identification of subclinical or nonconvulsive seizures for patients on long-term epilepsy video-EEG monitoring units. Another common clinical use is automated scoring of sleep architecture in digital polysomnogram recordings (see also Chapter 26). In both instances, the computer flags or scores possible events or states, with varying degrees of success. For many spike or seizure detectors, frequent false-positive identification of artifacts or nonepileptic transients occurs. Expert screening of flagged events or states clarifies these false-positive events. Overall, automated event detection facilitates human review of the data by flagging or prescoring, allowing the expert to scan through or audit data much more rapidly.

Monitoring and trending the EEG is useful in the operating room (OR) or intensive care unit (ICU). Most often this is an aid to detect gradual changes in the EEG that result from changes in the patient's clinical status. In the OR, this can be a sign of gradually developing cerebral ischemia. In the ICU, changes can be due to lightening of coma or development of new complications. Such complications include ischemia, poor tolerance of raised intracranial pressure, postoperative development of subdural hematoma, or occurrence of nonconvulsive seizures (6,8,22,23,25,34,40,48,51) (see Chapter 25). Monitoring the EEG over hours or days allows for identification of such long-term trends or events in ways difficult to appreciate just from occasional 20-minute-long routine EEG testing.

Source analysis is a technique for deducing the likely generator of brief transients such as epileptic spikes or evoked potentials. Multichannel scalp voltage values are used to estimate a likely three-dimensional location of a generator. Sometimes these are displayed superimposed on magnetic resonance imaging (MRI) sections, a technique known as co-registration. As an example, mesial temporal–generated epileptic spikes can be separated from neocortical temporal epileptic spikes (see Chapter 23).

Frequency analysis transforms the EEG into its frequency components. The magnitude of each frequency or frequency band is calculated. As an

example, relative amounts of posterior-dominant alpha rhythm can be quantified. *Coherence analysis* takes this method one step further, assessing the relationships between frequency components at different scalp-recording sites. The results of frequency and coherence analysis can be presented as a table of numbers or a multidimensional graph or in a topographic display.

Topographic EEG Displays

Topographic EEG displays most often are stylized maps of the scalp presenting localized electrical features such as frequency content in a particular band. These stylized maps, often collectively referred to as "EEG brain maps," superficially resemble computed tomography or MRI displays. Figure 24.1 shows some EEG brain maps. Actually, the relationship to neuroimaging displays is very superficial, because EEG brain maps are a stylized representation rather than an anatomically accurate rendering. The term *EEG brain maps* should not be confused with functional cortical brain mapping by direct cortical stimulation or with brain mapping by neuroimaging techniques, which have no direct relationship to EEG brain mapping.

Statistical Analysis

Statistical analysis is a way of comparing between EEG recordings or between the EEG recording of an individual subject and those of a group of normal control subjects. Most often such comparisons are made on the basis of signal analysis features such as frequency analysis, and may be displayed as numerical tables or topographic EEG brain maps.

Comparison to normative values uses group statistics to assess a particular EEG feature from an individual. The feature is compared to the same feature in a group of normal control subjects. These statistical techniques identify when a subject's EEG values differ from the expected values based on the control population. Techniques should be used to adjust these for age, nonnormal statistical distributions, and other factors. The results highlight ways in which a particular EEG sample differs from average or expected values.

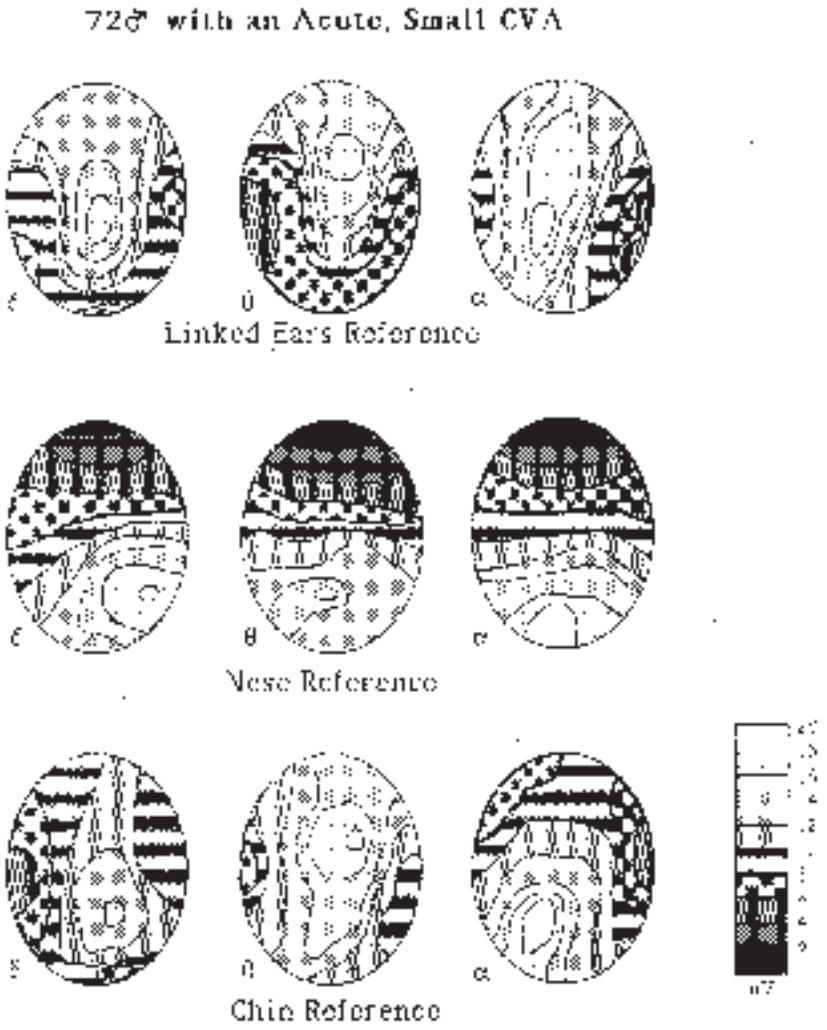

FIG. 24.1. EEG brain maps of the same data compiled using three different references: linked ear, nose, and chin sites. The EEG was recorded on a 72-year-old man who had had a small acute stroke. Right parasagittal slowing is evident as precentral theta and postcentral delta activity. Note how different the maps look depending on the reference chosen. The linked ears reference tends to squeeze the topographic contours toward the sagittal midline. The nose reference tends to flatten the contours and push them toward the occiput. The chin reference is probably the most accurate here. This is an example of the *contaminated reference effect*. (From Nuwer MR. Quantitative EEG: 1. Techniques and problems of frequency analysis and topographic mapping. *J Clin Neurophysiol* 1988;5:1–43, with permission.)

Diagnostic discriminant analysis compares an individual's selected EEG features to a template of features commonly found in a particular disease category. A patient's EEG might be compared with several possible disease categories to see with which the patient's EEG best fits statistically.

PROBLEMS

Various types of problems can interfere with recording of records suitable for qEEG assessments or with their interpretation (31–33).

Artifacts

Artifacts contaminate portions of all EEG records. The sources are many, including eye movements, blinks, electromyograms, electrocardiograms, electrode pops, breathing, nearby electrical equipment, or even intravenous lines. When examining a routine EEG by visual analysis, the expert electroencephalographer is trained to read past these artifacts, seeking the real EEG through or between contaminated regions. In contrast, the computer has great difficulty assessing artifact. Expert human review is needed. Even with such review, many routine clinical EEGs are sufficiently contaminated that finding several minutes of completely artifact-free segments of awake EEG may be challenging or impractical.

"Garbage in, garbage out" is an oft-quoted maxim in the data processing community. This certainly applies to qEEG. Actual qEEG analysis may be contaminated with artifact to some extent. Recognizing and accounting for this is important. One lesson is that the qEEG results cannot be understood unless the raw EEG is visually analyzed by an expert electroencephalographer simultaneously, and referenced back and forth between quantitative results and visual analysis of the EEG tracings. Quantitative results cannot be trusted or interpreted on their own.

"Different" Versus "Diseased"

Statistical analysis can identify ways in which an individual patient's particular EEG segments differ from average or expected values. However, the meaning of this difference can be difficult to interpret, because "different" does not equal "diseased." The fact that a patient's EEG contains features that are different from the ideal average does not imply that this difference is due to a disorder or a disease. Analogously, some people are taller than average and other people are shorter than average, but this height variation does not imply that the differences are due to a pathological cause. Such differences should not be considered "abnormal" unless they pass further tests. For example, the difference must represent a type of change that is commonly accepted as indicative of pathology. Artifactual causes also need to be excluded. Other changes may simply reflect the diversity of normal EEG features in the general population, just as the population at large has great diversity in facial or other physical features.

Similarly, the EEG community has long been aware of "*normal variant*" waveforms. Certain features are well known to occur in a minority of patients. Although they may trigger alarm in the uneducated observer, the knowledgeable expert knows to discount these features as nonpathological. Various such features include mu rhythm, rhythmic temporal theta activity (psychomotor variant), and 14- and 6-Hz spikes. These are just some examples of statistical outliers of no clinical significance, but they serve as reminders of how statistical qEEG analysis can yield highly statistically "abnormal" features that are well known to be nonpathological.

Contaminated References

Contaminated references are commonly encountered in EEGs. Many electroencephalographers would concede that there is no optimal montage useful for all patient situations. Digital EEG allows for montage reformatting to help control for this commonplace problem. Yet many qEEG techniques are based on a specific montage, such as using linked ear leads. When either ear lead is contaminated by artifact or normal variant waveforms, the quantitative results can be substantially altered in adverse ways. Even with pathological slowing near one ear lead, the actual location of the slowing may show up at the wrong qEEG scalp sites because of this effect.

Figure 24.1 shows an example of such a problem. One can see how technical differences in processing and displaying can cause major differences in the clinical impression one receives from the brain maps. In these cases, the differences are due simply to changing the reference electrode used. The EEG data themselves are the same. Even an expert electroencephalographer could become confused by such misleading displays.

Alertness

Alertness is assumed for certain qEEG tests, such as comparison to normal controls. Yet all clinicians who routinely read EEGs appreciate how quickly any individual slips into early drowsiness with its concomitant changes in EEG characteristics. The changes in EEG features resulting from drowsiness mimic changes that can be seem with some types of brain damage.

Medication Effects

Medication effects also can cause slowing or other EEG changes. As with drowsiness, these changes may be confused with brain damage by some qEEG analysis techniques. Knowledge of the recent medication history of a patient may be very relevant to understanding the kinds of changes that are seen in any EEG. qEEG worsens the situation when its statistical techniques flag such changes as "abnormal," subverting the usual differential diagnostic process in visual EEG interpretation.

Statistical Problems

Statistical problems are commonplace when assessing large amounts of data with statistical techniques. False-positive "abnormalities" may average about 5% among large numbers of statistical tests run in some applications, but the number can reach 15%–20% in some individual normal control subjects, and even higher numbers may be reached in occasional normal individuals (9). Many statistically generated EEG "abnormalities" are probably clinically meaningless, but flagging them as such can easily mislead an electroencephalographer. Other statistical complexities exist that have yet to be clearly understood, having to do with the lack of independence of EEGs recorded at adjacent sites, the failure of EEG statistics to meet initial tests for a normal distribution, and the use of large numbers of tests simultaneously.

Small Technical Changes

Small technical changes in the collection of EEG data can also cause exaggerated "abnormal" qEEG results. Use of electrode caps can speed conducting the test, but caps sometimes fail to remain adequately in place, becoming slightly tipped or yawed and not ideally accounting for differences in patient head shapes. Sometimes electrodes make poor contact with the scalp or further technical issues intrude. Sometimes filters are set differently from the settings with which the initial normative group of EEGs was run. Each such technical problem can compound itself when processed through qEEG.

Selection of Results

Selection of results is necessary in most qEEG applications. The electroencephalographer must choose among various recorded epochs of EEG. Each epoch may represent 2 seconds of recording. Dozens of such epochs are needed for many qEEG applications. Each must be selected by a knowledgeable electroencephalographer so as to exclude artifact, drowsiness, normal variants, and other problems. The skill with which this selection is done is a critical factor in determining the outcome of the test. Furthermore, the selection process can skew results. Intermittent abnormalities truly present in the EEG might be excluded, or certain artifacts might be erroneously included in the epochs chosen. If the electroencephalographer comes to the process with a preconceived bias that a certain result is likely to occur, he or she may bring that bias to the selection process. For example, a record may contain intermittent slowing seen over the left or the right hemisphere at separate times during the recording, but an electroencephalographer seeking just the left-sided slowing could identify those epochs selectively for further processing. In that case the quantitative results will show left-sided slowing. Similarly, frontal slow eye movements of early drowsiness can contaminate the record and produce frontal slow activity in the qEEG. Identification of which epochs are selected for qEEG processing is key for understanding the meaning of the qEEG results. Review of a qEEG test should include review of the concomitantly recorded routine EEG tracings as well as review of the specific epochs chosen.

Some tactics diminish selection bias (10), but, despite such suggestions, commonplace qEEG applications can still be quite problematic. Problems often outweigh the value of specific qEEG tests; however, valuable clinical applications have been found in certain settings, typically when the technique addresses specific quantitative questions, and is used in expert hands with good clinical judgment along with simultaneous visual interpretation of the EEG tracings.

CLINICAL SETTINGS

The American Academy of Neurology (AAN) and the ACNS undertook a joint assessment of the clinical utility of qEEG (35). This evidence-based assessment was conducted through a panel of experts. It widely sought published evidence about qEEG and its potential clinical uses. The panel determined that criteria for assessing the literature should include several ideal elements or concepts (5,7,11–18,20,21,24,26–30,38,39,41–47,49,50). First, the disease study should be clearly defined. Explicit, clear criteria for test abnormality should be defined prospectively. Control groups also should include patient groups with other diseases in the differential diagnosis of the disorder evaluated. Control groups should be different from those originally used to develop the normal limit of the qEEG test. Disease severity should simulate that encountered in the proposed test application. Test–retest relia-

bility should be high. Various validity measures should be calculated and compared to those of other tests already clinically used in that differential diagnosis. Blinded observations are considered more objective. The efficacy or goal of the test (i.e., how will it affect patient care) should be clear. Incremental changes to existing accepted tests require less proof, whereas novel techniques require a greater degree of demonstrated validity and utility. Publications by authors with a potential conflict of interest should preferably be replicated by others. Various gold standards should be taken into account, depending on the clinical question for which a test is being evaluated.

In the end, these societies accepted a series of recommendations about digital EEG, qEEG, and EEG brain mapping. The following is a summary of those recommendations:

A. Digital EEG is an established substitute for recording, reviewing, and storing a paper EEG record. It is a clear technical advance over previous paper methods. It is highly recommended (see Chapter 3).
B. EEG brain mapping and other advanced qEEG techniques should be used only by physicians highly skilled in clinical EEG, and only as an adjunct to and in conjunction with traditional EEG interpretation. These tests may be clinically useful only for patients who have been well selected on the basis of their clinical presentation.
C. Certain qEEG techniques are considered established as an addition to digital EEG in
   C.1. Epilepsy—for screening for possible epileptic spikes or seizures in long-term EEG monitoring or ambulatory recording to facilitate subsequent expert visual EEG interpretation (see Chapter 22).
   C.2. OR and ICU monitoring—for continuous EEG monitoring by frequency trending to detect early, acute intracranial complications in the OR or ICU, and for screening for possible epileptic seizures in high-risk ICU patients (see Chapter 25).
D. Certain quantitative EEG techniques are considered possibly useful practice options as an addition to digital EEG in
   D.1. Epilepsy—qEEG may be useful for topographic voltage and dipole analysis in presurgical evaluations (see Chapter 23).
   D.2. Cerebrovascular disease—based on class II and III evidence, qEEG in expert hands may be useful in evaluating certain patients with symptoms of cerebrovascular disease whose neuroimaging and routine EEG studies are not conclusive.
   D.3. Dementia—routine EEG has long been an established test in evaluation of dementia and encephalopathy when the diagnosis remains unresolved after initial clinical evaluation. In occasional clinical evaluation, qEEG frequency analysis may be a useful adjunct to interpretation of the routine EEG when used in expert hands (see Chapter 13).
E. On the basis of current clinical literature, opinions of most experts, and proposed rationales for its use, qEEG remains in vestigational for clinical use in postconcussion syndrome, mild or moderate head injury, learning disability, attention disorders, schizophrenia, depression, alcoholism, and drug abuse.
F. On the basis of clinical and scientific evidence, opinions of most experts, and the technical and methodological shortcomings, qEEG is not recommended for use in civil or criminal judicial proceedings.
G. Because of the very substantial risk of erroneous interpretations, it is unacceptable for any EEG brain mapping or other qEEG techniques to be used clinically by those who are not physicians highly skilled in clinical EEG interpretation.

CONDITIONS FOR CLINICAL USE

Even within the confines of those clinical circumstances in which qEEG testing is considered established or promising, certain caveats need to be recognized before embarking on test interpretation. First and foremost, quantitative results cannot be interpreted on their own. They can be understood only by referring back and forth between any quantitative tables, charts, graphs, and the like and the visual interpretation of the EEG tracings from which those analyses were made. The individual epochs used should be identified. For multiple-day monitoring or long-term epilepsy EEG monitoring, selected portions are reviewed and interpreted at times when suspicious activity is automatically flagged or at randomly audited other times.

The technical quality of these EEG recordings must be satisfactory for clinical interpretation. The standard guidelines for EEG recordings should be followed (e.g., those from the ACNS and IFCN) (1–7). There is no clinical application for qEEG analysis apart from interpretations by physicians with appropriate skills, training, knowledge, and ability in routine EEG analysis, as well as additional knowledge and experience with the relevant additional technical problems, artifacts, normal variants, and statistical issues encountered in qEEG.

qEEG can be a useful adjunct to traditional visual EEG analysis, in the sense that it acts as a "ruler" that measures certain features more carefully and searches for subtle features of interest. However, qEEG can often be

misleading, especially in the hands of practitioners with limited skills in routine EEG interpretation.

As this field gradually develops, a careful evaluation of proposed new applications is needed to separate those that actually work and add clinical value from those that do not. With careful progress, qEEG may come to be a commonly used adjunct to EEG interpretation. Such tools may give us further insights into the pathophysiology of disease as well as further sensitive methods for measuring and diagnosing neurological and psychiatric disorders.

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Chapter 25

Continuous EEG Monitoring in the Intensive Care Unit

Kenneth G. Jordan and Thomas P. Bleck

The Problem, Its History, and Its Context
Scientific Basis for Continuous EEG
Environmental and Technical Considerations for Continuous EEG
Electrodes and Montages
Artifacts and Pitfalls
Clinical Factors that Confound Continuous EEG in the Intensive Care Unit
Technical Adjustments and Suggestions for Troubleshooting
Training of ICU Personnel for Continuous EEG
Supervision of Continuous EEG Using Network Technology
Clinical Applications and Impact of Continuous EEG
Continuous EEG in Status Epilepticus
Continuous EEG in Acute Focal Cerebral Ischemia
Continuous EEG in Diagnosis and Prognosis of Coma
Continuous EEG in Acute Severe Head Trauma
Management of Increased Intracranial Pressure
Non-convulsive Status Epilepticus in Acute Severe Head Trauma
Detection of New or Increasing Intracranial Masses
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Cost Benefit, Cost Effectiveness, and Outcome Studies of Continuous EEG
Summary
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THE PROBLEM, ITS HISTORY, AND ITS CONTEXT

Although catheters, transducers, digital readouts, and alarms in the intensive care unit (ICU) enable medical personnel to monitor patients' hearts, lungs, kidneys, blood, and other organs, cerebral function usually remains hidden in the "black box" of the cranial vault, monitored primarily by bedside observations. As treatment options for acute neurological disease have expanded, and as neurologists and neurophysiologists have become more involved in neurological intensive care units (NICU), many clinicians have become uncomfortable relying on the traditional neurological examination for detecting potentially remediable changes in cerebral function. Even in the best circumstances, with expert personnel, intermittent clinical assessment is hampered by discontinuity and subjectivity. In addition, contrary to the goal of a physiological monitor, changes in examination findings occur *after* clinical deterioration. As a result, the intensivist is confronted with the sisyphean task of simultaneously preventing further clinical deterioration while striving to reverse damage that has already occurred. Bedside assessment becomes progressively uninformative when patients are heavily sedated or given neuromuscular junction blocking agents.

Encouraged by the application of the electroencephalogram (EEG) as an intraoperative monitor, neurophysiologists developed methods of employing continuous EEG (CEEG) in the ICU to illuminate the "black box" of cerebral function (14,37,49,84). Traditionally, the raw EEG generated cumbersome amounts of data and was too complex for interpretation by nonexperts. In the 1970s, data compression techniques were introduced in an attempt to simplify EEG interpretation. These techniques entailed the use of quantitative analysis of EEG frequency and amplitude in place of the real-time display of EEG. Examples included compressed spectral array (CSA) (15,21), the cerebral function monitor (73,84), and topographic brain mapping (78,86). In the ICU setting, data reduction—particularly with CSA—was used primarily to predict outcome of patients in a coma (16,20). Until the 1990s, technological limitations and logistical barriers made raw EEG impractical as a real-time physiologic monitor. During that decade, however, digital EEG overcame many of these impediments, making bedside CEEG a clinically relevant tool (51,79,80).

An optimal ICU monitoring system should be:

- More sensitive and specific than clinical observations.
- Noninvasive.
- Simple to operate and interpret by nonexperts.
- Compatible with medical and nursing care of the patients.

Examples of other successful monitors include the bedside electrocardiographic monitor and transcutaneous pulse oximetry. CEEG monitoring in the ICU has not yet reached its potential in simplicity and utility. Advances in digital EEG technology will probably further facilitate its application, online interpretation, and clinical applicability. The early use of CEEG led to the recognition of important and somewhat surprising EEG abnormalities in patients with acute cerebral injuries, including non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) (51). CEEG in the ICU has gradually became more widespread as studies supported its value in providing important and often otherwise unobtainable information (12,19,25,54,80,115). CEEG has more recently been employed in emergency medicine (59,60).

This chapter reviews use of CEEG in the ICU and addresses its scientific basis and the technical and logistical issues of its implementation. It also examines established, emerging, and potential clinical applications; the numerous (often unique) artifacts found in CEEG; and troubleshooting suggestions. Finally, reflecting the maturation of CEEG, we discuss preliminary efforts to assess its cost benefit, cost effectiveness, and impact on patient outcomes.

SCIENTIFIC BASIS FOR CONTINUOUS EEG

Seven major neurobiological and clinical attributes underlie the rationale for CEEG:

1. *The EEG is tightly linked to cerebral metabolism.* A multitude of electrochemical processes produce the extracellular electrical currents that generate the scalp EEG (83; Chapter 1). Measurable activity is generated by the spatial and temporal summation of postsynaptic excitatory and inhibitory potentials in the superficial layers of the cortex. These are modulated by ascending diencephalic input. As a result, the EEG closely reflects cerebral metabolism, becoming abnormal if any of the interdependent components is disrupted.
2. *The EEG is sensitive to two of the most common causes of cerebral injury: ischemia and hypoxia.* Pyramidal neurons in cortical layers 3 and 5 are mainly responsible for EEG generation and are selectively vulnerable to hypoxia and ischemia.

3. *The EEG detects neuronal dysfunction at a reversible stage.* EEG abnormalities arise when cerebral blood flow (CBF) declines to between 25 and 30 mL/100 g/min (5). Progressive changes in EEG morphology, amplitude, and frequency correlate with the severity of cerebral ischemia (92,98) (Fig. 25.1). Synaptic transmission is preserved to 17 mL/100 g/minute, but energy failure and loss of cell membrane integrity (cell death) do not occur until 10 to 12 mL/ 100 g/minute. This "window of reversibility" between the appearance of EEG abnormalities and neuronal death suggests that appropriate intervention during this time might improve or restore cerebral function (26).
4. *The EEG detects neuronal damage or recovery, whereas the clinical examination cannot.* Two common clinical phenomena illustrate this principle. First, during carotid endarterectomy, EEG changes occur within 60 seconds if clamping of the carotid artery produces significant focal cerebral ischemia. Timely placement of a shunt produces resolution of these EEG abnormalities within minutes (see Fig. 25.1). Because the patient is anesthetized, detection and reversal of cerebral injury would not be possible without EEG monitoring (98). Second, during treatment for refractory status epilepticus, the clinical examination loses much of its value. Seizure activity can persist despite loss of all visible motor activity. When this occurs, only EEG can reveal whether seizure activity has been controlled.
5. *The EEG is the best available method for detecting epileptiform activity.* Acute, observable seizures occur in 10% to 27% of patients with acute brain injuries (38). CEEG has documented a surprisingly high incidence of NCS and NCSE in patients with acute cerebral ischemia, intracranial hemorrhages, head trauma, and convulsive status epilepticus (Fig. 25.2). Conversely, EEG is the only method of confirming absence of EEG seizure activity in NICU patients with motor movements that might be convulsive in origin (50,51,85,101,108).

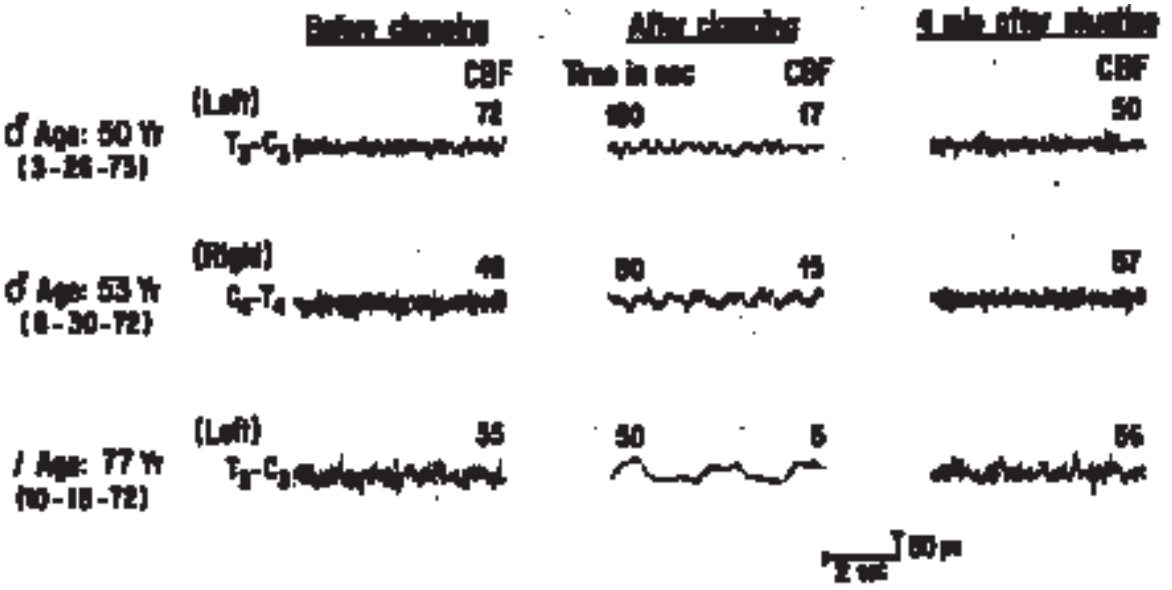


FIG. 25.1 Intraoperative EEG activity in three patients undergoing carotid artery endarterectomy. After carotid clamping, EEG changes correlate with the severity of the drop in cerebral blood flow (CBF). After a shunt is placed and CBF restored, EEG returns rapidly to baseline. (From Sundt TM Jr, Sharbrough FW, Piepgras DG, et al. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy with results of surgery and hemodynamics of cerebral ischemia. *Mayo Clin Proc* 1981;56:533–543.)

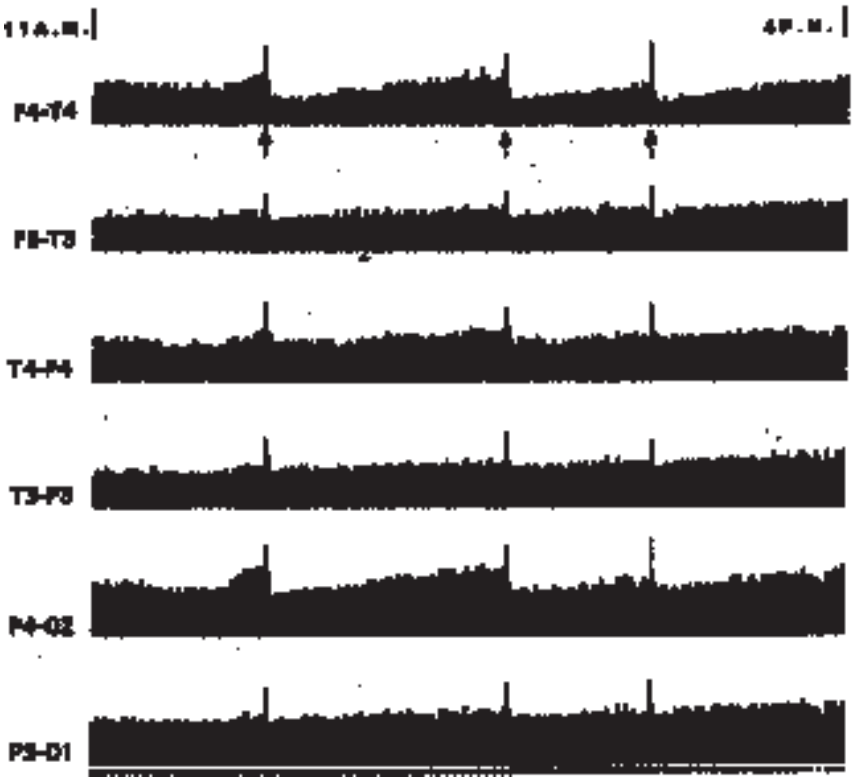


FIG. 25.2. Quantitative EEG detection of non-convulsive seizures. The patient had a hypertensive left thalamic hemorrhage, was comatose, and had no outward signs of seizures. Six EEG channels are displayed, and time is on the horizontal axis. Alpha activity is shown as a percentage of the overall EEG activity from 1 to 30 Hz. Three non-convulsive seizures are characterized by an abrupt jump in percentage of alpha activity *(arrows)* followed by attenuation of alpha activity. Review of the stored raw EEG confirmed that these events were generalized epileptiform discharges. (From Nuwer MR. Electroencephalograms and evoked potentials. Monitoring cerebral function in the neurosurgical intensive care unit. *Neurosurg Clin North Am* 1994;4:647–659.)

6. *CEEG provides dynamic information.* Just as long-term monitoring is necessary to capture spontaneous seizures, the capriciousness and variability of cerebral function in NICU patients necessitate continuous monitoring. Routine bedside EEG provides only a "snapshot" of cerebral activity within a 30- to 45-minute window. Such fragmented testing often misses significant events (Fig. 25.3).
7. *The EEG provides useful information about localization.* The EEG can be used as a bedside tool to approximate localization of cerebral injury to the anterior, posterior, or lateralized head regions. The International 10-20 System of Electrode Placement establishes a consistent relationship between electrode scalp placement and underlying cerebral topography (46). Although this falls short of the anatomical detail provided by modern brain imaging, it can usefully influence the decision to transport a critically ill patient for an imaging study. The transport of critically ill patients out of the ICU for procedures is a logistically intense and potentially hazardous undertaking. Typical adverse events during transport include endotracheal tube mishaps, equipment malfunction, loss of oxygen supply, hypercapnia, and hypotension (103).

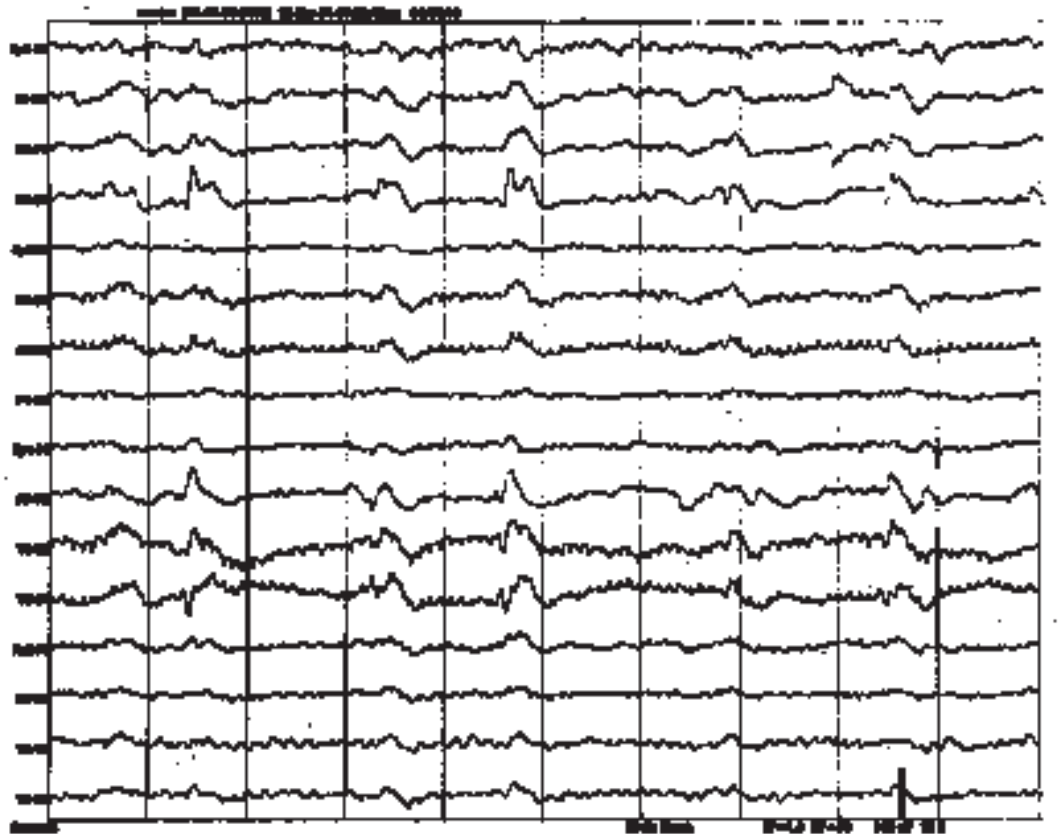


FIG. 25.3. Two samples from continuous EEG recording illustrating why standard EEG might miss significant events. **A:** Periodic lateralized epileptiform discharges (PLEDs) without ictal activity are seen in the left hemisphere. *(Figure continues.)*

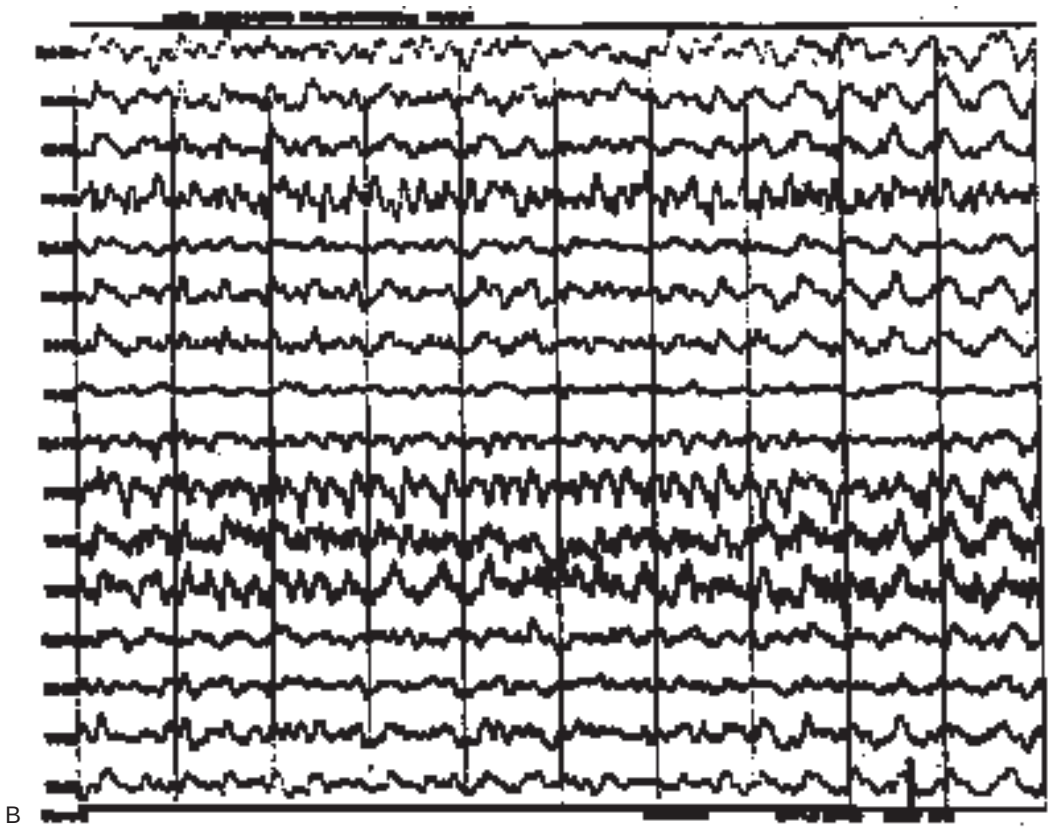


FIG. 25.3. *Continued.* **B:** With continuous monitoring, a prolonged, ictal event is seen arising from the area of PLEDs.

ENVIRONMENTAL AND TECHNICAL CONSIDERATIONS FOR CONTINUOUS EEG

The ICU environment is replete with sources of electrical noise as well as electrical hazards. CEEG is performed on patients who may be restless, agitated, delirious, or combative. Many have altered cranial anatomy, including skull defects, scalp edema, drains, or intracranial catheters. Artifacts of biological, electrical, and environmental sources are seen more frequently, and are more difficult to eliminate, in the ICU than in the EEG laboratory or epilepsy monitoring unit. Duration of monitoring can range from one to many days (the average at the authors' institution is 4.2). During this time, patients require routine medical and nursing care, are often physically manipulated for respiratory and physical therapy, and may be transported out of the ICU for procedures. In this challenging environment, CEEG changes must be identified promptly, accurately interpreted, and correctly correlated with other physiological and clinical data. In comparison with less complex forms of monitoring, such as electrocardiography and pulse oximetry, CEEG generates large amounts of data that require timely review and documentation. Standards for data storage have yet to evolve. Textual notations entered concurrently with patient care maneuvers and any interventions are important for proper interpretation of the EEG data (94).

These challenges can be met with proper equipment, training, and supervision. Digitized real-time EEG (DEEG) is the preferred technological method for CEEG. DEEG allows for on-line or *post hoc* filtering, montage reformatting, and data management. DEEG samples can be saved at preset intervals as well as on an *ad hoc* basis. The record can be annotated, timed, and correlated with other digitized physiological data such as intracranial pressure (ICP) and measurements of cerebral perfusion pressure. Hard copies can be printed and posted for baseline comparisons and documentation, or faxed offsite for expert review. Many commercial systems have automated algorithms for detecting spikes and seizures, although their value in CEEG remains to be determined (51).

A number of commercial DEEG units have programs for quantitative EEG (qEEG). qEEG transforms DEEG signals into frequency and amplitude (or power) measurements using the fast Fourier transformation. The resulting components can be displayed in a variety of formats, including bar graphs, CSA, and topographic scalp maps. Several statistical variables can be analyzed and compared, although the validity of some statistical methods remains to be established (78). The appeal of qEEG resides in its data compression and visual display capabilities, which are perceived as more easily interpretable than raw DEEG data.

The "bispectral index" is one of the more commonly described attempts to process EEG data for the non–EEG-trained user (30). Another approach—automated segmental analysis—holds considerable promise in this regard (3). The expert systems approach may also prove useful (93). qEEG may therefore be easier for non-EEG professionals to identify significant changes. qEEG detects cerebral ischemia earlier than visual analysis, but it remains unclear if these early changes are clinically significant (1).

Vespa et al. (108) analyzed the percentage of alpha-range EEG activity (relative alpha) and found its variability to be a useful tool for detecting cerebral ischemia due to vasospasm. Nuwer (80) used relative alpha to detect NCSE in patients with acute brain injury (see Fig. 25.2). Bleck (12) employed spectral edge frequency and CSA for detecting seizures when sedation or anticonvulsants had suppressed background activity. Another potentially useful area for qEEG is trend analysis of focal slow activity. In patients with baseline encephalopathic slowing, it may be difficult using visual analysis alone to detect progressive regional slowing or further attenuation of background activity. qEEG, such as CSA, may detect these subtle but potentially important changes.

Technical and physiological variables, however, can produce misleading qEEG displays. For this reason, EEGers generally agree that the raw EEG signal must be available for comparison when qEEG is used (78). Sources of potential qEEG misinterpretation include skull asymmetries, scalp edema, and fluctuating states of alertness. Seizures in the delta frequency range, brief seizures, burst-suppression, periodic lateralized epileptiform discharges, and spike discharges may go undetected by qEEG. In addition, a false-negative incidence of up to 10% has been reported, in comparison to raw EEG for the detection of focal abnormalities documented on cerebral imaging studies (81). qEEG has difficulty identifying episodic slowing and variable alertness (personal observation).

ELECTRODES AND MONTAGES

In many patients, including those with head trauma, craniotomies, skull defects, surgical drains, intracranial catheters, fresh suture lines, and head wounds, electrode positions must be modified from those specified by the conventional 10-20 System. Electrode placement should maintain symme-

try and be in areas topographically correlated to the cerebral pathological process of interest. Either disk or needle electrodes can be used. Disk electrodes obviate the risk of accidental needle puncture and are more comfortable for conscious patients. However, they produce more artifact on imaging studies than do needle electrodes. Needle electrodes can generally be applied more quickly than disk electrodes, and comfort is not an issue in patients with altered levels of consciousness. Use of collodion to secure the electrodes for long-term recording is mandatory. In the relatively closed environment of the ICU, personnel should be advised of the potentially offensive odor of collodion. Air purifiers, filters, and fans should be used to minimize and disperse the vapors. Reapplication of gel to disk electrodes, at least daily, should be done.

ARTIFACTS AND PITFALLS

When CEEG is used in the ICU, many artifacts are more frequent and may be more difficult to eliminate than those in the EEG laboratory or epilepsy monitoring unit (113). Reasons for this include the following:

- EEG electrodes, wires, and amplifiers are close to electronic devices that generate alternating current fields (automated intravenous pumps, ICU monitors, and ventilator equipment) and to structures that generate static charges (dripping intravenous fluids, condensed water moving in ventilator tubing).
- Long-term recording provides more opportunities for dislodging electrodes and drying of electrode gel, which result in impedance mismatching.
- Patient-generated artifacts are more numerous and also more difficult to control, inasmuch as the patients are critically ill. Artifacts include many of the same body movement and muscle potentials seen in a standard laboratory, but they also include intractable hiccups, myoclonic jerks, palatal myoclonus, nystagmus, asymmetric oculomotor paralysis, and flexor or extensor posturing.
- The scalp and calvaria of patients may be damaged or distorted by trauma, surgery, or disease. Changes include scalp edema, which can be prominent enough to produce artifactual reduction in amplitude either regionally or over an entire hemisphere, mimicking intracranial disease. Skull asymmetries, postcraniotomy defects, or head trauma produce strikingly asymmetrical eye movement, pulse, or electrocardiographic artifacts.
- EEG electrodes and wires can be disturbed by routine nursing activities, including patient turning, manipulation of dressings, suctioning, and placement of nasogastric tubes.

Advances in automated techniques for artifact identification and rejection should greatly increase the utility of CEEG and qEEG in the near future (102).

CLINICAL FACTORS THAT CONFOUND CONTINUOUS EEG IN THE INTENSIVE CARE UNIT

Many clinical variables in ICU patients affect the EEG but do not reflect cerebral abnormalities. For example, most ICU patients receive medications that alter the EEG, including benzodiazepines, barbiturates, narcotics, and neuroleptics. Patients on ventilators may be hyperventilated (intentionally or unintentionally). It is useful for clinicians to know a patient's pH and arterial carbon dioxide tension ($PaCO_2$) when interpreting the EEG. Patients who have been hyperventilated and are being weaned off controlled ventilation may show physiological EEG changes as their hypocapnia normalizes. Most ICU patients have disrupted sleep patterns, or they may lack sleep entirely despite appearing asleep. In patients who are "locked-in," EEG evidence of normal sleep-wake cycling leads to the correct diagnosis.

TECHNICAL ADJUSTMENTS AND SUGGESTIONS FOR TROUBLESHOOTING

It is impossible to avoid the many technical, electrical, mechanical, and physiological sources of artifacts encountered in the ICU. The following suggestions may be valuable:

1. Adjusting the bandpass of the displayed activity can remove some of the bothersome low- and high-frequency transients. With qEEG equipment, the actual data should be stored at wide bandpass. Maintaining the low-frequency filter at 1 Hz usually removes respiratory and other low-frequency artifacts. If epileptiform discharges are superimposed on high-amplitude, low-frequency activity, changing the low-frequency filter setting to 3 or 5 Hz (time constant of 0.03 seconds) attenuates the slow-wave activity and accentuates the sharp signals of interest. Some use a 60-Hz notch filter routinely in the ICU. Reducing the high-frequency

filter to 50 Hz diminishes high-frequency artifacts such as those originating in muscle. Lowering it to 35 Hz risks losing moderate-frequency activity that may have physiological importance. Bipolar montages are usually preferred over referential ones.

2. If generalized or widespread abnormalities appear with atypical waveforms, reference and ground electrode impedances should be checked, as should the preamplified connection to the computer cable.
3. Frequent, simple text notations should be made on the EEG to document nursing and physical therapy treatments, medication administrations, and other variables that can disrupt or affect the EEG record. Without these notations, related EEG changes can easily be misinterpreted as pathological. Developing a standard menu simplifies this task.
4. A database or reference binder with CEEG samples of commonly encountered artifacts is helpful for ICU nurses. As additional or unique examples are identified, these can be added.

TRAINING OF ICU PERSONNEL FOR CONTINUOUS EEG

The word "monitor" is derived from the Latin *monere,* meaning "to warn." CEEG functions much as binoculars do for the lookout on a ship: it provides early warning by extending the viewer's powers of observation. Although impressive technological advances in monitoring devices have improved clinicians' ability to observe physiological and pathophysiological events, the success of a monitoring system depends on a highly trained, skilled, and dedicated team. Like a ship's crew, the monitoring team functions as a feedback loop, consisting of: observation → recognition → communication → analysis → decision making → response → observation, and so forth. Team members must be proficient in use of the equipment, communicate their observations clearly, analyze data thoughtfully, make accurate decisions rapidly, and implement responses appropriately. Key members of the team include the ICU bedside nurse, the EEG technologist, the supervising EEGer, the neurointensivist, and other attending physicians. The team's proper training, continuing education, motivation, compensation, and administrative support require no less commitment than other complex ICU tasks (54).

Our experience of training more than 300 ICU and emergency department nurses in CEEG contradicts the traditional view that the EEG is too complex and visually confusing for non-experts to use. ICU nurses approach EEG already comfortable with waveform recognition from their experience with electrocardiography, pulmonary artery catheters, intraaortic balloon pumps, and ICP monitoring. They consider CEEG a natural extension of physiological monitoring to the brain. Using a structured workshop (51), we have trained a large cadre of ICU nurses to be comfortable with and competent in, recognizing basic CEEG patterns and common artifacts. The workshop

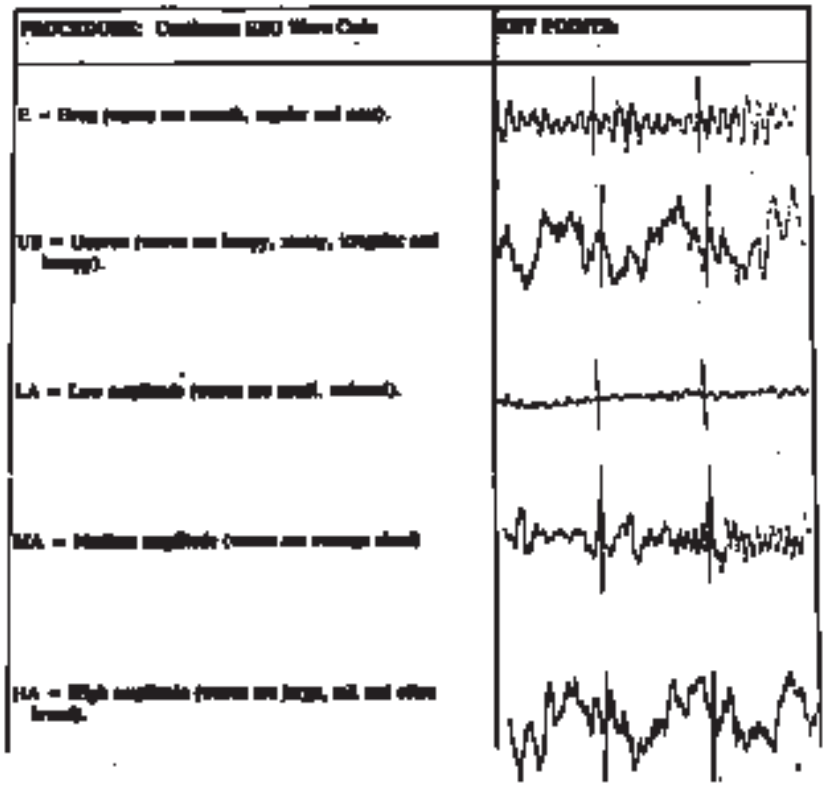


FIG. 25.4. Codes used by nurses to describe CEEG activity. Symbols and respective waveforms from CEEG training manual. (From Jordan KG. Continuous EEG and evoked potential monitoring in the neuroscience intensive care unit. *J Clin Neurophysiol* 1993;10:445.)

includes a training manual, workbooks, a library of CEEG samples with clinical correlations, and hands-on practice with equipment (Fig. 25.4). Neurologists, EEG technologists, and previously trained ICU nurses assume mentoring roles at the bedside. Vespa et al. (106) reported a similar experience. After going through a training program, their nurses achieved 94% accuracy in identifying generalized seizures, burst-suppression, and reduced alpha variability. In a few institutions, CEEG training is a requirement for all ICU nurses, and their competency in this area is regularly assessed. Only nurses who have achieved this competency are assigned to patients requiring CEEG.

SUPERVISION OF CONTINUOUS EEG USING NETWORK TECHNOLOGY

For CEEG to be fully effective and credible, expert supervision must be readily available to ICU nurses and physicians. They may be supervised by a neurointensivist-electroencephalographer or by an EEGer sufficiently experienced in neurological critical care to provide meaningful correlations between EEG and clinical data. In view of its increasing use, CEEG is likely to become part of the curriculum in fellowship programs for clinical neurophysiology and neurointensive care.

Stand-alone bedside EEG units are isolated from expert oversight. Even when CEEG equipment is part of a local ICU network, effective and credible supervision is limited because EEG experts are not in the ICU most of the time. As a computer-based modality, CEEG can be remotely transmitted to experts in an offsite laboratory, office, or home for real-time or *post hoc* interpretation. This makes expert supervision available 24 hours a day. Although speed is a concern because of the voluminous data generated by CEEG, modems at 33.8 or 56 kbps produce a transmission delay of only 10 to 15 seconds for 16 channels of real-time CEEG. Faster and more reliable transmission can be achieved with newer technology.

It is likely that expert supervision via CEEG networking will become increasingly important for at least two reasons. First, management decisions for many acute neurological conditions, such as acute ischemic stroke and status epilepticus, are critically time dependent. With effective treatment now available, it becomes difficult to justify delays in interpretation. Studies have already documented delays in the diagnosis and treatment of NCSE in the emergency department that result in significant rates of morbidity and mortality (59,60). Second, because there are relatively few certified EEGers to meet the potential demand for CEEG, it may become increasingly important to leverage the limited pool of expertise to an increasing number of patients through a multivenue CEEG network.

CLINICAL APPLICATIONS AND IMPACT OF CONTINUOUS EEG

Table 25.1 lists the diagnoses in 200 patients consecutively monitored in one NICU. Table 25.2 demonstrates the impact of CEEG on the clinical management of these patients, expanding a previously reported experience with 73 patients (51). Jordan (51) examined three specific clinical decisions that commonly arise in the ICU: (a) transporting the patient for cerebral imaging studies; (b) initiating or modifying anticonvulsant drug therapy; and (c) hemodynamic manipulation for cerebral perfusion. Using a retrospective chart review, he categorized the impact of CEEG as "decisive" when the CEEG findings alone led to one or more of these decisions; as "contributing" when CEEG was combined with clinical findings to make one or more decisions; and as "non-contributory" when CEEG data did not assist with any of these decisions. The impact was decisive in 54%, contributing in 32%, and non-contributory in 14% (52). The impact varied somewhat with the specific diagnostic category, as indicated in the Table. Vespa et al. (106) reviewed data from 300 monitored patients to determine

TABLE 25.1. *Indications for continuous EEG in the intensive care unit*

Admitting diagnosis	No. of patients	% of total
Acute cerebral ischemia	57	28
Intracranial hemorrhage	43	22
Uncontrolled seizures	44	22
Metabolic coma	20	10
Brain tumor	16	8
Intracranial infection	13	6
Head trauma	7	4
Total	200	100

K.G. Jordan (unpublished data).

TABLE 25.2. *Impact of continuous EEG in the intensive care unit on clinical management (N = 200)*

Impact	No. of patients	% of total	ACI	HEM	SZ	MC	BT	INF	HT
Decisive	109	54	28	22	36	9	8	4	2
Contributing	64	32	16	16	5	10	5	8	4
None	27	14	13	5	3	1	3	1	1
Total	200	100	57	43	44	20	16	13	7

ACI, acute cerebral ischemia; BT, brain tumor; HEM, intracranial hemorrhage; HT, head trauma; INF, intracranial infection; MC, metabolic coma; SZ, uncontrolled seizures.

the impact of CEEG on clinical decisions in the ICU. They studied 200 patients retrospectively and 100 prospectively. The critical determinations analyzed included decisions to (a) continue aggressive care, (b) send a patient out of the unit for a computerized tomographic (CT) scan, (c) adjust sedation, and (d) determine seizure activity. In more than 90% of their patients, CEEG was used as a daily guide for one of more of these decisions at the bedside.

These data also strongly support the contention that when CEEG is implemented systematically by a well-trained team, it positively influences bedside clinical management decisions (54).

In the following sections, established, emerging, and potential uses of CEEG in patients with status epilepticus, acute focal cerebral ischemia, coma, and acute severe head trauma are reviewed.

CONTINUOUS EEG IN STATUS EPILEPTICUS

Acute seizures, including those of status epilepticus, are common following acute brain injuries. Early convulsive seizures occur in 10% to 27% of patients with various types of acute brain injury (38). More than half of the reported cases of generalized convulsive status epilepticus (GCSE) arise from ischemic trauma, intracranial hemorrhage, cerebral hypoxia, hypoglycemia, drug intoxication, and withdrawal syndromes (33,39,67). Of patients without a history of epilepsy, 59% with status epilepticus have acute brain trauma (7). A new acute brain injury precipitates status epilepticus in about 25% of patients with known epilepsy (8). In other words, various acute brain injuries seen in the ICU and emergency department are commonly associated with status epilepticus. NCSE cannot be reliably diagnosed by clinical examination, and acute brain injury itself can alter consciousness and behavior, confounding the diagnosis of NCSE. Using CEEG, Jordan (50) found that 34% of 124 NICU patients had nonconvulsive seizures (NCS) and that 76% of these (33 patients) had NCSE. Privitera et al. (85) obtained emergency EEGs from 198 patients with altered consciousness and found that 27% (53 patients) had NCSE. Among their 49 patients with NCS and NCSE, Young et al. (115) found that acute brain injuries were the cause in almost half. Vespa et al. (108) identified seizures in nine (16%) of 56 patients with acute severe head trauma, of whom seven (78%) had NCS. In the Veterans Affairs Cooperative Study of status epilepticus, Treiman et al. (101) found that of patients with overt GCSE who received "adequate" treatment, 20% continued to have NCS and NCSE. Similarly, DeLorenzo et al. (32) found that in 12% of 170 patients with GCSE, NCSE developed after overt convulsive activity stopped. Clinical detection of NCSE could be determined only by CEEG.

In the absence of CEEG, the diagnosis of NCS and NCSE is likely to be delayed or missed. Of 89 ICU patients with NCSE, 77% were not recognized as having seizures at the time of first EEG (34). There was a median delay of 24 hours for the diagnosis of NCSE in those who had had clinical seizures, and a delay of 72 hours for those without clinical seizures. Some of the patients of Young et al. (115) with NCSE were obtunded for hours before an EEG was obtained that led to the correct diagnosis. Conversely, CEEG allows the exclusion of status epilepticus in critically ill patients with unusual movements (88).

Kaplan (60) reported substantial delays in the diagnosis of NCSE in the emergency department. In another study (59), the average time from patients' arrival in the emergency department to the diagnosis of NCSE was 2½ hours, and misdiagnosis of NCSE occurred in 93% (Fig. 25.5). In these

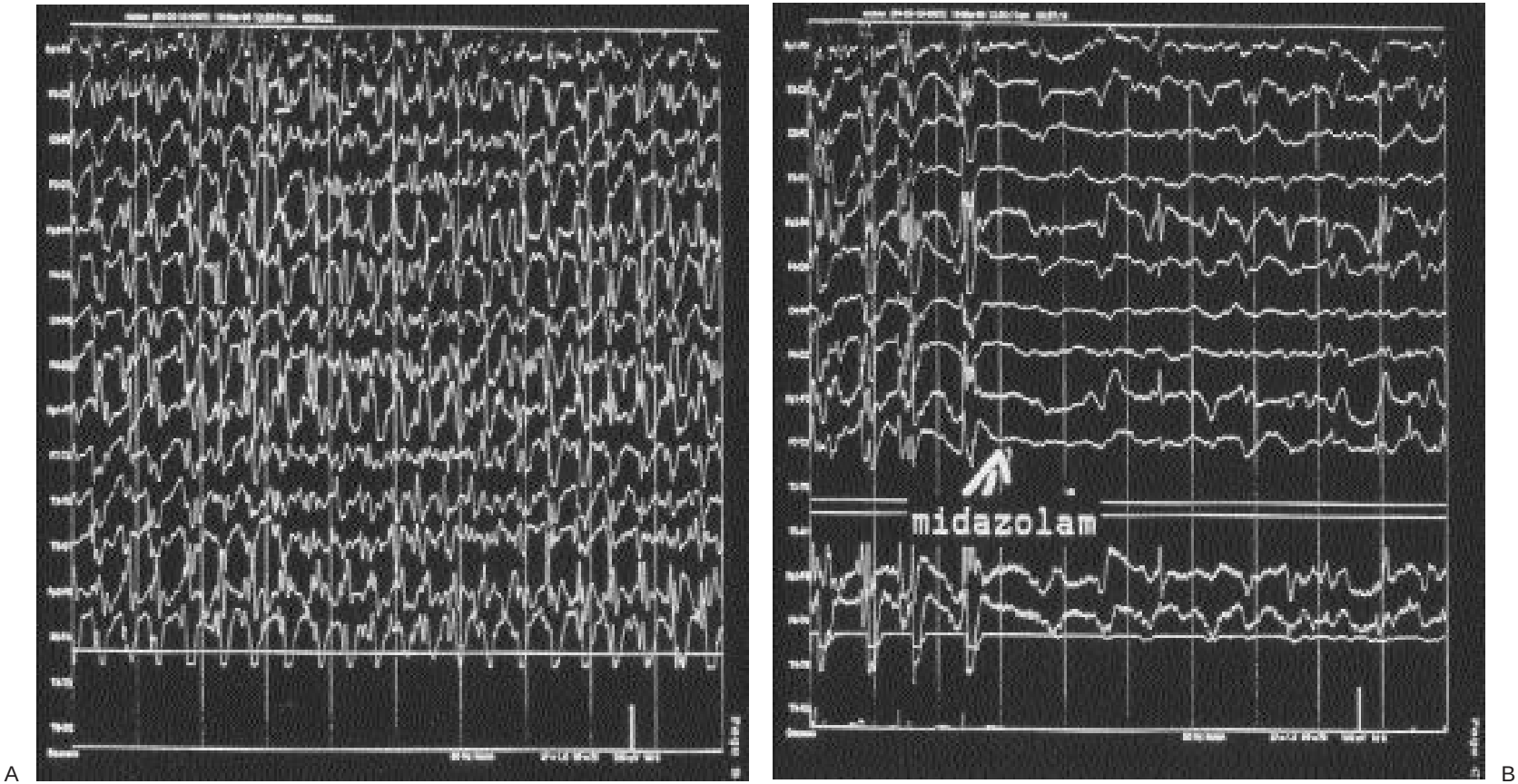


FIG. 25.5. Non-convulsive status epilepticus (NCSE) in an emergency department patient with acute cerebral infarction and theophylline toxicity. The delay from the patient's arrival to diagnosis of NCSE was 210 minutes. **A:** Generalized, highly rhythmic polyspike–slow-wave discharges (channels 15 and 16 turned off). **B:** Once NCSE was identified, intravenous midazolam produced immediate cessation of seizure activity.

two studies from emergency departments, NCSE was often misdiagnosed as postictal state, psychiatric disorder, stroke, or metabolic encephalopathy.

These data lead to the following conclusions:

- GCSE and NCSE are common accompaniments or sequelae of acute brain injury.
- After GCSE convulsions are controlled, NCSE is a common cause of persisting obtundation or behavioral changes.
- Without CEEG, the diagnosis of NCSE is delayed or overlooked.

The longer GCSE or NCSE persists, the more difficult it is to treat, and the higher the rate of mortality. Among patients in whom GCSE lasts more than 1 hour, the mortality rate rises from 3% to 36% (100). After 3 hours, the mortality rate approaches 50% (115). Etiology is an important determinant of progress (67), but multivariate logistic regression analysis has revealed that the variables that most increase the rates of morbidity and mortality in NCSE are seizure duration and delayed diagnosis, independent of etiology (115). Prolonged NCSE is particularly refractory to treatment and carries a higher mortality rate than does GCSE. Of the 30 patients with NCSE in the emergency department study by Jordan et al. (59), only 25% were controlled within 3 hours of treatment, and only 50% were controlled by 5 hours.

In the Veterans Affairs Cooperative Study of status epilepticus, Treiman et al. (101) used definitions somewhat different from those used here. However, many of their cases of "subtle status epilepticus" correspond to NCSE. Their "overt status epilepticus" category includes GCSE and some other forms of status epilepticus as well. Among 518 patients with status epilepticus, the first treatment regimen was successful in 55% with overt status epilepticus but in only 15% with subtle status epilepticus. Mortality rates in those groups were 27% and 65%, respectively.

The concurrence of acute brain injury and status epilepticus appears to compound the risk of morbidity and mortality (57,114). In patients with acute brain injury, GCSE is often resistant to treatment and associated with substantially higher morbidity and mortality rates than is GCSE occurring in nonacute processes (66). In a prospective study, Waterhouse et al. (109) found that when status epilepticus complicated acute ischemic stroke, mortality was three times higher than in stroke without status epilepticus. They also found a highly significant difference in mortality between these two groups that was not attributable to lesion size or to stroke severity. A logistic regression model indicated that the effects of status epilepticus and acute stroke on mortality rate were synergistic, not simply additive (Fig. 25.6). In the Veterans Affairs Cooperative Study of status epilepticus (101), patients with persistent subtle status epilepticus had a mortality rate twice as high as that of patients with overt status epilepticus (30% versus 16%). In addition, with acute brain injury, subtle status epilepticus was 36% more likely to occur than overt status epilepticus, and more than twice as likely with acute systemic illness. Jordan et al. (59) found a dramatic increase in mortality among patients with acute brain injury associated with prolonged NCSE, with an odds ratio of 23.8 for acute over remote brain injury. In addition, Young et al. (115) found a highly significant difference in mortality between patients with NCSE and acute brain injury and those with remote brain injury (Fig. 25.7). Severe disability or death was seen in 75% of NCSE patients with acute brain injury, in contrast to 38% without acute brain injury (59). There is biochemical evidence sup-

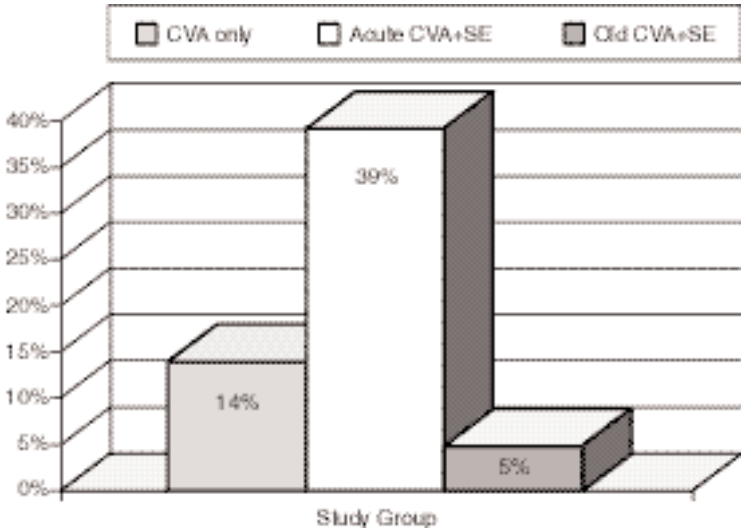


FIG. 25.6. Synergistic effect of status epilepticus and acute ischemic stroke on mortality. The rate of mortality of acute cerebral vascular accident (CVA) with status epilepticus (acute CVA + SE) was significantly higher than that from acute CVA without status epilepticus (CVA only: $p < 0.001$) and also higher than remote CVA with status epilepticus (old CVA + SE; $p < 0.001$). (From Waterhouse EJ, Vaughan JK, Barnes TY, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. *Epilepsy Res* 1998;29:175–183.)

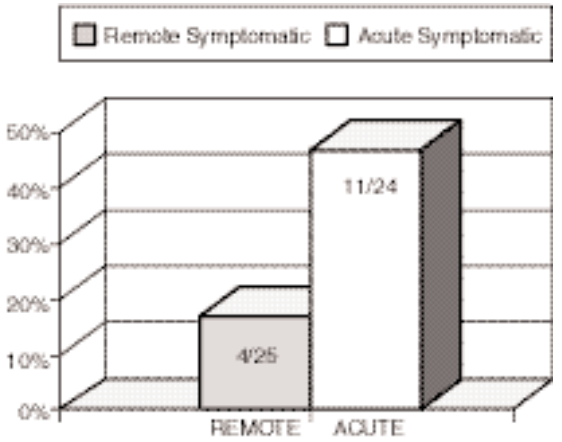


FIG. 25.7. The effect of concurrent acute brain injury and non-convulsive status epilepticus (NCSE) on mortality. In comparison with patients with remote symptomatic etiologies, patients with NCSE and acute symptomatic etiology (called acute brain injury in text) showed a nearly threefold increase in mortality (p = 0.009, odds ratio = 6.0). (Based on data from Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996;47:83–89.)

porting this deleterious synergy. In a study of unselected patients with status epilepticus, DeGiorgio et al. (31) found the highest levels of serum neuron-specific enolase, a marker of neuronal injury, in patients who had both status epilepticus and acute brain injury.

These data are consistent with the accepted concept of secondary neuronal insult described by Miller and Becker (74). Acutely injured neurons are more likely than intact neurons to suffer irreversible injury or death when exposed to comparable levels of ischemic, metabolic, or hypoxic insults. Waterhouse et al. (109) drew an analogy to head injury, in which the combination of two acute injuries produces a worse outcome than either injury alone.

The conclusion from these findings is that in patients with acute brain injury and altered mentation or behavior, an EEG should be obtained promptly to exclude or confirm the diagnosis of NCSE and to guide management. We believe that for patients with acute brain injury and GCSE, it is urgent to obtain complete control of seizure activity, and control should be confirmed by EEG. Suggested primary and secondary criteria for the EEG diagnosis of NCS are listed in Table 25.3. EEG evolution of NCSE is shown in Figure 25.8.

TABLE 25.3. *Criteria for non-convulsive seizures*

Guideline: To qualify, at least *one* primary criteria *and one or more* secondary criteria, with discharges >10 seconds

Primary criteria

1. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at > three/second
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at < three/second *and* secondary criterion 4
3. Sequential rhythmic waves and secondary criteria 1, 2 *and* 3 with or without 4

Secondary criteria

1. Incrementally increasing onset: increase in voltage and/or frequency
2. Decrementally decreasing offset: decrease in voltage and/or frequency
3. Postdischarge slowing or voltage attenuation
4. Significant improvement in clinical state or EEG patterns after intravenous antiepileptic drug administration

CEEG provides objective information for physiologically targeted management of both GCSE and NCSE. Without CEEG, the patient may be undertreated, remaining exposed to the effects of unremitting epileptic cerebral activity, or overtreated, subjected to the risk of iatrogenic ventilatory failure, cardiovascular instability, and prolonged coma. After control of status epilepticus, CEEG patterns are useful for prognosis as they are highly correlated with morbidity and mortality, independent of etiology (48). The cumulative published experience from 1995 to 2000 suggests that CEEG is approaching a standard of care in the management of status epilepticus (12,32,77,101).

In cases of refractory GCSE, CEEG is necessary to guide therapy. High-dose pentobarbital has been the agent used most frequently. More recently, midazolam and propofol have been introduced with success and fewer complications (22). Whichever agent is used, CEEG is necessary to guide the intensity and duration of treatment. Different protocols have been recommended, but no optimal regimen has emerged, nor is there consensus about which EEG

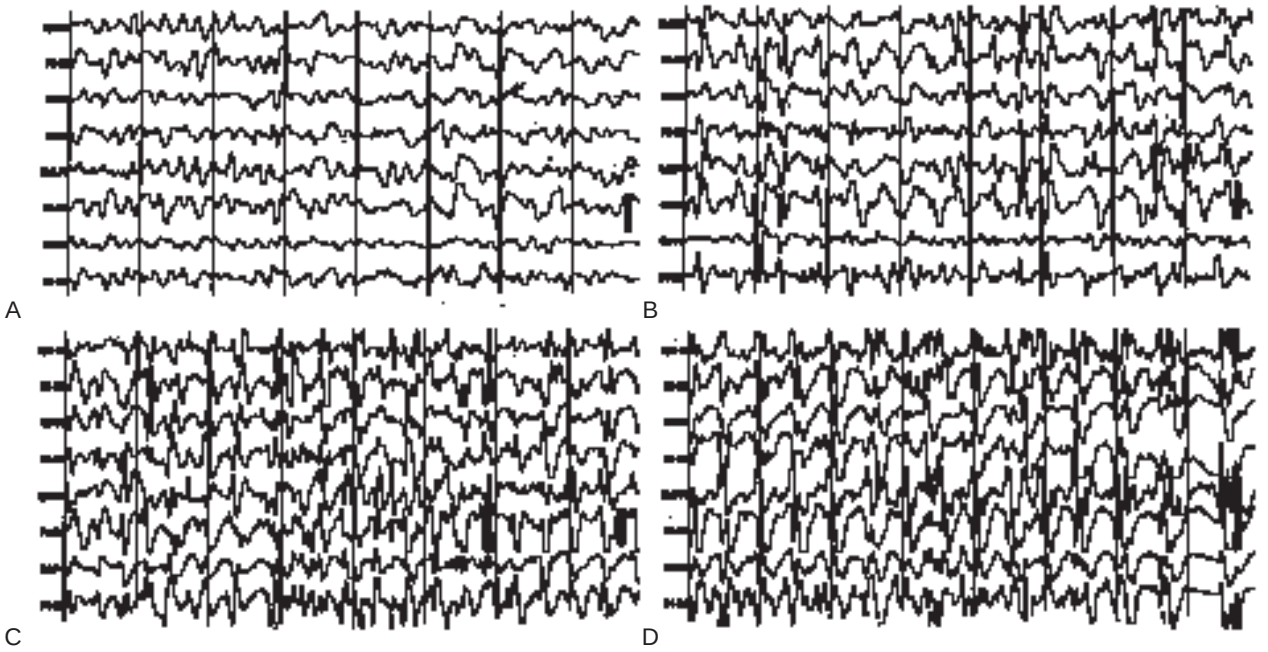


FIG. 25.8. Evolution of generalized non-convulsive status epilepticus (NCSE). **A:** Generalized, low- to medium-voltage theta-delta activity. **B:** Variable but incrementally increasing pattern of generalized spike, spike-wave, and sharp-wave discharges. **C** and **D:** Progressively rhythmic and stereotyped spike, polyspike, and spike-wave generalized discharges. Thick vertical calibration bar is 50 mV. Time interval between vertical dividing lines is 1 second. (From Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996;47:83–89.)

endpoint is required for treatment to be successful (69,82). Based on our experience, we recommend administering the lowest dose necessary to produce cessation of all EEG epileptiform activity for 12 hours, during which time the patient receives loading doses of maintenance anticonvulsants. After this, the infusion is decreased guided by CEEG (53). As the infusion is decreased by spikes, polyspikes, spike-wave complexes, periodic lateralized epileptiform discharges, and bilateral independent periodic lateralized epileptiform discharges may emerge, which might suggest pending relapse into status epilepticus. However, these "emergent" epileptiform patterns are usually distinct in field distribution and morphological features from the patient's ictal activity, and represent a temporary effect of medication withdrawal. They are not clearly associated with a risk of recurrent seizures. Misconstruing these "medication-emergent" findings can lead to unnecessary, repeated treatment to suppress EEG activity (4) (Fig. 25.9).

Patients in the NICU exhibit a wide variety of non-epileptic involuntary and semipurposeful movements. These can be confused with, and mistakenly treated as, seizures (90). They include struggling movements, tremulousness, tetanic spasms, septic rigors, neuroleptic-induced rigidity and extrapyramidal movements, myoclonic jerks, tonic head or eye deviations, and decerebrate or decorticate posturing. Routine bedside EEG may capture only a fraction of the movements. CEEG can advantageously identify cerebral activity before, during, and after the movements. In the mechanically ventilated unconscious patient, CEEG during neuromuscular blockade can determine the presence or absence of epileptogenic activity (Fig. 25.10).

Patients with some neurological diseases are at risk for potentially fatal hyperkalemia if given depolarizing neuromuscular junction blocking agents (104). Although this scenario is most commonly encountered in patients with lower motor neuron disorders, nondepolarizing agents are preferable to succinylcholine for this purpose. Vecuronium, 0.1 mg/kg provides adequate blockage for about 20 minutes. Adequate ventilatory support must be provided during this time (e.g., the ventilator mode may require temporary alteration if the patient is receiving pressure support ventilation). Patients with substantial renal dysfunction should receive cisatracurium, 0.1 to 0.2 mg/kg, because vecuronium is renally excreted.

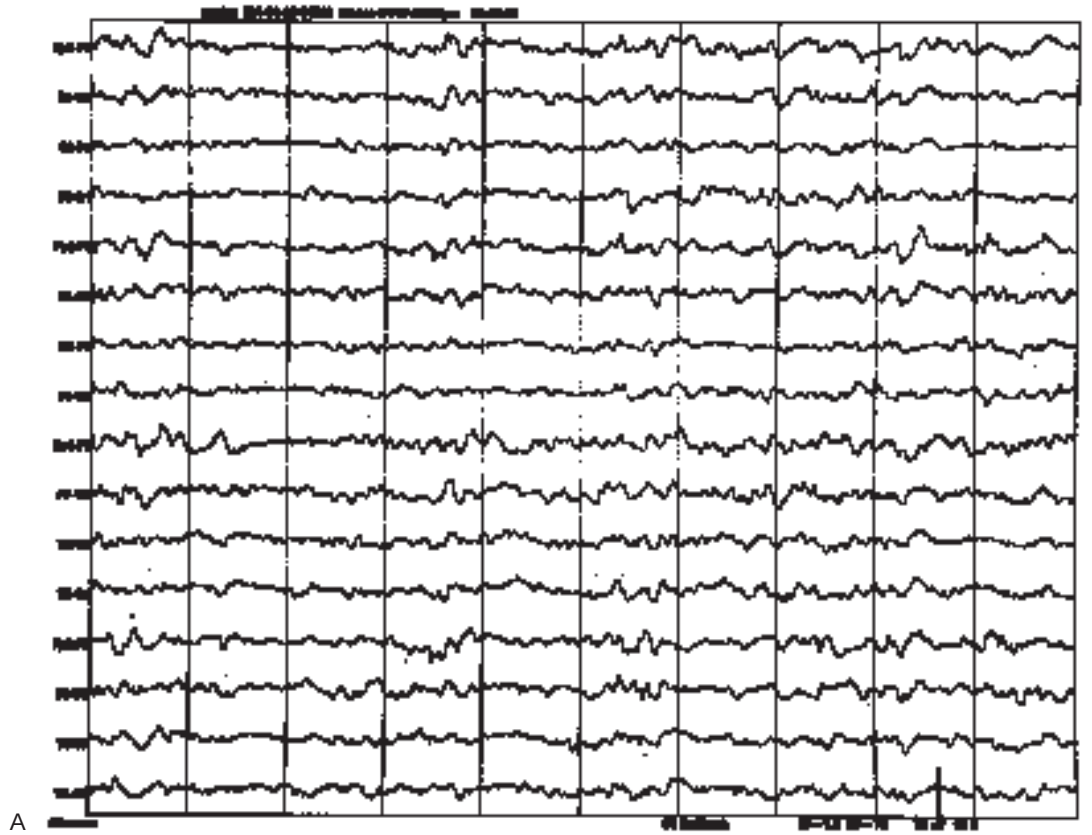


FIG. 25.9. Emergence from pentobarbital-induced cerebral suppression for status epilepticus. **A:** Low-amplitude mixed frequencies with residual burst-suppression. (*Figure continues*.)

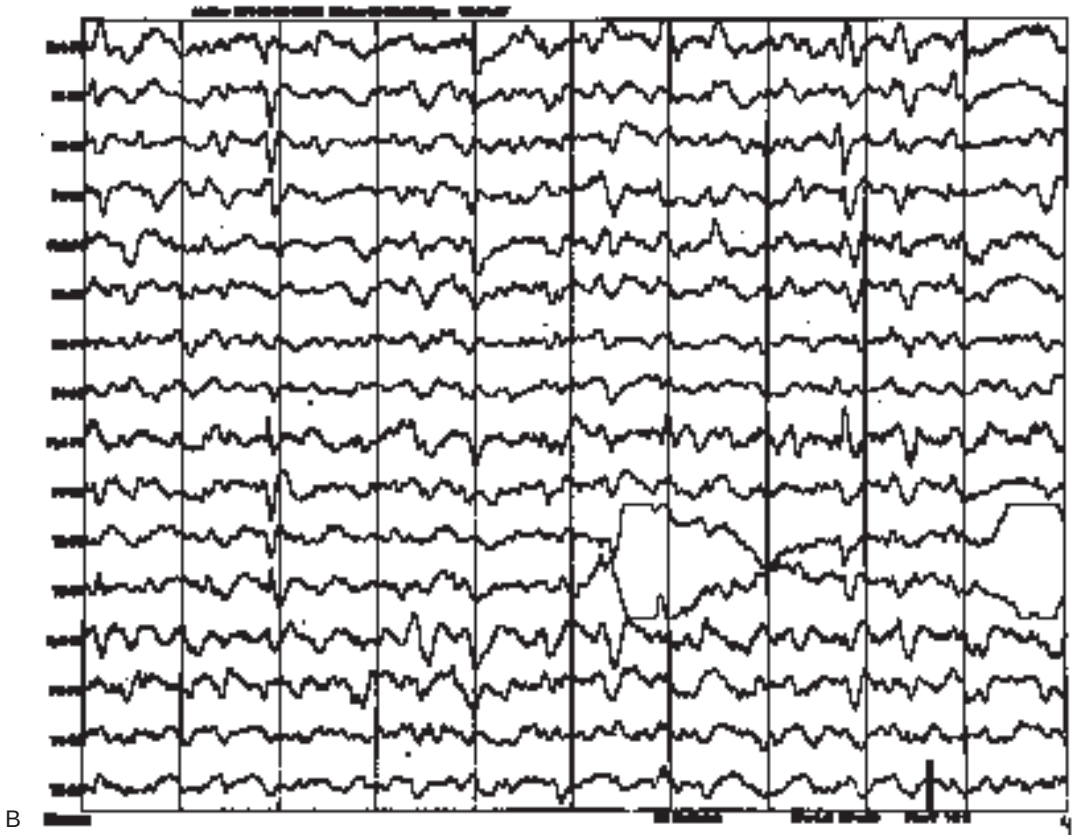
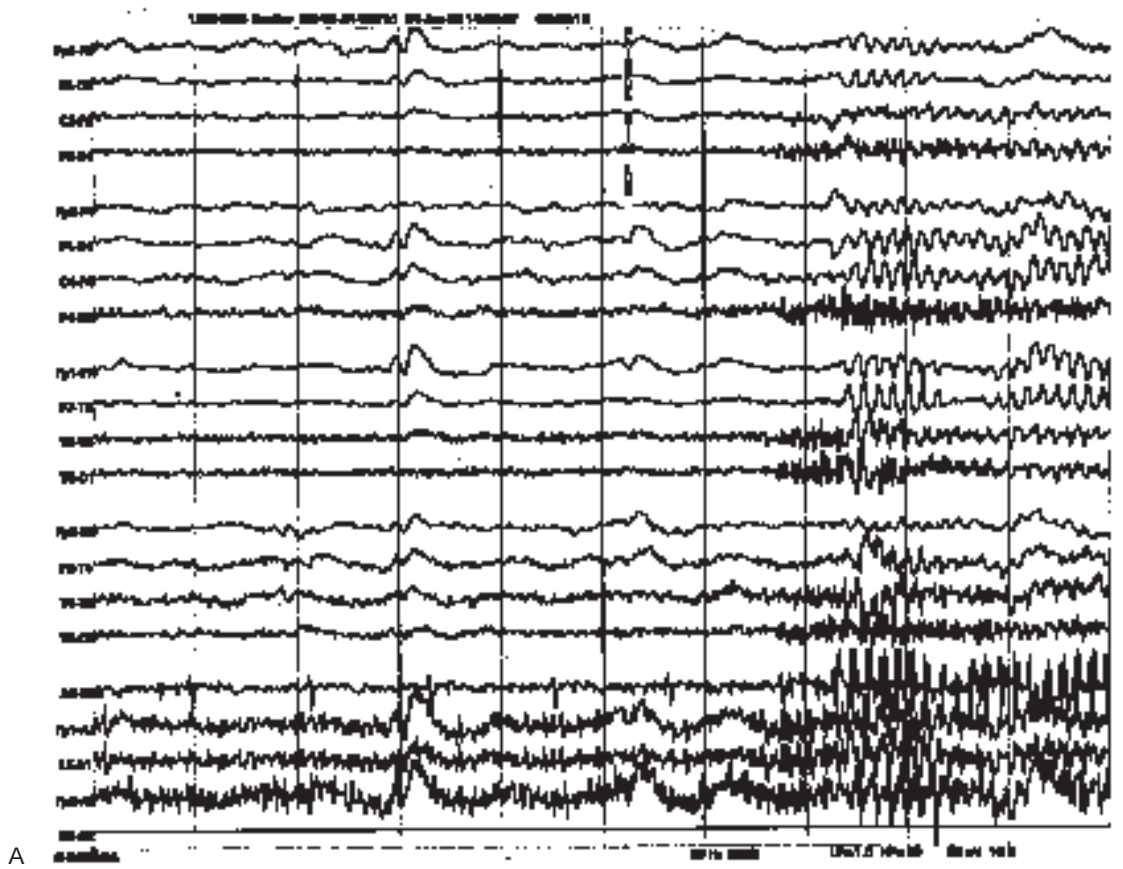


FIG. 25.9. *Continued.* **B:** A variety of epileptiform activity is present, including left hemisphere spikes, right frontal sharp waves, and right frontotemporal triphasic semiperiodic sharp waves. These activities resolved as the patient's coma lightened. (From Jordan KG. Continuous EEG monitoring in the neuroscience intensive care unit and emergency department. *J Clin Neurophysiol* 1999;16:14–39.)



A

FIG. 25.10. Continuous EEG in a patient with acute severe head trauma and stimulus-induced "seizures." These proved to be non-epileptic. **A** and **B:** Patient stimulation produced incrementally increasing, generalized rhythmic activity. The morphological pattern in the left posterior hemisphere strongly resembles incrementally increasing ictal polyspike activity. (*Figure continues*.)

B

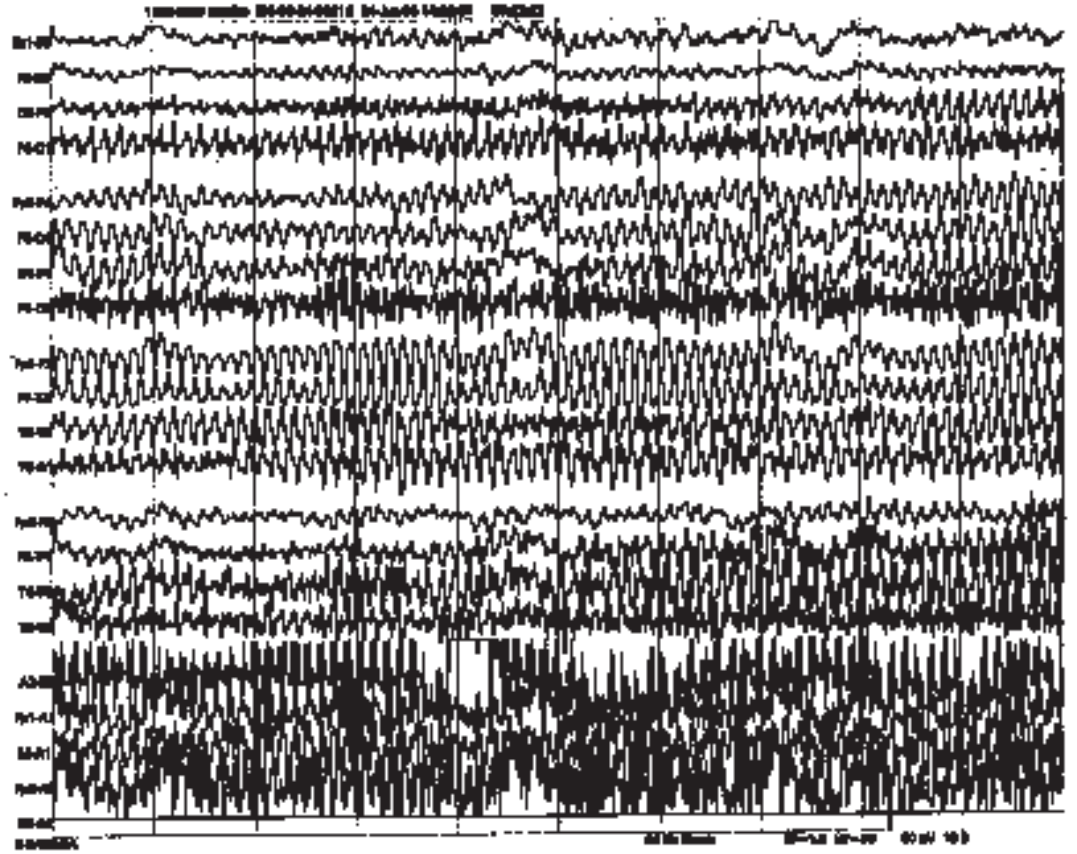
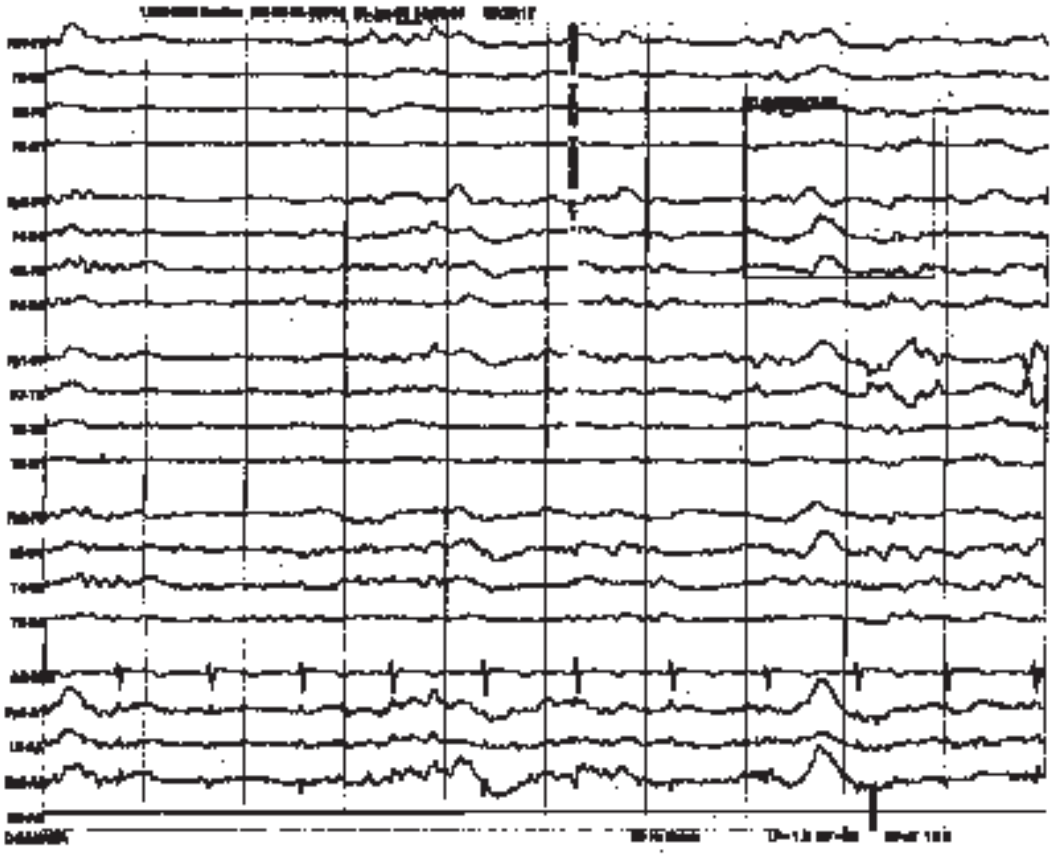


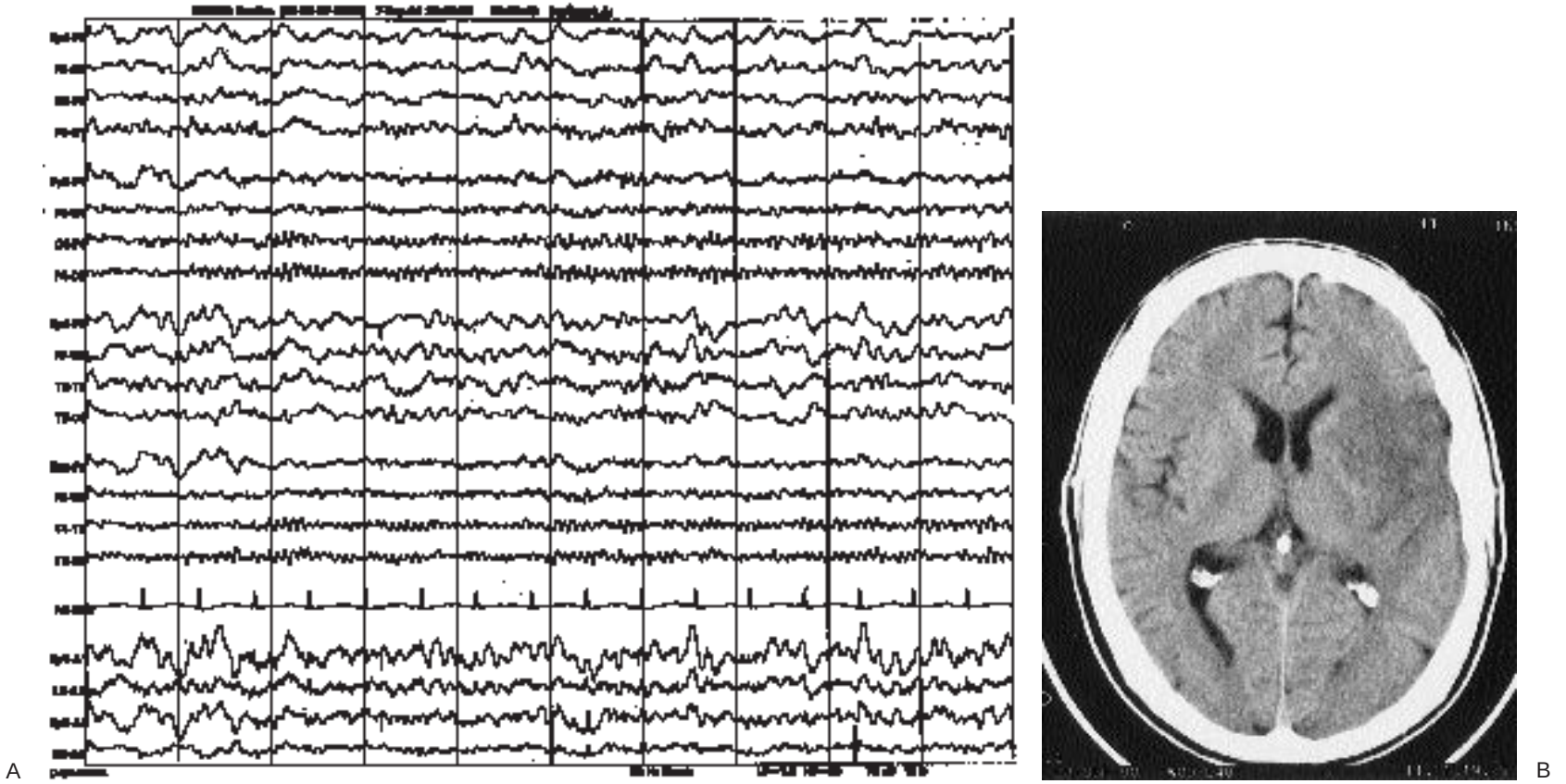
FIG. 25.10. *Continued.*



C

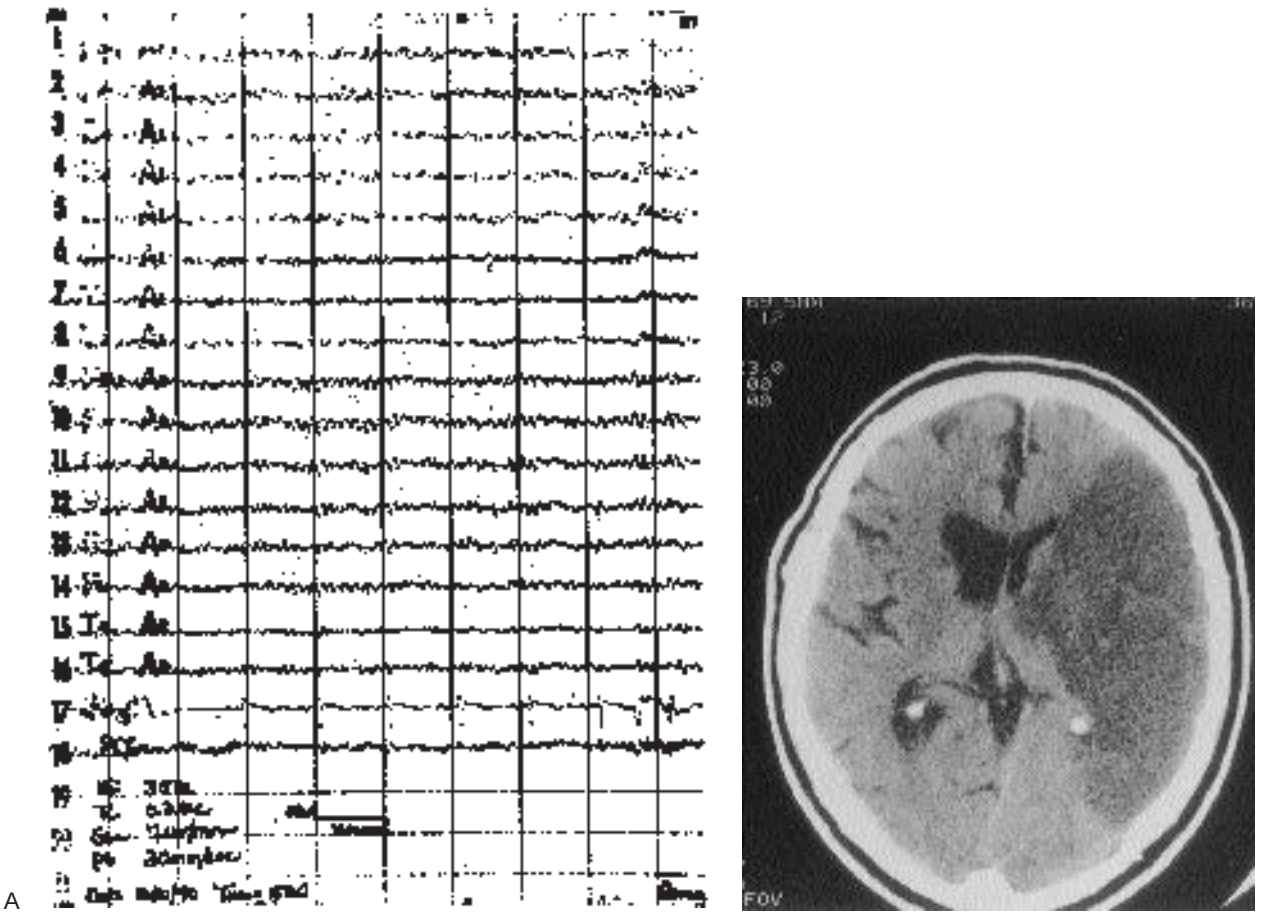
FIG. 25.10. *Continued.* **C:** After administration of a neuromuscular blocking agent, there was no evidence of epileptiform activity, even with stimulation. (From Jordan KG. Continuous EEG monitoring in the neuroscience intensive care unit and emergency department. *J Clin Neurophysiol* 1999;16:14–39.)

The possibility of psychogenic status epilepticus must also be kept in mind. In one specialized epilepsy center, almost 20% of patients in the emergency department with intractable GCS had psychogenic seizures, and several had psychogenic GCSE (38). Psychogenic GCSE can appear genuine even to experts, and CEEG is the only way to determine if the convulsive activity is accompanied by ictal discharges (70). Although convulsive motor activity often obscures the CEEG record, the prompt appearance of a normal alpha rhythm during pauses is strong evidence for psychogenic status epilepticus.



A B

FIG. 25.11. EEG and CT scan in a patient with acute left infarction of the anterior temporal lobe. **A:** Continuous polymorphic delta activity in the left hemisphere, maximal temporally, with well-preserved right hemisphere background activity. **B:** CT scan showing acute left temporal infarction.



A B

FIG. 25.12. EEG and corresponding CT scan with extensive left hemisphere infarction secondary to middle cerebral artery occlusion. **A:** Referential montage showing marked attenuation of all EEG frequencies over the left hemisphere. **B:** CT showing extensive left hemisphere infarction with mass effect invading the entire middle cerebral artery territory.

CONTINUOUS EEG IN ACUTE FOCAL CEREBRAL ISCHEMIA

EEG abnormalities with large hemispheric infarctions were described as long ago as 1948 (28). In order of increasing severity, these changes include (a) widespread polymorphic delta activity in the involved hemisphere, maximally in the temporal and frontotemporal regions (Fig. 25.11); (b) ipsilateral attenuation or loss of alpha activity, beta activity, and sleep spindles; (c) with extensive hemispheric infarction, marked suppression of all EEG activity (Fig. 25.12); and (d) contralateral frontal delta activity and intermittent projected rhythmic delta activity with mass effect and midline shift. Patients with acute focal ischemia often have precarious cerebral perfusion: in up to 43%, perfusion worsens within the first 24 hours (17). Among patients with subarachnoid hemorrhage vasospasm, 25% to 40% suffer symptomatic ischemia (45). Therefore, a bedside monitor warning of impending deterioration would be helpful. Because of its dependence on CBF, CEEG changes appear within minutes of the onset of ischemia (98). In 45% of 22 such patients, CEEG deterioration was characterized by focal slow activity, appearance of epileptiform discharges, or generalized slowing (49). CEEG abnormalities preceded clinical changes in several patients. The severity of EEG abnormalities in acute focal cerebral ischemia correlates closely with the degree of ischemia measured by xenon CT determination of cerebral blood flow (58). When hypertensive hypervolemic therapy was used to elevate regional CBF above the ischemic threshold, CEEG documented resolution of the focal slow activity. Wood et al. (111) also studied volume expansion therapy and likewise found that CBF and qEEG improved together (111).

TABLE 25.4. *Early xenon CT cerebral blood flow studies in patients with regional voltage attenuation without delta (RAWOD)*

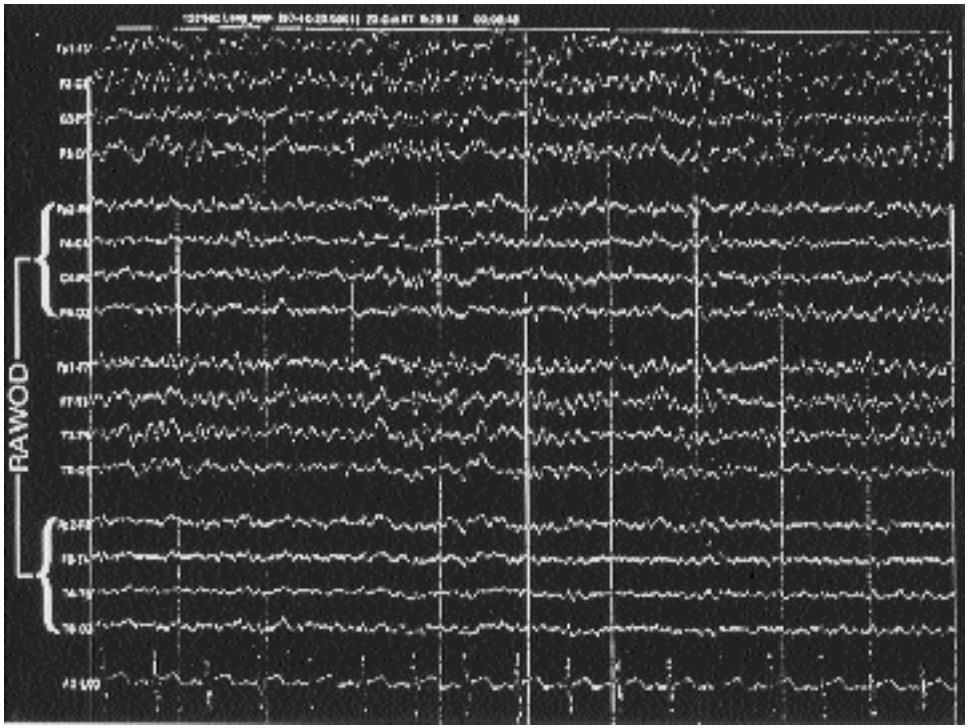
Patient	MINHSS (NIHSS)	V_i (%)	$mCBF_i$ (mL/100 g/min)	Infarct on initial CT scan
JM	10 (35)	52.9	10.5	+
GN	10 (35)	47	6.8	+
SS	8 (28)	60.6	10.1	–
TP	8 (28)	43.4	10.0	+
HH	10 (35)	53.9	5.7	–
AC	10 (35)	49.8	8.3	–
Mean results	9.3 (33)	51.2 ± 6.6	8.6 ± 2.2	

$mCBF_i$, mean ischemic cerebral blood flow; MINHSS (NIHSS), National Institutes of Health Stroke Scale; V_i, percent volume of ischemic tissue (in affected hemisphere).

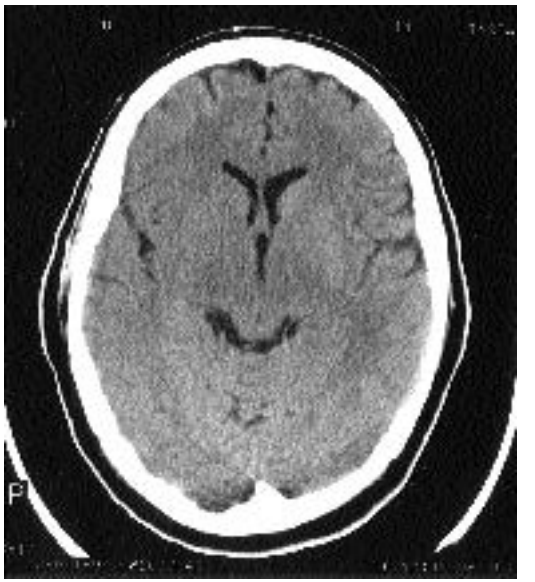
In the emergency department, there may be a role for urgent EEG in selected patients with suspected stroke. In one study (65), the rate of stroke misdiagnosis in the emergency department was 13% to 19%; misdiagnosis was caused by conditions that mimicked ischemia (Table 25.4). Another study (40) found that the rate of misdiagnosis by emergency medicine specialists was 9% (16 of 185), and by family physicians 15% (8 of 52). Conversely, a number of stroke syndromes manifest without motor or sensory loss and can be confused with non-stroke conditions, including psychiatric disorders. These include receptive (Wernicke's) aphasia, visual agnosia, Gertsmann's syndrome, alexia with or without agraphia, and right parietal lobe ischemia. In acute stroke, the CT scan is often normal or equivocal early, increasing the likelihood of misdiagnosis. Because the EEG changes within minutes of the onset of ischemia, it provides a strong clue to the presence of ischemia or infarction as the basis of the patient's symptoms. This has obvious implications for the appropriate use of intravenous thrombolytic therapy. The relative roles of CEEG and the newer techniques of diffusion and perfusion magnetic resonance imaging remain to be determined.

The introduction of thrombolytic therapy for stroke has raised both hope and uncertainty within the medical community (21,76). Data support its benefits, but there is also evidence of a low but significant risk of intracranial hemorrhage (27). Jordan (55) studied 49 patients in the emergency department with focal ischemia using acute EEG. Eighteen patients had widespread voltage attenuation of all frequencies without accompanying delta activity, a pattern described by the acronym RAWOD (regional attenuation without delta) (Fig. 25.13*A*). This is equivalent to the third pattern described by Cohn et al. (28). It is also similar to the EEG pattern seen when clamping of the carotid artery produces cerebral ischemia sufficient to cause infarction (97).

Important clinical, physiological, and anatomic correlations were found with RAWOD: (a) Severe neurological deficits were present in all patients (mean National Institutes of Health Stroke Scale score, 31); (b) regional CBF was decreased to infarction levels in all patients studied (mean regional CBF, 8.6 mL/100 g/min); (c) ipsilateral cortical somatosensory evoked potentials were absent; (d) ipsilateral internal carotid artery and middle cerebral artery transcranial Doppler (TCD) velocities were markedly abnormal; (e) all RAWOD patients had poor outcomes, including a mortality rate of 67% (12 of 18); and, (f) in 56% of RAWOD patients (10 of 18), the ini-



A



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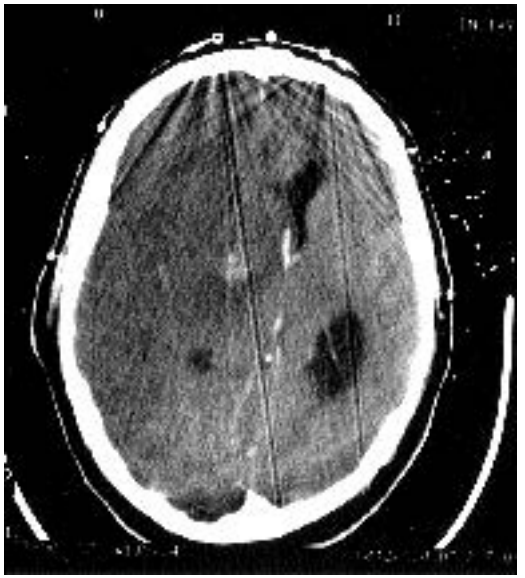


C

FIG. 25.13. Emergency room EEG and CT scans in a patient with massive acute right hemisphere ischemia. **A:** Acute emergency room EEG shows widespread attenuation of all frequencies in the right hemisphere (regional attenuation without delta [RAWOD]). There is diffuse 6-Hz theta slowing and some intermixed delta activity in the left hemisphere. **B:** Initial CT scan taken shortly before emergency room EEG. This scan was interpreted as normal. There may be early cortical edema in the right sylvian fissure. **C:** Repeat CT scan obtained 20 hours after the initial scan. This scan shows massive right hemisphere edema with midline herniation. The streak artifacts are caused by EEG needle electrodes in the patient's scalp.

tial CT showed no new areas of infarction, but on follow-up 48 hours later all 10 showed massive infarctions, often with malignant edema (see Fig. 25.13*B* and *C*). Among 20 patients with clinically severe acute focal cerebral ischemia within the middle cerebral artery territory, xenon CT showed a mean CBF of 10.4 mL/100 g/min in the symptomatic patients who developed severe edema (41). Among those who clinically herniated, mean CBF was 8.6 mL/100 g/min. These values are in the same range measured in the cerebral hemisphere ipsilateral to the RAWOD pattern (personal observation). RAWOD is a distinctive EEG pattern found in extensive and irreversible focal ischemia, and it signifies a high risk of malignant cerebral edema.

Such observations suggest that urgent EEG in the emergency department may be a practical, cost-effective, and objective method for early identification of hemisphere infarctions. If confirmed, this could be a method that contributes to better selection of patients for therapeutic intervention.

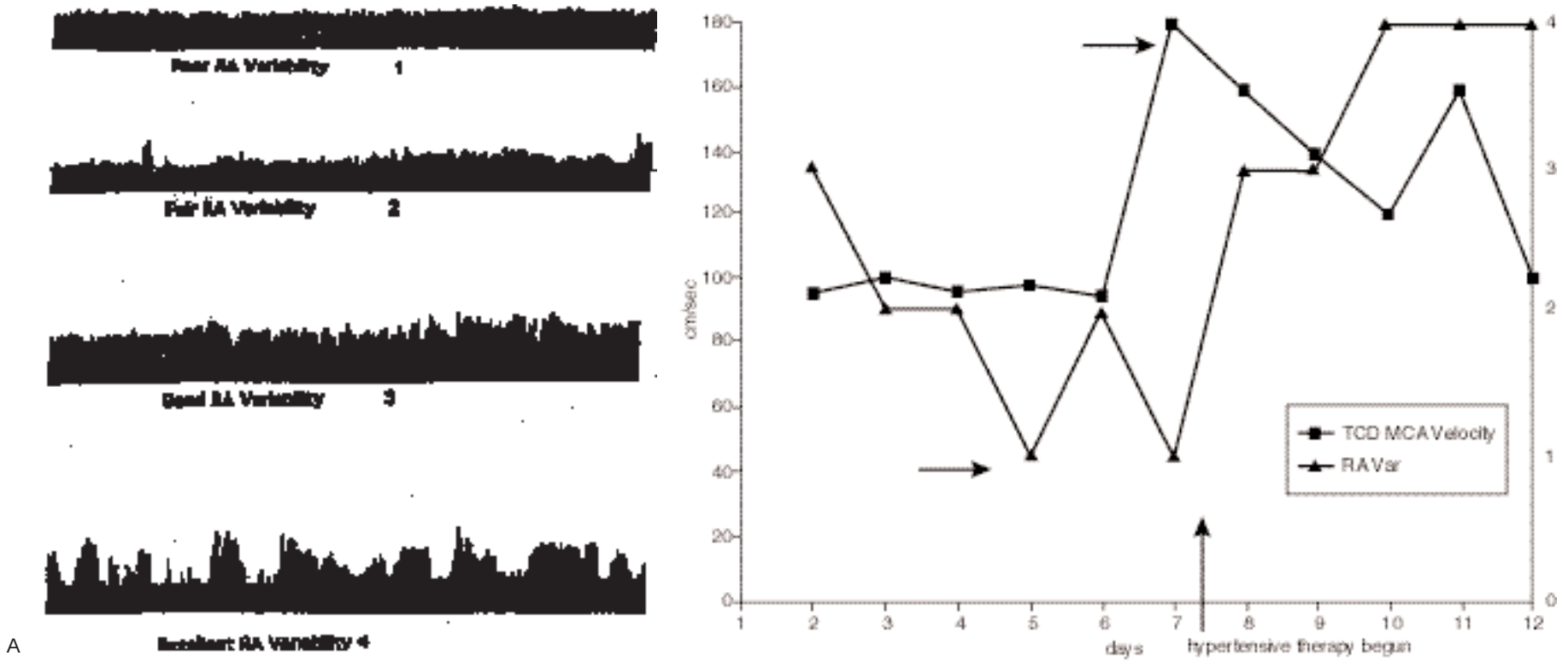


FIG. 25.14. Relative alpha variability on quantitative electroencephalogram (qEEG) correlated with transcranial Doppler (TCD) velocities in subarachnoid hemorrhage vasospasm. **A:** qEEG samples displaying relative alpha variability, graded 1 (abnormal) to 4 (normal). **B:** Graph shows relative alpha variability worsening to grade 1 on day 5. This precedes TCD evidence of vasospasm, detected on day 7. (From Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *J Neurosurg* 1999;91:750–760.)

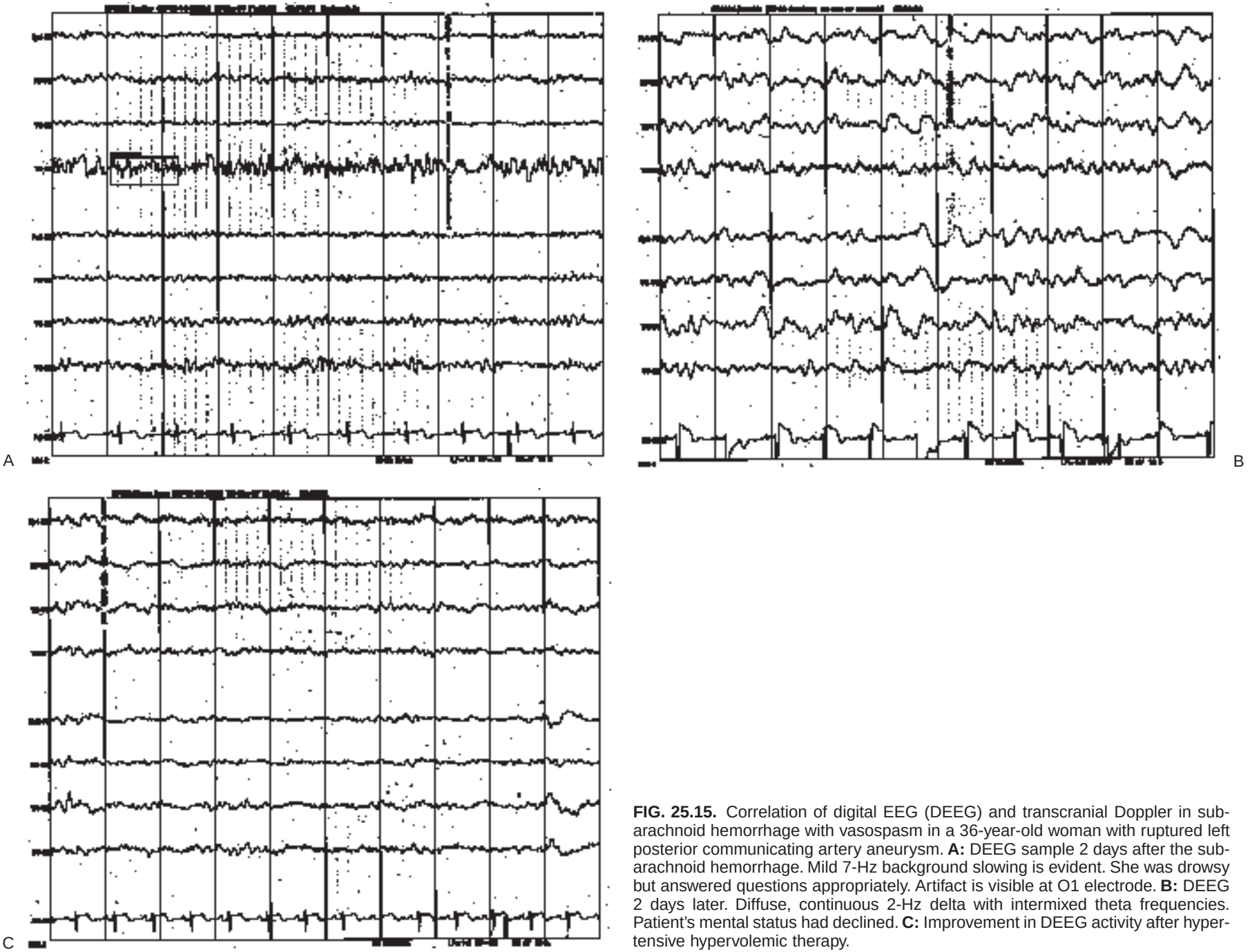


FIG. 25.15. Correlation of digital EEG (DEEG) and transcranial Doppler in subarachnoid hemorrhage with vasospasm in a 36-year-old woman with ruptured left posterior communicating artery aneurysm. **A:** DEEG sample 2 days after the subarachnoid hemorrhage. Mild 7-Hz background slowing is evident. She was drowsy but answered questions appropriately. Artifact is visible at O1 electrode. **B:** DEEG 2 days later. Diffuse, continuous 2-Hz delta with intermixed theta frequencies. Patient's mental status had declined. **C:** Improvement in DEEG activity after hypertensive hypervolemic therapy.

CEEG has been used to monitor patients at risk for vasospasm-induced focal ischemia. Rivierez et al. (87) found that broad, repetitive slow waves were predictive of vasospasm-induced ischemia. Labar et al. (62) reported that qEEG changes preceded clinical evidence of vasospasm in four (36%) of 11 cases. Vespa et al. (107) used qEEG to study 32 consecutive patients with subarachnoid hemorrhage. Data were analyzed blindly and compared with TCD velocities, cerebral angiograms, and CT scans. In 19 (59%) of 32 patients, vasospasm developed. The variability of relative alpha was significantly decreased in all patients with vasospasm, a finding that enabled clinicians to detect vasospasm before TCD studies in over 70%. As vasospasm resolved, baseline relative alpha variability returned (Fig. 25.14).

Raw CEEG data can also help detect vasospasm-induced cerebral dysfunction before TCD findings are diagnostic (Fig. 25.15). In managing vasospasm patients, CEEG may be helpful in targeting therapeutic goals for mean arterial pressure, intravascular volume, and cardiac output (see Fig. 25.15*C*).

CONTINUOUS EEG IN DIAGNOSIS AND PROGNOSIS OF COMA

CEEG assesses the dynamic reactivity, variability, and wake-sleep integrity of the cortex. All of these have prognostic importance in coma. Bricolo et al. (16) reported unfavorable outcomes in 95% of patients with monotonous delta activity, in contrast to 30% of patients with variable or sleep-wake patterns. Other researchers have verified that the presence of physiological sleep-wake cycles suggests a favorable prognosis (9). In a study of posttraumatic coma, Stone et al. (96) found that EEG reactivity was prognostically more useful than the dominant frequency. In their study, reactivity was immediate or delayed and was characterized by desynchronization, attenuation, appearance of new delta or theta activity, or the appearance of sleep spindles. In both traumatic and anoxic-ischemic coma, a poor prognosis is implied by invariant, unreactive alpha activity, burst-suppression patterns, and periodic bursts of epileptiform discharges (99) (see Chapter 14).

In an attempt to provide a systematic approach to EEG in coma, Young et al. (116) developed and validated a grading system that was based on 100 EEGs in comatose patients. Through blinded interpretation by two electroencephalographers, their system achieved a κ score of 0.90, indicating almost perfect agreement. They found that prognosis worsened from grade I to VI but could be further refined by use of "subcategories," including reactivity, generalized or focal distribution, and epileptiform activity.

CEEG may provide clues to the etiology of coma and help exclude competing possibilities. Spindle or alpha coma patterns can be seen in patients with overdoses of tricyclic agents, benzodiazepines, or barbiturates. In the absence of drug overdose, alpha-theta coma is almost always caused by a generalized hypoxic-ischemic insult. Fluctuating, generalized theta-delta activity, especially if accompanied by triphasic wave activity, suggests a metabolic encephalopathy, but the pattern can also be seen in severe hypercapnia, opiate toxicity, and lithium overdose (43). Septic encephalopathy can produce a similar appearance, with the severity of the EEG abnormalities paralleling the degree of mental status impairment, systemic severity of the condition, and correlating with death (112). When severe hydrocephalus produces coma, intermittent bursts of diffuse rhythmic delta activity (FIRDA) can be seen; these may fluctuate dramatically with changes in intraventricular pressure (Fig. 25.16*A* and *B*). Coma caused by structural lesions with mass effect tends to be characterized by attenuated background activity ipsilateral to the lesion, plus bilateral frontal and asymmetric rhythmic delta activity (Fig. 25.20*A* to *D*). Coma can also be a deceptive, nonspecific manifestation of NCSE. Lowenstein and Aminoff (68) reported that of 38 comatose patients with EEG-proved NCS, 10% had no clinical signs of seizures, and 70% had only "subtle motor movements." Corroborating this observation, Jordan (50) reported that of 43 patients with NCS, 37% were comatose without distinguishing clinical motor features (see Fig. 25.17).

In the evaluation of coma, routine bedside EEG can mislead the clinician and result in incorrect conclusions. For example, sleep patterns may not be detected during routine recording times, and prolonged cycles or autonomous activity may not be recognized. In addition, an EEG "snapshot" of a distinctive pattern, such as burst-suppression with epileptiform activity (Fig. 25.18*A*), may lead to management decisions based on the assumption of a hopeless prognosis. The dynamic element of CEEG may, in fact, suggest a more favorable outcome (see Fig. 25.18*B* to *D*). Furthermore, in a comatose patient with NCSE, a nonspecific encephalopathy may be suggested by a routine EEG recorded during an interictal period. Conversely, a number of metabolic encephalopathies can precipitate NCS or NCSE, such as hyperglycemia or hypoglycemia, hypernatremia or hyponatremia, and hepatic encephalopathy (51) (Fig. 25.19).

A

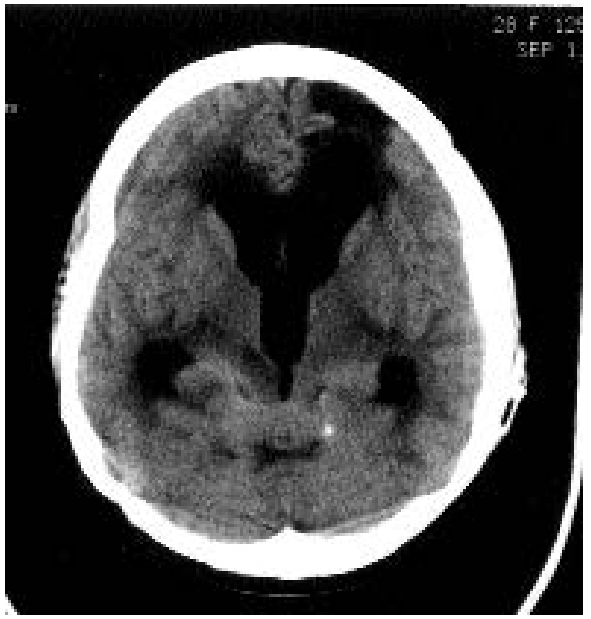
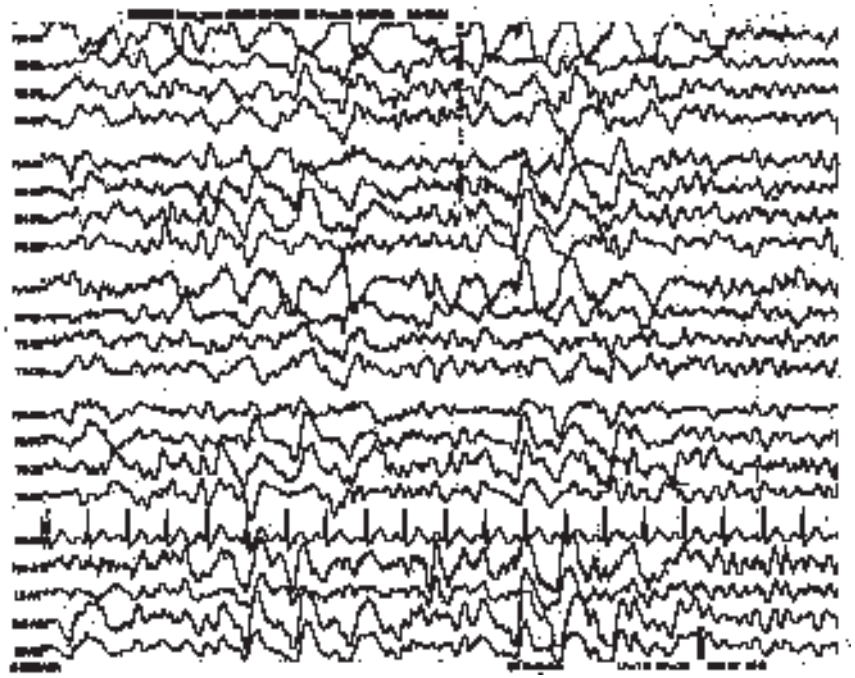
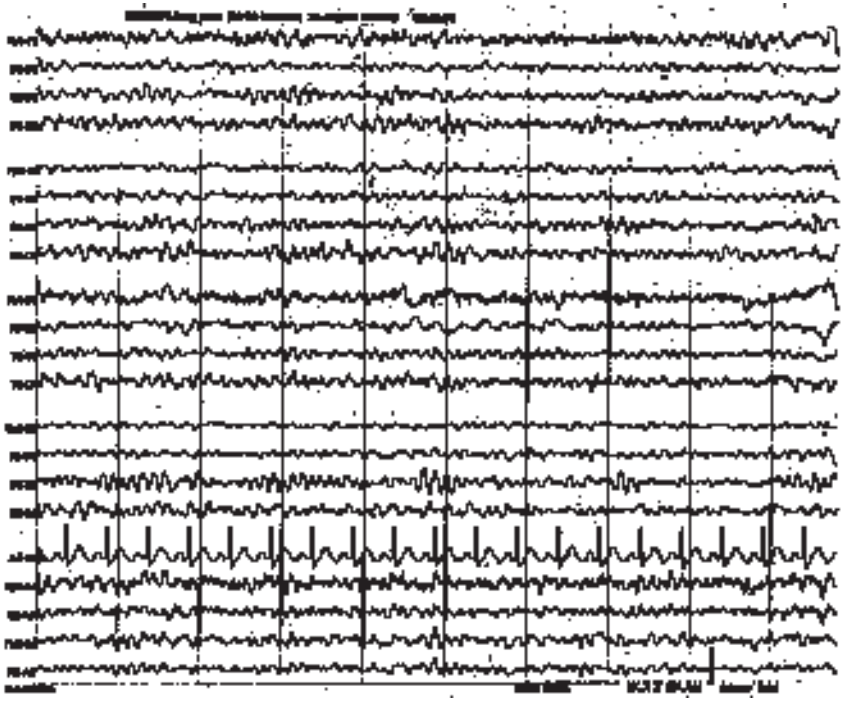


FIG. 25.16. CT scan and continuous EEG samples in comatose 28-year-old woman with obstructive hydrocephalus and tuberculous meningitis. **A:** Noncontrast CT scan shows severe dilatation of the supratentorial ventricular system. A right ventriculoperitoneal shunt is not visualized. The left focal encephalomalacia is from prior removal of a tuberculoma. **B:** Semicontinuous delta-theta pattern is punctuated by high-amplitude, generalized, intermittent, rhythmic delta bursts. At the notation "button press," the patient's shunt reservoir is "pumped." **C:** Dramatic improvement in continuous EEG after "pumping" of shunt reservoir.

B





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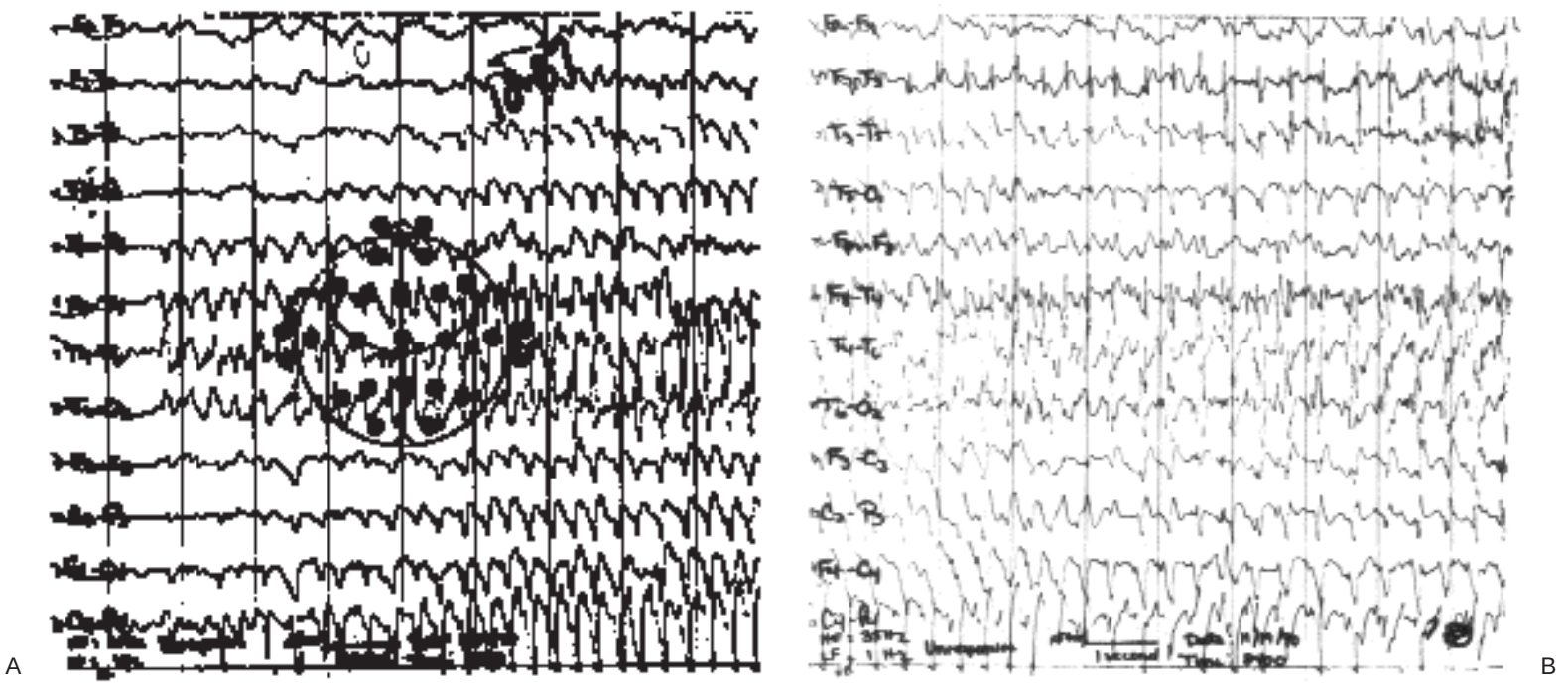
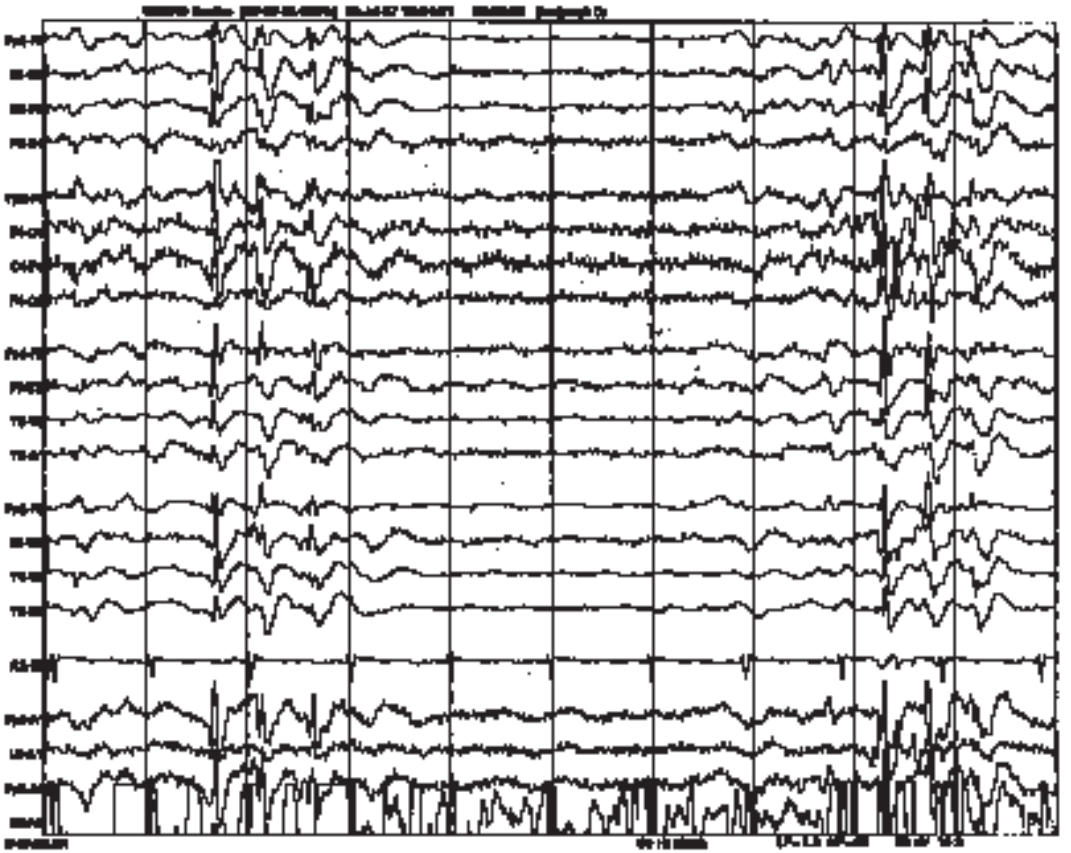
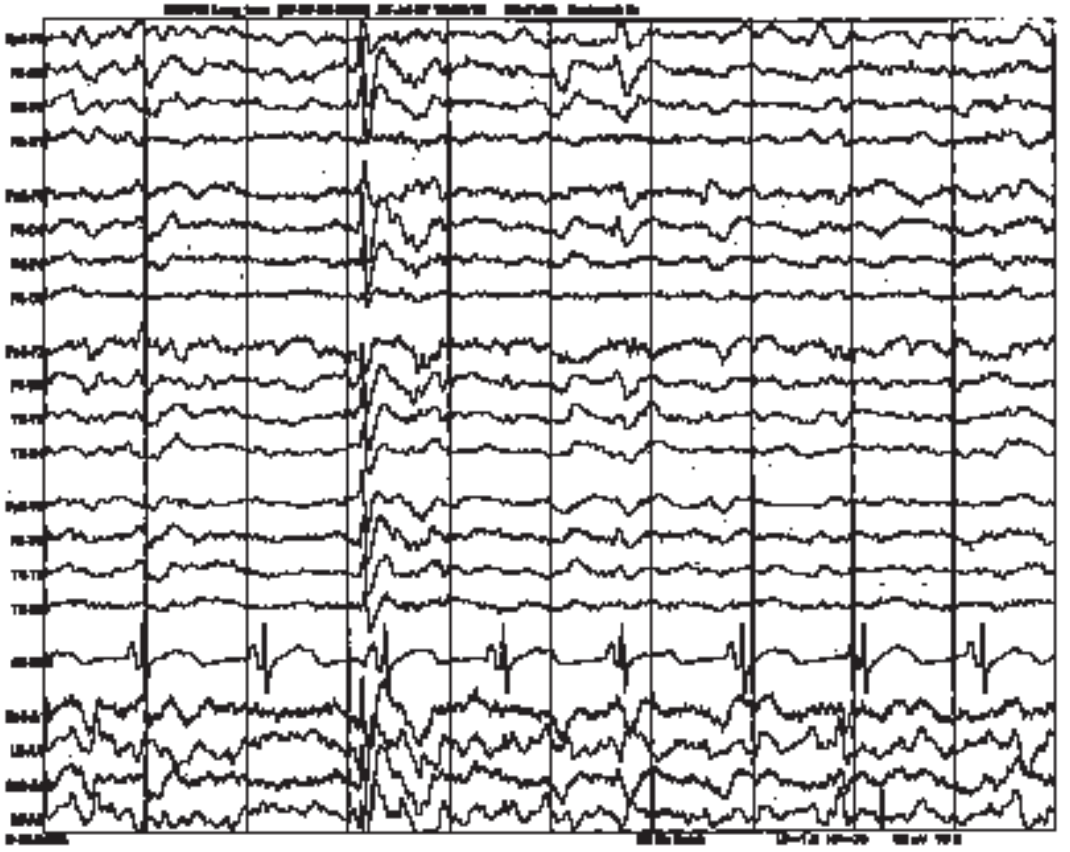


FIG. 25.17. EEG from a comatose patient with small right temporal lobe abscess. The cause of the patient's coma was nonconvulsive status epilepticus (NCSE) arising from the right temporal lobe. No convulsive activity or distinguishing motor features were present. **A:** Focal onset of seizure from the right midtemporal region with beginning secondary generalization. **B:** Generalized seizure activity, during which the patient remained unresponsive without motor activity.



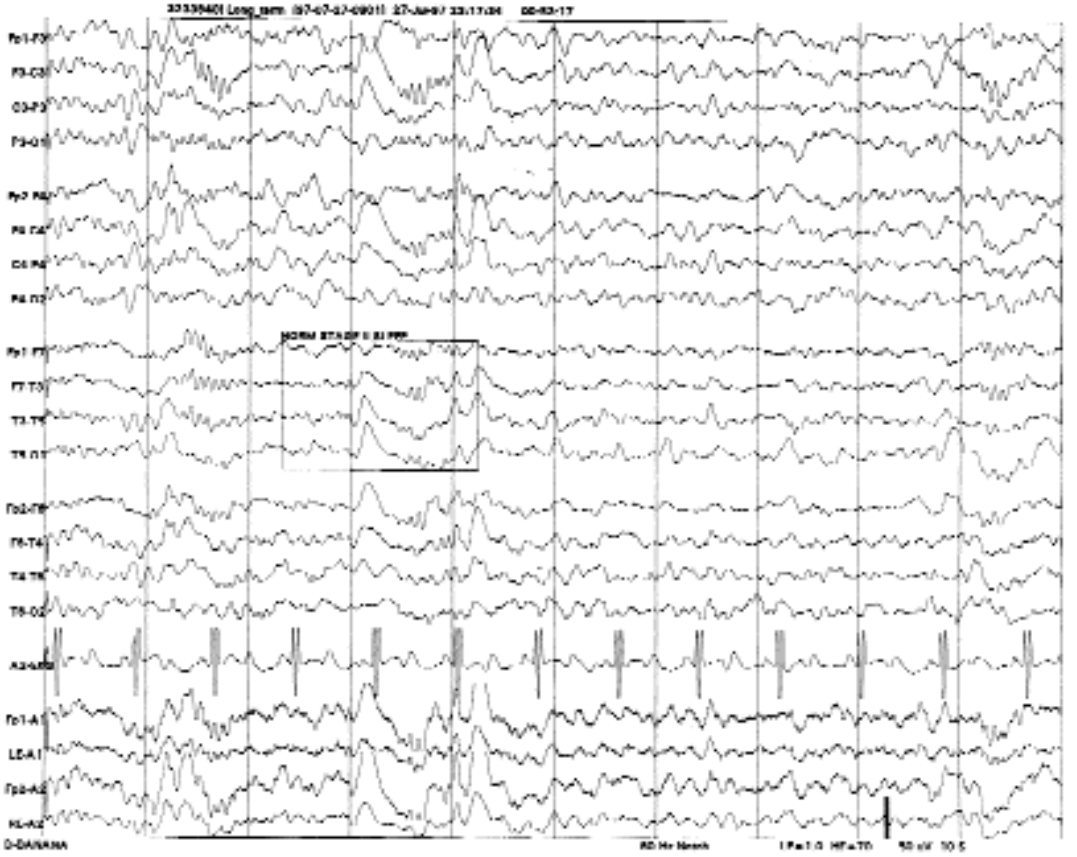
A

FIG. 25.18. Continuous EEG in a 41-year-old woman with anoxic encephalopathy resulting from generalized convulsive status epilepticus (GCSE). The patient also had elevated ammonia levels in association with chronic valproic acid use. Initial examination revealed deep coma, decerebrate posturing, and bilateral Babinski signs. **A:** Markedly suppressed, unreactive record with bursts of generalized spike discharges. No clinical convulsive activity was seen. (*Figure continues.*)



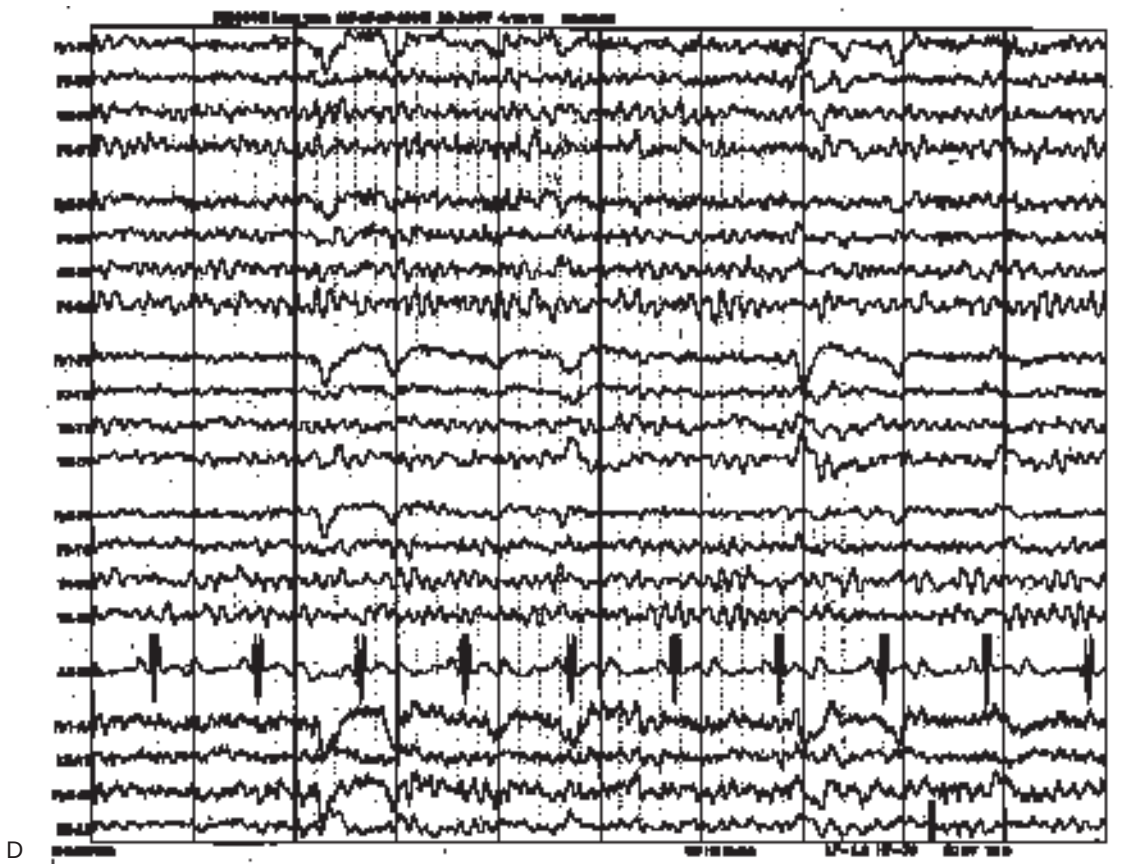
B

FIG. 25.18. *Continued.* **B:** Two days later, continuous semirhythmic delta activity is present, and occasional generalized spike discharges are still seen. (*Figure continues.*)



C

FIG. 25.18. *Continued.* **C:** Two days after the recording in *B.* Generalized theta activity with epochs of physiological stage II sleep patterns is present. (*Figure continues.*)



D

FIG. 25.18. *Continued.* **D:** One day after the recording in part *C.* EEG activity is nearly normal. Only mild posterior background slowing is present. The patient made a complete recovery.

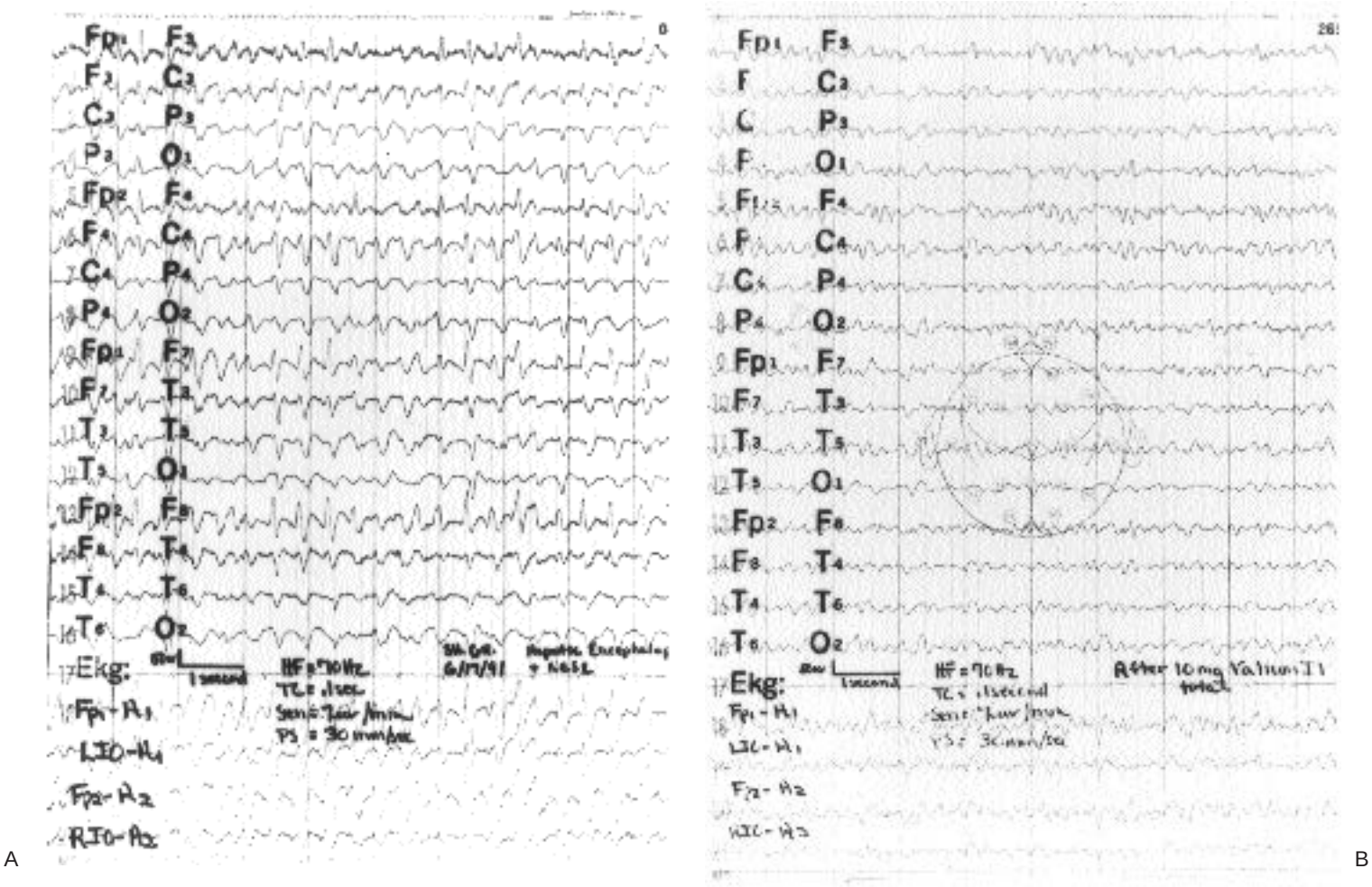


FIG. 25.19. Continuous EEG of a comatose patient with coexisting NCSE and hepatic encephalopathy. The blood ammonia level was elevated to four times normal. **A:** Continuous 2.5- to 3-Hz spike-wave and triphasic sharp waves. The nurse observed occasional jaw-thrusting movements, suggestive of epileptic automatisms. **B:** After intravenous administration of 10 mg of diazepam, the record rapidly evolved to a generalized rhythmical theta pattern. The patient's level of alertness also improved markedly. (From Jordan KG. Continuous EEG and evoked potential monitoring in the neuroscience intensive care unit. *J Clin Neurophysiol* 1993;10:445.)

Patients with de-efferented ("locked-in") states present a special challenge in the NICU. Their cerebral function is inaccessible by bedside evaluation because motor responses, including facial and bulbar muscles, are absent. In such patients, CEEG reveals normal alertness and responsiveness to various stimuli. Inadequate sedation may leave the paralyzed patient conscious and anxious, whereas excessive sedation may prolong ventilatory dependence, induce coma, or both. CEEG can also reveal superimposed encephalopathic insults, which can be caused by hypercapnia, sepsis, metabolic imbalance, or medication side effects. Some patients are so profoundly de-efferented that clinical findings suggest brain death. In this circumstance, CEEG can confirm normal or near-normal cortical activity, reactivity, and sleep-wake cycles.

The addition of EEG analysis to other systems to predict outcome for ICU patients also improves the utility of these systems (117).

CONTINUOUS EEG IN ACUTE SEVERE HEAD TRAUMA

Since the early 1980s, there have been a number of major breakthroughs in understanding the pathophysiological processes associated with traumatic brain injury. Much of the neurological damage does not occur at the moment of impact. Over the ensuing hours and days, delayed insults cause secondary injury that is apparent biochemically and clinically (23). This discovery spurred renewed interest in neurophysiological monitoring of trauma patients to identify impending secondary brain injury in time to control or reverse it.

In traumatic injury, sequential brain imaging is commonly used to assess structural abnormalities, but, as Sloan (95) pointed out, the functional integrity of the cerebrum and brainstem can be determined only by clinical examination or neurophysiological testing. In many trauma patients, sedative and neuromuscular blockading agents used to control ventilation or agitated behavior render the neurological examination uninformative. In these patients, the functional state of the brain can be determined only by neurophysiological monitoring. The use of CEEG as a management tool in head trauma is in its early stages. Correlative and prospective studies are beginning to appear (10,105,108). Emerging information suggests that CEEG can be beneficial in detecting posttraumatic NCSE, in the management of increased ICP, and in the early detection of cerebral mass effect. From extrapolation of studies in related conditions, CEEG has a potential role in the early detection of posttraumatic vasospasm and, perhaps, injurious levels of hyperventilation.

An important caveat in using EEG in head trauma patients is the common occurrence of skull fractures, surgical defects, edema, and subgaleal hematomas. These extracerebral factors can produce significant abnormalities and asymmetries in the EEG.

Management of Increased Intracranial Pressure

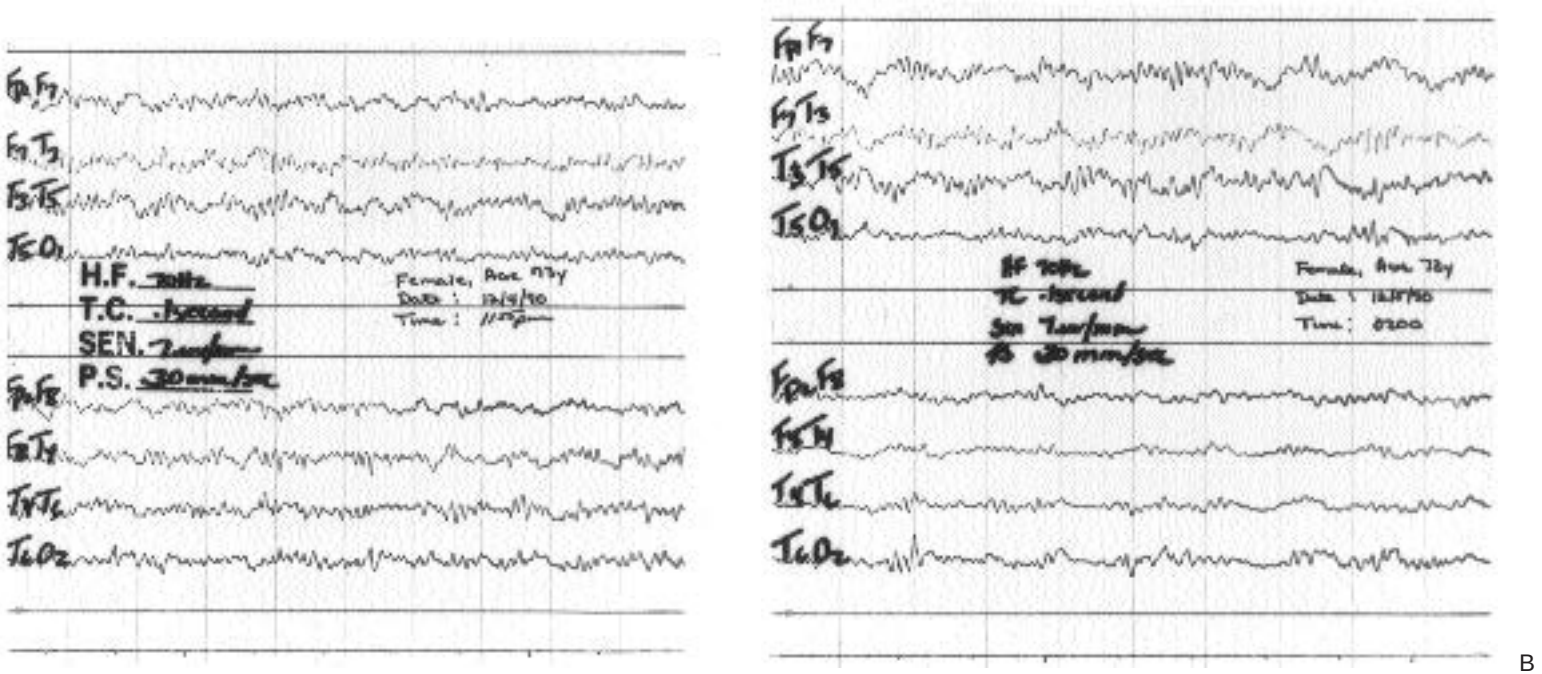
Current guidelines for the management of traumatic brain injury patients (18) suggest ICP monitoring for any patient whose CT scan shows compressed basal cisterns, midline shift, or multiple high- or low-density lesions. When increased ICP does not respond to conventional measures, high-dose barbiturate therapy is effective in lowering it (36). Pentobarbital has been the most widely used barbiturate for this purpose. Neither serum nor cerebrospinal fluid pentobarbital levels correlate with therapeutic efficacy or systemic toxicity (110). CEEG is the most reliable guide to barbiturate dosing, and most experts recommend achieving a burst-suppression pattern, because it correlates with maximal reductions in cerebral oxygen use (as estimated by the cerebral metabolic rate of oxygen [$CMRO_2$]). Increasing the barbiturate dose to induce electrocerebral silence does not diminish $CMRO_2$ further, but it does add to the risk of cardiovascular instability (61). If systemic hypotension complicates barbiturate use, the benefits of the treatment are negated and may be reversed (91).

Non-convulsive Status Epilepticus in Acute Severe Head Trauma

In a small study, Jordan (51), used CEEG to identify NCS in two (29%) of seven patients with head trauma. In a larger, prospective study, Vespa et al. (108) identified seizures in nine (16%) of 56 patients with acute severe head trauma, of whom seven (12.5% of total) had NCS or NCSE. Only one (11%) of the nine patients with seizures had a good outcome, in contrast to 21 (47%) of 45 of the patients without seizures. Bergsneider et al. (10) studied 13 head trauma patients with combined positron emission tomographic (PET) scanning and CEEG. Five of these (38%) showed NCS, and two (15% of the total) had NCSE. PET scans showed that both patients with NCSE had hyperglycolysis in the epileptogenic brain areas.

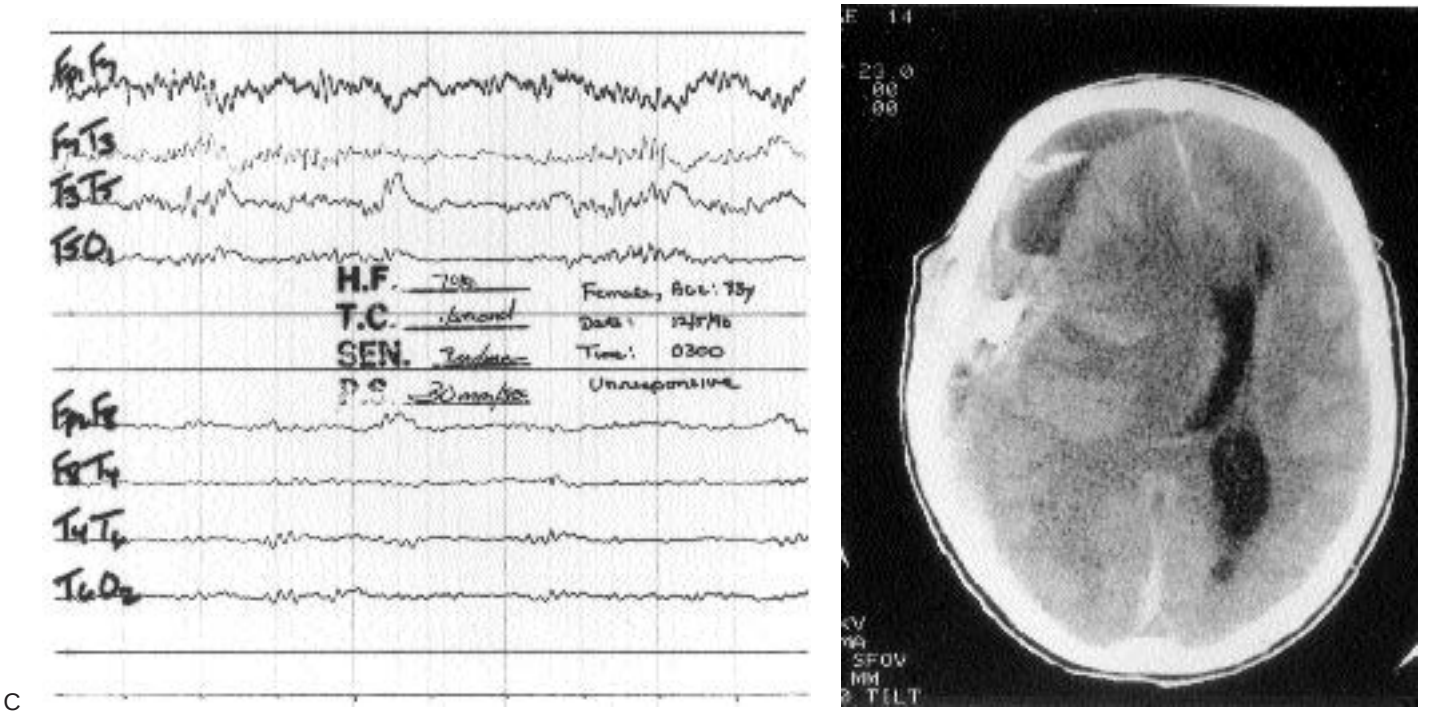
Armon and Dayes (4) reported NCSE as a complication of acute subdural hematoma. In three cases, the epileptic focus localized to cortex dis-

torted by fresh blood on imaging studies. NCSE was refractory in all patients; two patients required high-dose barbiturates. One patient died, and the two survivors required 65 and 89 days of hospitalization with subsequent custodial care. These observations may relate to an earlier report by Inglis et al. (47), who described glucose hypermetabolism in acute subdural hematoma. The hypermetabolism could be ameliorated by blocking excitatory amino acid receptors, which suggests that it was a manifestation of excitotoxic depolarization, a common substrate for epileptogenic activity. Supporting the observations of Armon and Dayes, Jordan observed a similar association between acute subdural hematoma and NCSE (personal observation). Of four patients with subdural hematoma, three became alert and interactive after surgical evacuation of the clot. The fourth was in NCSE preoperatively and never regained consciousness after surgery. Within the first two postoperative days, the three alert patients had simple partial seizures. Postoperative CT scans showed successful evacuation of clot with no new abnormalities. Nonetheless, the patients became progressively obtunded and CEEG confirmed NCSE in all three. Aggressive treatment was associated with complete neurological recovery in one patient and good recovery in the other two. These observations suggest the possibility that acute subdural hematoma may impart an excitotoxic vulnerability to status epilepticus and NCSE on the injured cortex.



A B

FIG. 25.20. Continuous EEG of a stuporous patient after drainage of right subdural hematoma. **A:** Diffuse spindle-like activity with underlying, continuous 2-Hz delta activity. **B:** Two hours later, right hemisphere activity decreases in amplitude, and left hemisphere delta becomes more prominent. (*Figure continues.*)



C D

FIG. 25.20. *Continued.* **C:** One hour after the recording in part *B,* the right hemisphere develops a very attenuated burst-suppression pattern. Left hemisphere delta activity is more prominent. **D:** Noncontrast computed tomographic scan taken after the recording in part *C.* There is a fresh hemorrhage below burr hole site with massive right hemisphere edema and transfacial herniation. (From Jordan KG. Continuous EEG and evoked potential monitoring in the neuroscience intensive care unit. *J Clin Neurophysiol* 1993;10:445.)

Detection of New or Increasing Intracranial Masses

Patients with traumatic brain injury may deteriorate as a result of new mass lesions unseen on the initial CT scan, or from rapid enlargement of lesions that initially appeared relatively innocent (23). After the evacuation of large intracranial hemorrhages, the decompression effect can lead to delayed enlargement of contralateral mass lesions. In addition, post-traumatic or postoperative systemic coagulopathies may cause hematomas to enlarge or reaccumulate. Although imaging studies are the best way to identify new or enlarging mass lesions, they require transport of patients out of the ICU. Patients with acute severe head trauma often have multi-organ trauma and cardiovascular instability, which increase the hazard of transport. CEEG can be considered a useful adjunctive tool for suggesting the presence of new or expanding mass lesions (Fig. 25.20), adding objective data to the decision of whether to transport the patient for brain imaging.

Potential Role of Continuous EEG in Traumatic Vasospasm and Therapeutic Hyperventilation

Studies have shown that posttraumatic vasospasm is more common than previously thought (72). CBF measurements have documented the occurrence of severe cerebral ischemia from posttraumatic vasospasm, including cerebral infarctions. Lee et al. (64) demonstrated a close association between posttraumatic vasospasm and poor outcome, which was independent of the admitting Glasgow Coma Scale score. They suggested that early identification of such patients could lead to corrective medical measures similar to those used for treating vasospasm due to subarachnoid hemorrhage vasospasm.

Hyperventilation to a $PaCO_2$ of 25 to 30 mm Hg has been advocated for increased ICP in trauma patients. However, one study suggested that lowering the $PaCO_2$ to about 25 mm Hg may be deleterious in comparison with a $PaCO_2$ in the range of the mid-30s mm Hg (75). Supporting data from CBF, TCD, and $CMRO_2$ studies have led to a consensus that, in severe head trauma, overly vigorous hyperventilation may produce ischemia in vulnerable brain regions (71). Current guidelines therefore no longer recommend hyperventilation as prophylactic therapy. The EEG changes produced by hyperventilation include generalized theta or delta slowing, activation of epileptogenic activity, and accentuation of focal slowing (29). Even moderate hypocapnia ($PaCO_2$ of 35 mm Hg) produces EEG slowing (44).

COST BENEFIT, COST EFFECTIVENESS, AND OUTCOME STUDIES OF CONTINUOUS EEG

Cost benefit and cost effectiveness are complicated and controversial subjects in health care. Their use as analytic tools to examine resource use in ICUs inevitably overlaps with issues of quality of care and medical ethics. In examining a particular variable, cost benefit can be considered as the benefits gained in dollar terms and cost effectiveness as the benefits gained in quality-adjusted life years (63). Therefore, if CEEG provides a *cost benefit* to an institution, the ratio of its setup and operational costs to the sum of the savings that it provides in health care expenditures, plus the monetary value of the increase in lives saved and lives lengthened, will be low. If CEEG is *cost effective,* the ratio of its costs to the sum of the number of lives it saves, years of lives saved, and quality of lives saved will be low.

Vespa et al. (106) calculated the "cost efficiency" for CEEG in the ICU in 100 patients with severe head trauma. They found significant cost effectiveness and cost benefit for CEEG. Its average cost was $560 per patient, which was 1% of the total hospital cost. Over the 4-year period of study, in which CEEG was part of the standard protocol, hospital costs per patient declined from $88,690 to $49,578, a 44% reduction. Median length of stay declined from 24.3 to 13.6 days, also a 44% reduction. The discharge Glasgow outcome score improved from a mean of 2 to a mean of 3 ($p < 0.01$). Despite the use of needle electrodes, no cases of scalp cellulitis or skin infection were detected. In summary, this study found that inclusion of CEEG in the ICU as standard protocol for management of trauma patients resulted in a cost savings of 44%, a reduction in length of stay by 44%, and relative improvement in outcome of patients by 50%. These preliminary data support the cost benefit and cost effectiveness of CEEG.

The costs of developing a CEEG program include those for personnel, training, continuing education of the monitoring team, purchasing and maintaining equipment, and establishing a computer network. Because CEEG personnel do not dedicate all their time to performing or interpreting CEEG, these costs need to be apportioned accordingly. We estimate that a modest but effective CEEG program can be established at an initial cost of $100,000 to $150,000. As discussed earlier in this chapter, CEEG can have a major impact on the clinical management decisions affecting ICU patients (see Table 25.2). In a retrospective and prospective study of 300 CEEG patients, Vespa et al. (106) found that CEEG was used daily in more than 90% of patients to guide one or more clinical decisions made at the bedside. The impact on care involved both physicians and nurses: nurses increasingly reported suspect EEG ischemia, changes caused by sedative and other drug administration, and EEG patterns contributing to early prognosis. Vespa et al. concluded that "the use of CEEG is cost effective and appears to offer additional quality to intensive care."

CEEG may also help clinicians tailor sedative doses more closely to patient needs, thereby improving efficiency, decreasing costs, and shortening duration of mechanical ventilation. Albrecht et al. (2) demonstrated the utility of a closed-loop control system for sedation that was based on the median frequency of the EEG power spectrum.

It is informative to compare benefit, effectiveness, and outcomes with and without the use of a monitoring device in matched populations. For example, according to historical controls, before electrocardiographic monitoring for acute myocardial infarction was introduced, costs were lower, but there was a significant loss in number of lives saved and in quality-adjusted life years in comparison to similar measures after its introduction. The use of

CEEG in NICU trauma patients improves outcomes, is cost effective, and cost beneficial (106).

Outcome studies examining the role of CEEG in GCSE, NCSE, acute ischemia, and coma remain to be done. The data from reports reviewed for this chapter provide evidence that the rates of morbidity and mortality of GCSE and NCSE can be positively influenced by its use. As the application of CEEG expands in other diagnostic areas, outcome studies should become feasible and informative. It is worth remembering, however, that for outcome studies to have validity and credibility, as Bleck (12) has emphasized, they must carefully define criteria for the competent use of monitoring devices, as well as the management to be followed on the basis of the data obtained. As emphasized earlier, the monitoring device itself has a limited effect on outcome; how the monitoring team extracts information from it and the subsequent clinical decisions and interventions will determine its impact on the patient's course.

SUMMARY

This chapter has placed the current state of CEEG in the ICU in its historical context, reviewed its scientific rationale, presented logistical and technical challenges in its use and implementation, and provided guidelines to meet these challenges. It described major sources of artifacts and methods to reduce them. It presented the rationale and the authors' paradigm for training and supervising ICU bedside nurses in CEEG. It also presented established, emerging, and potential benefits of CEEG emphasizing the clinical importance this monitoring technique brings to the bedside in a variety of NICU and emergency department situations. Increasing numbers of neurointensivists, electroencephalographers, and neurological colleagues are no longer content to rely on bedside examination alone to evaluate cerebral function in critically ill patients. They have thus begun to join with their colleagues in other critical care specialties who have long benefited from physiological monitoring to assess target organs at risk. Network technology and DEEG have made it easier to implement and oversee the use of CEEG in the ICU and emergency department. qEEG is finding a credible role in seizure detection and early identification of cerebral ischemia to complement DEEG. EEG in the emergency department is beginning to carve out a legitimate role in the pre-ICU management of patients with status epilepticus, ischemia, and coma.

Abundant supportive data indicate that in patients with status epilepticus, CEEG may be indispensable for timely and optimally effective management. In this context, it is close to becoming a standard of care. The high incidence of NCS and NCSE in acute brain injury, suggested by early studies, has been confirmed by more recent ones, particularly in patients with GCSE. Without CEEG, the recognition of NCSE is commonly delayed or missed, which likely contributes to the increased rates of morbidity and mortality of NCSE compared to GCSE. As a monitor of the effects of cerebral ischemia, the role of CEEG has expanded to include evaluation of post–subarachnoid hemorrhage vasospasm. CEEG may also be emerging as a valuable tool in focal ischemia. For comatose patients, CEEG can provide otherwise unobtainable prognostic and diagnostic information. Its role in trauma has expanded from monitoring high-dose barbiturate therapy to early detection of NCSE, targeting cerebral perfusion in increased ICP, and providing early detection of progressive mass effect.

One conclusion stands out: In patients with acute brain lesions, unexplained alteration of mental status requires rapid diagnosis and treatment to ensure the best possible outcome. In the clinical settings reviewed in this chapter, this requirement may be impeded without the availability, prompt use, and rapid interpretation of CEEG in the emergency department and NICU. We believe that the timely use of EEG in the emergency department and CEEG will help eliminate diagnostic ambiguity, accurately guide therapy, and prevent potentially harmful delays in treatment.

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Chapter 26

Sleep Disorders: Laboratory Evaluation

Rodney A. Radtke

Polysomnography: Technical Aspects
Electroencephalographic Sleep Recording
Anterior Tibialis Electromyography
Ventilatory Monitoring
Alternative/Screening Techniques
Polysomnography: Interpretation
Electroencephalography-Related Variables
Respiration-Related Variables
Movement-Related Variables
Multiple Sleep Latency Test (MSLT)
Multiple Sleep Latency Test Procedure
Multiple Sleep Latency Test Interpretation
Clinical Evaluation of Sleep Disorders
Evaluation of Excessive Daytime Sleepiness
Approach to Nocturnal Behavioral Events (Parasomnias)
Approach to the Patient with Insomnia
References

The rapid growth of sleep disorder medicine in the United States has led to an increasing role for clinical electroencephalographers in the evaluation of sleep and its disorders. However, most clinical neurophysiology training programs still do not incorporate the neurophysiological or clinical aspects of sleep disorders into their curricula. This chapter provides an introductory overview of the sleep laboratory evaluation of sleep disorders that is aimed at the practitioner or trainee in clinical electroencephalography (EEG).

The investigation of sleep and its disorders is a relatively new medical discipline; the greatest development has occurred since 1980. The use of prolonged EEG recording to investigate sleep was pioneered by Kleitman and culminated in his historic discovery (with Aserinsky) of rapid-eye-movement (REM) sleep in 1953 (6). In the 1960s, early investigations described sleep-onset REM periods in narcolepsy (83,102) and defined sleep apnea (39,58). Important progress in standardizing sleep investigation occurred in 1968 when a committee of sleep researchers published a manual for scoring sleep; this system, known by the editors' names, Rechtschaffen and Kales, became the accepted standard that is still used today (82). The Association of Sleep Disorder Centers (ASDA) was formed in 1976 to enhance patient care and standardize the practice of sleep disorders medicine. This group of clinical sleep specialists created an extensive classification system for the diagnosis of sleep and arousal disorders, which was initially published in 1979 (7) and then revised in 1990 (53). The ASDA (which later changed its name to the American Academy of Sleep Medicine) also spearheaded the development of a certification board in sleep medicine, which now functions as the free-standing American Board of Sleep Medicine.

Clinical investigation of sleep disorders relies primarily on two major techniques: the overnight polysomnogram (PSG) and the multiple sleep latency test (MSLT). The overnight PSG allows evaluation of nocturnal sleep and focuses primarily on identification and characterization of respiratory abnormalities in sleep. PSG is also useful in evaluation of movement disorders, parasomnias, and nocturnal sleep disruption. The MSLT offers (a) an objective assessment of daytime sleepiness and (b) a determination of possible early-onset REM sleep. These two study techniques serve as the gold standard of sleep evaluation and are reviewed in detail. A brief overview of the initial assessment of a patient with excessive daytime sleepiness, unusual nocturnal behavior, or insomnia is also presented.

POLYSOMNOGRAPHY: TECHNICAL ASPECTS

Overnight sleep studies are usually performed in a facility dedicated to sleep investigations. Most sleep laboratories have one or more bedrooms in which environmental noise, ambient temperature, lighting, and decor are controlled, thus facilitating the patient's sleep. The technologist and polygraphic equipment are located in a separate room, to minimize any disruption to the patient's sleep. An intercom is used to monitor and communicate with the patient as needed. Most laboratories also videotape the night's sleep so that behavioral or respiratory events that occur can be reviewed. Overnight sleep recordings can be obtained adequately with a standard EEG machine. However, polygraphs that provide several channels with direct current (DC) amplifiers and wider pen excursions offer improved quality of respiratory monitoring and allow simultaneous recording of oxygen saturation directly on the paper record.

The patient is scheduled to arrive for the nocturnal study 60 to 90 minutes before his or her usual bedtime. During electrode application, the technologist reviews the patient's history and offers an explanation of the study procedure. Medical information from the referring physician should be available at the time of the study to ensure that the correct procedure is performed, to assist in decision making during the study, and to complement the interpretation subsequently provided. The usual study duration is 6 to 8 hours, depending on the specific clinical problem. When the patient awakens in the morning, the technologist obtains the patient's impression of the night's sleep and how it may have varied from his or her usual night's rest. This information may be important in the clinical correlation of the sleep study results. Sleep studies are routinely scored by the sleep technologist. The sleep study tracing and scored data are then reviewed by a polysomnographer, who provides the interpretation and clinical correlation.

Digital EEG technology has proved to be an extremely useful tool for PSG studies. It has simplified the handling and storage of large amounts of neurophysiological data. The ability to expand the number of channels also allows a greater EEG sampling, which can then be reviewed at routine EEG paper speed (30 mm per second) to allow better assessment of a possible epileptic event, which can be very difficult to interpret when available only at 10 mm per second (38). The digitalization of the information certainly lends itself to computer analysis. At this time, however, manual scoring of sleep stages according to standard Rechtschaffen and Kales criteria (82) is still the standard, in view of the unreliability of most sleep staging programs (51). Improvement in computer-aided sleep scoring may make sleep study scoring a less laborious task in the future. Computer analysis also has a potential to go beyond the standard (and somewhat arbitrary) epoch-by-epoch scoring of sleep and capture information about the microstructure of sleep that may have important clinical or research implications.

Minimal polygraphic requirements to score sleep adequately include two channels of EEG: one channel for the electro-oculogram (EOG) and one channel for the submental electromyogram (EMG). In routine PSG, additional channels are used to assess respiration, leg movements, oxygenation, and cardiac rhythm. The following is a brief review of "standard" technology involved in PSG recordings. Other reviews of PSG technique may also be helpful to the reader (13,80).

Electroencephalographic Sleep Recording

As with routine EEG, nonpolarizable silver–silver chloride or gold electrodes are standard and are attached with collodion to maintain adequate contact for the 6 to 10 hours required for an overnight study. The International 10-20 System is used for electrode placement (55), but a much more limited EEG montage, described later, is selected. Early sleep investigators were limited by channel availability and could commit only one channel to EEG recording (central EEG lead to contralateral ear; e.g., C4-A1). As a result, the scoring manual of Rechtschaffen and Kales (82) is based on that single lead derivation. However, the poor sampling of waking alpha activity by this montage has led most investigators to add at least one additional channel (occipital lead to more anterior reference; e.g., 01-A2) for better separation of wakefulness from stage 1 (drowsiness). In addition, many laboratories commit at least two additional channels to EEG. A transverse vertex montage (e.g., T3-Cz, Cz-T4) is often preferred because it is sensitive to the identification of sleep spindles and vertex waves. Bilateral central, occipital, and ear electrodes are routinely placed so that in the event of electrode failure, the

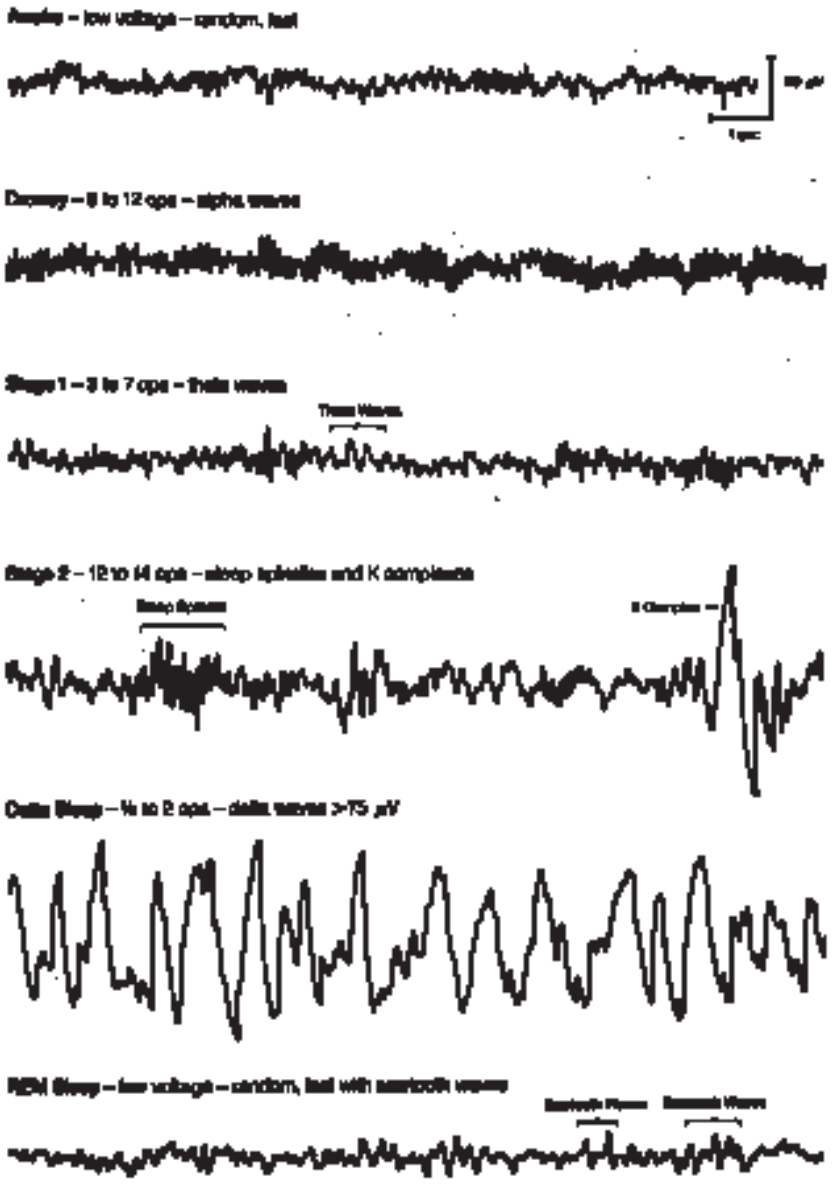

FIG. 26.1. EEG activity characteristic for each of the major sleep stages. The activity is recorded from the usual sleep study derivation (C4-A1) at a paper speed of 10 mm per second. *Delta sleep* is an alternative name for slow-wave sleep. (From Hauri P. *The sleep disorders.* Kalamazoo, MI: Upjohn Co., 1982:5–62.)

homologous contralateral derivation can be used without disturbing the patient. Occasional patients, such as those with possible nocturnal seizures, require a more extensive EEG montage for adequate assessment.

Routine recording or display speed for the PSG is 10 mm per second (82). This is initially disconcerting to the electroencephalographer trained in using a paper speed of 30 mm per second. The slower paper speed was chosen to reduce paper use and to improve visualization of events (e.g., apneas) that occur over a relatively long time. Slow paper speeds still allow clear visualization of alpha rhythm and sleep spindles. In fact, the characteristic appearance of sleep spindles, "sawtooth" waves, and eye movements is more easily recognized at slower paper speeds once the interpreter has adjusted to the altered appearance (Fig. 26.1). The EEG low-frequency filter (LFF) setting is 0.3 Hz, and the high-frequency filter (HFF) setting is 70 Hz. The extended low-frequency band is important for assessing the prominent slow-wave activity seen during deeper stages of non-REM sleep. The amplifier sensitivity setting is usually 5 to 10 μV per millimeter; 7 μV per millimeter is used most commonly. Because voltage of the delta range activity is important in determining sleep stage, any change in EEG channel sensitivity must be clearly flagged to avoid sleep scoring errors.

Electro-oculogram

The EOG is obtained primarily to identify phasic bursts of rapid eye movements, which are the cardinal sign of REM sleep. In addition, these electrodes allow identification of slow lateral eye movements, which are often the first and most dependable manifestation of drowsiness (92). Gold-plated or silver–silver chloride EEG cup electrodes are used to record the EOG, but collodion should be avoided because of possible corneal injury. EEG electrolyte paste with additional sticky tape over the electrodes offers adequate attachment and avoids the risk of eye injury. Two different electrode montages can be used to monitor eye movements. Most commonly (and as recommended in Rechtschaffen and Kales' manual [82]), a referential recording is made from an electrode 1 cm lateral and 1 cm superior to the outer canthus and referred to the ipsilateral ear. A second channel records activity from a location 1 cm lateral and 1 cm inferior to the contralateral outer canthus and referred to the ipsilateral ear. This two-channel derivation shows eye movements as out-of-phase potentials, thus increasing the interpreter's confidence in correctly identifying REMs (Figs. 26.2 and 26.3). Alternatively, eye movements may be recorded from a single bipolar linkage between two electrodes placed near each outer canthus, as described earlier. The advantage of this derivation is that (a) the conjugate eye movements have twice the potential and (b) the EOG

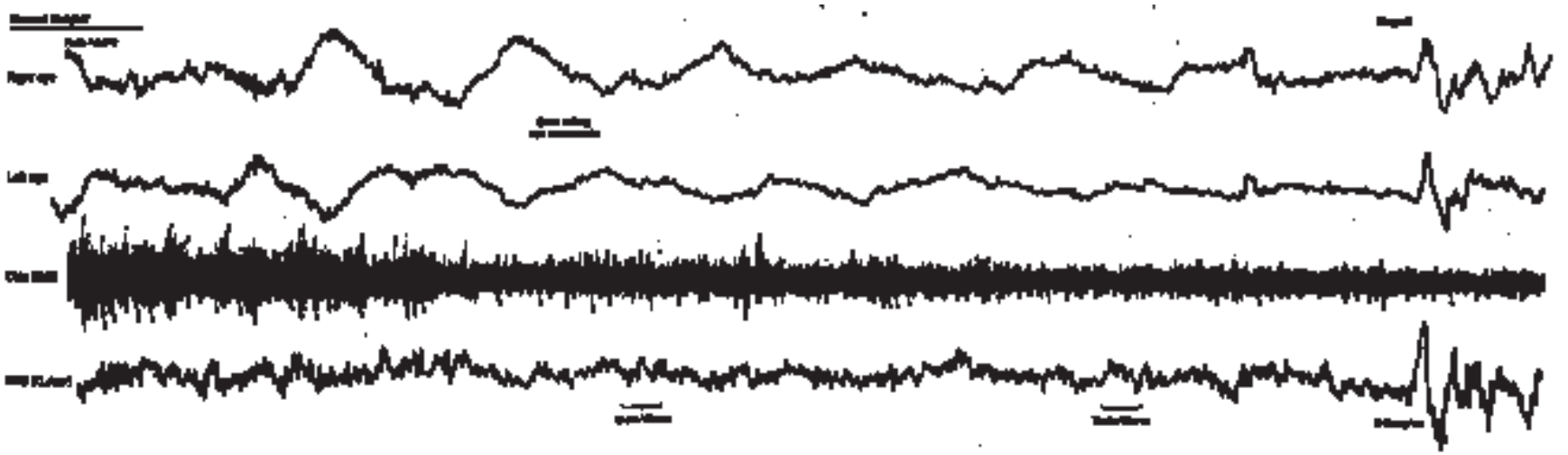

FIG. 26.2. Slow eye movement. Note the slow, rolling eye movements appearing as out-of-phase activity in electro-oculographic (EOG) channels. Slow eye movements accompany the appearance of mixed-frequency theta activity typical for stage 1 sleep. The K complex near the end of the epoch denotes onset of stage 2. The K complex appears as in-phase activity in EOG channels, which reflects its cerebral origin. (From Rechtschaffen A, Kales A, eds. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.)

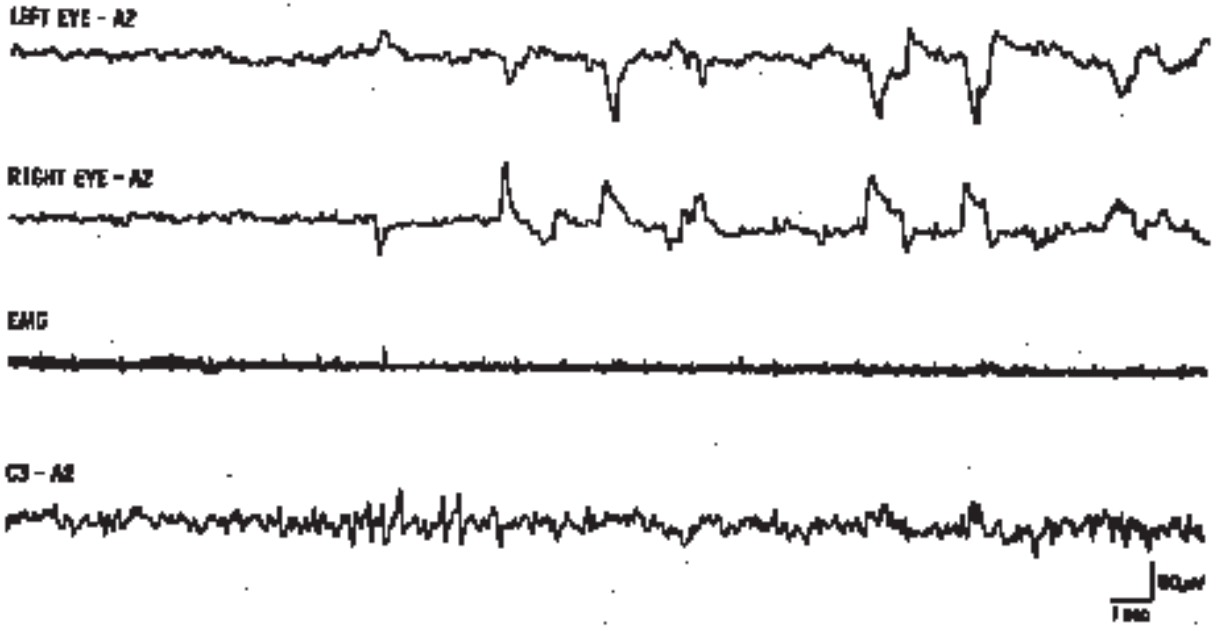

FIG. 26.3. Unambiguous rapid eye movement (REM) sleep with relatively low-voltage, mixed-frequency electroencephalogram, REMs, and tonic electromyogram at lowest level during sleep. Note series of typical "sawtooth waves" at onset of REM activity. (From Rechtschaffen A, Kales A, eds. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.)

occupies only a single polygraph channel. Absence of a phase reversal complicates visual identification of eye movements. Sensitivity and filter settings for the EOG are similar to those used for EEG recording.

There is no standard definition of what constitutes a rapid eye movement as opposed to a slow one. Slow eye movements have a frequency of 0.25 to 0.5 Hz, and the sharpest slope has a duration consistently greater than 0.5 seconds. In comparison, REM waveforms have a sharp slope lasting 50 to 200 milliseconds and a waveform frequency of greater than 1 Hz. Obviously, the rate of return to baseline of any EOG waveform is dependent on the alternating current (AC) filter setting and the superimposition of any additional eye movements. Thus, the abrupt slope of the EOG waveform is the most reliable differentiating feature. A reasonable cutoff is the requirement that the rapid slope of a rapid eye movement be shorter than 300 milliseconds in duration and have an amplitude of at least 20 μV.

Axial Electromyogram

Submental (chin) EMG activity reflects axial muscle tone and is used as one criterion for identifying REM sleep and movement arousals. Submental EMG is recorded by regular EEG electrodes placed over the mylohyoid muscle. One electrode is placed on the tip of the jaw, and the second electrode is placed 3 cm posterior and lateral. This second electrode should be placed bilaterally, functioning as a backup electrode from which to select the most reliable EMG recording.

Tonic EMG activity from axial musculature gradually decreases from wakefulness through stages 1 to 4 of sleep and is usually entirely absent during REM sleep. Sensitivity of the submental EEG channel should be adjusted during drowsiness to reflect moderate activity. Subsequent adjustments should be avoided during the night to permit comparison of EMG activity during different portions of the record. The typical sensitivity setting of the EMG is 2 μV per millimeter, the LFF setting is 5 Hz, and the HFF setting is 70 Hz.

Anterior Tibialis Electromyography

Anterior tibialis EMG activity is monitored to detect periodic leg movements (30,31). Regular EEG electrodes are placed over the anterior tibialis muscle bilaterally. The anterior tibialis muscle can be easily identified on the anterior lower leg by having the patient dorsiflex the foot against resistance. Two electrodes 3 cm apart are placed over each anterior tibialis muscle. A bipolar recording from each anterior tibialis muscle is usually obtained. Sensitivity and filter settings are similar to those described for submental EMG recording. A semistandardized baseline is obtained before the study by asking the patient to dorsiflex a foot gently. Figure 26.4 is an example of periodic leg movements (PLMs) of sleep recorded from the anterior tibialis EMG electrodes.

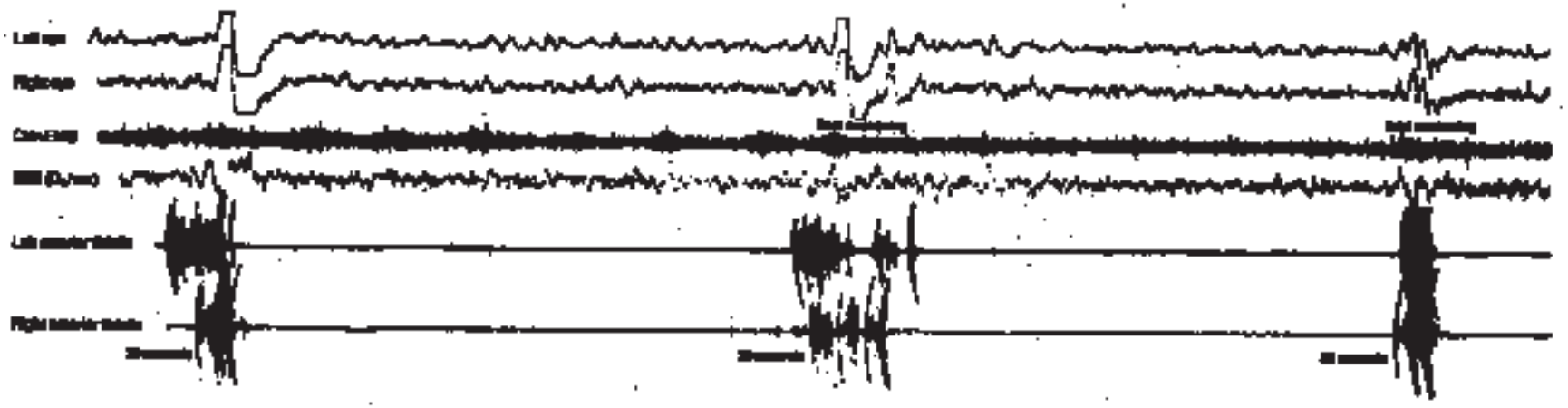

FIG. 26.4. Periodic leg movements (PLMs) of sleep. The anterior tibialis electromyographic (EMG) recording demonstrates bursts of periodic EMG activity associated with electroencephalographic arousals. (From Hauri P. *The sleep disorders.* Kalamazoo, MI: Upjohn Co., 1982:5–62.)

Ventilatory Monitoring

Inasmuch as the suspicion of sleep apnea is the most common indication for overnight PSG, ventilatory monitoring is arguably the most important technical aspect. Although measurements of airflow and ventilatory effort are technically the most difficult of all polygraphic variables to obtain, they are essential for adequate assessment of breathing during sleep. Both airflow and a measure of ventilatory effort must be recorded in order to distinguish among central, mixed, and obstructive apneic events (Fig. 26.5). In central (or nonobstructive) apnea, absence of respiratory drive causes all mechanical efforts to cease, and no airflow occurs at the nose or mouth. In obstructive apnea, ventilatory efforts continue but no airflow occurs; this is because the airway is occluded. A mixed apnea begins as a central apnea (without ventilatory effort or airflow), but then the picture of obstructive apnea develops (ventilatory effort without accompanying airflow). Apneas are arbitrarily defined as cessation of airflow for 10 seconds or longer (1,12). In addition, hypopneas (decreased airflow) may also be clinically significant. Specific scoring criteria for respiratory events are discussed in the section on polysomnographic interpretation.

For all measures of airflow or ventilatory effort, an LFF setting of 0.5 Hz is used. DC amplification is preferred; it is routinely used if a dedicated polygraph machine is available. However, adequate respiratory monitoring is possible with routine EEG AC amplifiers if the lowest LFF available is selected. Polygraph machines have a greater pen excursion, which also aids in assessment of respiratory parameters.

Airflow Monitoring

Thermistors and Thermocouples

Thermistors or thermocouples are the least expensive and most commonly used method of monitoring airflow (1,12,13). Thermistors are small glass beads or wires whose electrical resistance changes as a function of temperature. When they are powered by a 1.5-V battery, the voltage drop across the thermistor varies with temperature. Expired air warms the thermistor and pro-

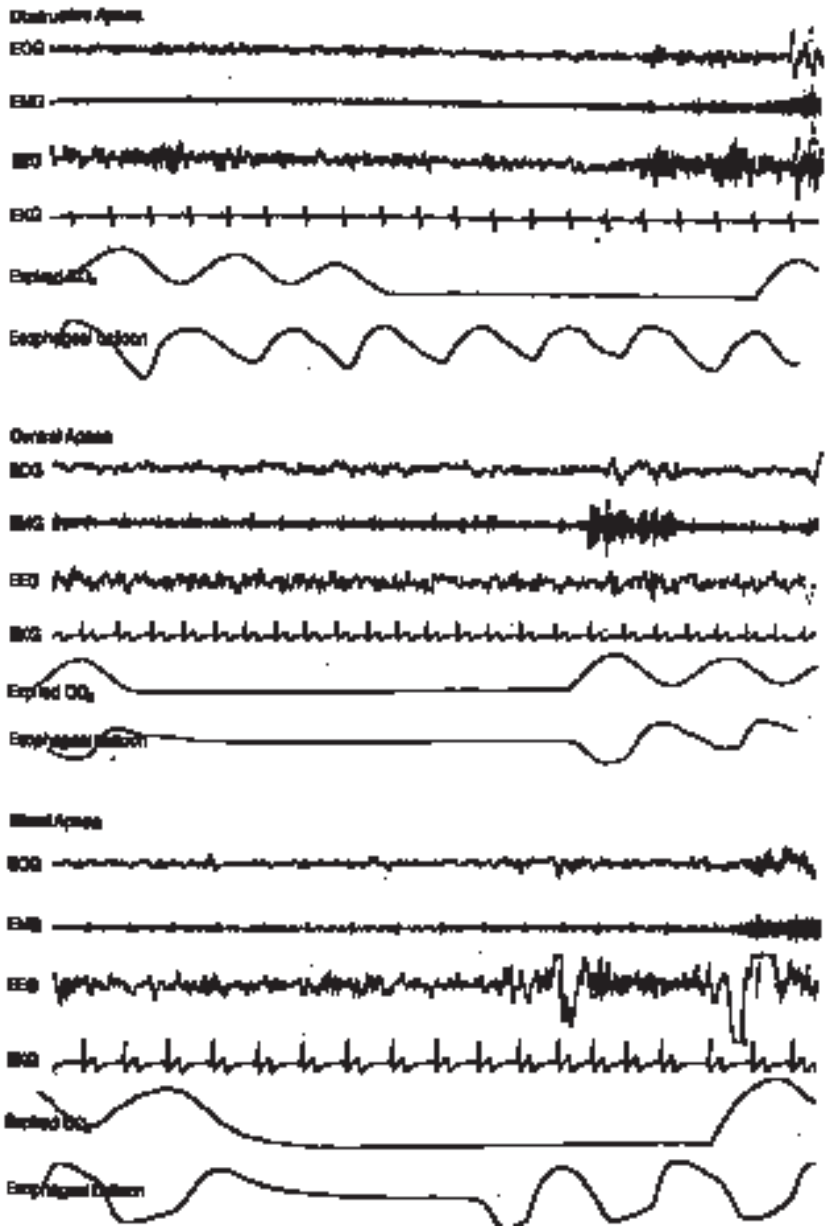

FIG. 26.5. Examples of obstructive, central, and mixed apneas. Compare airflow (measured by CO_2 analysis) and ventilatory effort (measured by intraesophageal balloon). (From Hauri P. *The sleep disorders.* Kalamazoo, MI: Upjohn Co., 1982:5–62.)

duces a signal that can be displayed on a polygraph. A thermocouple consists of two dissimilar metals in electrical contact, which produces a low-voltage signal that varies with the temperature change caused by expired air.

Small, lightweight thermistors (or thermocouples) are taped, under each nostril and in front of the mouth. It is crucial to monitor both nostrils because the airflow path frequently changes during the night as a function of patient position. Activity from the two nasal thermistors can be summed and displayed in a single channel. Patient movement may disturb the position of the thermistors and result in loss of signal. Thus, careful attention needs to be paid to thermistor position throughout the night.

Carbon Dioxide Detectors

Measuring the carbon dioxide (CO_2) of expired air can serve as an alternative method of monitoring airflow (1,76). It is based on the principle that 6% to 7% of exhaled air is CO_2, whereas inhaled air contains negligible amounts of CO_2. In order to sample CO_2 content, a cannula is inserted just inside the nostril and is connected to an infrared or mass spectroscopy analyzer. For routine clinical PSG, the small increase in sensitivity for detecting air movement by using CO_2 detectors does not usually warrant the added expense and technical demands. However, end-tidal carbon dioxide tension (PCO_2) monitoring is an essential component of assessing sleep-disordered breathing in children. The clinical importance of PCO_2 monitoring in pediatric sleep apnea has led to its wide application in pediatric sleep laboratories. Because of the technical difficulties in maintaining adequate end-tidal PCO_2 measurement, transcutaneous CO_2 may be used to complement the end-tidal PCO_2 measurement (76).

Nasal Cannula/Pressure Transducer

Reports have described the successful application of a simple, noninvasive pneumotachygraph consisting of a standard nasal cannula connected to a 2-cm water pressure transducer (52,75,77). These initial reports identified sensitivity to airflow changes comparable with that of thermistor/thermocouples (in identifying hypopneas) and greater sensitivity in recognizing additional events (characterized only by flow limitations) that may be helpful in identifying the respiration-related arousals that are a significant part of the upper airway resistance syndrome (45) (Fig. 26.6). Commercial products are now available, and their use is becoming more widespread. Greater experience is necessary to determine how readily the apparent benefits of this technology can be extended to routine PSG.

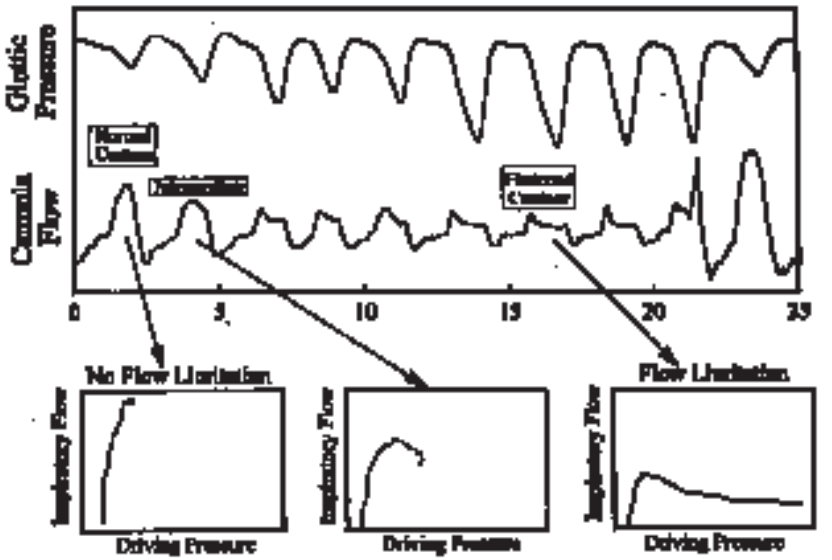

FIG. 26.6. Pressure/flow relationships from nasal cannula/pressure transducer during a single respiratory event. The x-axis shows time in seconds. Breaths with normal, intermediate, and flattened flow contours are labeled, and a plot of the driving pressure/flow relationship is shown. The flattened flow/time contour shows a nonlinear flow/pressure relationship characteristic of flow limitation. (From Hosselet JJ, Norman RG, Ayappa T, et al. Detection of flow limitations with a nasal cannula/pressure transducer system. *Am J Respir Crit Care Med* 1998;157:1461–1467.)

Pneumotachography

Pneumotachography is the only method that allows direct quantification of ventilation during sleep. However, the technique involves an uncomfortable tight-fitting mask and a flow-to-pressure transducer that offers considerable resistance to respiration. Although it is technically superior to the other methods of monitoring airflow, the sleep disruption and increased respiratory resistance preclude the routine use of pneumotachography in PSG (101).

Ventilatory Effort Monitoring

Esophageal Pressure Monitors. An esophageal pressure monitor can be either a catheter-tip or balloon transducer that is placed through the nose into the distal esophagus (72). The output signal of the pressure/voltage transducer shows absolute pressure (with a DC amplifier) or variations in pressure (with

an AC amplifier) on the polygraphic record. Esophageal pressure monitors measure pleural pressure swings and are the most accurate devices for assessing ventilatory effort. However, because of their invasive placement and the inability of many patients to tolerate them, esophageal monitors are less than ideal for routine PSG. Nonetheless, in difficult cases, intraesophageal pressure measurement can accurately resolve ambiguities as to the nature of the apnea.

Piezoelectric Belts. This device incorporates a piezo crystal element transducer in an elastic belt. When stretched, the piezo crystal element provides a voltage signal proportional to the stress applied. It requires no power and connects simply to the electrode board or input cable. It incorporates good sensitivity to ventilatory effort with simple and reliable technical application.

Impedence Pneumography. When a high-frequency electrical signal is applied to the chest wall through two electrodes, the electrical impedance between the two electrodes varies, depending on the position of the chest wall. In practice, an AC carrier signal is applied directly to the chest (or abdominal) wall. The voltage drop across the body wall varies with chest wall movement and modulates the amplitude of the carrier signal. A demodulator system then converts the signal variation into a form that can be displayed on a standard AC or DC polygraph channel.

Impedance pneumography has proved to be a reasonable technique for qualitatively monitoring ventilatory effort (78). The simplicity of the commercially available devices and the stability of this method are significant advantages. The two input electrodes are placed over the point of greatest excursion of the chest wall or abdomen. As with strain gauges, placement on both chest and abdomen increases sensitivity to ventilatory effort and makes identification of paradoxical respirations possible (Fig. 26.7).

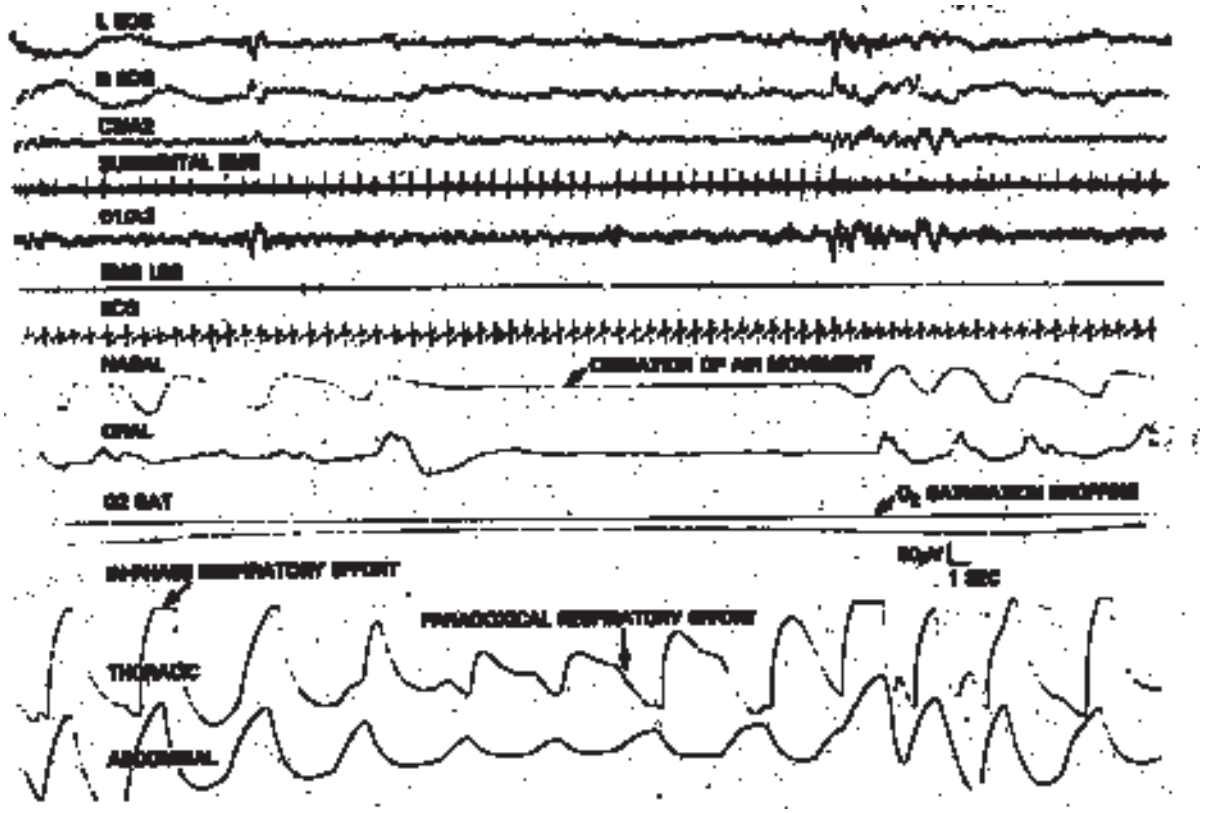

FIG. 26.7. Obstructive apnea. Note the development of out-of-phase or paradoxical movement of thoracic and abdominal monitors during period of obstructive apnea. (From Mendelson WB. *Human sleep.* New York: Plenum Press, 1987:159.)

Inductive Plethysmography. In inductive plethysmography, a conductive wire is sewn into an elastic band or mesh that encircles the chest or abdomen. With expansion of the body wall, the circle of wire enlarges and the inductance of the loop is changed. When an AC current is applied to this wire, the variable inductance can be displayed on an AC or DC polygraph channel. This technique is much more powerful than the methods already described, inasmuch as it provides a quantitative measure of airflow. This method also permits more accurate determination of lung expansion, regardless of patient position (16,27). The instrument is carefully calibrated so that the sum of the chest and abdominal signals is proportional to the volume of airflow. If the airway is obstructed, no air is exchanged; any change in chest volume is associated with an opposite change in abdominal volume (paradoxical respiration), and the sum of the two is zero (representing no airflow). Theoretically, complete ventilatory monitoring can be accomplished with two bands around the chest. The three output channels are rib-cage movement, abdominal movement, and total volume. Obstructive apneas are recorded as continued respiratory movement of both thorax and abdomen but with no significant change in total volume signal (Fig. 26.8). In central apneas, all three signals are suppressed. Mixed apneas, as expected, show a central pattern followed by an obstructive picture. Hypopneas may also be quantified by this technique. Theoretically, an independent measure of airflow (thermistor) is unnecessary. However, because of difficulties in calibration (especially in obese patients) and slippage of coils, this technique usually requires an additional monitor of airflow. Although it increases cost and is more technically demanding, inductive plethysmography offers significant advantages over other methods.

Strain Gauge. Strain gauges are among the most convenient methods of qualitatively recording respiratory effort. Most strain gauges consist of a distensible tube filled with mercury. The electrical resistance of the mercury column varies directly with its length and inversely with its cross-sectional area. The strain gauge tube is strapped to the chest or abdominal wall in the area identified as having the greatest expansion with inspiration, and it is then connected to a battery. Each inspiration stretches the tube, decreasing its diameter and increasing its resistance. The voltage change across this varying resistance can be displayed on the polygraph record. Separate strain gauges should be placed over both the thoracic and abdominal walls. This provides a more sensitive measure of inspiratory effort and also helps identify paradoxical ventilatory effort (e.g., increase in thoracic circumference with decrease in abdominal circumference) seen with obstructive apnea (96). Although convenient and inexpensive, strain gauges depend greatly on stable positioning and are sensitive to artifact created by even small amounts of patient movement.

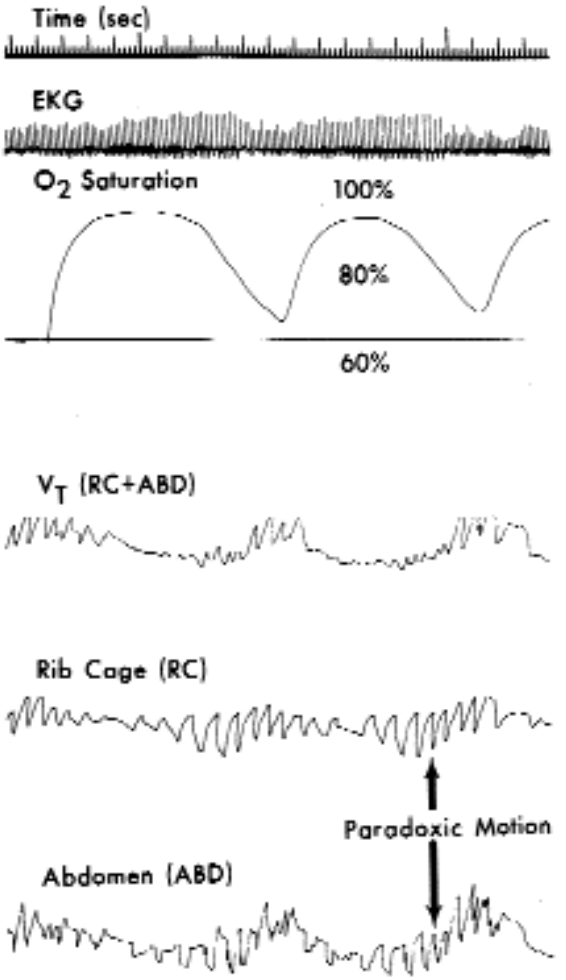

FIG. 26.8. Inductive plethysmography demonstrating paradoxical motion of ribcage and abdominal signals along with absence of significant volume signal (V_T[RC + ABD]), indicating decreased or absent airflow. Note accompanying oxygen desaturation. (From Cohn M. Respiratory monitoring during sleep: respiratory inductive plethysmography. In: Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques.* Menlo Park, CA: Addison-Wesley, 1982:213–223.)

Intercostal Electromyography. Intercostal EMG can be recorded by surface electrodes placed over the intercostal space. This technique identifies thoracic ventilatory movements, but it is frequently inadequate in obese patients. Thus, although sometimes useful as a complementary technique, intercostal EMG alone is not an adequate index of ventilatory effort.

Arterial Oxygen Assessment

Determination of arterial oxygen desaturation is an important adjunct in assessing the severity of apneic episodes (23,34,100). Finger pulse oximetry is the technique that is most commonly used. It measures oxygen saturation by light transmission through the fingernail bed. Oxygen saturation (SaO_2) values obtained from pulse oximetry are continuously recorded, usually through a DC polygraphic channel. The accuracy of pulse oximetry is compromised by the presence of carbon monoxide, hyperbilirubinemia, oxygen saturations of less than 50%, dark skin pigmentation, or significant hypotension. It is important to note that the change in SaO_2 associated with a respiratory event appears 20 to 40 seconds after the actual event. Incorporated in the delay is partial circulation time to the finger and machine measurement delay.

Electrocardiogram

The ECG is monitored during sleep studies to detect arrhythmias that may be associated with sleep-disordered breathing events. Documentation of an associated cardiac arrhythmia can affect treatment decisions in a patient with sleep apnea. In PSG, the ECG is usually derived from two electrodes placed over the anterior chest wall. This placement avoids much of the movement artifact seen with the use of limb leads alone. It is adequate for monitoring heart rate, extrasystoles, and other arrhythmias. However, the differences in recording display, along with the limited derivation, do not allow adequate assessment of P wave and QRS abnormalities. If the precise rhythm disturbance cannot be determined from the PSG alone, then independent evaluation with a Holter monitor or another dedicated ECG recording device is required. The routine LFF setting for ECG is 1 Hz, and the routine HFF setting is 70 Hz; the sensitivity setting is approximately 50 μV per millimeter.

Nocturnal Penile Tumescence

Nocturnal penile tumescence is frequently measured to help differentiate organic from psychogenic causes of impotence. Normal REM sleep-related erections usually persist in the presence of psychogenic causes but are absent with organic causes. Strain gauges are placed on the penis, one at the base and the other just below the glans. Several sizes are commercially available and are selected to fit snugly on the flaccid penis. These devices are very similar to the strain gauges described for monitoring ventilatory effort. Before the study, amplifier signals are carefully calibrated, and the output of each strain gauge is recorded on a DC polygraph channel.

In addition to measuring tumescence, nocturnal penile tumescence studies also record EEG, EOG, and submental EMG. It is important to evaluate sleep continuity and architecture to ensure the validity of the REM-related tumescence observations. Nocturnal penile tumescence studies also include some evaluation of penile rigidity. Karacan (63) gave a description of nocturnal penile tumescence techniques and their clinical interpretation.

Recording Montage

PSG montages are selected in accordance with the clinical question. For screening studies of patients with possible sleep apnea, PSG variables should include EEG, EOG, axial EMG, anterior tibialis EMG, airflow, ventilatory effort, and SaO_2. A representative montage for a 16-channel machine is given in Table 26.1. If there is a more specific clinical question, the montage can be adjusted accordingly. For example, if the primary con-

TABLE 26.1. Screening polysomnographic montage

Channel	Sensitivity (μV/mm)	Filters (LFF/HFF) (Hz)
1. C4-A1	7	0.3/70
2. O1-A2	7	0.3/70
3. T3-Cz	7	0.3/70
4. Cz-T4	7	0.3/70
5. Left outer canthus-A1	7	0.3/70
6. Right outer canthus-A2	7	0.3/70
7. Submental electromyogram (EMG)	2	5/70
8. Electrocardiogram	70	1/70
9. Left anterior tibialis EMG	3–7	5/70
10. Right anterior tibialis EMG	3–7	5/70
11. Snore monitor		
12. Nasal thermistor	—	0.1/15
13. Oral thermistor	—	0.1/15
14. Thoracic movement	—	0.1/15
15. Abdominal movement	—	0.1/15
16. Sao_2 (oximetry)	—	DC/70

HFF, high-frequency filter; LFF, low-frequency filter; Sao_2, oxygen saturation.

cern is involuntary motor activity during sleep, arm and leg EMG monitors can be added. For patients with possible seizures, additional EEG channels are needed (38). The newer digital machines with expanded channel capabilities (e.g., 32 channels) allow greater flexibility in recording all physiological variables and a choice of variables on which to focus in review. In general, assessment for nocturnal seizures is best performed with dedicated video-EEG monitoring designed for recording seizures. If sleep laboratory equipment is used for such a purpose, additional channels of EEG accompanied by simultaneous time-locked video are required and should be able to be reviewed at a 30-mm-per-second display.

Alternatives/Screening Techniques

The laboratory PSG represents the gold standard for the evaluation of patients with sleep disorders. Because of its cost, cumbersome nature, and limited access, alternative approaches have been presented in the literature. Daytime nap studies have been shown to be inappropriate for most noninfant patients. Nap studies have the potential to disrupt sleep or produce an erroneous estimation of apnea severity (4,40).

Nocturnal oximetry has been proposed as a screening tool for patients in whom sleep apnea is suspected. Obviously, this may totally miss the upper airway resistance syndrome or brief apneas without significant oxygen desaturation. In one large study, the sensitivity of nocturnal oximetry was 90%, and specificity was 75% (111). The researchers concluded that, even when used by the most experienced clinicians, nocturnal oximetry has significant limitations that preclude its routine use as a screening tool at this time. In addition, it is totally inadequate in evaluating any other cause of excessive daytime sleepiness (EDS), such as narcolepsy or periodic movements (80,100).

Ambulatory recording of EEG or other physiological recorders have been used extensively in evaluation of patients with EDS (81). Most techniques suffer from limitation of data acquisition (fail to record either adequate EEG or respiratory data), which precludes routine application. Those that do provide comparable physiological sampling to attended PSG still retain some technical limitations and have only minor cost savings. In 1994, the Standards of Practice Committee of the ASDA published practice parameters for the use of portable recording of obstructive sleep apnea (97). The consensus presented is that portable recordings currently have a very limited role (e.g., follow-up studies after diagnosis established with in-laboratory studies). With further technological advances and cost reduction, ambulatory PSG may assume an increasing role but will require careful validation studies.

POLYSOMNOGRAPHY: INTERPRETATION

The clinical interpretation of polysomnographic sleep studies is based primarily on the analysis of three main variables: EEG-related variables (i.e., sleep stage, arousals), respiration-related variables (i.e., apneas or hypopneas), and movement-related variables (i.e., periodic leg movements). This discussion focuses on the guidelines for the scoring of these variables and the subsequent assignment of clinical significance. Both of these areas continue to evolve, and any statement may be outdated within a few years. Because of inconsistency in technique and variability in interpretative guidelines (i.e., criteria for hypopnea [41,108]), it is difficult to compare sleep study results across laboratories (1,5). However, there has been progress (i.e., definition of arousals [11]) that makes sleep scoring today more of a science than it was as practiced during the 1980s.

In contrast, because of the large amount of data demonstrating the presence of apneic or movement events in asymptomatic persons, the assignment of clinical significance today is even more problematic than it was years ago (9,10,19,66,68,112). Previously, a study result was considered abnormal and diagnostic of sleep apnea if the patient had more than five apneic episodes per hour of sleep (46). Today, an apnea index of 5 to 10, particularly in an older patient, is probably best considered normal. The exact limit for attaching clinical significance remains unclear. Guidelines in this area that are based on the author's own standard of practice are provided here, but with the understanding that other experienced practitioners may have different opinions and that these standards are continually evolving.

Electroencephalography-Related Variables

Basic Sleep Scoring

Normal sleep has a clearly defined architecture that is relatively stable from childhood through senescence (86). Sleep onset begins with a transition from wakefulness to stage 1. Stage 1 is normally brief and is followed by stage 2. Slow-wave sleep comes next and is usually sustained, especially in children and young adults. Sleep then briefly lightens to stage 2 before an initial brief REM period. This REM period occurs approximately 90 minute after sleep onset and completes the first sleep cycle. This complete cycle is then repeated three to five times during the night, but the amount of slow-wave sleep diminishes during ensuing cycles, whereas the amount of REM increases. Histograms are useful for visually displaying the ultradian cycle within a night's sleep (Fig. 26.9) (61). Predictable changes in sleep architecture occur with age. Beginning in middle age, slow-wave sleep becomes less prominent, the number of awakenings increase, and sleep efficiency decreases (109). Published information on

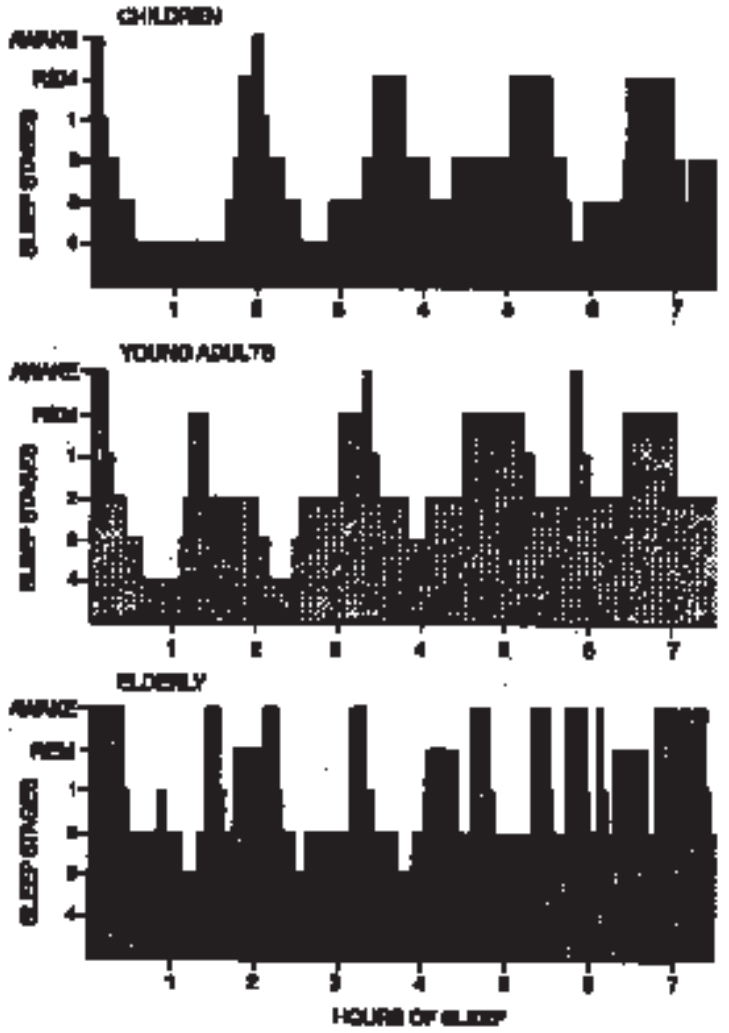

FIG. 26.9. Histograms representing normal sleep cycles for age. Rapid-eye-movement (REM) sleep (darkened area) occurs cyclically throughout the night at intervals of approximately 90 minutes. REM sleep shows little variation in the different age groups, whereas stages 3 and 4 sleep can be seen to decrease with age. Note also the frequent awakenings and increase in total awake time seen in the elderly. (From Kales A, Kales J. Recent findings in the diagnosis and treatment of disturbed sleep. *N Engl J Med* 1974;209:487–499.)

TABLE 26.2. *Average values for men of different ages*

	Age (years)		
Index	20–29	40–49	60–69
Time in bed (TIB) (min)	442	429	451
Total sleep time (TST) (min)	419	389	407
Sleep efficiency (TST/TIB)	95%	91%	90%
Wake (after sleep onset)	1%	6%	8%
Stage 1	4%	8%	10%
Stage 2	46%	55%	57%
SWS	21%	8%	2%
REM sleep	28%	23%	23%
Sleep latency (min)	15	10	8

REM, rapid eye movement; SWS, slow-wave sleep.

(From Williams RI, Karacan I, Hursch CJ. *Electroencephalography (EEG) of human sleep: clinical applications.* New York: John Wiley and Sons, 1974.)

normal sleep can serve as an outline for normal values in PSG (Table 26.2), but each laboratory must study control subjects to identify any significant effects on sleep that result from differences in technique or environment.

Scoring is usually done on an epoch-by-epoch basis, with epoch lengths varying from 20 to 60 seconds. Thirty-second epochs are used as a standard by most laboratories. Epochs are scored according to the guidelines of Rechtschaffen and Kales (82); each epoch is scored as the stage that occupies more than 50% of that epoch (see Fig. 26.1). The following is an abbreviated summary of sleep scoring:

Stage W corresponds to the waking stage and is characterized by alpha activity or low-voltage, mixed-frequency EEG activity. REMs, eye blinks, and tonic EMG activity are usually present.

Stage 1 is scored when more than 50% of an epoch is low-voltage, 2- to 7-Hz activity. Vertex waves may occur in late stage 1. Slow rolling eye movements lasting several seconds are routinely seen early in stage 1, but K complexes and sleep spindles are absent by definition. Tonic EMG activity is usually less than that of relaxed wakefulness.

Stage 2 requires the presence of sleep spindles or K complexes, and less than 20% of the epoch contains delta activity. Sleep spindles bursts must last at least 0.5 second before they can be scored. K complexes are defined as biphasic vertex sharp waves with a total duration of greater than 0.5 second.

Stage 3 is scored when 20% to 50% of an epoch consists of delta activity that is 2 Hz or slower and is greater than 75 μV in amplitude. Sleep spindles may or may not be present.

Stage 4 is scored when more than 50% of an epoch consists of delta activity that is 2 Hz or slower and is more than 75 μV in amplitude. Reliable differentiation of stages 3 and 4 sleep is difficult by visual inspection, and most laboratories combine stages 3 and 4 into a single determination of slow-wave sleep.

Stage REM is characterized by relatively low-voltage, mixed-frequency EEG activity with episodic REMs and absent or markedly reduced axial EMG activity. Phasic EMG activity may occur, but tonic activity must be at a level that is as low as, or lower than, that during any other time in the study. Sleep spindles and K complexes are absent. Series of 2- to 5-Hz vertex-negative "sawtooth waves" occur, particularly just before phasic REM activity. The requirements to score sleep as REM are REMs, low or absent axial EMG, and the typical mixed-frequency EEG recording that does not preclude the scoring of REM (i.e., no sleep spindles can be seen).

Movement time is scored when more than 50% of an epoch is obscured by movement artifact. Movement time must be preceded or followed by sleep and is thus distinguished from movement occurring during wakefulness. If more than 50% of an epoch can be scored as sleep, it is assigned the stage that best describes the majority of the interpretable portion.

Additional sleep values are determined from each sleep study and contribute to the clinical interpretation of the study. These additional variables include the following:

1. Recording time is the time elapsed between "light outs" and "lights on" at end of study.
2. Total sleep time is the total time occupied by stage l, stage 2, slow-wave sleep, and REM sleep.
3. Sleep efficiency is defined as total sleep time divided by recording time and is expressed as a percentage.
4. Sleep latency is the time from "lights out" to the first epoch scored as sleep. Some authors prefer to use the first epoch of stage 2 in order to be more confident about identifying the onset of sustained sleep. However, when sleep is very disrupted, there may be an extended period of time from recognition of stage 1 until an epoch than can be scored as stage 2.
5. REM latency is the time from sleep onset (as described earlier) to the first epoch scored as REM, minus any intervening epochs scored as wakefulness.
6. Sleep stage percentages (percentages spent in stage 1, stage 2, slow-wave sleep, and REM) are determined by dividing time recorded in each sleep stage by total sleep time.
7. Wake after sleep onset is time spent awake after sleep onset.

The scoring principles of Rechtschaffen and Kales (82) function well when applied to sustained sleep. However, the frequent arousals and movement artifacts seen in a patient with severe sleep apnea can preclude scoring of a study by conventional criteria. Bornstein (12) suggested modified sleep scoring rules to help "smooth over" many of the arousals and sleep stage transitions seen in patients with extremely disrupted sleep.

Arousals and Awakenings

Traditionally, there had been no reasonable consensus about the scoring of arousals from sleep. In Rechtschaffen and Kales' system (82), an awakening was defined as a return of the patient's waking background for at least 30 seconds. An arousal, by Rechtschaffen and Kales' criteria, was scored when a patient's waking alpha activity returned for more than 3 seconds but less than 30 seconds. However, most arousals from sleep are more subtle than that just described, and there previously existed no exact requirements to define these. Standard sleep stage scoring systems are intended to identify sleep stage and not transient interruptions in that stage. The transient nature of these arousals caused them to be overlooked in the standard 30-second-epoch sleep scoring system. These brief arousals are usually characterized on a standard polysomnogram by an abrupt change in EEG frequency with or without brief increase in EMG amplitude. With the increasing recognition that arousals result in fragmented sleep, which in turn leads to increased daytime sleepiness, the need for specific and reliable criteria for the identification of arousals became sorely evident (99). The Sleep Disorders Atlas Task Force of the American Sleep Disorders Association has published a preliminary guide with illustrations (11). These recommendations are summarized as follows.

An EEG arousal is an abrupt shift in EEG frequency, which may include theta waves, alpha waves, and/or frequencies greater than l6 Hz but not spindles, subject to the following rules and conditions:

1. Subjects must be asleep, defined as l0 continuous seconds or more of any stage of sleep, before an EEG arousal can be scored. Arousal scoring is independent of the Rechtschaffen and Kales' (82) epoch scoring (i.e., an arousal can be scored in an epoch of recording that would be classified as wakefulness by Rechtschaffen and Kales' criteria).
2. A minimum of 10 continuous seconds of intervening sleep is necessary to score a second arousal.
3. The EEG frequency shift must be 3 seconds or longer in duration to be scored as an arousal (Fig. 26.10).

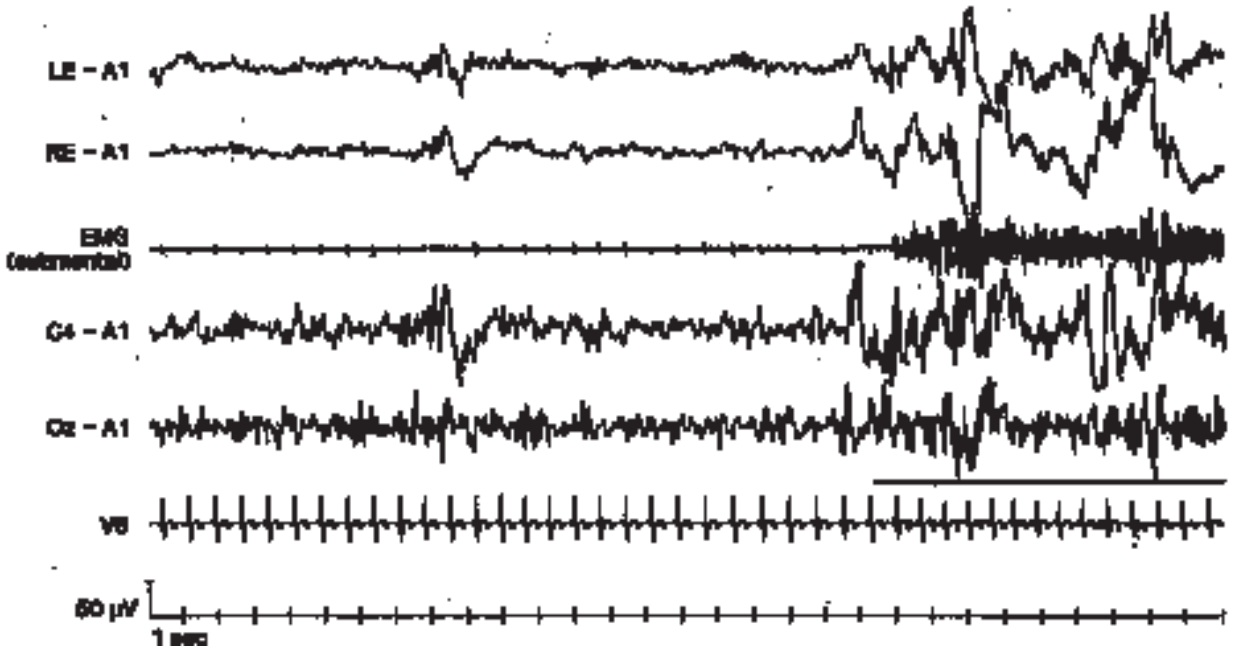

FIG. 26.10. This is a greater-than-3-second electroencephalographic (EEG) change with frequencies higher than 16 Hz and alpha activity. This EEG arousal also has increased electromyographic amplitude. There are more than 10 seconds of sleep preceding this event, and it is scored as an arousal. (From Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples. *Sleep* 1992;15: 173–184.)

4. Arousals in non-REM sleep may occur without concurrent increases in submental EMG amplitude (Fig. 26.11).
5. Arousals are scored in REM sleep only when accompanied by concurrent increases in submental EMG amplitude (Figs. 26.12 and 26.13).
6. Arousals cannot be scored on the basis of changes in submental EMG amplitude alone.
7. Artifacts, K complexes, and delta waves are not scored as arousals unless accompanied by an EEG frequency shift (as previously defined) in at least one derivation. If such activity precedes an EEG frequency shift, it is not included in reaching the 3-second duration criteria. When occurring within the EEG frequency shift, artifacts or delta wave activity are included in meeting duration criteria.
8. The occurrence of pen-blocking artifact should be considered an arousal only if an EEG arousal pattern is contiguous. The pen-blocking event can be included in reaching duration criteria.
9. Nonconcurrent but contiguous EEG and EMG changes, which were individually less than 3 seconds but together more than 3 seconds in duration, are not scored as arousals.
10. Intrusion of alpha activity of less than 3 seconds' duration into non-REM sleep at a rate higher than one burst per l0 seconds is not scored as an EEG arousal. Three seconds of alpha sleep is not scored as an arousal unless a l0-second alpha-free episode precedes.
11. Transitions from one stage of sleep to another are not sufficient by themselves to scored as EEG arousals unless they meet the criteria just indicated.

These EEG arousal criteria are based on EEG changes alone with one exception: An increase in submental EMG is required for demonstration of arousal from REM sleep. The criteria of defining arousal as being 3 seconds or greater in duration is simply a methodological one and is of uncertain physiological significance. It was simply chosen to increase the reliability between observers for scoring arousals.

In the author's opinion, these current EEG arousal scoring rules underestimate the frequency of arousals. Specifically, rhythmic delta activity or a series of vertex waves is ignored as an arousal (Fig. 26.14). These events, particularly when accompanied by another change in the polysomnogram

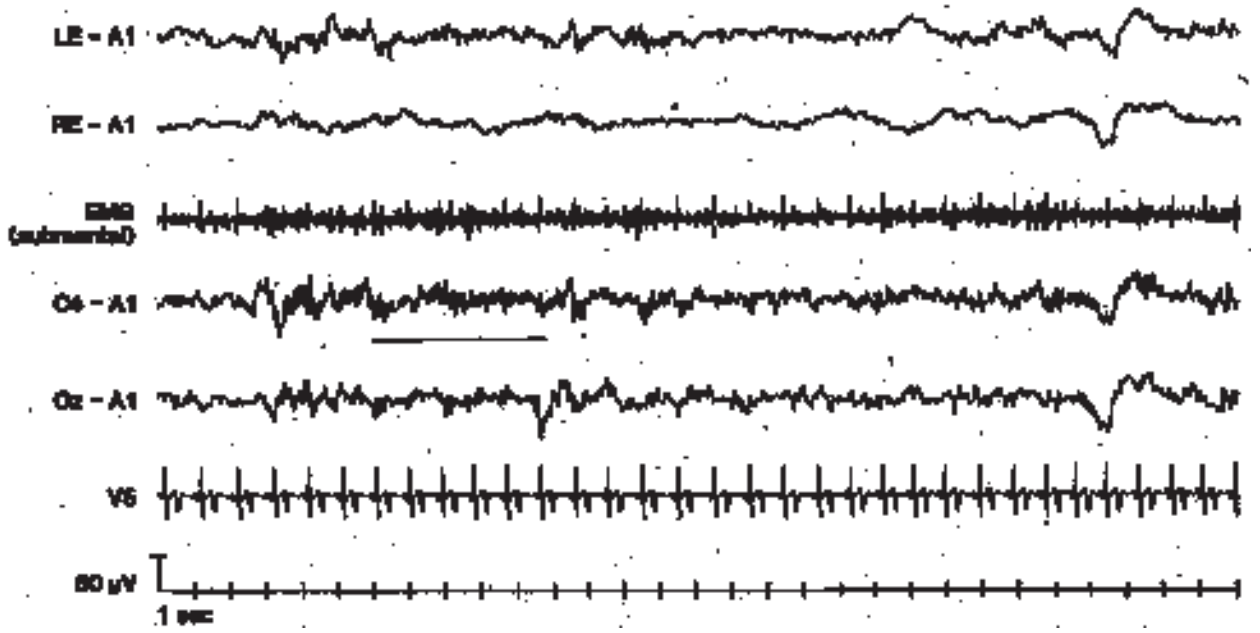

FIG. 26.11. The EEG frequency change in this epoch of non–rapid-eye-movement sleep is scored as an arousal despite the absence of an electromyographic amplitude increase. (From Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples. *Sleep* 1992;15:173–184.)

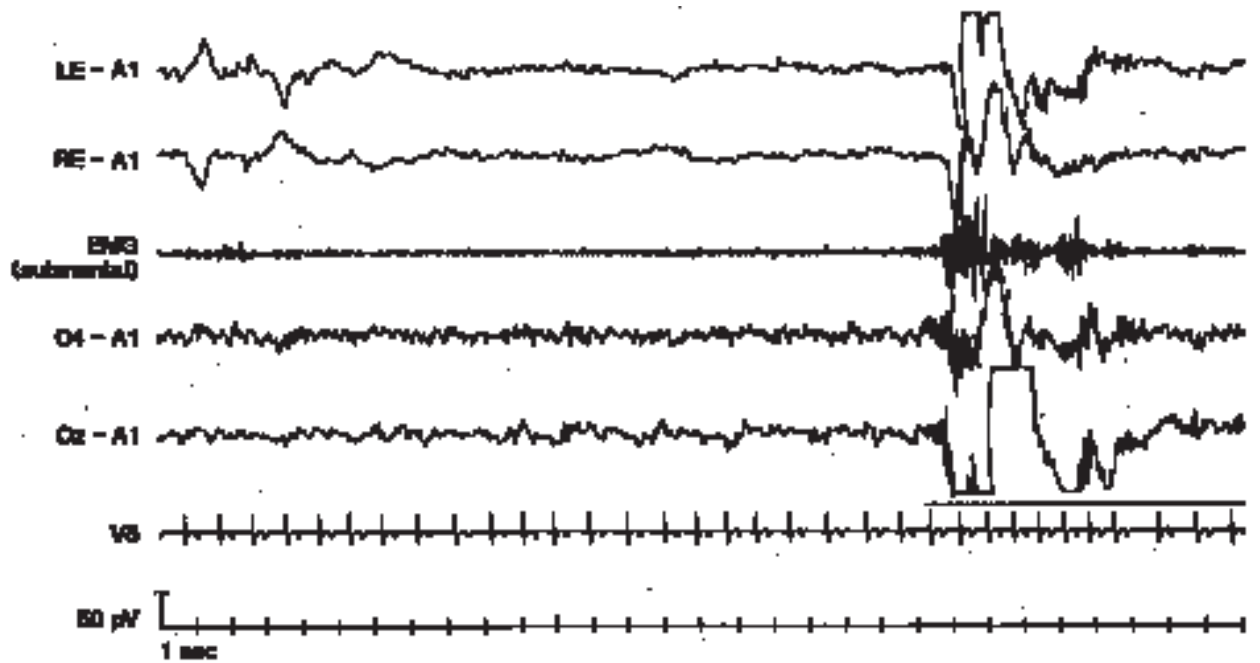

FIG. 26.12. The EEG frequency change in this epoch of rapid-eye-movement sleep is scored as an arousal because there are both an electromyographic amplitude increase and an EEG change of more than 3 seconds' duration. (From Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples. *Sleep* 1992;15:173–184.)

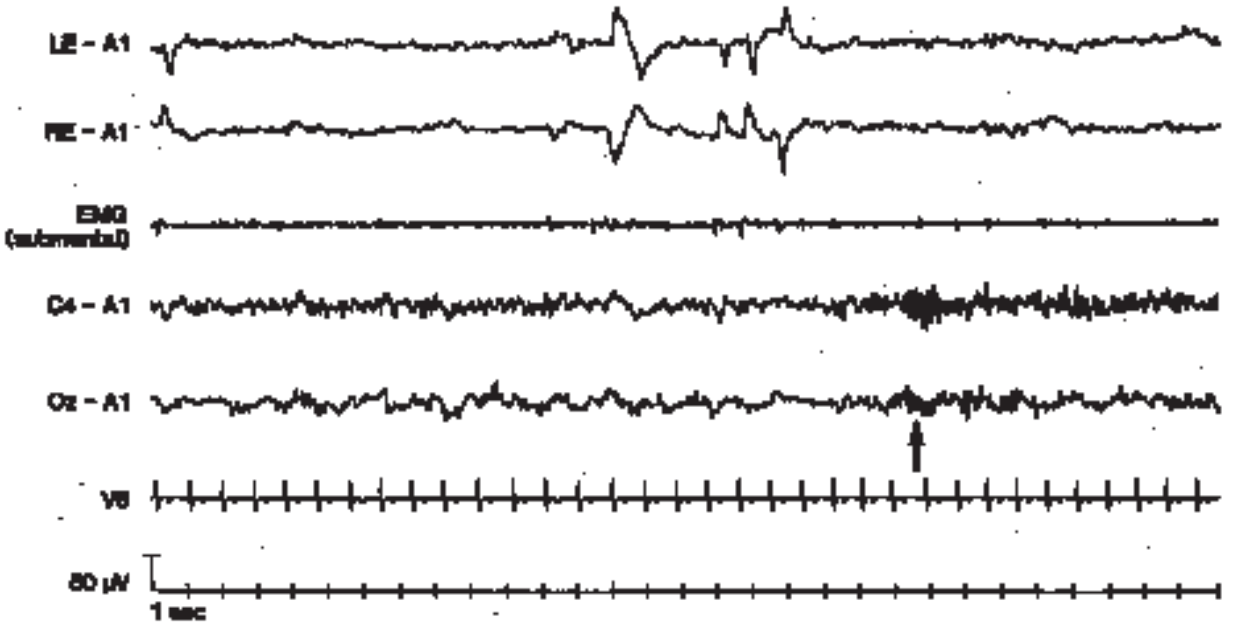

FIG. 26.13. The EEG frequency change on this epoch of rapid-eye-movement sleep *(arrow)* is not accompanied by an increase in electromyographic amplitude and thus is not scored as an arousal. (From Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples. *Sleep* 1992;15:173–184.)

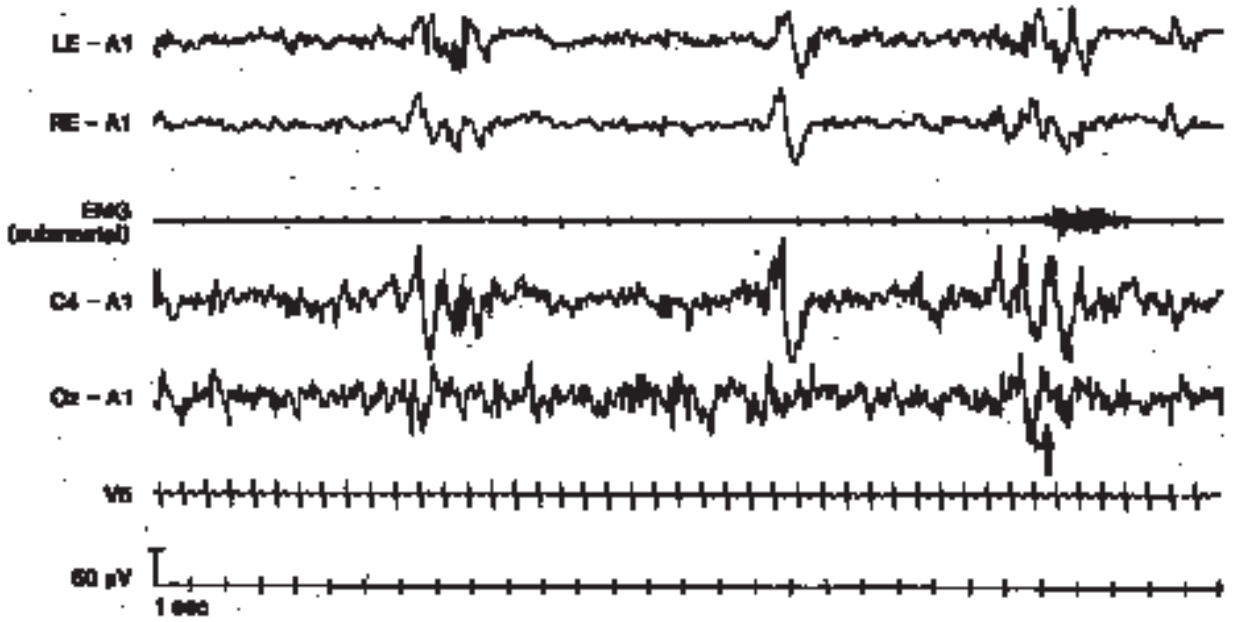

FIG. 26.14. The delta burst of this example *(arrow)* is not scored as an arousal because there is no arousal-type EEG pattern, although there is an electromyographic amplitude increase. (From Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples. *Sleep* 1992;15:173–184.)

(i.e., increase in submental EMG or return of ventilation) almost assuredly represent a comparable physiological arousal. In any case, the current availability of rules defining EEG arousals is a major advance in standardizing the scoring of sleep studies.

Respiration-Related Variables

Other than the duration (10 seconds), there is no consensus about the decrement in airflow required for scoring respiratory events as apneas or hypopneas. This ambiguity is further complicated by (a) the variable techniques used in different laboratories, (b) the qualitative nature of airflow measurement by any technique, and (c) the effects of position change on measured airflow and respiratory effort. Many events without complete cessation of airflow are associated with oxygen desaturation and arousal. As a result, most laboratories score both apneas (cessation of airflow) and hypopneas (significant decrease in airflow) as contributing to a respiratory disturbance index (RDI): apneas plus hypopneas, divided by hours of sleep (1,12).

An apnea episode is defined as a cessation (or greater than 90% decrease) of baseline airflow from nasal and mouth thermistors that persists for 10 seconds or more (1,12) (see Fig. 26.5). Baseline airflow is defined by the airflow before and after the respiratory event in question. The event is scored as an obstructive apnea if there is evidence on chest and abdominal monitors of continued respiratory effort throughout the period of apnea. The event is scored as a mixed apnea if there is no apparent ventilatory effort for more than 6 seconds at onset of the apnea, followed by return of ventilatory effort. Central apnea is scored if no respiratory effort can be detected throughout the entire period of apnea. An apparent central apnea that is consistently terminated by a loud snort should be reviewed carefully to confirm the presence or absence of any obstructive component. It should be emphasized that obstructive apneas with feeble accompanying inspiratory efforts may be incorrectly interpreted as purely central apneas by all commonly used techniques for assessing ventilatory effort except for esophageal pressure monitoring (95).

Physiological apneas occur in nearly every study. These are brief (10- to 20-second) central apneas that occur during the transition from wakefulness to sleep or during bursts of phasic REM activity during REM sleep. These events are scored and contribute to the calculation of the respiratory disturbance index. Brief hypopneic periods during REM sleep not associated with arousal or oxygen desaturation are usually ignored.

There is no universal agreement about the polysomnographic criteria necessary to score a hypopnea. The author's criteria has been a more than 50% decrease in airflow at the nasal and oral thermistors associated with an arousal, an awakening, or more than a 3% decrease in oxygen saturation. Whyte et al. (108) demonstrated that hypopneas could be more accurately scored by using the criteria of a 50% decrease in thoracoabdominal movement lasting at least 10 seconds. They used inductive plethysmography as the ventilatory monitoring technique. The same research group had previously demonstrated (41) that examining thoracoabdominal movement was a more sensitive indicator of hypopnea than was airflow monitoring alone. However, the usual standard of practice is currently to use a definition of some noticeable decrement in airflow at the nasal and oral airflow monitors associated with oxygen desaturation or an arousal (1).

Regardless of the definition of an episode of hypopnea, there are frequently other events, presumed to be respiratory in character, that cannot be scored according to the criteria described earlier. These are recurrent episodes of loud snoring and apparent increases in ventilatory effort associated with a brief arousal. However, they do not meet the criteria for a decrease in airflow or an accompanying oxygen desaturation. In view of the lack of objective criteria, these events are usually not scored as respiratory events, although they are most likely part of a continuum that includes apneas and hypopneas. Investigators using an esophageal balloon have demonstrated a similar increase in negative intrathoracic pressure; these events reflect a pathophysiological mechanism similar to that of obstructive apneas and hypopneas. A task force of the American Academy of Sleep Medicine (AASM) labeled these events *respiratory event–related arousals* (RERAs). Such events contribute significantly to sleep disruption and subsequent daytime symptoms. Guilleminault et al. (44) coined the term *upper airway resistance syndrome* to encompass patients who have clinical manifestations of sleep apnea in the absence of respiratory events that can be scored. However, the AASM task force proposed the inclusion of the RERAs as part of the quantification of breathing abnormalities in obstructive sleep apnea. In view of the similar pathophysiological processes, they proposed using the frequency of apneas, hypopneas, and RERAs to define disease severity (1). However, at this time the inclusion of RERAs in assigning obstructive sleep apnea severity is not widely practiced.

In patients who have recurrent hypopneas, no attempt is made to characterize these events as central or obstructive, inasmuch as there are no reliable criteria with current technology. Similarly, it must be recognized that there may be a significant overestimation of central apneas, because of the limitations of routinely used monitoring devices. When a patient has predominantly central apneas, consideration should be given to the use of

intraesophageal pressure monitoring to confidently rule out an obstructive component to the patient's respiratory dysrhythmia.

Monitoring of oxygen saturation via pulse oximeter is part of a standard polysomnogram. However, the exact manner in which the results of oxygen saturation monitoring are reported is variable. Several measures of oxygen desaturation have been employed. Most sleep report programs are able to generate a convenient graphic format of the cumulative oxygen saturation histogram (Fig. 26.15). In the histogram, the total percentage of sleep time spent at or below each saturation is demonstrated. From this format, a number of parameters can be derived, such as the percentage of sleep time spent below 90%, 80%, or another identified level of oxygen saturation. In addition, an oxygen desaturation index is frequently determined, such as the number of oxygen desaturations (greater than 3%) per hour of sleep. This desaturation index can complement the RDI in determining disease severity. Of note is the greater importance of the oxygen desaturation index in pediatric patients as episodes that can be scored as apneas are rare in that population.

Diagnosis of Sleep Apnea

The diagnosis of sleep apnea has traditionally been based on recording five or more respiratory events (apneas and hypopneas) per hour of sleep

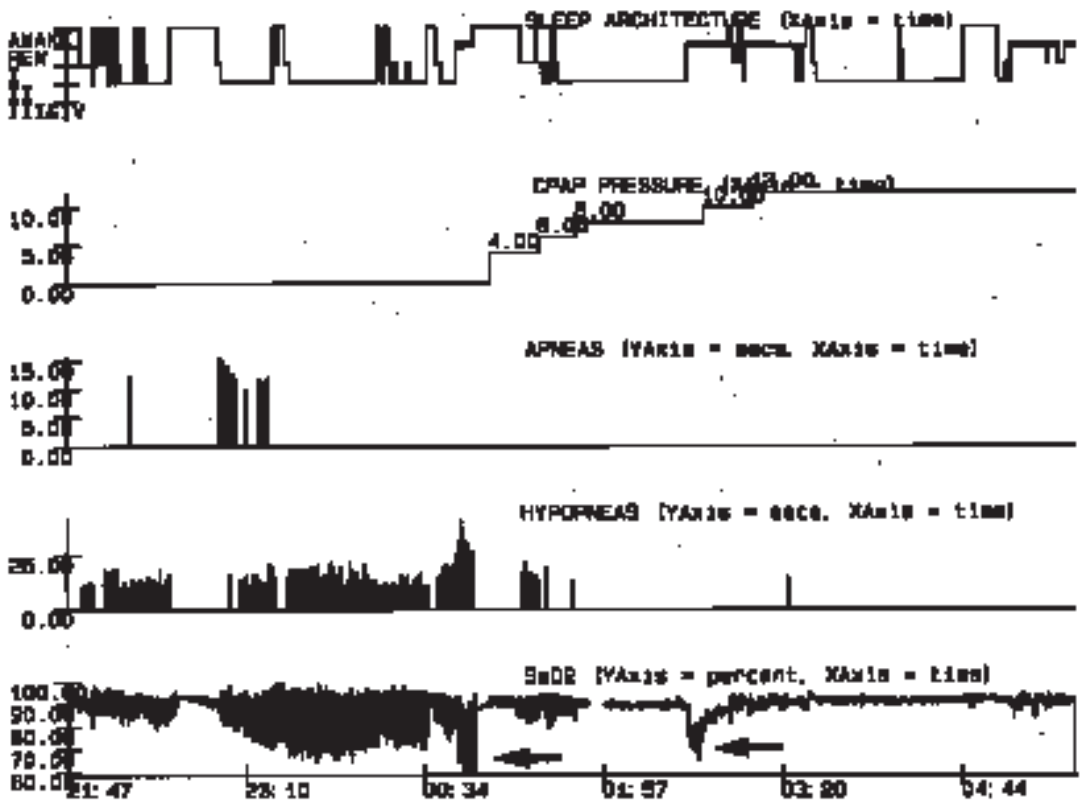

FIG. 26.15. Sleep histogram, continuous positive airway pressure (CPAP), apneas, hypopneas, and oxygen desaturation displayed for overnight polysomnography. Note prominent oxygen desaturations associated with recurrent hypopneas. More severe desaturations (*arrows*) are noted during rapid-eye-movement (REM) sleep (*darkened line*). Marked improvement in respiratory events and oxygen desaturations are noted with CPAP pressure of 8 cm H_2O and above. Slightly higher CPAP pressures were necessary to control desaturations in REM sleep.

(RDI > 5) (46). This standard derived from investigation of a small population of middle-aged control subjects free of sleep complaints. More recent studies, however, indicated that a significant percentage (approximately 40%) of normal subjects older than 60 years have sleep apnea according to that criterion (9,19,66). Knight et al. (64) reported a subtle increase in daytime sleepiness in this "apneic" population, but otherwise these persons have no neuropsychological or general medical complications. Therefore, the rigid use of the RDI of more than 5 as diagnostic of sleep apnea will lead to the overdiagnosis of the sleep apnea syndrome, particularly in an elderly population (9). A more reasonable RDI criterion may be 10 in middle-aged patients and 15 in patients older than 60 years. In the author's experience, this is the minimal degree of sleep apnea that is associated with daytime complaints. Data in the literature have documented that patients with an apnea index exceeding 20 have a significant increase in subsequent mortality during long-term follow-up (49).

Multiple factors must be analyzed in determining the severity of sleep apnea. Certainly the RDI is of great importance, but apnea duration, degree of oxygen desaturation, and associated cardiac dysrhythmias must be incorporated into the decision-making process. The positional nature needs to be assessed, because many patients have severe apnea when lying supine but with little or no apnea when lying on their side. The exact factors that contribute to long-term morbidity or mortality from sleep apnea have not been identified. Surprisingly, the degree of sleepiness is not closely correlated to the RDI or to degree of oxygen desaturation. Rather, sleepiness is more closely correlated to the degree of sleep fragmentation, as reflected by an increase in awakenings, arousals, and percentage of time in stage 1 sleep with an accompanying decrease in percentages of time in stage 3 and 4 sleep (29,43,89). Table 26.3 provides a guide for characterizing disease severity in apneic patients. The AASM task force published their own categorization for obstructive sleep apnea severity but emphasized that there are currently no adequate prospective studies to validate these criteria (1).

Sleep-Disordered Breathing in Pediatric Patients

In the preceding discussion, the emphasis is obviously on adult patients. The diagnosis and sleep laboratory evaluation of pediatric patients for obstructive sleep apnea is much more problematic. Clinically, the patients usually come to medical attention with witnessed snoring and struggling nocturnal respiration. They are much less likely to be sleepy during the day or to have accompanying obesity. The abnormalities identified on polysomnography in pediatric patients are much less profound, and a greater degree of clinical judgment is necessary for evaluation.

The polysomnographic evaluation of normal children indicates that apneas are much less frequent in children than in adults. In 50 normal children studied by Marcus et al. (69), the mean apneic index was 0.1. The mean number of desaturations greater than 4% per hour of sleep was 0.3. Only nine children (18%) had *any* obstructive apnea identified, and only two children (4%) had apnea lasting 10 seconds. Only one child had more than two episodes of obstructive apnea in a night's sleep. From these data, Marcus et al. recommended a "normal value" of less than one for an apnea index in a child. In addition, the mean minimum SaO_2 was 96%, and in only one child did the oxygen saturation ever fall below 90%. Marcus et al. recommended a value of 92% as the minimum SaO_2 in children. The recommended normal value for the number of desaturations greater than or equal to 4% per hour of sleep was less than 1.4.

In an additional study, Rosen et al. (87) examined polysomnographic data from 20 children who had clinical evidence of upper airway obstruction dur-

TABLE 26.3. *Characteristics of sleep apnea by severity*

Degree of apnea	RDI	Apnea duration (sec)	Oxygen saturation (%)	Electrocardiographic findings
Mild	<20	<20	>85	Mild bradytachyarrhythmia
Moderate	20–40	20–40	75–85	Brief asystole (<3 seconds) or prominent bradytachyarrhythmia
Severe	>40	>40	<75	Asystole (>3 seconds) or ventricular tachycardia

RDI, respiratory disturbance index [(apneas + hypopneas)/hours of sleep].

ing sleep (loud snoring and labored breathing) and who had accompanying oxygen desaturations during sleep. The condition of these children was confidently thought to represent a clinical syndrome of obstructive sleep apnea in children. Remarkably, the mean apnea index was only 2 in this population. This was despite the fact they experienced an average of 175 oxygen desaturations greater than 5% each night and with an average minimum SaO_2 of 66%. Rosen et al. concluded from this study that episodes of complete obstructive apnea are generally rare in children, even in the setting of serious sleep-related upper airway obstruction, and that the adult criteria for obstructive sleep apnea fail to identify apnea in the majority of children with serious upper airway obstruction. Although widely accepted normative data in the pediatric population do not currently exist, it is clear that the mere extrapolation of adult values is inappropriate. The presence of any obstructive apneas lasting l0 seconds in a child should be met with suspicion of indicating significant airway compromise. Similarly, greater attention needs to be paid to episodes of oxygen desaturation.

In view of the lack of overt apneas and the possible lack of sensitivity of O_2 changes, additional markers of sleep-disordered breathing have been sought in pediatric patients. The most useful measure identified to date is the end-tidal CO_2. Several defined guidelines have been provided, but the most useful appears to be defining the persistence of an end-tidal PCO_2 equal to or greater than 50 mm of mercury for more than 8% to 10% of the total sleep time. Investigators believe this value to reliably distinguish snoring from clinically significant obstructive hypoventilation (17).

Movement-Related Variables

Periodic leg movements (PLMs) (also called periodic movements of sleep) are repetitive, stereotyped movements of the lower extremities that occur during sleep (28,68,81). They were previously called nocturnal myoclonus, but the movements are not truly myoclonic, and also there might otherwise be confusion with other true myoclonic events that can occur during sleep. PLMs are characterized by tonic extension of the great toe, with occasional superimposed clonic activity, variably accompanied by ankle dorsiflexion and knee flexion. Lower extremity movements are scored as PLMs when anterior tibialis EMG activity lasts 0.5 to 5 seconds and at least five movements occur in a cluster with an intermovement interval of 5 to 90 seconds. The most common intermovement interval is 20 to 40 sec (see Fig. 26.4). Although many authors also require EMG amplitudes to be at least 50% of those of baseline foot dorsiflexion EMG recordings, movements with much smaller amplitudes are frequently associated with an arousal and are potentially significant. Thus, it seems unwise to apply an absolute amplitude requirement for scoring PLMs.

Movement-associated arousals (also termed PLM-associated arousals) are routinely scored with each PLM if there is no associated respiratory dysrhythmia and if the EEG arousal follows the movement within a few seconds. Oftentimes, EEG arousal varies in its relation to anterior tibialis EMG activity. It may occur just before, synchronously with, or just after EMG activity (65). As a result, some authors score arousals occurring 2 to 4 seconds before or after a PLM as being a PLM-associated arousal. Obviously, care must be taken to ensure that there is no other cause (e.g., recurrent hypopneas) for these recurrent arousals. Although arousals that immediately precede the leg movements may not seem to be movement-associated, Lugaresi et al. (68) postulated an internal "pacemaker" that gives rise to both the arousal and leg movement. As such, the leg movement and EEG arousal occur frequently in a mildly asynchronous manner.

Scored PLMs events are counted and divided by hours of sleep to yield a movement index or a PLM index. The number of movement-associated arousals is also divided by the hours of sleep to yield a movement arousal index (or a PLM arousal index). The movement arousal index is believed to be the most clinically relevant measure for assessing the significance of PLMs (28,88).

The basis for diagnosing periodic limb movement disorder was originally determined to be five movements per hour of sleep (31). However, it soon became apparent that there was a large population of asymptomatic persons who had more than five movements per hour (28). Bixler et al. (10) demonstrated an 11% incidence of PLMs (using a movement index greater than 5) in normal subjects and noted a marked increase in incidence with age. However, none of these subjects had more than five arousals per hour related to these leg movements. Other studies have shown that in patients with hypersomnolence, the degree of sleep disruption is correlated with the severity of EDS (46,98). Therefore, the emphasis in PLMs has subsequent been placed on the movement arousal index as a measure of sleep disruption that more closely correlates with clinical symptoms.

PLMs that are associated with few arousals (movement arousal index < 5) are considered clinically insignificant, and patients are classified as having an asymptomatic parasomnia. Even if a movement arousal index of more than 5 is used, there is a large population of asymptomatic individu-

als who have "significant" periodic limb movement disorder (28,68). As with the RDI, a cutoff of 15 for the movement arousal index appears reasonable, especially in evaluation of an elderly population. The author emphasizes that PLMs are present in a broad range of sleep disorders, and their pathophysiological processes and exact clinical significance remain poorly understood (30,68).

The ASDA Atlas Task Force published standardized rules for scoring, which have not gained wide application to date, at least partly because of the nonintuitive nature of the scoring system and the difficulty in immediately extracting a value comparable to the currently used movement arousal index. The complex guidelines are not repeated here.

TABLE 26.4. *Montage*

Channel	Sensitivity (μV/mm)	Filters (LFF/HFF) (Hz)
1. C4-A1	7	0.3/70
2. O1-A2	7	0.3/70
3. T3-Cz	7	0.3/70
4. Cz-T4	7	0.3/70
5. Left eye-A1	7	0.3/70
6. Right eye-A2	7	0.3/70
7. Submental electromyogram	2	5/70
8. Electrocardiogram	75	1/15

HFF, high-frequency filter; LFF, low-frequency filter.

MULTIPLE SLEEP LATENCY TEST (MSLT)

The multiple sleep latency test (MSLT) is a multiple-nap trial designed to quantify the patient's sleepiness and assess the presence of sleep-onset REM (SOREM) periods (3,21). It serves as the gold standard for the assessment of EDS, but it clearly has significant limitations. Other measures of sleepiness (pupillometry [95], the Epworth Sleepiness Scale [24,56]) are either too technically cumbersome or too subjective to warrant widespread clinical use. The MSLT provides an objective quantification of "sleepiness" and is useful in the clinical determination of hypersomnolence. Opportunities to nap are given at 2-hour intervals throughout the day, thereby allowing the investigators to obtain a sampling of the diurnal variation of the patient's sleep tendency.

Multiple Sleep Latency Test Procedure

1. The patient obtains a usual night's rest before the study. Most investigators require that the preceding night's sleep be documented by PSG to ensure adequate sleep and exclude sleep disruption (e.g., sleep apnea, PLMs) as a contributing cause of EDS.
2. The patient arrives at the laboratory in time to allow application of electrodes. At a minimum, electrodes are placed to monitor central and occipital EEG, submental EMG, EOG, and ECG. A sample montage is displayed in Table 26.4. The first nap trial is initiated 1.5 to 3 hours after the patient has awakened from nocturnal sleep. Four or five nap times are scheduled during the day (e.g., 9:30 a.m., 11:30 a.m., 1:30 p.m., 3:30 p.m., and 5:30 p.m.). For each scheduled nap time, the patient lies down in street clothes and assumes a comfortable sleep position. In order to standardize physical activity, a 15-minute quiet period immediately precedes each scheduled nap time. The sleep room should be quiet, dark, and free of environmental noise. As the nap time is about to begin, the technician instructs the patient to "close your eyes and attempt to sleep," turns off the lights, exits the room, and begins recording.
3. The MSLT is routinely scored in 30-second epochs. Sleep onset is usually defined as the first 30-second epoch scored as stage 1 or deeper sleep. However, there is some confusion in the literature and some laboratories use the first of three consecutive epochs scored as sleep to define sleep onset. Sleep offset (awakening) is defined as two consecutive epochs of wakefulness after sleep onset. All scoring is done according to the criteria of Rechtschaffen and Kales (82).
4. Each nap is reviewed for evidence of REM sleep (Fig. 26.16). REM sleep is scored as per Rechtschaffen and Kales' criteria (82) and its onset is determined by the first epoch scored as REM sleep. REM latency (latency to REM onset after sleep onset) is usually determined, but the most important observation is the presence or absence of REM during each nap trial.
5. Each nap is terminated (a) 20 minutes after the nap time started if no sleep has occurred, (b) after 15 minutes of continuous sleep as long as sleep onset criteria are met before the end of 20 minutes, or (c) after 20 minutes if the patient awakens, even if the patients has been asleep less than 15 minutes.
6. The patient is instructed to maintain wakefulness (and is observed if at all possible) between nap periods.

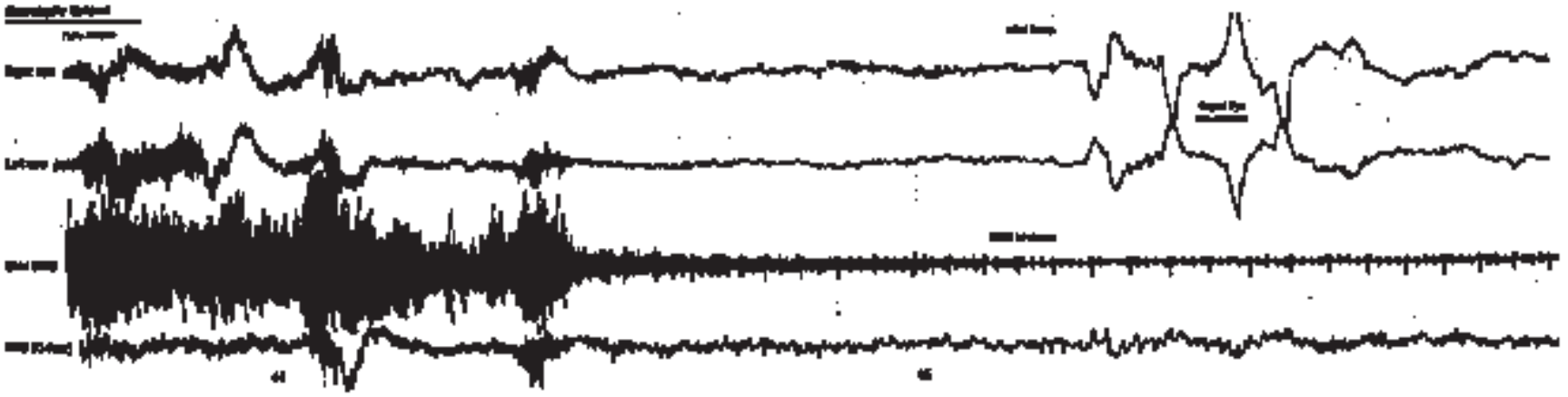

FIG. 26.16. Sleep-onset rapid-eye-movement (REM) period. Polysomnographic record demonstrates the appearance of a low-voltage, mixed-frequency electroencephalogram, accompanied by the abrupt loss of tonic electromyographic activity and the appearance of REM activity. (From Hauri P. *The sleep disorders.* Kalamazoo, MI: Upjohn Co., 1982:5–62.)

Multiple Sleep Latency Test Interpretation

The interpreter determines the latency to sleep onset and the presence or absence of REM sleep for each nap trial. Sleep onset is usually interpreted as the first 30-second epoch of stage 1 sleep or deeper sleep stage. A 30-second epoch is scored as wakefulness if the majority of the 30-second period demonstrates a waking pattern. Stage 1 is determined if the majority of the 30-second epoch is stage 1 sleep. Thus, a brief return of alpha activity for 5 to 10 seconds does not result in an awakening, nor does it necessarily prevent the scoring of an epoch as sleep.

As mentioned previously, there has been some confusion and inconsistencies in the MSLT literature regarding the determination of sleep onset. Richardson et al. (85) used three consecutive epochs scored as stage 1 sleep to determine sleep onset. The most commonly cited "normative data" come from that approach (see Table 26.6). However, starting in 1986 (21) with the publication of the MSLT practice guidelines, many laboratories have begun using the one-epoch criterion, and it is the most widely used definition of sleep onset.

Benbadis et al. (8) examined the various criteria for determining sleep onset and their impact on the MSLT results. Requiring only one epoch of stage 1 sleep resulted in a mean sleep latency of 6.2 minutes, as opposed to 7.5 minutes for the three-epoch criterion. Use of the briefer sleep onset criterion resulted in a change in category (e.g., normal to moderate EDS) in 16 of 100 studies.

Difficulties occasionally occur in determining the exact time of sleep onset or in the interpretation of an ambiguous REM event. Each laboratory needs to develop rules or define approaches to these problems. The most common approach is to require that sleep onset be unambiguous (i.e., cessation of alpha activity and onset of slow eye movements) and not score a decrease in alpha amplitude or frequency as adequate for sleep onset. In the absence of a well-defined posterior alpha rhythm, evidence of increased theta activity (particularly centrally) accompanied by slow eye movements or a vertex wave is usually necessary to score sleep confidently. Similar ambiguities surrounding REM onset sometimes occur. Again, adhering to a strict interpretation for scoring REM sleep is probably the best approach. However, as is evident throughout sleep study interpretation, much has been left to the judgment of the individual polysomnographer.

Individual sleep latencies are then averaged to determine mean sleep latency (MSL). MSLT results from different populations are shown in Table 26.5. A MSL of less than 5 minutes is considered indicative of

TABLE 26.5. *Mean sleep latency test (five nap trials)*

Group	Mean sleep latency (minutes)	Number of REM-sleep episodes (% of group)		
		None	One	Two or more
Narcoleptics (*n* = 49)	2.9 (±2.7)	2	2	96
Nonnarcoleptic, non–sleep apneic EDS (*n* = 63)	8.7 (±4.9)	92	8	0
Controls (*n* = 13)	13.4 (±4.3)	100	0	0

EDS, excessive daytime sleepiness; REM, rapid eye movement.

pathological hypersomnolence. It is a direct indication of the individual's vulnerability to falling asleep in a low-stimulus situation and is associated with performance decrements and unintentional episodes of sleep. A MSL of more than 10 minutes is considered normal and does not reflect significant sleepiness. A MSL between 5 and 10 minutes is the "gray zone" into which some normal persons and some hypersomnolent patients fall. There is no consensus as to the clinical significance that should be applied to results in this range. Labeling a MSL in this range as suggestive but not diagnostic of pathological hypersomnolence is probably the most reasonable approach. Some authors suggest that if a single cut-off value is used, 8 minutes is a rational dividing point between normal (>8 minutes) and abnormal (<8 minutes) (91).

Nonpathological factors affect the MSLT in important ways. MSL is related to the amount of sleep on one or several preceding nights, age, continuity of sleep, time of day, and drug use (18,20,22,33,90). It is therefore necessary to review carefully, preferably with a sleep diary, the patient's sleep pattern over the 7 to 10 days before the study. This need to ensure adequate nocturnal sleep for accurate MSLT results has led most sleep clinicians to require overnight PSG the night before the MSLT. However, sleep deprivation occurring only the night before the study must usually result in less than 4 to 5 hours of total sleep to prominently affect mean sleep latency (18). Drugs also affect sleep latency (sedatives and hypnotics, antihistamines, and stimulants) or REM latency (tricyclic antidepressants, monoamine oxidase inhibitors, and stimulants) (73). Therefore, withdrawal from these medications is necessary before the MSLT is performed. A 2-week period of drug abstinence is empirically required, although there are no good data on the exact time course of medication withdrawal effects. If surreptitious drug use is of concern, a urine drug screen is appropriate on the day of the study.

Somewhat surprisingly, the MSLT has not been an effective measure of treatment response in most patients with narcolepsy. Treated narcoleptic patients do not have a significant change in MSL even though they report improved alertness. Mitler (74) and other researchers (47), in an attempt to be more sensitive to this improvement, devised a "maintenance of wakefulness" test. The main difference from MSLT is that the subjects are instructed to remain awake during each trial. This results in some increased sensitivity to treatment effects, but the test is not widely used clinically.

Premature onset of REM sleep in narcoleptic patients was first noted by Vogel (105) and linked to narcolepsy by Rechtschaffen et al. (83). A single daytime nap to detect early-onset REM was used initially, but it proved to be less than ideal because of its insensitivity in identifying REM sleep pathological processes. The MSLT was developed to allow repeated sampling of sleep and to increase the sensitivity to SOREM periods. When first described by the Stanford University sleep group, each nap allowed a 10-minute period of sustained sleep, and two of five naps had to demonstrate REM sleep onset in order to be diagnostic of narcolepsy. More recently, the recommended protocol for the MSLT was changed to allow the patient a 15-minute period of sustained sleep (21). Because SOREM periods are extremely rare in normal rested persons, some clinicians interpret a single REM-onset nap as adequate for the diagnosis of narcolepsy. However, just as there are many factors that affect MSL, there are circumstances other than narcolepsy that may result in SOREM periods (15,89). Medications, sleep deprivation, time of day, and even subject position have all been described to affect the incidence of SOREMs (73). Nonetheless, a single SOREM period, with documentation of adequate and uninterrupted sleep the night before the study, is certainly abnormal but must be assessed in view of the clinical history or other diagnostic studies. Two REM-onset naps are clearly abnormal and consistent with abnormal REM pressure. Most commonly, this is caused by narcolepsy but also has been described in sleep apnea, drug withdrawal, severe depression, and myotonic dystrophy (27,73,79).

CLINICAL EVALUATION OF SLEEP DISORDERS

The most common sleep-related complaints seen in a sleep center are EDS, disturbed nocturnal breathing, unusual nocturnal behavior (parasomnia), and difficulty with initiating or sustaining sleep (insomnia) (71). The clinical approach to evaluating patients presenting with these common complaints is briefly described in this section. Comprehensive reviews that include discussion of pathophysiological processes and treatment of these disorders are available elsewhere (26,37,67).

Evaluation of Excessive Daytime Sleepiness

A wide range of diagnoses must be entertained in the evaluation of EDS. Table 26.6 lists the final diagnoses in a multicenter report on patients with the complaint of EDS (32). As in nearly every series, sleep apnea, narcolepsy, and idiopathic hypersomnia were the most frequent diagnoses. Figure 26.17 presents a diagnostic algorithm, as proposed by an ASDA task force, that can be applied to the clinical assessment of the "sleepy" patient (4).

The initial evaluation of a hypersomnolent patient focuses on the patient's history. The patient's complaint of EDS must be judged as inappropriate and undesired sleep, as opposed to lethargy, fatigue, or tiredness, which can be reported in a large number of psychiatric and medical conditions. In patients with moderate to severe sleepiness, the history should include episodes of actual inappropriate sleep (e.g., falling asleep at a stoplight). Although the character of the patient's sleepiness often varies among these disorders, there is significant overlap that prevents a confident diagnosis based on the character of the patient's sleepiness alone. An observer history is required to corroborate the reports of sleepiness and also to report on the possible presence of loud snoring, witnessed apneic episodes, or excessive motor activity in sleep. Patients frequently deny or underestimate the degree of sleepiness present and are usually unaware of any snoring or nocturnal apneas.

TABLE 26.6. *Disorders of excessive somnolence (*N = *1983)*

Diagnostic category	Total %	Range/center (%)
Sleep apnea	43.2	23.9–81.2
Narcolepsy	25.0	7.7–32.2
Idiopathic hypersomnia	8.8	0.0–26.9
No hypersomnolence disorder	5.4	0.0–16.4
Other hypersomnias	6.1	1.9–7.9
Psychiatric disorders	3.7	0.0–25.3
PLM/RLS	3.5	0.0–13.7
Medical, toxic, environmental	2.7	0.0–5.1
Drug/alcohol dependency	1.5	0.0–4.4

PLM, periodic leg movement; RLS, restless legs syndrome.

Adapted from Coleman RM, Pollak C, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep-wake disorders. *Ann Neurol* 1980;8:416–421.

The presence of cataplexy is essentially a pathognomonic feature of narcolepsy. Cataplexy is the sudden development of muscle weakness affecting the head, neck, or entire body. It is usually precipitated by strong emotion (e.g., laughter, anger) and is not associated with impairment of consciousness. The muscular weakness lasts from seconds to minutes and then resolves. A history of unambiguous cataplexy in combination with EDS is sufficient for diagnosing narcolepsy, and further sleep study evaluation is not necessarily indicated. However, the possible coexistence of other sleep disorders (sleep apnea, periodic movements) that may also be clinically significant must not be overlooked. Sleep paralysis and hypnagogic hallucinations are the other auxiliary symptoms of narcolepsy, but they are less specific to narcolepsy and do not serve as pathognomonic markers of the disease.

The initial assessment of a patient's sleep-wake complaint is usually aided by the completion of sleep diaries for 1 to 2 weeks before the appointment. These are particularly helpful in identifying sleep restriction or sleep cycle abnormalities that may be contributing to the patient's complaints.

Routine medical evaluation is appropriate for all patients with EDS. Screening for general medical concerns (e.g., hypothyroidism) is appropriate before sleep center evaluation. Attention to possible psychiatric symptoms is also appropriate. Many patients with EDS present with a picture that resembles depression, and therefore the differentiation is sometimes quite difficult. However, if no overt medical problem is identified and the patient has a history clearly suggestive of pathological sleepiness, sleep laboratory evaluation is appropriate.

The usual recommendation is for overnight PSG and possibly MSLT. If there is a strong clinical suspicion of obstructive sleep apnea, PSG alone is usually adequate. If on the overnight PSG an adequate explanation for the patient's EDS is documented, MSLT is not usually performed. Some sleep laboratories perform the MSLT in all patients in order to quantify sleepiness, which may subsequently influence treatment decisions. However, the associated expense and effort seem unnecessary for patients in whom severe obstructive sleep apnea is demonstrated, in that treatment is

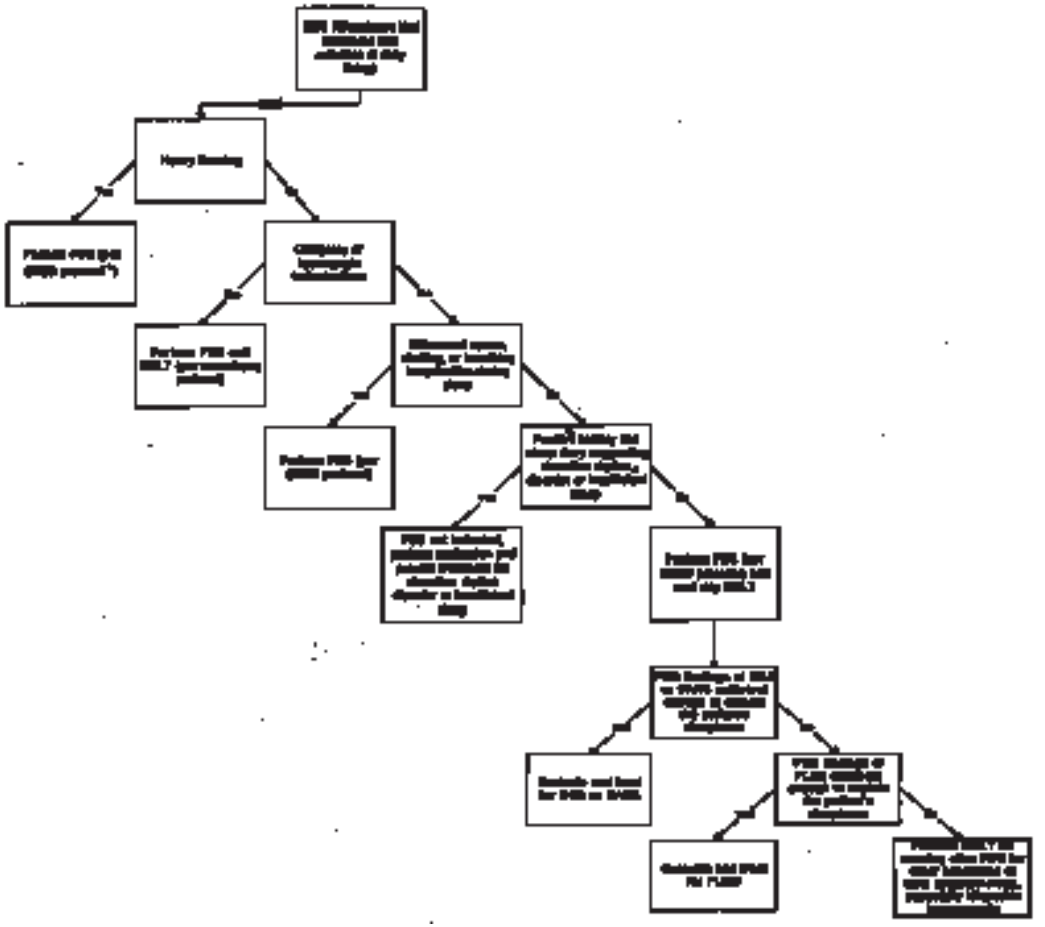

FIG. 26.17. Algorithm for evaluation of patient with a chief complaint of excessive daytime sleepiness. EDS, excessive daytime sleepiness; MSLT, multiple sleep latency test; PLMD, periodic limb movement disorder; PLMs, periodic limb movements; PSG, polysomnography; SRBD, sleep-related breathing disorder; UARS, upper-airway resistance syndrome. (From American Sleep Disorders Association Polysomnography Task Force. Practice parameters for the indications for polysomnography and related procedures. *Sleep* 1997;20:406–422.)

focused on the severity of the PSG abnormality in combination with the patient's subjective complaints.

If the PSG does not demonstrate an obvious cause of EDS, then MSLT is performed the following day to quantify the degree of sleepiness. An overnight PSG before the MSLT is usually required for adequate interpretation of the MSLT to ensure that sleep deprivation or sleep disruption has not artifactually contributed to an abnormal MSLT result. If MSLT is performed without proceeding to PSG, careful historical assessment (e.g., with a sleep diary) of the preceding night's sleep is required at the time of testing.

MSLT results can be used to confirm the diagnosis of narcolepsy and idiopathic hypersomnolence or to refute the complaint of hypersomnolence (21). If the patient has a MSL of less than 5 minutes and at least two REM-onset nap periods, a diagnosis of narcolepsy can be made. It is important to emphasize that the diagnosis of narcolepsy requires both EDS and documentation of REM abnormality. The REM disorder can be represented by cataplexy or by SOREM periods on the MSLT. If a single SOREM period is documented, a diagnosis of possible narcolepsy can be made, and consideration can be given to repeating the MSLT in an attempt to find additional

confirmatory evidence of REM pathology. If the MSLT documents hypersomnolence but no REM abnormality, the diagnosis is idiopathic hypersomnia (previously called idiopathic central nervous system hypersomnolence). This is an unfortunate but necessary "wastebasket" category at present. Some of these patients have narcolepsy, but the REM fragmentation has not yet become clinically evident. Other patients appear to have a syndrome characterized by EDS that can be resisted more successfully, resulting in fewer episodes of daytime sleep (42). These patients are not refreshed by daytime naps and respond poorly to stimulant medications. Many also have headaches, syncope, and peripheral vascular complaints, which raises the possibility of accompanying autonomic nervous system dysfunction.

More problematic is what to do for the patient in the "gray zone" with a mean sleep latency of between 5 and 10 minutes. Clinical judgment is needed to assess the appropriateness of stimulant drugs in this setting. Repeating the MSLT may yield more definitive information. A MSL of more than 10 minutes does not support the diagnosis of EDS, and treatment is not generally warranted. In the patient with a convincing clinical complaint of EDS but in whom hypersomnolence is not documented, the clinician must consider syndromes producing episodic hypersomnolence and the possible need to repeat the MSLT.

Approach to Nocturnal Behavioral Events (Parasomnias)

By virtue of their intermittent nature, the parasomnias are less easily investigated with PSG studies. Historical information therefore assumes greater importance. The differential diagnosis in a patient suffering from unusual nocturnal behaviors includes somnambulism, night terrors, confusional arousals, seizures, REM behavior disorder, and nightmares. Table 26.7 lists characteristics that can be useful in differentiating these nocturnal events. If the nocturnal events are ambiguous or occur with predictable frequency, PSG with closed-circuit television recording usually enables diagnosis.

Somnambulism and night terrors are disorders of arousal and classically occur during the first part of the night; the EEG demonstrates a normal awake or paroxysmal slow-wave pattern during the event (54,60,62,103). Night ter-

TABLE 26.7. *Differential diagnosis of common parasomnias*

Type of parasomnia	Usual age at onset	Time of night	Sleep stage	Type of behavior	Postictal confusion	Effect of stimulation	Recall of event	Duration
Somnambulism	Childhood	First half	NREM	Clumsy, trance-like	Absent	Stops episode	Minimal	Seconds to minutes
Night terrors	Childhood	First third	NREM	Intense terror, vocalization autonomic changes	Absent	Variable	Minimal	Seconds to minutes
Nightmares	Variable	Variable	REM	Terror in response to dream content, limited autonomic changes	Absent	Stops episode	Dream content	Seconds to minutes
REM behavior disorder	Elderly	Last third (most common)	REM	Acting out of dream content, frequently aggressive	Absent	Stops episode	Dream content	Seconds to minutes
Confusional arousal	Variable (usually childhood)	First third	NREM	Confusion, incomplete responsiveness, automatic behavior, rarely aggressive	Present	Variable	Minimal	Seconds to minutes
Epileptic seizure	Variable	Variable	Variable	Stereotyped, variable complexity	Present (often agitation)	No effect	Minimal	Seconds to minutes

NREM, non–rapid eye movement; REM, rapid eye movement.

rors resemble nightmares, but the child has intense autonomic arousal, is subsequently amnestic for the event, and cannot recall any precipitating dream content. Nightmares are seen in patients of all ages and are manifested by emotional upset from disturbing dream content with only limited autonomic arousal. Confusional arousals (also called nocturnal sleep drunkenness) arise in patients of all ages who are frequently considered "deep sleepers"; these occurrences are thought to be caused by an inability to rouse from non-REM sleep. During these events, the patient may manifest several minutes of bizarre confused behavior, for which he or she is subsequently amnestic (14). Violent or aggressive behavior is much less common with confusional arousals than that seen with the REM behavior disorder.

REM behavior disorder is believed to arise from the loss of the usual muscle atonia of REM sleep, which results in the acting out of dream content (93,94). This disorder may be a human analogue (50) of an animal model described by Jouvet and Delorme in 1965 (57). These authors observed complex motor activity in cats during REM sleep after they received pontine tegmental lesions. However, only a few humans have had identifiable brainstem disease. Patients with this disorder are most commonly men older than 60 years with no other underlying neurological or psychiatric illness. These patients present with wild dream enactment behaviors that are frequently violent and result in injury to themselves or their bed partners. PSG with video analysis demonstrates that the motor activity is restricted to REM sleep and may allow confirmation of the diagnosis.

Epileptic seizures are almost always accompanied by an ictal discharge on scalp EEG, followed by postictal slowing. However, the limited EEG montage and slow paper speed used in PSG impairs identification of ictal and interictal epileptic activity. Use of expanded EEG montages and a paper speed of 30 mm per second are necessary in order to evaluate possible epileptic events properly (Fig. 26.18). Even with these adjustments, however, some epileptic events have ambiguous scalp correlates or have no scalp correlates whatsoever (14,38,106,107,110). Absence of an EEG correlate during behavioral events has led to symptomatic description of patients in whom the pathophysiological basis of their nocturnal attacks is uncertain. However, most authors believe that syndromes such as hypnagogic paroxysmal dystonia are caused by frontal lobe epilepsy, despite the lack of a consistent electrographic seizure correlate. If nocturnal seizures are likely to occur, evaluation is better carried out in an epilepsy monitoring unit more suited to extended EEG and video analysis.

Hysterical dissociative reactions, including fugue states, are demonstrated by an alert patient (with normal waking EEG) who manifests complex pur-

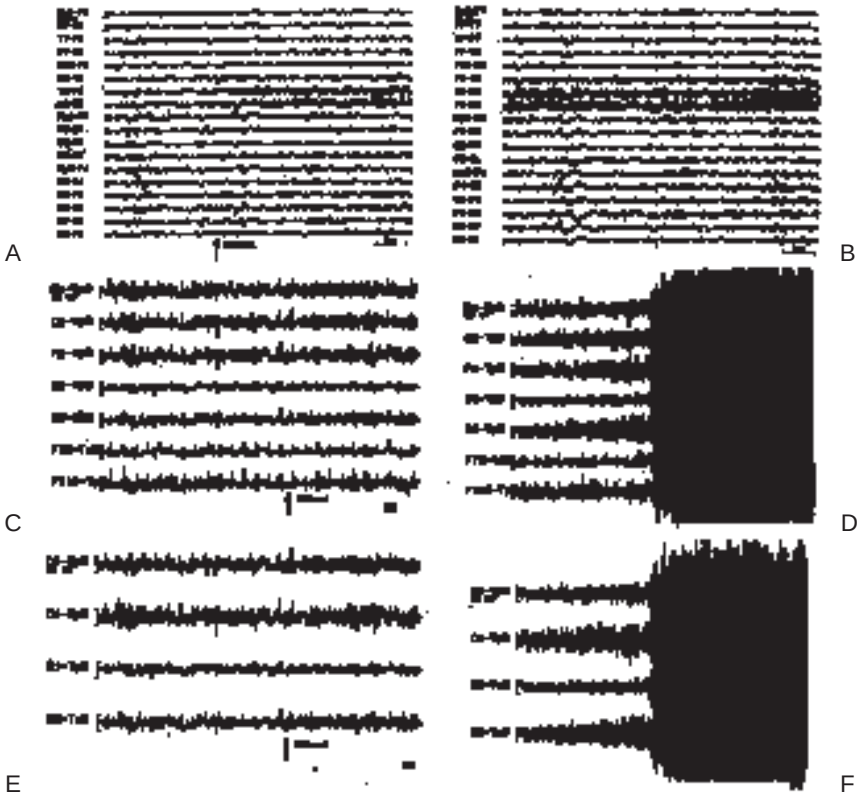

FIG. 26.18. Right temporal lobe seizure in a patient with epilepsy. The electroencephalographic onset (*arrow*) consisted of rhythmic alpha activity in the right temporal region that preceded the clinical onset by 26 seconds, as shown in consecutive 10-second epochs on the 18-channel anteroposterior bipolar montage **(A** and **B).** The evolution of rhythmic activity in the right temporal region (FT10) can be appreciated with difficulty on the seven-channel montage at a paper speed of 10 mm per second but would be extremely difficult to interpret in isolation **(C** and **D).** The pattern is not clearly evident on the four-channel montage **(E** and **F).** (From Foldvary N, Caruso AC, Maschaa E, et al. Identifying montages that best detect EEG seizure activity during polysomnography. *Sleep* 2000;23:221–229.)

poseful behaviors during apparent "sleep" that can last for hours or even days (62). Activity resembling sleepwalking or night terrors in an elderly patient is frequently associated with underlying organic intellectual impairment and is simply an episode of confusion resulting in nocturnal wandering (36).

Approach to the Patient with Insomnia

PSG plays a more limited role in the clinical evaluation of patients complaining of difficulties in initiating or maintaining sleep. The differential diagnosis, as outlined in Table 26.8, includes a wide range of psychiatric and psychological problems that do not routinely necessitate PSG evaluation. However, sleep apnea and periodic movements of sleep (with or without restless leg syndrome) has been identified in 5% to 29% of patients with insomnia (32,59,113).

The author's experience with 100 consecutive chronic insomniac patients evaluated with ambulatory cassette PSG revealed that 34% of the studies provided useful information that was not otherwise available and that sometimes contradicted historical evidence (35). Twenty-five patients had PLMs (mean movement index, 48; mean movement arousal index, 23). Three patients had significant obstructive sleep apnea (mean RDI = 22), subsequently confirmed with laboratory PSG. Six patients had only subjective insomnia because PSG sleep time was five times greater than the amount they had self-reported; four of these patients reported no sleep during the study night even though their total sleep time ranged from 190 to 401 minutes! Age was an important factor in identifying a population more likely to benefit from PSG. Forty-five percent of patients older than 40 years had sleep apnea, PLM, or subjective insomnia identified on PSG, in contrast to 15% of patients younger than 40.

Although there is disagreement among sleep specialists regarding the necessity of PSG evaluations in patients with insomnia, the author's data argue for at least selective use of PSG. Certainly, patients with difficulties in initiating and maintaining sleep who have clinical evidence of possible sleep apnea or PLM should be evaluated by a PSG. In other such patients, the decision to conduct PSG should be individualized, depending on the chronicity and severity of the sleep problem as well as the age of the patient. In most patients with insomnia, it is reasonable for the sleep clinician to formulate a diagnosis on the basis of clinical judgment and to proceed with initial treatment. For patients failing to respond to treatment efforts, PSG could then be offered in order to provide a more comprehensive diagnostic picture (2,84).

TABLE 26.8. *Disorders of initiating and maintaining sleep*

Diagnostic category	% (*N* = 1,214)	Range/center %
Psychiatric disorder	34.9	3.9–66.8
Psychophysiological	15.3	1.0–32.9
Drug/alcohol dependency	12.4	2.9–25.2
PLM/RLS	12.2	2.8–26.3
No insomnia abnormality	9.2	0.0–28.7
Sleep apnea	6.2	0.0–18.4
Medical/toxic	3.8	0.0–12.6
Other	5.9	0.0–12.6

PLM, periodic leg movement; RLS, restless legs syndrome.

Adapted from Coleman RM, Pollak C, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep-wake disorders. *Ann Neurol* 1980;8:416–421.

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Chapter 27

Visual Evoked Potentials

Charles M. Epstein

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The visual evoked potential (VEP) is the largest evoked potential in common use, the easiest to record in cooperative subjects, and, it has been argued, the most sensitive to alteration by neurological disease. However, its deceptively simple waveform is affected by many variables, including nature of the stimulus, choice of recording techniques, and idiosyncrasies of subjects to be tested. There is correspondingly large variation in clinical practice; at times, different authorities appear to give conflicting recommendations. Specific implementations improve the utility of VEPs for some applications but reduce it for others. Two central goals of this chapter are to explain the bases for different techniques and to provide rational criteria for selecting among them. Because the VEP reflects the organization of the human visual system, relevant aspects of visual anatomy and physiology are reviewed.

ANATOMY AND PHYSIOLOGY OF THE HUMAN VISUAL SYSTEM

Retina and Optic Nerve

Light entering the eye crosses behind the lens; thus, images from the temporal field are formed on the nasal portion of the retina, and those from the nasal field appear on the temporal retina (Fig. 27.1). Superior and inferior fields are inverted in a similar manner. Within the human retina, photoreceptor cells classified as rods and cones hyperpolarize in response to light. Rods are more sensitive than cones but function only in dim light and are found predominantly in the peripheral retina. Cones detect color and function in brighter light; they are concentrated especially in the macular region. After adaptation to a dark environment, the physiological state of the retina is referred to as *scotopic:* rod function predominates. In bright light, in which cone function dominates, the physiological state is *photopic.* Cones sensitive to red light waves are most prominent in the macular region, whereas those sensitive to blue light waves lie almost exclusively outside it.

The output of rods and cones projects to bipolar cells and then to ganglion cells, whose axons form the retinal nerve fiber layer and the optic nerve. Developmentally and physiologically, the retina is part of the central nervous system, and the optic nerve is invested with central myelin. An extensive network of amacrine and horizontal cells mediates lateral interactions between adjacent parts of the retina. These interneurons appear to use a large variety of neurotransmitters, including dopamine.

The macular area at the posterior pole of the retina is specialized for high-acuity vision. The foveal pit, a 1.5-mm depression in the center of the macula, contains only slender cones that are packed densely for maximum resolution. This high-resolution region corresponds to the central 3 degrees of the visual field. The layer of myelinated axons emerging from the fovea is denser than that from other portions of the retina and courses directly to the optic nerve head in the papillomacular bundle. In the optic nerve and cortex, the percentage of fibers devoted to the macula is magnified far out of proportion to the actual size of the macula (see Fig. 27.1). The much larger peripheral retina projects to a proportionally smaller fraction of the visual cortex; it serves predominantly to detect patterns of light and movement and to direct the high acuity of central vision toward appropriate targets. In persons with normal vision, the output of these different retinal areas is integrated so well that people are generally unaware of their different functions.

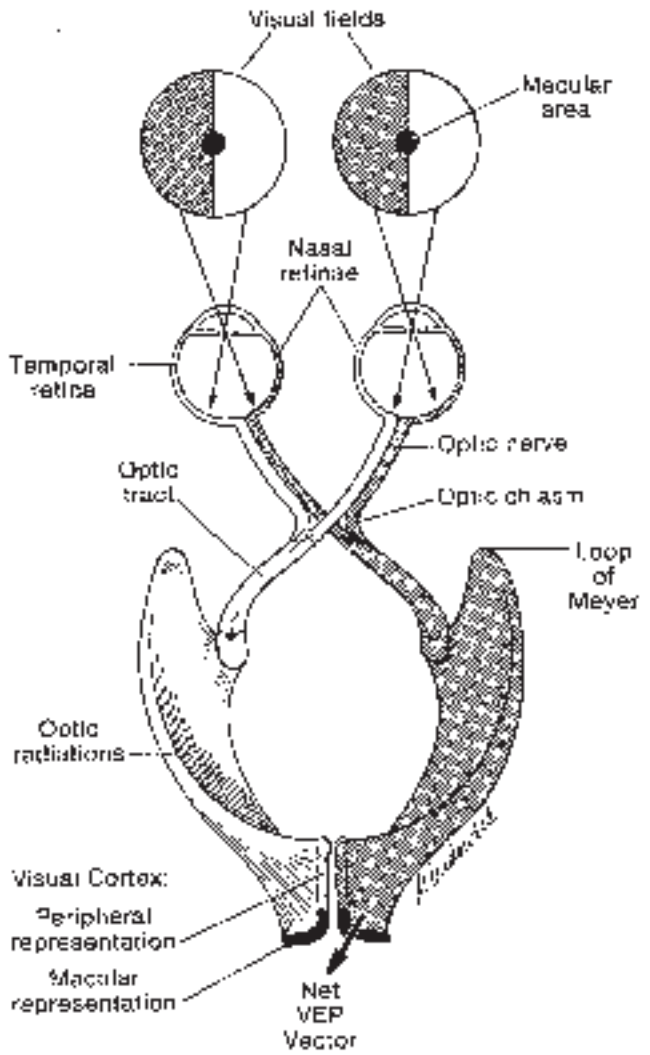

FIG. 27.1. The primary visual pathways, illustrating (i) the crossing of nasal fibers in the optic chiasm, (ii) the macular and peripheral retinal projections to the striate cortex, and (iii) the magnification of the macular area in the visual cortex (shown in black.) The *large arrow* shows the usual direction of the net visual evoked potential vector from hemifield stimulation, which slants obliquely back across the opposite hemisphere.

Each retinal neuron responds to a limited field of photoreceptor cells. For the simplest bipolar and ganglion cells, this receptive field is circular, consisting of a center area and a larger surrounding area. The center and the surrounding area produce opposite responses to light. "Center-on" retinal ganglion cells depolarize and produce more action potentials when light strikes the center of their receptive fields, whereas the firing rate falls when light hits the surrounding area. "Center-off" neurons reduce their firing rate with illumination of the center and increase firing when more light reaches the surrounding area. In the fovea, the center receptive field of a retinal ganglion cell is confined to the width of a single slender cone (1.0 to 1.5 μm), but receptive fields enlarge progressively in the parafoveal and peripheral retina, in which they include multiple photoreceptor cells. Because their input is divided into inhibitory and excitatory fields, retinal neurons are much more sensitive to borders and contrast than to diffuse illumination. This sensitivity to contrasting edges continues with increasing sophistication through the later stages of visual processing (82). Because the primary visual system is arranged to emphasize detection of boundaries and movement, sensitivity to contrasting patterns is a more appropriate way to describe visual function than is simple light detection or even conventional visual acuity.

Overall retinal function is assessed neurophysiologically by the electroretinogram (ERG), which shows the mass response to a bright flash of diffuse or patterned light (Fig. 27.2). Because the peripheral retina is many times larger than the fovea, its response dominates the ERG. The ERG "a" wave represents an early light response from photoreceptors. The ERG "b" wave, peaking at about 50 milliseconds, reflects activity of deeper cell layers; it probably originates in glia rather than in neurons. Retinal processing is relatively slow in comparison with that of other sensory receptors: Direct measurements in humans suggest that the response to a flash of light appears in the optic nerve with a latency of about 40 milliseconds (113).

Optic Tract, Optic Radiations, and Visual Cortex

At the optic chiasm, fibers from the temporal portion of the retina pass ipsilaterally into the optic tract, whereas those from the nasal half of the retina decussate to travel in the contralateral optic tract toward the thalamus (see Fig. 27.1). In primates, there is a small but important exception: For the few degrees around the nasal half of the fovea, a dense ring of ganglion cells also projects ipsilaterally (98). Some crossing fibers for the superior temporal field are said to swing forward into the contralateral optic nerve before turning back in the optic tract. (This bulge is known as Wilbrand's knee,

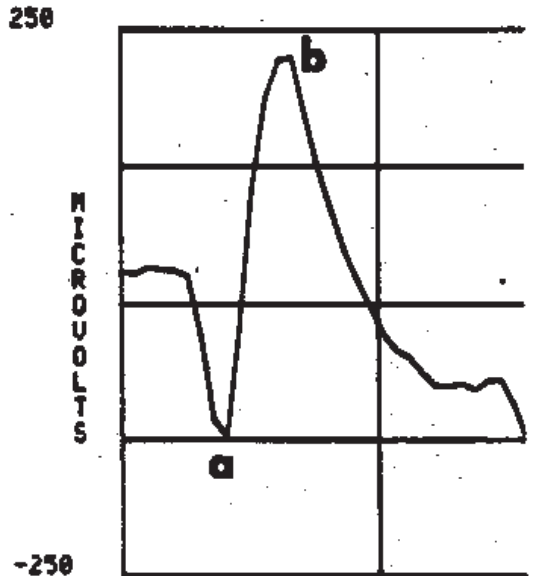

FIG. 27.2. White-flash electroretinogram under scotopic conditions, showing normal "a" and "b" waves from the retina.

although doubts have been raised about its existence in primates (81)). Within the optic tract proper, fibers representing corresponding portions of the visual field are not fully congruous. Thus, lesions at this level produce visual field defects that are nonhomonymous (i.e., they are different in the two eyes). Optic tract fibers from each eye enter alternating layers of the lateral geniculate nucleus.

Myelinated axons projecting from the lateral geniculate nucleus to the cortex form the optic radiations, which swing superiorly and laterally around the lateral ventricle in the temporal and parietal lobes. One portion of the radiations tends to loop especially far forward towards the tip of the temporal horn; known as the loop of Meyer, it contains fibers representing the superior visual field from the contralateral side (see Fig. 27.1). As the radiations near the visual cortex, homologous fibers from the two eyes come closer together; therefore, lesions at a parieto-occipital level produce homonymous field defects. Visual sensory fibers enter the primary visual cortex in Brodmann's area 17. Here, layer IV is markedly thickened and forms a visible stripe in the calcarine fissure, known as the band of Gennari. Its presence has led to the designation of the primary visual area as *striate cortex.*

As a result of foveal magnification, approximately one-third of the primary visual cortex is devoted to the 3 degrees of central vision. The macular projection area occupies the posterior portion of the calcarine cortex, extending in the medial portion of the hemisphere approximately to the occipital pole (see Fig. 27.1). There is considerable anatomical variability in the gross configuration of the occipital lobes, and there is equally wide variability in the representation of macular vision over the occipital pole and medial occipital cortex (162).

LUMINANCE AND CONTRAST SENSITIVITY

The brightness of a light source is commonly measured in candelas; the luminance of a two-dimensional surface is expressed in candelas per square foot, candelas per square meter, or foot-lamberts (1 f-L = 3.426 cd/m^2). The contrast between two adjoining areas has been described in several ways, but in the most common formula, contrast is expressed as a percentage, where *Lmax* is the luminance of the brighter area and *Lmin* represents the dimmer one:

$$\text{contrast} = 100 * \frac{L_{max} - L_{min}}{L_{max} + L_{min}}$$

Contrast sensitivity is the eye's ability to detect small differences in illumination between adjacent areas and is measured with the use of striped patterns or gratings of different sizes. The level of contrast between light and dark stripes is varied to determine the threshold for detection of the pattern. A contrast sensitivity curve can be generated by plotting the size of the grating against the visual threshold for pattern detection (Fig. 27.3). For central vision, peak sensitivity to contrast between light and dark stripes is 3 to 4 cycles per degree (75); the width of individual stripes is 7-10 minutes of arc. At a distance of 1 m, this corresponds to a line 2 to 3 mm wide. Outside the fovea, peak sensitivity is for larger patterns, approaching 1 cycle per degree.

Video-based VEP systems can produce a large variety of stimulus patterns, including solid bars that have uniform luminance within the light and dark areas (Fig. 27.4*A*) and stripes whose luminance varies according to a sine wave function (see Fig. 27.4*B*). Although solid bars may appear to represent the simpler pattern, their optical effects are more complex. The sinusoidal stripes can be represented, through Fourier analysis, by a single fundamental spatial frequency, which is usually given as the number of light-dark cycles in 1 degree of arc. In contrast, Fourier analysis of uniform

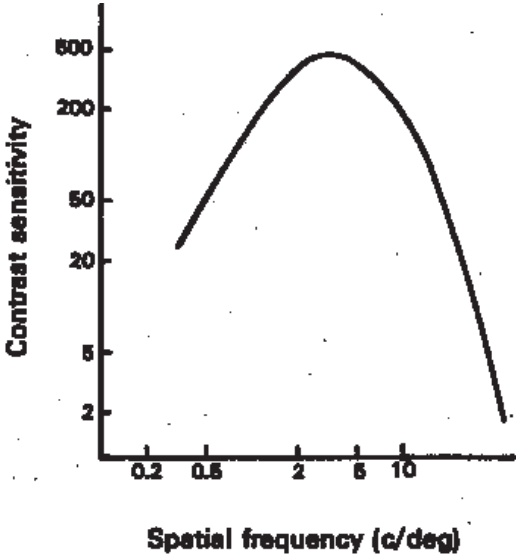

FIG. 27.3. Idealized contrast sensitivity curve, indicating that the human eye is most sensitive to spatial dimensions around three to four cycles per degree. (Modified from Kelly D. Pattern detection and the two-dimensional Fourier transform: flickering checkerboards and chromatic mechanisms. *Vision Res* 1975;16:277–287.)

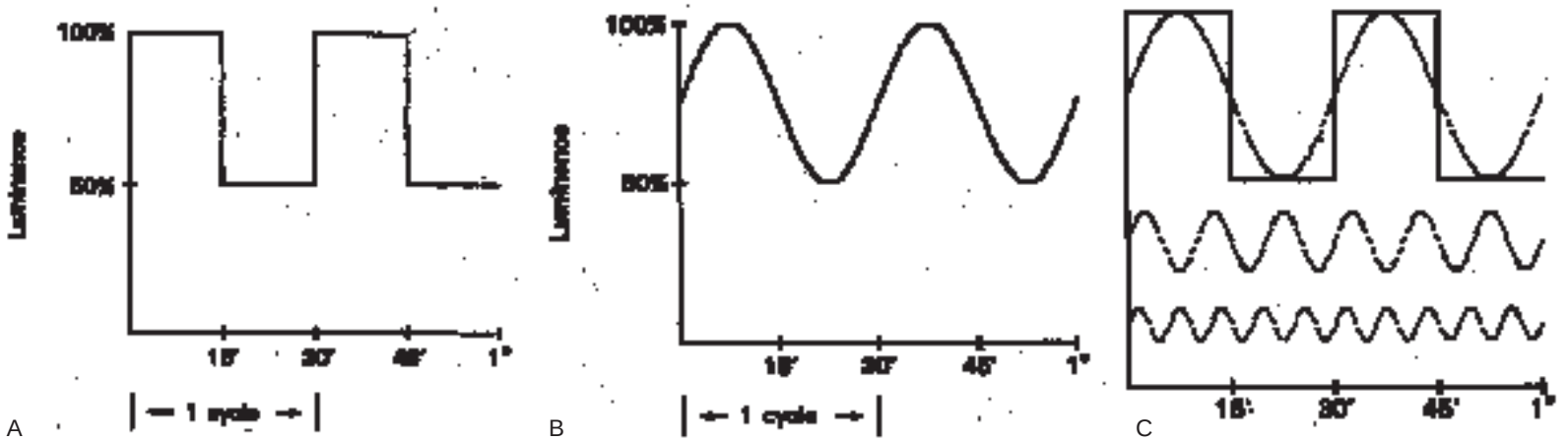

FIG. 27.4. A: Luminance profile for a pattern of solid bars, in which the light elements have twice the brightness of the dark ones and one full cycle is equal to 30 minutes of arc. Individual elements are 15 minutes wide, and the spatial frequency is 2 cycles per degree. **B:** Luminance profile for a sinusoidal grating. Contrast is $100 \times (100 - 50)/(100 + 50) = 33\%$. **C:** A pattern of solid bars shown with the first three sine-wave harmonics of the equivalent Fourier series (*dotted curves*).

bars reveals a whole series of spatial frequencies. The fundamental frequency is still the width of one full light-dark cycle, but there is also an infinite series of weaker harmonics whose frequencies are an odd multiple of the fundamental (see Fig. 27.4*C*). Thus, a simple-appearing pattern of solid bars may actually stimulate the visual system at many spatial frequencies.

Frequency analysis of a conventional checkerboard pattern yields results that are even more surprising and seem counterintuitive: a two-dimensional Fourier transform shows only components along the diagonals rather than along the edges of the individual checks (75). Thus, if the visual system responds to the underlying frequency components of the pattern, a checkerboard pattern actually stimulates the retina at the oblique angles of 45 and 135 degrees. Data consistent with this hypothesis have been found at both low (87) and high (159) contrast levels with checkerboard stimuli.

Some investigators have argued that the choice of VEP pattern stimuli should be based on these physiological observations: that is, stripes should be used in preference to checks, the luminance profile of the stripes should be sinusoidal rather than uniform, and their size should be near the peak of the contrast sensitivity curve at 3 to 4 cycles per degree. It is further argued that the brightness of the pattern stimulus must be balanced very precisely so that the VEP is not contaminated with any trace of conflicting input in the form of changing luminance. These points are obviously important for research applications in which specifying the exact nature of the stimulus is crucial to understanding the corresponding output. They are less compelling for clinical practice, in which the most important criteria of VEP utility are stable and robust responses, sensitivity, and specificity for certain types of visual dysfunction rather than others. In medical applications, stimuli with the "ideal" characteristics preferred by researchers turn out to have a number of potential drawbacks that are discussed later in this chapter.

SOURCE AND TOPOGRAPHY OF THE FULL-FIELD PATTERN VISUAL EVOKED POTENTIAL

As shown in Fig. 27.1, stimuli confined to half the visual field activate the primary visual cortex of only one hemisphere. Under typical test conditions, checkerboard pattern reversal in one hemifield produces a net pattern VEP (PVEP) vector that points diagonally back across the opposite occipital lobe and is represented by the large arrow in Fig. 27.1 (19,96,152). This net vector reflects almost entirely activity in macular and paramacular areas of the visual cortex (119). The macular area of visual cortex is closer to scalp recording electrodes, and is more responsive than peripheral areas to pat-

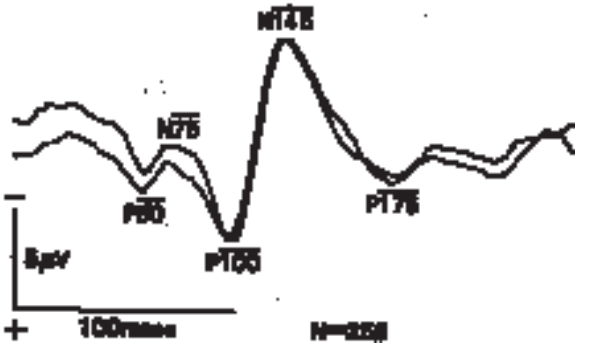

FIG. 27.5. The normal midline pattern visual evoked potential, recorded in an Oz-Cz derivation from an average of 256 responses. Light-emitting diode stimulator with checks measuring 40 minutes of arc, in a 4 × 4 degree pattern; passband is 1.0 to 100 Hz. The major positive and negative peaks are labeled according to their mean latency in normal subjects.

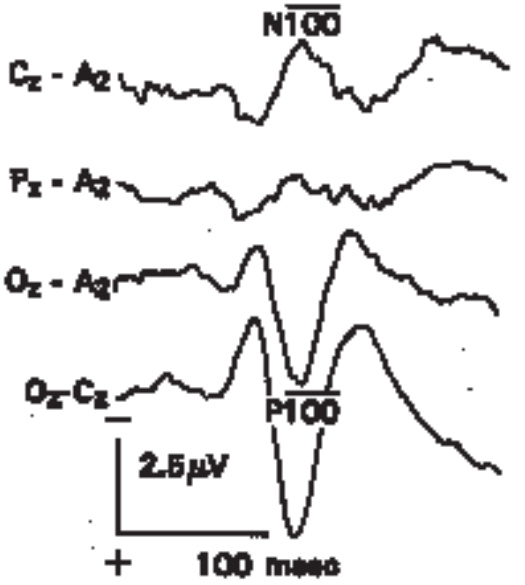

FIG. 27.6. A normal pattern visual evoked potential recorded from a chain of sagittal derivations, showing the occipital P100, the frontocentral N100, and their summation in the Oz-Cz derivation.

terns of the sizes most commonly used. When the full visual field is stimulated, vectors from the two hemispheres sum to produce a PVEP maximum at the occipital midline. This full-field PVEP usually has a negative-positive-negative configuration between 70 and 140 milliseconds; maximal positivity occurs at around 100 milliseconds (Figs. 27.5 to 27.7). The most commonly accepted convention is to display relative positivity at the occiput by a downward deflection. Peaks are labeled with nominal latency values derived from the average in normal subjects: N$\overline{75}$, P$\overline{100}$, and N$\overline{145}$ (see Fig. 27.5). In this system, the bar over the numeral means that this number represents an average (*not* a normal limit.) Depending on test conditions, a smaller positive peak may be recorded between 50 and 60 milliseconds and is usually designated either P$\overline{50}$ or P$\overline{60}$.

Electrodes placed more anteriorly along the midline often show a negative wave in the frontocentral region, which occurs at about the same time as the P$\overline{100}$ (see Fig. 27.6, top channel). If a recording derivation interconnects the area of this N$\overline{100}$ and the occiput (e.g., Fz-Oz), then the P$\overline{100}$ and N$\overline{100}$ sum to give a larger and better-defined PVEP (see Fig. 27.6, bottom channel).

All portions of the PVEP are probably of cortical origin and are classified as middle-latency evoked potentials. However, the exact sources of different PVEP components are unresolved. The earliest definable wave, P$\overline{50}$, begins within 50 milliseconds after pattern reversal. This is barely 10 milliseconds after the earliest flash responses that can be recorded directly from the optic nerve and indicates that the "conduction time" in optic nerve, tract, and radiations is only a small fraction of the total latency from pattern-shift to the peak of P$\overline{100}$. Findings from animal studies with flash stimuli have been interpreted to suggest that N$\overline{75}$ may represent the initial excitation associated with the arrival of visual signals at layer IV of the calcarine cortex (91). Kraut et al. (91) proposed that P$\overline{100}$, the most stable and most commonly measured VEP component, arises from a secondary wave of inhibition at pyramidal cells, mediated by γ-aminobutyric acid (GABA). Experiments using several types of stimuli in anesthetized cats demonstrated that the GABA antagonist bicuculline substantially alters the VEP (183). In similar preparations, anticholinesterases reduced VEP amplitudes (88). However, in human studies, γ-vinyl GABA, which increases GABA levels, did not alter P$\overline{100}$ (73). Experiments with magnetic interference over the occipital cortex indicate that the interval from 80 to 100 milliseconds after a retinal stimulus is critical to visual perception. This time frame corresponds fairly well to P$\overline{100}$ and suggests that the latter does in some way reflect active processing of visual information (2).

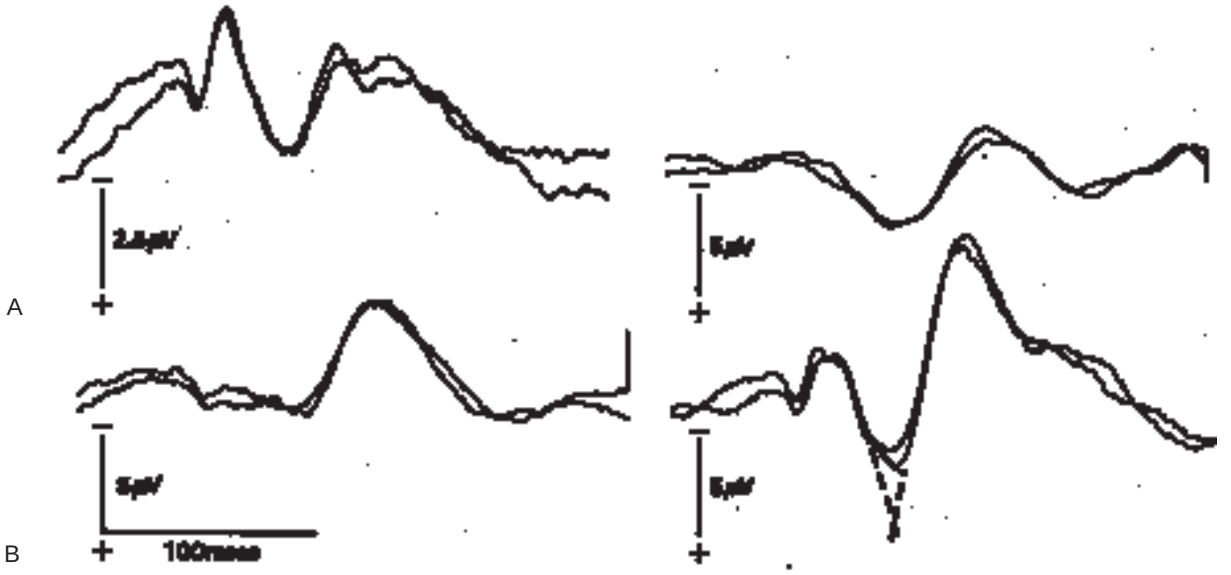

FIG. 27.7. Normal waveform variability of the pattern visual evoked potential in four subjects, all recorded from Oz-Cz as in Fig. 27.5. N$\overline{75}$ may be the largest peak **(A),** or it may be entirely absent **(B).** P$\overline{50}$ is seen in *A, B,* and *D* but not in *C.* P$\overline{100}$ is consistently present at about 100 milliseconds. *Dashed lines* in *D* show one technique for estimating the latency of P$\overline{100}$ when the center is ambiguous.

TRANSIENT AND STEADY-STATE VISUAL EVOKED POTENTIALS

When the interval between visual stimuli is greater than the duration of the VEP and responses are averaged individually, the result is termed a *transient VEP*. This is the type generally used in clinical studies and emphasized in this chapter. At stimulus rates faster than about four per second, sequential VEPs begin to run together and form trains of rhythmic activity. Such trains, seen by electroencephalographers in the form of photic driving, are called *steady-state VEPs*. With increasing stimulus rates, the steady-state VEP resembles a series of sine waves; individual components and individual latencies related to a specific stimulus become difficult to define. However, the much faster stimulus rates that are possible with steady-state VEPs allow presentation of multiple stimuli in a much shorter time. They also enable direct application of special techniques such as phase-locked amplifiers and Fourier analysis (54,120). Although steady-state VEPs sacrifice direct measurement of latency and wave shape, they provide extremely sensitive estimates of evoked potential amplitude and allow distinction among simultaneous responses at closely adjacent frequencies.

Steady-state VEPs have been used most often in attempts to measure visual acuity objectively, as discussed later in this chapter. Alternatively, frequency analysis allows simultaneous stimulation of multiple sectors in the visual field.

INTERPRETATION OF FULL-FIELD PATTERN VISUAL EVOKED POTENTIALS

P$\overline{100}$ latency at the occipital midline is the central measurement for PVEP interpretation. This choice is not attributable to any special physiological significance of P$\overline{100}$; it is neither the earliest component nor even necessarily the largest. In view of the wide range of PVEP variability, it is simply the one that is most stable and most consistently identified in all normal subjects (see Fig. 27.7). P$\overline{50}$, N$\overline{75}$, or P$\overline{175}$ may be absent in some normal persons, and N$\overline{145}$ may be too poorly defined for accurate measurement. Thus, these latter components are difficult to use in distinguishing normal PVEPs from abnormal ones.

P$\overline{100}$ Latency Measurement

P$\overline{100}$ may be narrow or broad, and it may be symmetrical or asymmetrical in shape. A broad P$\overline{100}$ may appear intuitively suspicious and, in fact, has been interpreted as a sign of temporal dispersion in the visual signal. However, there are currently no simple and precise criteria by which P$\overline{100}$ width can be used as an index of disease. In a narrow, symmetrically shaped PVEP, measurement of peak latency is unequivocal. When the response is noisy or asymmetrical, the choice of "peak latency" is more ambiguous. If N$\overline{75}$ is absent (see Fig. 27.7*B*), P$\overline{100}$ should be considered the beginning of the upstroke to N$\overline{145}$. A bifid P$\overline{100}$ should be approached as described later in this chapter. Otherwise, different laboratories deal with ill-defined peaks in different ways. One technique is to extrapolate the downward slopes from N$\overline{75}$ and N$\overline{145}$, taking the P$\overline{100}$ latency as the point of their intersection (see Fig. 27.7*D*). Another is to estimate, simply by gestalt, the center of the entire complex from N$\overline{75}$ to N$\overline{145}$. Whichever criterion is used, it must be applied consistently in collecting normative data, in interpreting clinical studies, and in comparing latencies from the two eyes. Sometimes, P$\overline{100}$ cannot be estimated to better than 2 or 3 milliseconds, and the result lies close to the upper limits of normal. This situation should be described as borderline. The interpretation should not be forced into an "either/or" category beyond the precision allowed by the data.

PVEP latencies have a gaussian distribution in normal subjects, and so conventional parametric statistics may be used to calculate normal limits. Recordings from both eyes in 20 normal subjects are considered the minimum data base for establishing normal values of P$\overline{100}$ latency. There is no clinical interest in recognizing unusually short PVEP latencies, and so one-tailed statistics are appropriate for establishing an upper limit of normal (3). This boundary is commonly set at the 99% tolerance limit, 2.5 standard deviations (SD), or 3.0 SD. For 20 to 30 subjects, the mean plus 2.5 SD and the 99% tolerance limit are similar. These statistics result in classifying about 1% of normal subjects as "abnormal." A one-tailed limit of 2.0 SD results in classifying 5% of normal subjects as abnormal and in an excess number of false-positive findings.

P$\overline{100}$ latency may change appreciably in serial studies of normal volunteers. Oken et al. (127) reported an average absolute latency change of 2.9 milliseconds in controls, with a maximum of 11 milliseconds in one subject. However, Hammond et al. (74) and Stockard et al. (163) found less prominent variability.

Inter-eye latency differences are more sensitive than absolute latency to the presence of subtle disease. They show a less gaussian distribution but also vary far less than absolute latency among different laboratories. Inter-eye differences are also less affected by age than are absolute latency measurements (163). In published normal series, upper limits for interocular latency difference usually lie between 6 and 8 milliseconds. However, patients are generally more likely than controls to have small differences

between the two eyes that result from refractive error, changes in pupillary size, retinal disease, cataracts, or other opacities. Patients' PVEPs are less likely to be exquisitely well defined. Thus, a more conservative limit of 10 milliseconds or more is appropriate for defining an abnormal inter-eye latency asymmetry. Mild asymmetries in this range should be considered pathological only when the whole VEP envelope, including N75 and N145—not just the tip of P100—is asymmetrical. On serial studies, inter-eye latency differences have changed by an average of 2.5 milliseconds, with individual shifts of up to 9 milliseconds (127).

P100 Amplitude Measurement

PVEP amplitude is considerably more variable than latency; consequently, it is more difficult to use in identifying neurological disease. Different laboratories measure amplitude from the peak of N75 to P100, from P100 to N145, as the sum of the two, or as whichever is best defined in a given subject. P100 amplitude distribution in normal individuals is non-gaussian; consequently, attempts to calculate normative data by parametric statistics such as mean, standard deviation, and tolerance limits can be inaccurate and misleading. The lower limit of normal for N75 to P100 amplitude is zero (3). Normal limits for P100 to N145 are best determined by non-parametric techniques. In simple terms, this means collecting PVEPs from 100 or so normal persons, measuring the amplitudes, and defining "abnormal" as a value smaller than 99% of these amplitudes.

Comparison of relative PVEP amplitude between the two eyes is somewhat easier than assessment of absolute amplitude. Even here, however, the distribution of raw data and possible data transformations should be evaluated by a trained statistician before "normal limits" are calculated. In various series, amplitude ratios greater than 2:1 or 2.5:1 are considered "abnormal." Such statistical amplitude abnormalities may result from a wide variety of nonneurological factors and should be assessed very carefully before they are interpreted as evidence of neurological disease. Serial studies in normal volunteers have shown amplitude changes of 2:1 for the same eye (127).

Other Statistical Considerations

An important and often-neglected aspect of calculating normal limits is that probability thresholds should be adjusted according to the number of independent parameters that are considered. For example, P100 latency may be measured with three different orientations of the pattern (28). If the latencies under each condition are independent variables (which is, after all, the underlying assumption when they are measured separately) and if the normal limits for each condition include 95% of controls, then three separate statistical tests may produce false-positive results in almost 15% of the normal population!

A large fraction of the VEP literature consists of demonstrating that adding new test conditions and measurements results in a larger number of abnormal VEPs. This is a normal consequence of performing more tests, and without statistical adjustments, the number of false-positive results may rise faster than the number of true abnormalities (62). In testing for disorders such as multiple sclerosis, most clinicians consider that misclassifying a normal subject as diseased is far more deleterious than temporarily missing the diagnosis in a patient with mild illness. To avoid such errors, measurement of increasing numbers of VEP parameters should be accompanied by increasingly conservative statistics, to the level of 3 SD or beyond.

Aberrant Waveforms and Normal Variants

If average background noise is acceptably low (1 μV or less), a nonreproducible PVEP should be considered absent. In cooperative subjects, its absence should be confirmed by additional recordings at Pz and the inion (see Fig. 27.10*B*). A reproducible waveform is "aberrant" if an unequivocal P100 cannot be determined. Many of these aberrant responses appear to contain too many peaks rather than too few, and the origin of each peak must be analyzed individually. Morphological variants that include a prominent P50 should not be confused with aberrant waveforms (see Fig. 27.7).

Apparently bifid, or "W," potentials may be recorded in normal subjects when the frontal N100 and occipital P100 components are asynchronous (161,163). The apparent double peak is seen only with the use of a frontal or central reference. In such cases, P100 latency can be identified easily in simultaneous ear-reference recording (Fig. 27.8). When small check sizes are used, true bifid potentials that fail to resolve with a change of reference are rare in normal persons; many authors consider them pathological. True bifid potentials are best analyzed with hemifield stimulation (85); see later discussion.

Background entrainment is familiar to electroencephalographers as the photic driving response that is seen routinely in conventional EEG. On occasion, the photic response contains higher harmonics at two or more times the actual stimulus rate. This phenomenon, termed *frequency doubling* (134), is seen commonly in steady-state VEPs and more rarely in transient VEPs.

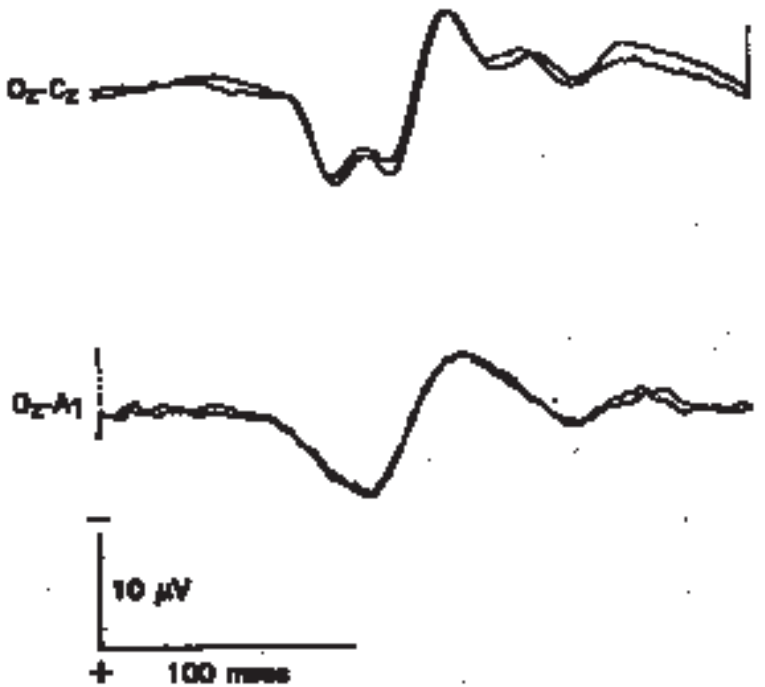

FIG. 27.8. Bifid P100 with a vertex reference (*top*) resolved to a single peak with a simultaneous ear reference (*bottom*). The W-shape of the P100 is caused by an asynchronous N100 picked up by the vertex electrode.

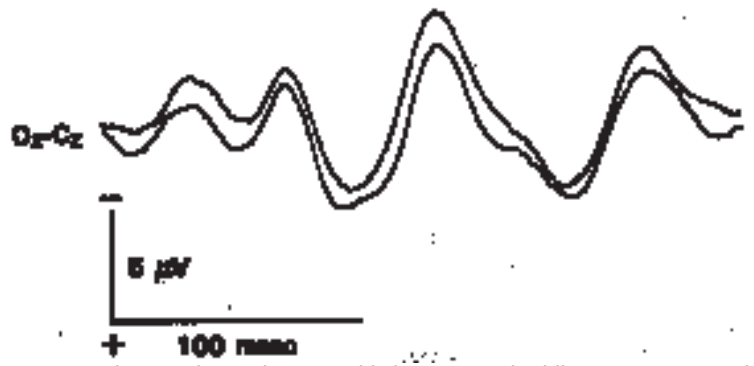

FIG. 27.9. Background entrainment with frequency doubling at 3.7 reversals per second. The very early peaks falling sooner than P50, as well as the exaggerated P175, result from driving of harmonics above the actual reversal rate.

PVEPs with frequency doubling appear to contain an excessive number of independent peaks. Usually, P175 is very large, and there are reproducible components shorter in latency than P50 (Fig. 27.9). These very early waves can be interpreted only as a late but synchronous response to the penultimate stimulus. Frequency doubling tends to occur at stimulus rates higher than two per second. It can usually be diminished by reducing the reversal frequency and avoiding exact fractions of the original rate.

STIMULI FOR ELICITING PATTERN VISUAL EVOKED POTENTIALS

Pattern Reversal

The most commonly used stimulus for PVEP recording is a pattern of light and dark checks, bars, or stripes that is repeatedly reversed: that is, the light portions of the pattern abruptly become dark, and the dark portions become light. Most clinical laboratories use black-and-white checkerboard patterns.

In the earliest pattern reversal systems, moving mirrors were used to deflect the position of a slide projected on a screen. Such mechanical devices could produce rapid pattern shifts (5 milliseconds) but were clumsy, fragile, and lacking in flexibility. They have been supplanted almost entirely by video pattern generators, which are considerably more versatile. However, pattern reversal is actually slower with conventional video systems than with any other technique. Standard television monitors use an "interlace" mode, which generates only 30 new frames per second (25 in Europe); thus, fully replacing one picture with another requires more than 30 milliseconds. (Faster "noninterlace" modes used in some sophisticated systems require 15 milliseconds or less.) The video sweep generator may be synchronized to the power line, to minimize picture distortion. Synchronizing pattern reversal to sweep onset can then produce excess 60-cycle noise in the VEP. However, desynchronizing the moment of reversal from the sweep generator means that each new pattern begins on a different part of the screen, leading to further uncertainty in timing. This temporal smearing of video images affects the resulting PVEPs. The early, relatively narrow P50 is less likely to be seen with video pattern generators than with other techniques, and there is a small effect on P100 latency.

Pattern reversal can also be performed with grids of light-emitting diodes (LEDs), which turn on and off in a few microseconds (53). The luminance of LEDs is precisely controlled by the input current. LED stimulators are small, rugged, and portable, making them suitable for mounting above a supine patient or for the operating room. However, the size of the elements is fixed, and the total stimulus field is small.

Pattern Onset

A complex pattern may be rapidly flashed on and off with the use of LEDs, a tachistoscopic projector, or a computer-controlled video display. Although it is possible to hold luminance constant throughout (141), pattern onset commonly combines both pattern and luminance stimuli and is used less widely than pattern reversal. However, pattern onset produces more robust responses (4,141,149). Aminoff and Ochs (4) reported that this type of stimulus produced a higher yield of diagnostic abnormalities in patients with multiple sclerosis. In the operating room, goggles incorporating small grids of flashing red LEDs are used by some centers to monitor visual function during surgical procedures.

PATTERN VISUAL EVOKED POTENTIAL STIMULUS PARAMETERS

Check Size

As noted previously, the contrast sensitivity function of the fovea suggests that checks with a diagonal around 4 cycles per degree represent an optimal stimulus to central vision. Other considerations, however, mitigate against use of a pattern this fine for routine clinical testing. Many patients referred for PVEP testing have less than 20/20 acuity because of refractive errors, presbyopia, or cataracts; some arrive at the laboratory without their glasses or with the lingering effects of mydriatics that paralyze accommodation. With very small checks or gratings, latency of the PVEP is inordinately sensitive to many factors: blurring of the pattern by poor acuity (159); age (160); ophthalmological disorders such as central serous retinopathy, which can mimic optic neuritis (90,151); and non visual disorders such as Parkinson's disease (171). To the neurologist interested in searching for disease of the optic nerve or posterior visual pathways, latency prolongation produced by any of these factors is misleading and reduces the utility of the test. On the other hand, checks larger than 1 degree approach the size of the entire fovea, with increased stimulation of parafoveal and peripheral portions of the retina. As a compromise, the Evoked Potential Guidelines of the American Electroencephalographic Society (now the American Clinical Neurophysiology Society [ACNS]) recommend a check size in the range of 24 to 32 minutes of arc (3). At this size, effects of visual blurring are reduced, and foveal sensitivity remains high. In practice, checks up to 50 minutes of arc in size have proved to be clinically useful for full-field stimulation and are preferred in many laboratories specifically to avoid the confounding factors noted earlier. Checks between 50 and 90 minutes of arc in size are recommended when PVEPs are used for testing visual fields.

Check size also affects PVEP morphological pattern; smaller checks produce a relatively larger $N\overline{75}$, a more sharply defined $P\overline{100}$, and a reduced likelihood of recording a W-shaped $P\overline{100}$.

A simple formula for determining the visual angle of individual checks in a checkerboard pattern is

$$A = 57.3 * W/D$$

where A is the visual angle in degrees, W is the width of the check in millimeters, and D is the distance to the eye in millimeters.

Field Size

Checkerboard patterns used in PVEP testing have ranged in width from 3.0 (33) or 3.8 degrees (23) up to 48 degrees of arc (102). For full-field testing of central vision, a 4×4 degree pattern covers the macula and yields entirely adequate results. Larger fields produce only a small increase in PVEP amplitude. Some researchers suggest that smaller fields increase sensitivity of the PVEP to optic nerve demyelination, perhaps because the response of a large parafoveal area can "swamp" the latency delay produced by a small central scotoma (78). However, larger fields allow the patient's eye to wander more easily during testing. Field size significantly affects the direction of the PVEP net vector from hemifield stimulation. With large stimulus fields, the contribution of the peripheral retina directs the net vector obliquely through the contralateral hemisphere (see Fig. 27.1). With patterns whose size is only a few degrees across, the net vector tends to point straight back, so that the contribution from each hemisphere may be maximal ipsilaterally. In the past, this effect of field size on the PVEP vector led to conflicting experimental results. For hemifield stimulation, the ACNS Guidelines (3) recommend that the total field width subtend at least 16 degrees of arc.

Patient Distance

An eye-to-pattern distance between 0.7 and 1.5 m is generally satisfactory. With longer distances, blurring may result from severe uncorrected myopia or in reduced attention by uncooperative patients. With shorter distances, presbyopia may cause difficulty.

Contrast

PVEP amplitude increases with increasing pattern contrast up to the range of 20% to 40%. Beyond this, the effects of contrast saturate, and there

is no further change. In most clinical laboratories, regardless of stimulator type, contrast is well above saturation level.

Luminance

In normal subjects, average latency of P100 falls by about 12 milliseconds per logarithmic increase in luminance (29); that is, every time the brightness of the pattern is increased tenfold, latency decreases 12 milliseconds. A luminance difference of 100 times produces, on average, a P100 latency difference of 24 milliseconds. The dependence of PVEP normal values on luminance, and the difficulties in standardizing the brightness of video monitors, are the most important reasons that VEP laboratories must collect their own normative data rather than relying on published results.

The effect of luminance on latency is greater in patients with optic nerve disease, and use of lower luminance has been suggested as a method for increasing PVEP sensitivity (29). Unfortunately (from the neurologist's perspective), lower luminance may also increase sensitivity to other conditions such as retinal disease (151), poor visual acuity, and age (148).

The possibility of *inadvertent* luminance changes is critically important in the VEP laboratory, especially with television pattern generators. Luminance of the television screen is strongly affected by both brightness and contrast controls, and it may be altered by aging of the picture tube. Laboratories collecting normal data sometimes neglect to measure luminance of the screen at the outset or to mark the settings of the controls. At any future time, visitors to the laboratory may randomly twirl knobs, altering the range of normal values and opening the possibility of major errors in interpretation. Control settings should be clearly labeled, and the screen luminance should be checked periodically with a light meter.

PVEP testing should be performed in a moderately well-illuminated room similar to the patient's ordinary environment. This produces a photopic state in which vision is dominated by retinal cones and in which uniform test conditions are relatively simple to attain. In a dark-adapted scotopic test situation, the acuity, color sensitivity, and integrating functions of the retina are different and, of more importance, harder to control. Scotopic adaptation takes 30 minutes, and it is then altered unpredictably by the brightness of the pattern itself.

Color

Retinal cones sensitive to red light are largely confined to the foveal area, and red desaturation is a sensitive clinical sign of paracentral scotomata. On this basis, red/black patterns have been suggested as a means for increasing the sensitivity of the PVEP to central or paracentral lesions (118). In general, the use of different colors produces minor changes in PVEP amplitude and latency, but colored patterns have not been widely adopted for clinical testing.

Reversal Frequency

At "transient" PVEP testing rates, ranging between 0.5 and 4 reversals per second, the average latency of P100 rises by a few milliseconds with higher reversal frequency (163). Conventional television patterns begin to degrade at approximately two per second, and ACNS Guidelines recommend using patterns of less than four per second for routine clinical studies (3). With patterns of more than four per second, at the faster rates used in steady-state recording, the net VEP vector from pattern reversal swings posteriorly and is seen over the ipsilateral, rather than the contralateral, hemisphere (128). This effect is similar to that of reducing the stimulus field size, and it implies that visual field defects are more likely to be identified as slower reversal rates.

Note that reversal frequency and cycles per second are not the same thing; one full cycle equals two reversals.

PATTERN VISUAL EVOKED POTENTIAL RECORDING PARAMETERS

Passband

The ACNS Guidelines (3) recommend a low filter (high-pass) setting of 1.0 Hz and a high filter (low-pass) setting of 100 Hz. However, the literature includes some studies done with a tighter passband, occasionally as low as 70 Hz (85,141). Waveform distortion may be noticeable at this point.

Sixty-Hertz Filters

The frequency of some VEP components is close enough to 60 Hz that these filters should be avoided in VEP testing.

Sampling Rate

The analog data sampling rate should be fast enough to produce a new data point in each channel every millisecond or less. Thus, the minimum sampling rate for one channel is 1,000 per second; for eight channels, it is

8,000 per second. The inverse of the sampling rate is sometimes called the *dwell time.* At 8,000 samples per second, the dwell time is 0.125 milliseconds per sample.

Sweep Duration

Sampling should continue for at least 250 milliseconds after each stimulus.

Sensitivity

An optimal input range for the analog-to-digital converter is usually 50 to 100 μV. Lower values may lead to excessive distortion or rejection of normal brain activity; higher values may produce inadequate data resolution.

Number of Responses Averaged

Typically, 60 to 250 artifact-free samples are necessary to produce a good signal-to-noise ratio in the final average.

Replications

At least two averages should be taken in each test condition—more if responses are poorly reproduced. Well-reproduced responses should contain a P$\overline{100}$ latency difference of no more than 2.5 milliseconds and an amplitude difference of no more than 15%.

Recording Derivations

All VEP montages must include a midoccipital (MO) electrode. The popularly recommended "Queen Square" technique is to use an MO position 5 cm above the inion (3), which is meant to occupy the average topographic center of P$\overline{100}$. The International 10-20 System's location Oz lies about 1.4 cm below this. Neither MO nor Oz can be considered a fully reliable location in all subjects, however, because the center of P$\overline{100}$ may lie as high as Pz or as low as the inion in normal persons (Fig. 27.10*B*).

The most commonly used reference for PVEPs is Fz (or the Queen Square MF, which is 12 cm above the nasion). Some laboratories place a vertex reference at Cz, where electromyographic activity is usually less prominent. There is no consistent advantage in choosing one of these references over the others. All anterior midline reference sites record the anterior negativity, N$\overline{100}$, that accompanies P$\overline{100}$. This has the consequent advantage of maximizing apparent P$\overline{100}$ amplitude while minimizing noise (see Fig. 27.6), but it has the disadvantage that the contributions of N$\overline{100}$ and P$\overline{100}$ to an aberrant waveform may be impossible to separate. A large N$\overline{100}$ can mask an ectopic or small P$\overline{100}$ or its absence; asynchrony of these two components may lead to an apparently bifid or ambiguous P$\overline{100}$ (161). The easiest way to recognize and resolve such aberrant waveforms is to record routinely from midocciput to one or both ears in a second channel. The ears are relatively uninvolved by the PVEP, and they can be considered inactive for full-field recording. (They are not, however, inactive for hemifield studies.) The ear-reference channel serves as a constant check on the validity of the midline recording and helps identify normal variants that otherwise might lead to serious misinterpretation (see Fig. 27.10*A* and *B*).

For full-field testing, many laboratories use additional electrodes situated lateral to the midline. The International 10-20 System's locations 01 and 02 are generally considered too close together, and so the ACNS (3) recommends left occipital (LO) and right occipital (RO) positions 5 cm to each side of MO (see Fig. 27.10*A*). These additional derivations are most useful in screening for unsuspected field defects, which can then be better defined by subsequent hemifield recording. However, the sensitivity of full-field testing to such defects is limited (13,94,139), and the range of normal variation between LO and RO is large. Even P$\overline{100}$ amplitude asymmetries of greater than 2.5:1 should not be considered definitely abnormal in the absence of corroboration by hemifield studies.

In the author's and some other laboratories (161), an ear reference is considered even more essential than lateral occipital leads for full-field testing. Although the latter prevent a few false-negative results, the former avoids false-positive diagnoses, which are considerably more deleterious for the patients who receive them.

PATIENT FACTORS

Preparation

Ordinarily, each eye is tested individually, while the other eye is occluded by a patch. Binocular testing is occasionally helpful in patients who cooperate poorly, but it is much less sensitive to unilateral optic nerve disease. If possible, patients should not be tested within 24 hours of receiving mydri-

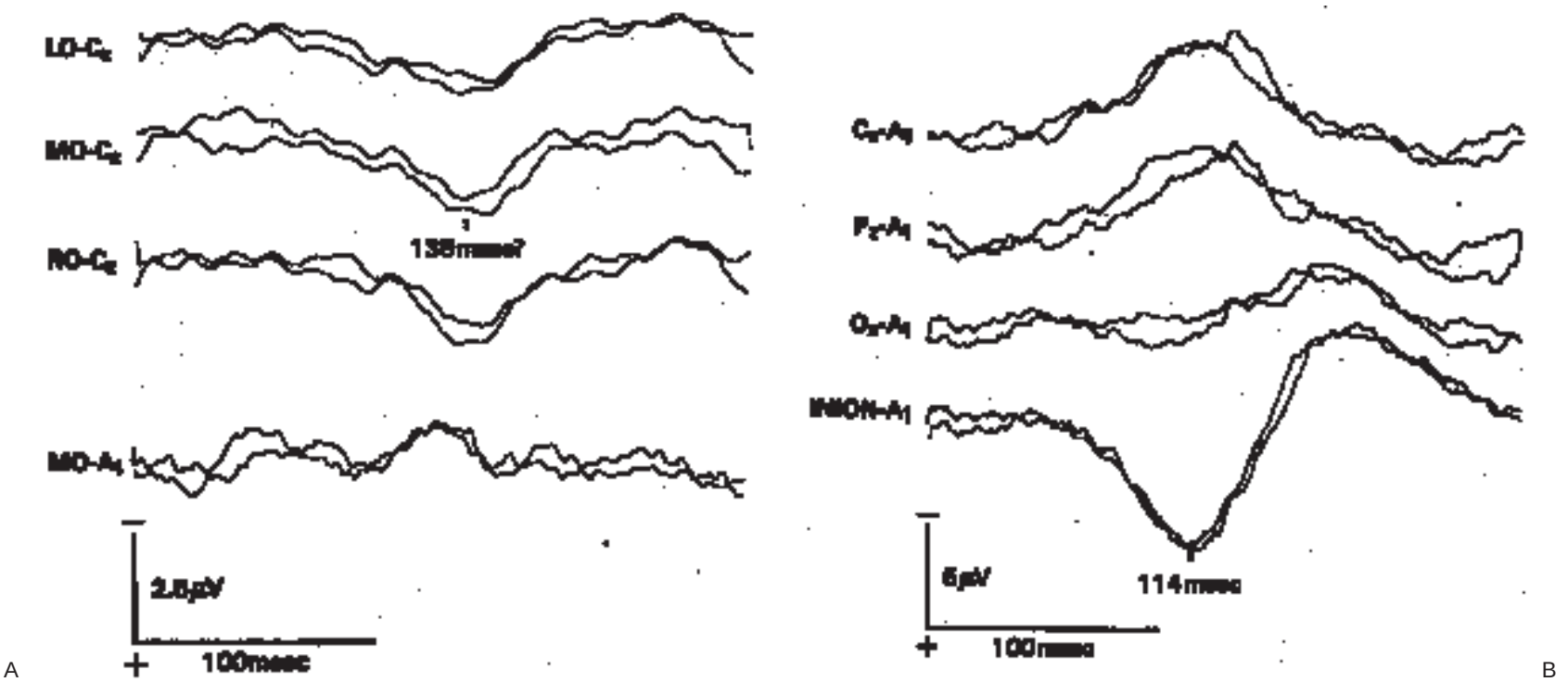

FIG. 27.10. A: Apparently small-amplitude, delayed pattern visual evoked potential to full-field stimulation. However, the response from MO-A1 is discrepant, which suggests an atypical distribution of the electric field. **B:** The same subject as in part *A* recorded 1 day later with a sagittal montage. P100 is located caudally at the level of the inion, and its latency is normal for this laboratory. The transition zone between P100 and N100 is located near MO and Oz, producing small and aberrant waveforms at those sites.

atic agents. Patients who use glasses should try viewing the pattern with and without them and should be tested under the condition in which the image is clearest.

Attention

A PVEP will not be recorded unless the subject is awake and concentrating on the stimulus. Amplitude and latency can be altered substantially if the subject's gaze is allowed to wander around the room, if there is excessive blinking, or if various extracerebral artifacts are generated (178). Unfortunately, other patient variables, more difficult to monitor, may also have an appreciable effect on PVEP amplitude and latency. The difference between relaxed and highly alert states can produce latency differences as large as 11 milliseconds in one eye in the same subject (44). Volunteers using maneuvers such as meditation (Fig. 27.11) and convergence with one eye covered (Fig. 27.12) have been able to abolish the PVEP or alter its latency by up to 15 milliseconds without detection by an attentive technician (27). Similar volitional changes have been demonstrated with different types of pattern stimuli in other laboratories (115,169). These effects may be reduced by the use of larger stimulus fields, larger checks, and binocular testing (169).

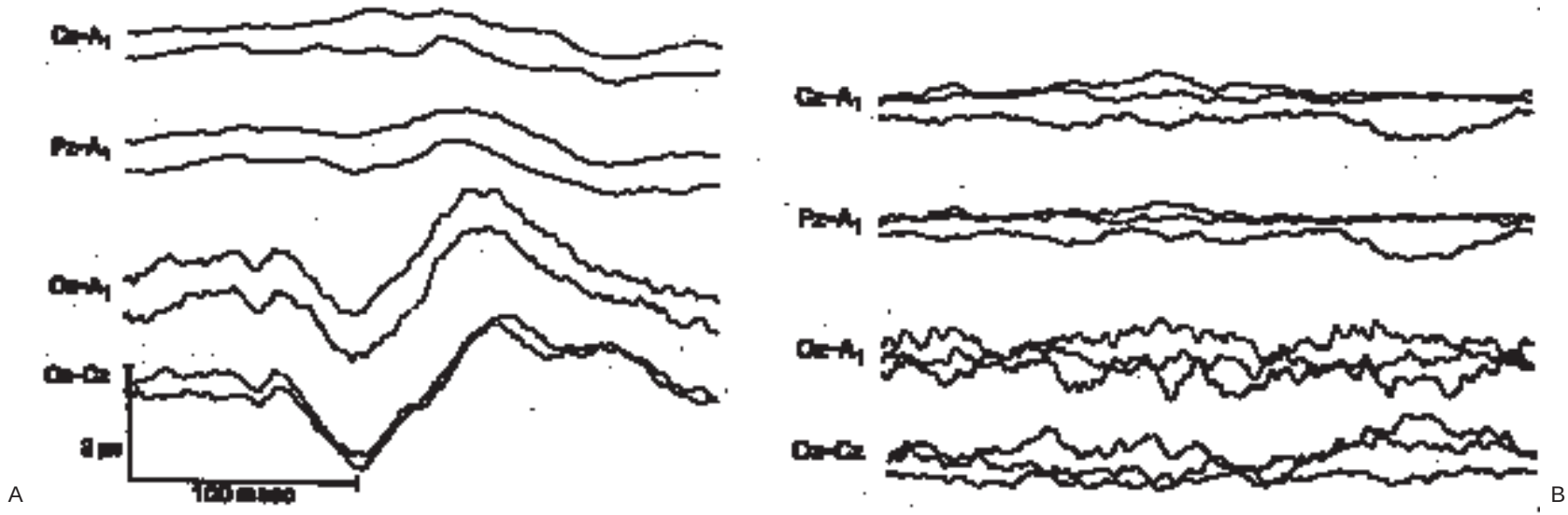

FIG. 27.11. A: Normal pattern visual evoked potential (PVEP) when the subject is attending to the stimulus, which is a light-emitting diode pattern generator with checks measuring 50 minutes of arc, 5-degree field, and maximum luminance of 100 cd per square meter. **B:** Apparently absent PVEP with the same subject performing transcendental meditation under otherwise identical conditions. Cooperation appeared good to the technician. (From Bumgartner J, Epstein C. Voluntary alteration of visual evoked potentials. *Ann Neurol* 1982;12:475–478.)

Only a minority of volunteers have been able to alter their PVEPs surreptitiously without special coaching. However, the PVEP is commonly used to evaluate patients suspected of hysterical visual loss or malingering. Such patients often exhibit unusual difficulty in maintaining fixation on the pattern and repeatedly allow the eye to close unless it is held open by the technician. How many are capable of more sophisticated manipulation is impossible to determine. In general, low-amplitude, absent, or even mildly delayed responses in this setting should be interpreted with caution.

Gender

In large series, women consistently show average latencies that are a few milliseconds shorter than those of men (43,163). In some studies, women have, on average, higher-amplitude PVEPs (43,45). This difference is greater with checks smaller than 30 minutes of arc (52).

Age

It can be difficult to test PVEPs in children until they are a few years old, although with checks of 30 minutes of arc or lager, latencies appear to reach adult values by the age of 20 weeks (158). Latencies for all check sizes are at adult values by the age of 5 years (45,158) and show no significant change from then until about age 40. Many normative studies have yielded conflicting results concerning the nature and degree of latency changes in healthy middle-aged and elderly persons. Some of these discrepant results have been clarified with the discovery that aging effects are dependent on both check size and luminance. Latency rises most rapidly with age with the use of smaller checks (37,159) and decreased luminance (148); these effects appear to be unrelated to pupil size (37,159). They can be minimized by the use of checks of 30 minutes of arc or larger and a luminance of 50 cd per square meter or greater. Otherwise, normative data should be calculated separately for older subjects.

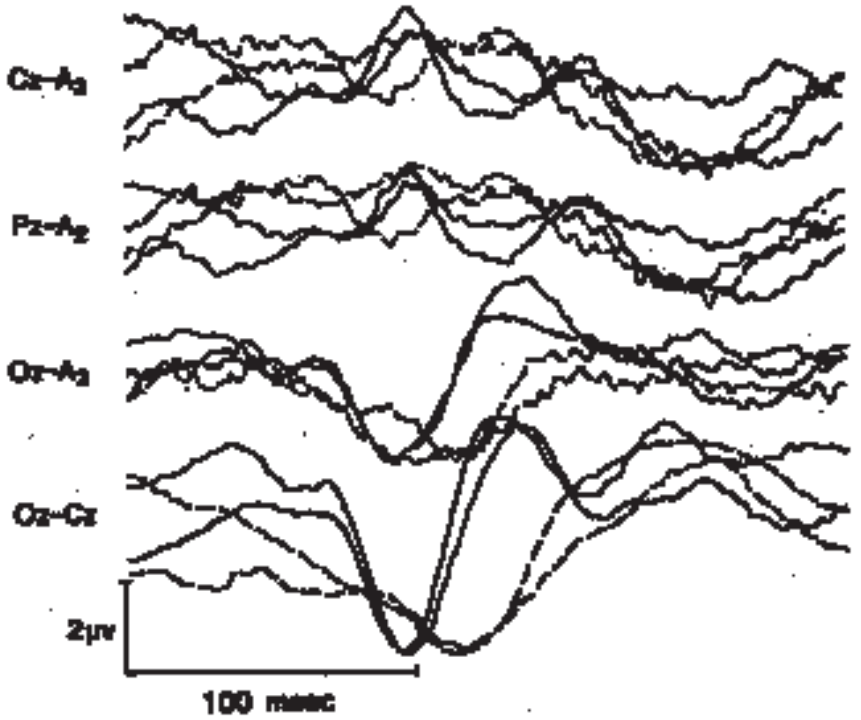

FIG. 27.12. *Solid lines:* normal PVEP with the subject attending to the stimulus, which is a video pattern generator with 21' checks, 10° field. *Dashed lines:* same eye, same subject performing forced convergence with one eye covered. The apparent latency difference is 15 msec. The maneuver was inapparent to the technician. (From Bumgartner J, Epstein C. Voluntary alteration of visual evoked potentials. *Ann Neurol* 1982;12:475–478.)

Pupils

Large pupillary asymmetries can change the amount of light reaching the two retinae by one logarithmic unit or more, and they can alter PVEP latencies by more than 10 milliseconds. Meiotics and cataracts can ha ve similar effects. Pupil size should be noted b y the technician and should be considered in evaluating small latency asymmetries.

NEUROLOGICAL APPLICATIONS OF VISUAL EVOKED POTENTIALS

The neurological utility of PVEPs is dependent on tw o properties: (a) their exquisite sensitivity to subtle lesions of the visual pathways, especially the optic nerve and chiasm, and (b) their relati ve *insensitivity* to alterations in visual acuity from ophthalmolo gical disorders. Man y studies ha ve demonstrated that prolonged P$\overline{100}$ latencies occur without detectable alteration in acuity (71,72), contrast sensiti vity (23,117,146), pupillary reactivity, color desaturation, funduscop y, or perimetr y (26). Con versely, it is extremely rare for clinical examination to show *any* abnormality of the anterior visual pathw ays when the PVEP is nor mal (26). If visual acuity is decreased but the PVEP is nor mal, a lesion of the optic ner ve or chiasm is very unlikely to be the etiology. Figures 27.13 to 27.15 illustrate mild, moderate, and mark ed latency increases, respecti vely, for P$\overline{100}$ after full-field monocular stimulation. Although neither these nor an y other PVEP abnor-

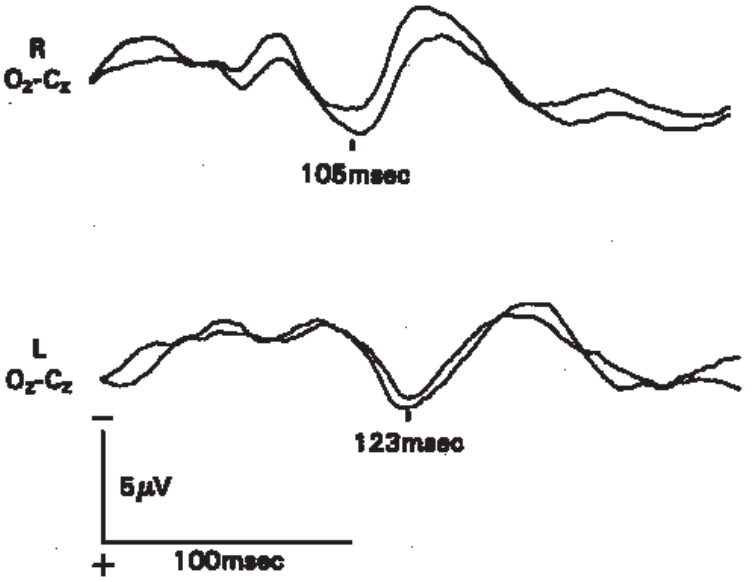

FIG. 27.13. Normal pattern visual evoked potential from right eye, and mild absolute latency prolongation from left eye, recorded as in Fig. 27.5 (99% tolerance limit, 120 milliseconds). In contrast to absolute latency, the interocular latency difference is markedly abnormal.

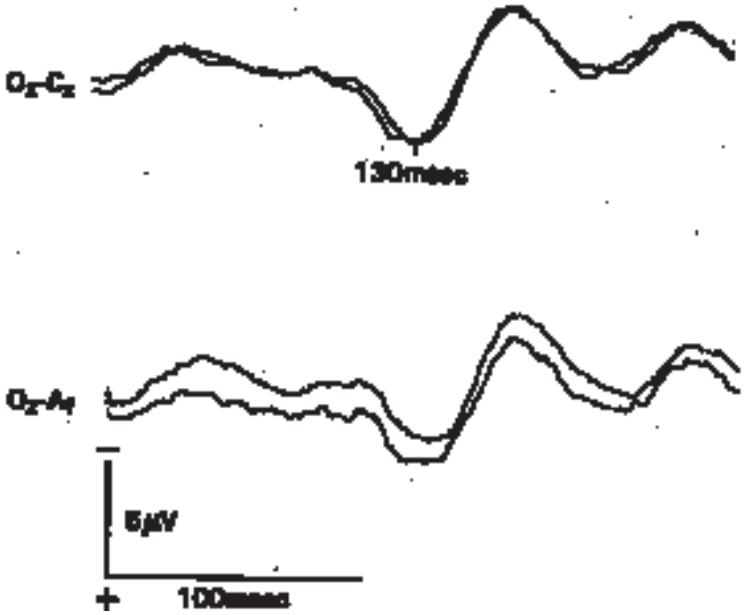

FIG. 27.14. Moderate midline latency prolongation in vertex and ear-reference derivations.

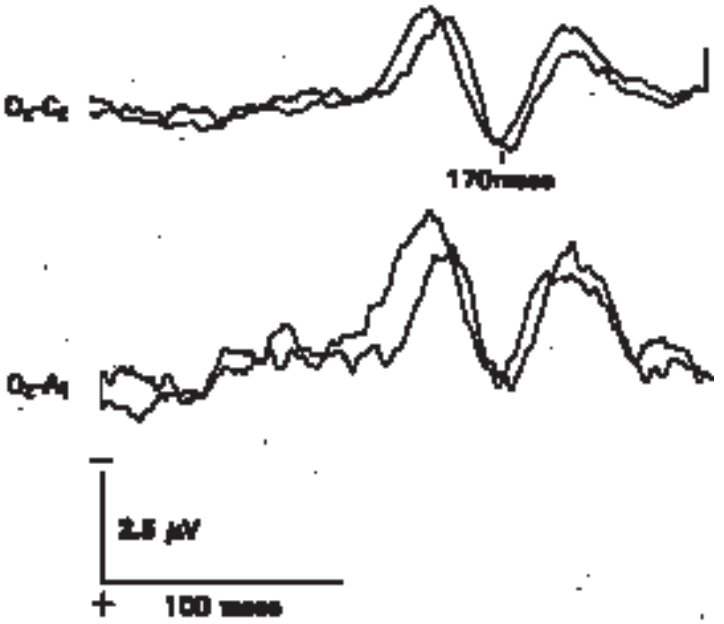

FIG. 27.15. Marked midline latency prolongation.

malities are pathognomonic for one disorder, marked latency prolongation with preservation of P100 amplitude is most characteristic of optic nerve demyelination.

Optic Neuritis and Multiple Sclerosis

Screening for asymptomatic lesions in multiple sclerosis is the most common clinical indication for PVEPs. A prolonged PVEP latency is the electrical equivalent of a pale optic disk with a Marcus Gunn pupil, and this helps to document the dissemination in space that is necessary for a diagnosis.

Across many studies on several continents, approximately 90% of patients with an unequivocal history of optic neuritis have abnormalities of the PVEP (8,29,41,71). During an acute attack, the proportion of patients with unobtainable PVEPs or prolonged P100 latencies approaches 100%. In most, latency abnormalities persist for many years, even after recovery of normal acuity.

In 1983, Chiappa (41) reviewed 26 clinical series involving nearly 2,000 patients with possible, probable, or definite multiple sclerosis. Overall, PVEP abnormalities were present in 37%, 58%, and 85%, respectively. Among 774 patients without clinical or historical evidence of optic neuritis, 54% had abnormal PVEPs, the majority of which were latency prolongations. Later series (55,84,112,121,126) documented a similar yield and a superior detection rate for asymptomatic lesions, in comparison with those found for somatosensory evoked potentials (SEPs) and brainstem auditory evoked potentials (BAEPs) (55,84). The classic PVEP pattern in multiple sclerosis is a unilateral, marked prolongation of P100 with relative preservation of amplitude (see Fig. 27.15). Such striking latency prolongations are unlikely to occur in other disorders; however, multiple sclerosis can commonly produce mildly prolonged PVEPs and their absence as well.

Many modifications have been proposed to increase the yield of PVEP abnormalities in demyelinating disorders. These include hyperventilation (47), decreased field size (32,78,118), smaller checks (121,126), LEDs (6), decreased luminance (29), red/black patterns (118), pattern onset stimulus

(4), hemifield stimulation (121,144), multiple orientations of gratings (28), and Fourier analysis (35). Hyperthermia has been tried as a provocative test; it usually decreases PVEP amplitudes both in normal subjects and in patients with multiple sclerosis but has no effect on latency (104,181). Addition of pattern ERG may help in clarifying the pathophysiological processes of abnormal PVEPs in multiple sclerosis but does not much affect the yield (36).

It is not possible to use all of these additional techniques simultaneously or sequentially in every patient. Some techniques, such as small check or field size and hemifield stimulation, are mutually exclusive. Patient tolerance and the need for multiple additional control studies also limit the number of variations that can be tried in a single subject before PVEPs deteriorate (155). A general screen for patients of varying age, acuity, and cooperation might incorporate full-field testing with checks 50 minutes of arc across and high luminance (at least 50 cd per square meter). For these conditions, a series of 20 to 30 normal controls is adequate. A higher sensitivity approach to cooperative patients with good acuity could involve a full-field pattern with low luminance (less than 40 cd per square meter) (29), small field size, and small checks, followed by hemifield testing. The latter approach would generate a higher yield of VEP abnormalities. It would also be expected to produce a higher percentage of false-positive results and to require a much larger control group compensated for age.

The widespread availability of magnetic resonance imaging (MRI) has modified the indications for evoked potentials (55,60,130). However, in one series (55), six of 11 patients with suspected multiple sclerosis and normal MRIs had abnormal PVEPs, and four of those six had cerebrospinal fluid immunoglobulin abnormalities. Conventional MRI is relatively insensitive to lesions of the optic nerve. Even with special techniques, MRI is less sensitive and less cost effective than PVEPs for detecting optic nerve lesions (111). Thus, the PVEP remains useful as an index of disease progression or improvement in clinical trials for treatment of multiple sclerosis (50,61,124).

Evoked potentials and especially MRI have influenced the criteria for diagnosis of multiple sclerosis, which include dissemination in time as well as in space. Multiple central nervous system lesions at the time of presentation increase the likelihood of progression to multiple sclerosis. However, the presence of other lesions accompanying optic neuritis may be a consequence of acute disseminated leukoencephalitis (130), vasculitis, or other multifocal disorders. A specific diagnosis will still depend on changes over time and on clinical judgment as well as on high technology. With the large number of neurophysiological, radiological, and immunological techniques now available to assist in the diagnosis of multiple sclerosis, clinical skills remain important in choosing and interpreting procedures efficiently and effectively.

Other Neurological Disorders

Diseases of the Optic Nerve

Anterior ischemic optic neuropathy is a common disorder of later life, often associated with temporal arteritis and other forms of vasculitis, tertiary syphilis and other infections, arteriosclerosis, or migraine. Thompson et al. (173) found that the PVEP was abnormal in all cases of ischemic optic neuropathy studied within 2 weeks of onset, as well as in 10 of 12 eyes studied more than 2 months later. Although the $\overline{P100}$ often appeared bifid or delayed, these investigators reported that detailed partial-field analysis showed the true pathophysiological process to be an alteration in PVEP topography resulting from macular field defects. PVEPs are absent or show mild latency increases in almost all cases of Leber's hereditary optic atrophy, but only subtle changes are found in presumed asymptomatic carriers (33).

Optic atrophy occasionally accompanies peripheral neuropathies, and PVEP latency prolongations have been reported in Charcot-Marie-Tooth disease (107,167), giant axonal neuropathy (101), and neuropathy associated with macroglobulinemia (10).

Increased intracranial pressure can produce papilledema and visual loss, and so it is not surprising that $\overline{P100}$ latency changes have been reported with hydrocephalus (49,150) and pseudotumor cerebri (164), although such abnormalities are not particularly frequent.

Sarcoidosis has multiple central nervous system and ocular manifestations, including optic neuropathy. Streletz et al. (166) studied PVEPs in 50 patients with systemic sarcoidosis. Abnormalities of latency and amplitude were found in all four patients with clinical brain involvement, as well as in seven of 29 who had no clinical evidence of ocular or neurological disease.

A variety of toxins may produce clinical or subclinical effects on the optic nerve. PVEPs have been used to monitor therapy with ethambutol (182), cisplatin (99), and deferoxamine (172). Latency prolongations have been described with quinine toxicity (59) and nitrous oxide toxicity (79). $\overline{P100}$ delays are reported in patients with chronic alcoholism (39). PVEPs are uniformly absent or delayed in patients with tobacco-alcohol amblyopia (92). In most of these conditions, improvement has occurred after discontinuation of therapy or after abstinence; no significant $\overline{P100}$ latency prolongation was

found in a carefully studied group of abstinent alcoholics (51) One patient who was transiently blind as a result of quinine toxicity had prolonged latencies after recovery (59).

Tumors

Most patients with extrinsic compression of the optic nerve or chiasm have abnormal PVEPs (63,70,80,128). In general, such lesions are expressed by a decrease in amplitude and by relatively modest prolongations in latency. In cases of pituitary adenoma, PVEPs may improve the serial assessment of visual function (80).

Leukodystrophies and Spinocerebellar Disorders

PVEPs are usually abnormal in central nervous system disorders that involve central myelin. Adrenoleukodystrophy, Pelizaeus-Merzbacher disease, and metachromatic leukodystrophy prolong PVEP latency (7,31,102, 103) and may produce abnormalities in presymptomatic affected children (102). The site of the responsible lesion is not clear, given the predilection of these disorders for the cerebral hemispheres. Prolonged latencies have been found in various proportions of patients with Friedreich's and other inherited ataxias (15,32,123,131), familial spastic paraparesis (15,75,131), tropical spastic paraparesis (8), subacute combined degeneration (vitamin B_{12} deficiency) (93), and vitamin E deficiency (86,109). Latency prolongation in this group of disorders is usually symmetrical. Abnormalities resulting from vitamin E and B_{12} deficiency may improve with treatment (86,93,109). Except for the early childhood leukodystrophies, all of these conditions share clinical features with multiple sclerosis, and abnormal evoked potentials should not be overinterpreted as proof of a specific disorder.

Miscellaneous Central Nervous System Disorders

PVEPs are delayed and "desynchronized" in cerebrotendinous xanthomatosis, and they improve after treatment with chenodiol (114). PVEP latencies were prolonged in a patient who suffered decompensation of phenylketonuria in adulthood (105).

PVEP abnormalities have also been found in central nervous system disorders whose major clinical and pathological features lie *outside* the sensory pathways. $P\overline{100}$ latency was delayed in three of eight patients with neurological involvement from Wilson's disease (42), as well as in patients with idiopathic Parkinson's disease (24). The changes in Parkinson's disease have been correlated with abnormalities of the ERG and have been ascribed to involvement of dopaminergic amacrine cells in the retina (64). However, the nature and existence of PVEP abnormalities in Parkinson's disease have been disputed by several other laboratories. Tartaglione et al. (171) reported that they occurred with sine-wave gratings of 2 cycles per degree but not with checks of 55 minutes of arc. In contrast, Bhaskar et al. (14) found that prolonged latencies occurred with both gratings and checks but that improvement after L-dopa treatment occurred only with checks. Because PVEPs have little practical application in the diagnosis of Parkinson's disease, prudent interpreters might choose to select test conditions that are *less* likely to be affected by it.

As with SEPs and conventional photic stimulation, PVEPs of unusually high amplitude occur in familial myoclonic epilepsies (69,142). Although otherwise nonspecific, this trait has proved to be useful within a large pedigree in screening for mild or asymptomatic mitochondrial encephalomyopathy (Fig. 27.16). VEP latency increases are also described in photosensitive epilepsies (108).

Both flash and pattern VEPs have been studied in patients with Alzheimer's disease and other dementias, with varying results. Changes in $P\overline{100}$ latency seem to be minimal (83) or nonexistent (76). In comparison

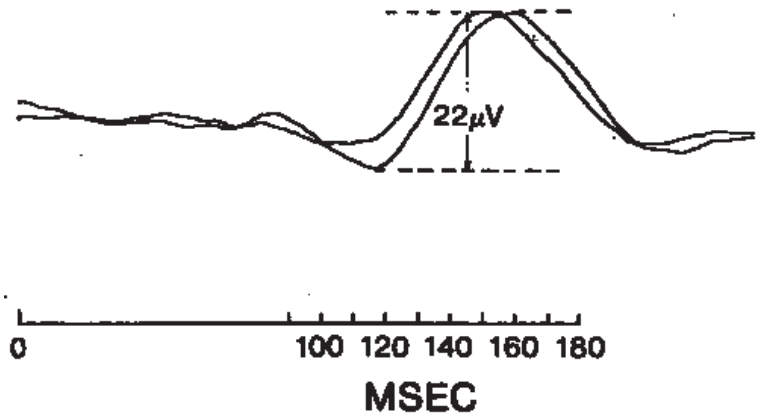

FIG. 27.16. Very high amplitude $N\overline{145}$ and waveform variability in an asymptomatic carrier of mitochondrial encephalomyopathy. (From Rosing H, Hopkins L, Wallace D, et al. Maternally inherited mitochondrial myopathy and myoclonic epilepsy. *Ann Neurol* 1985;17:228–237.)

with appropriate-aged controls, demented subjects have been reported to show latency prolongation in the late components of the PVEP (N145 and after) (83), as well as in some components of the flash VEP (FVEP) (76). Similar changes have been described with anticholinergics in normal subjects (9,138). Group differences were shown in Alzheimer's patients with the use of steady-state stimulation and Fourier analysis of frequencies from 15 to 30 Hz (174). These changes are not a consequence of diminished attention (83). However, because the affected components of the VEP are present less reliably than P100 and are more variable, the applicability of VEPs to individual cases of dementia is uncertain.

Migraine has been accompanied by increased high-frequency photic following on EEG (125,154), by increased oscillatory wave amplitude of the PVEP 250 to 500 milliseconds after a flash or pattern stimulus (see Fig. 27.5) (116), and by hemifield changes that are said to match the visual aura (168). However, the specificity and clinical utility of these changes have been disputed (179,180).

Visual Evoked Potentials in Coma

VEPs have been used in conjunction with SEPs and BAEPs to assess disability and attempt prognosis in prolonged coma, usually after closed-head trauma. In most published studies, the stimulus has been a stroboscopic flash, and the ERG has been monitored to verify retinal function. In some series, the FVEPs have been graded by overall configuration rather than by latencies and amplitudes (65), making comparisons among reports difficult. Anderson et al. (5) found that severely abnormal VEPs were accurately predictive of an unfavorable outcome after closed-head trauma. However, normal VEPs did not reliably predict a favorable result, and VEPs did not improve prognostic accuracy beyond that obtained with SEPs alone. Rappaport et al. (135,136) reported that in patients with head injury, the FVEP had a correlation of only 0.24 with disability ratings performed 1 year later. Pfurtscheller et al. (132) had difficulty making any correlation between VEPs and outcome. Gupta et al. (66) studied patients 6 to 24 months after head injury, when they had recovered consciousness and were able to cooperate for PVEPs. Abnormal PVEPs were present in one-third of all patients, as well as in half of those with severe residual cognitive impairment.

In most series, absence of the FVEP (with preserved ERG) appeared to be an accurate predictor of severe disability or death after closed-head trauma. However, a robust flash response is not predictive of recovery.

Visual Evoked Potentials in the Operating Room

Because the PVEP is sensitive to lesions of the optic nerve and chiasm, it has been employed intraoperatively to monitor surgical procedures that might endanger these structures. Unfortunately, the middle-latency PVEP is much more affected by level of consciousness, anesthesia (40,147,153, 177), and hypothermia (140,145) than are short-latency SEPs and BAEPs. Because of the difficulty in presenting true pattern reversal stimuli to the eyes of anesthetized patients, the typical stimulus is a flash from a strobe or from red LEDs mounted in small goggles, delivered through closed eyelids. The resulting evoked potentials are extremely labile, with a high incidence of false-positive changes that detracts from their utility (34,137). Harding et al. found that a combination of enflurane and nitrous oxide had minimal effect on VEPs and that disappearance of a previously normal VEP for more than 4 minutes correlated significantly with postoperative visual loss. Intraoperative evoked potentials are discussed more extensively in Chapter 31.

OPHTHALMOLOGICAL APPLICATIONS OF VISUAL EVOKED POTENTIALS

Visual Acuity

The most common applications of VEPs are chosen largely for their *lack* of correlation with visual acuity and ophthalmological disease. However, checkerboard patterns or gratings with sufficiently small elements can be used to estimate acuity comparable to the Snellen eye chart. Psychophysiological studies in adults indicate that reasonably accurate estimates can be made by plotting PVEP amplitude against spatial frequency for patterns of several different sizes. Amplitudes are then extrapolated to zero, which corresponds approximately to threshold for detection of the pattern (120,156). Sokol (156) used transient PVEPs from checkerboard patterns to determine visual acuity in infancy. He estimated acuities of 20/150 at 2 months of age, improving to 20/20 by age 6 months.

Much more rapid estimates of PVEP amplitude can be obtained with steady-state stimuli (i.e., rapid pattern reversal at 10 to 20 Hz) and signal analysis techniques such as the Fourier transform (54,170) (Fig. 27.17). Using a total test duration of 10 seconds, Norcia and Tyler (120) estimated an acuity of 4.5 cycles per degree in the first month of life; adult values of 20 cycles per degree were reached by the age of 8 months.

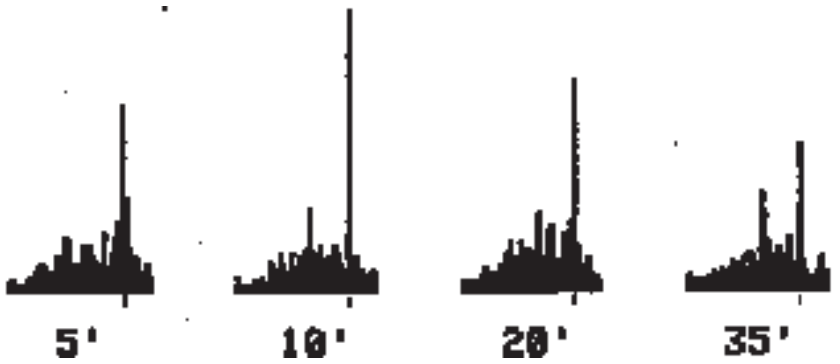

FIG. 27.17. Magnitude spectra obtained from Fourier transforms of steady-state visual evoked potentials, using four consecutive sets of patterns reversing at 15 per second with checks of the indicated dimensions. The histograms cover the range from 0.45 to 18.75 Hz, and the prominent 15-Hz peaks are indicated with tick marks at the bottom of each histogram. The patient, a 6-year-old boy, had normal acuity, and the checks measuring 10 minutes of arc are near the peak of his contrast sensitivity curve. Total recording time was 8.5 seconds. (From Epstein C, Gammon A, Gemmill M, et al. Visual evoked potential pattern generation, recording, and data analysis with a single microcomputer. *Electroencephalogr Clin Neurophysiol* 1984;56:691–693.)

Hysteria and Malingering

Hysterical visual loss or exaggeration of a mild impairment are common problems in neuro-ophthalmology and are frequent sources of referral to the VEP laboratory. Although good cooperation may be difficult to obtain in these patients, technically adequate PVEPs allow some useful conclusions. A normal P100 latency makes lesions of the optic nerve or anterior chiasm very unlikely as the cause of subjective visual loss. A well-defined response to checks of 10 minutes of arc indicates essentially normal acuity, and a good response to checks of 45 minutes of arc or smaller indicates vision of 20/200 or better (41). Long-latency PVEPs have also been used to document responses to stimuli that patients say they are unable to see (176). However, normal PVEPs do *not* rule out retrochiasmatic visual field defects, especially with full-field stimulation and recording at the occipital midline. Very rare patients with complete cortical blindness have recordable PVEPs when an island of striate cortex is spared by extensive parieto-occipital lesions (21). In general, such cases are easily identified by neurological and radiological evaluation.

As discussed in the section on patient factors, abolition of the PVEP (and even mild degrees of latency prolongation) may be accomplished volitionally by some subjects despite apparently good cooperation (27). In suspect situations, such findings should be assessed with caution before they are interpreted as proof of organic disease.

Amblyopia

With small checks or gratings, amblyopia ex anopsia in children is characterized by decreased amplitude and, occasionally, increased latency of PVEPs. Friendly et al. (57) used reversing checks of 15 minutes of arc on edge and were able to identify the amblyopic eye correctly in 22 of 27 children. They also misclassified one of four normal subjects as amblyopic. Sokol et al. (157) found that PVEPs with checks of 15 minutes of arc had a sensitivity of 96% when the acuity difference between eyes was three lines or more on a Snellen chart. However, sensitivity fell to 50% with a two-line acuity difference, and with a one-line difference, it was only 30%. The magnitude of amplitude asymmetry in amblyopic subjects correlated poorly with the asymmetry in acuity on the Snellen chart.

Glaucoma

PVEP latencies were abnormal at the occipital midline in a little over half of all eyes with glaucomatous field defects (30,175), but in less than one-quarter of those with ocular hypertension (175). Surprisingly, latency prolongation was most likely to be found with checks of 48 minutes of arc rather than with smaller checks of 12 minutes. Transient PVEPs were less sensitive than steady-state PVEPs at 7.5 alternations per second. Increased PVEP latency was associated with visible cupping and pallor of the optic disk.

Retinopathies

Central serous retinopathy is important in the differential diagnosis of optic neuritis. It often produces similar symptoms of central scotoma and decreased acuity, and it commonly produces PVEP delays. Papakostopoulos et al. (129) reported that in six patients with central serous retinopathy, PVEP latencies averaged 7 milliseconds longer in the affected eye. Sherman et al. (151) found significantly increased latencies in nine of ten involved eyes. In comparison with the normal eye, the mean delay was 10.6 milliseconds with checks of 56 minutes of arc and 21 milliseconds with checks of

14 minutes. One subject showed a latency difference of 43 milliseconds. Amplitudes were affected less than latencies, further mimicking PVEP changes seen in demyelinating disorders. Kraushar and Miller (90) reported on three patients in whom ophthalmologists mistook central serous retinopathy for evidence of multiple sclerosis. The retinal disorder most often improves spontaneously, and, in contrast to the usual outcome in optic neuritis, PVEP abnormalities generally remit with it.

PVEP delays have been reported with a variety of other acute and chronic retinal disorders (22,97). Because similar latency delays can be produced by retinal diseases and by optic neuritis, complete ophthalmological examination is *mandatory* in patients with symptomatic, nonhomonymous visual loss, regardless of PVEP findings.

PARTIAL-FIELD STIMULATION

The VEP after full-field pattern stimulation represents the sum of multiple components arising from both hemispheres and from both upper and lower quadrants (Fig. 27.18*A*). Its apparent simplicity is deceptive: The true complexity of the PVEP can be appreciated—and clinically used—only when portions of the visual field are stimulated selectively.

As previously noted, wide-angle pattern stimulation of either hemifield produces a net VEP vector that tends to point obliquely back through the opposite hemisphere. Thus, as implied by the direction of the arrow in Fig. 27.1, P$\overline{100}$ is most often maximal ipsilateral to the stimulus rather than contralaterally over the active occipital lobe (20,95,152). In addition to occipital electrodes LO and RO, hemifield studies require more lateral recording sites in the form of left and right temporal electrodes LT and RT, placed 5 cm lateral to LO and RO (3). With a circumferential array of five posterior electrodes referenced to a frontal site, normal subjects show an asymmetrical response across the temporal-occipital scalp. P$\overline{100}$ is recorded at the ipsilateral occipital lead, and a nearly simultaneous negative wave, N$\overline{105}$, appears at the contralateral temporal area (Fig. 27.18*B*) (11,16,67). N$\overline{105}$ is independent of the occipital P$\overline{100}$ and more variable; it arises from projections of the peripheral visual field rather than from the area of the macula (17,18,20,67). In about 50% of normal subjects, the lateral N$\overline{105}$ forms part of a full "PNP" complex, with surrounding P$\overline{75}$ and P$\overline{135}$ waves that roughly mirror the more familiar "NPN" waveform of the full-field response (67) (see Fig. 27.18*B*). The transition from NPN to PNP complexes usually occurs near the contralateral occipital lead.

If the peripheral retina is stimulated while central vision is occluded by a central scotoma, the contralateral N$\overline{105}$-P$\overline{135}$ complex is enhanced, whereas the ipsilateral P$\overline{100}$ is attenuated (Fig. 27.19) (17,18). The P$\overline{100}$ may disappear entirely with scotomata of 5 to 10 degrees. Under these circumstances, the enhanced N$\overline{105}$-P$\overline{135}$ complex may extend into midline and even ipsilateral leads, and it may be confused with a delayed P$\overline{100}$. If the absence of the true P$\overline{100}$ is not recognized, the preserved P$\overline{135}$ component will be misinterpreted as a latency prolongation. This is probably the mechanism for some apparent P$\overline{100}$ delays reported with macular disease (58) and partial central-field defects (173). In addition, the presence of a prominent P$\overline{75}$ component with the exaggerated P$\overline{135}$ may lead to a W-shaped waveform on full-field testing; this can then be misinterpreted as a bifid P$\overline{100}$ (85). Absence of a true P$\overline{100}$ can be confirmed directly by selective stimulation of the central field with a small field size (2 to 4 degrees) and small checks of 30 minutes of arc or less. Retinal disease—and, occasionally, central lesions—may delay one half-field response in comparison with the other in the same eye. (This is yet another explanation for some W-shaped responses seen on full-field testing.) Such cases can be resolved by testing each half-field separately.

The temporal-occipital asymmetries after hemifield stimulation are most reliably demonstrated with larger field sizes and larger checks than those that may be used for routine full-field testing. Small fields and checks emphasize contributions to the PVEP from the macular region, whereas they minimize input from peripheral elements that produce the N$\overline{105}$. Thus, hemifield testing is best performed with a relatively large stimulus field, extending at least 10 to 16 degrees from the midline, and with check sizes of at least 50 minutes of arc.

Accurate fixation and a consistent level of attention by the subject are even more crucial for partial-field recording than for full-field PVEPs. Partial-field studies produce the clearest results if visual fixation is maintained 1 to 2 degrees outside the edge of the reversing pattern, thereby preventing activation of uncrossed fiber systems in the fovea (98). If patterns occupying the right and left hemifields are reversed sequentially rather than together, the associated PVEPs can be sampled during a single average (143). This modification controls for changes in attention, and often improves the quality of hemifield recording (3).

Applications

Hemifield studies are more successful than full-field PVEPs for evaluating postchiasmatic visual field defects (19,68,94,100,128,139,165). A complete homonymous hemianopia characteristically results in decreased amplitude or complete loss of the response from the affected field (Fig. 27.20) (68,94,128), rather than increased latency (144). Because of the consider-

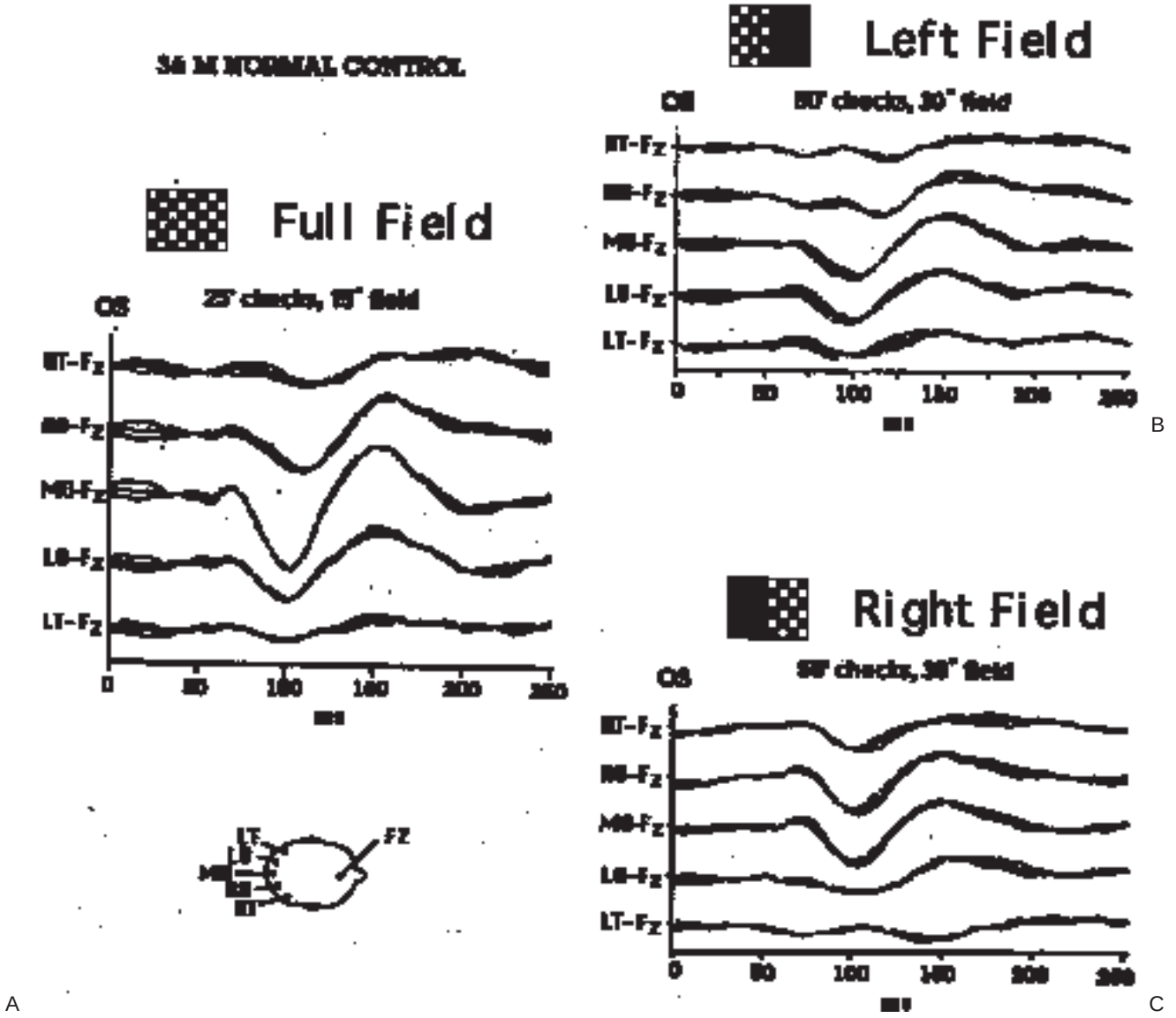

FIG. 27.18. Normal pattern visual evoked potentials from full-field and hemifield stimulation in a healthy control subject. **A:** The response to full-field stimulation is maximal at the midoccipital electrode and is symmetrical across the posterior temporal-occipital region. **B:** The response to stimulation of the left hemifield shows maximal positivity of P100 at the midline and the ipsilateral occipital area (LO). The contralateral occipital (RO) and temporal (RT) electrodes register an almost synchronous negativity, N105, surrounded by positive waves, P75 and P135. **C:** A complementary asymmetry is seen on right hemifield stimulation, although N105 is visible only from the LT electrode. (Figure courtesy of T. A. Pedley.)

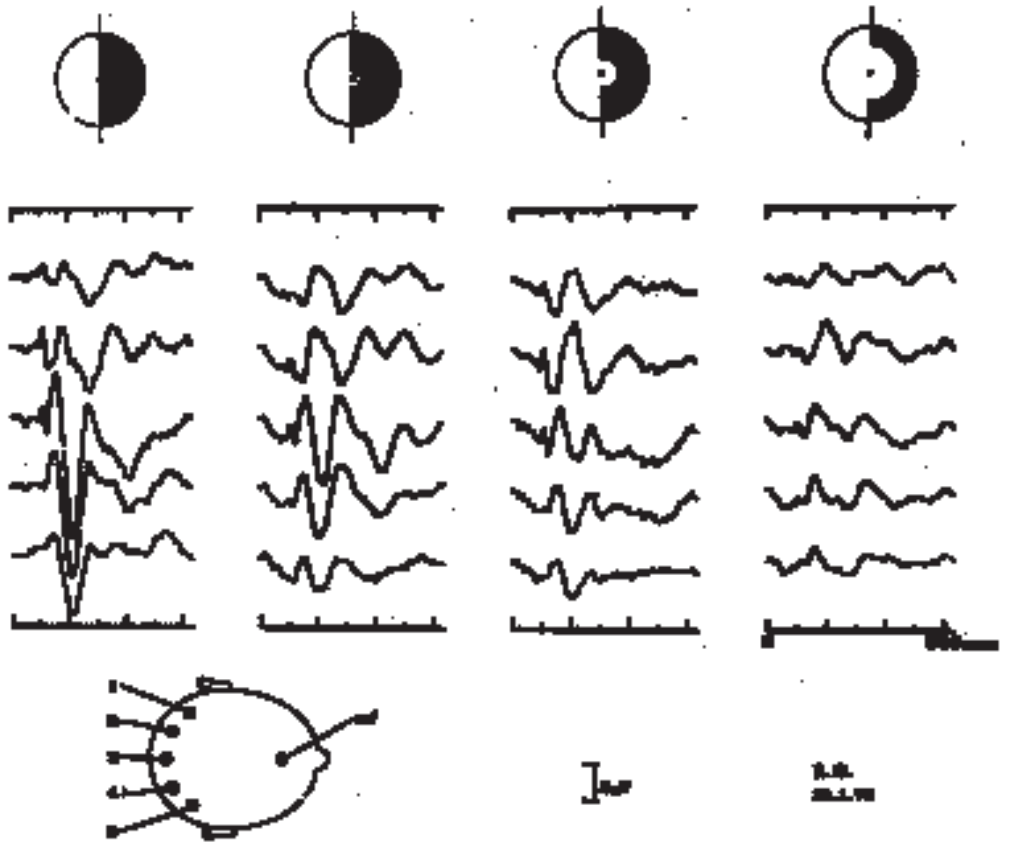

FIG. 27.19. The effect produced by a series of artificial central "scotomata" of increasing radii on the right half-field response in a single subject. The P100 is progressively attenuated, whereas the contralateral N105 is initially enhanced. Tracings from left to right show the complete half-field response, followed by responses with artificial scotomata of 2.5, 5.0, and 10.0 degrees in the central field. (From Blumhardt L, Barrett G, Halliday A, et al. The effect of experimental "scotomata" on the ipsilateral and contralateral responses to pattern-reversal in one half-field. *Electroencephalogr Clin Neurophysiol* 1978;45:376–392.)

able amplitude variability of hemifield responses in normal persons, it is best to interpret amplitude asymmetries conservatively. In laboratories with limited experience in recording half-field PVEPs, an abnormality should be identified only when the hemifield response is absent (68). In laboratories that have developed an adequate series of normative studies and recording experience, clinicians can interpret P100 amplitude asymmetries at the ipsilateral occipital electrode of greater than 3:1 as usually abnormal.

Hemifield latency asymmetries were rare in the reports of Blumhardt et al. (19) and Haimovic and Pedley (68), whose patients had destructive hemisphere lesions resulting from tumor, stroke, trauma, and surgery. Others (85,121,144), however, have reported more frequent half-field latency abnormalities in patients suspected of having multiple sclerosis or compressive lesions of the optic chiasm (25). In the latter studies, hemifield recording was also reported to increase the yield of abnormalities or improve analysis of aberrant PVEP waveforms; however, neurophysiological abnormalities were generally not correlated with visual field defects on conventional perimetry.

Unlike PVEPs from lateral hemifields, those from upper and lower fields are generally not symmetrical in normal persons and do not form mirror images above and below a midoccipital electrode. Instead, the full-field response reflects predominantly that from the lower field (96,110). Altitudinal PVEPs have not been widely used. Thus, although complete hemianopia can usually be identified, it has not been possible with partial-field PVEPs to

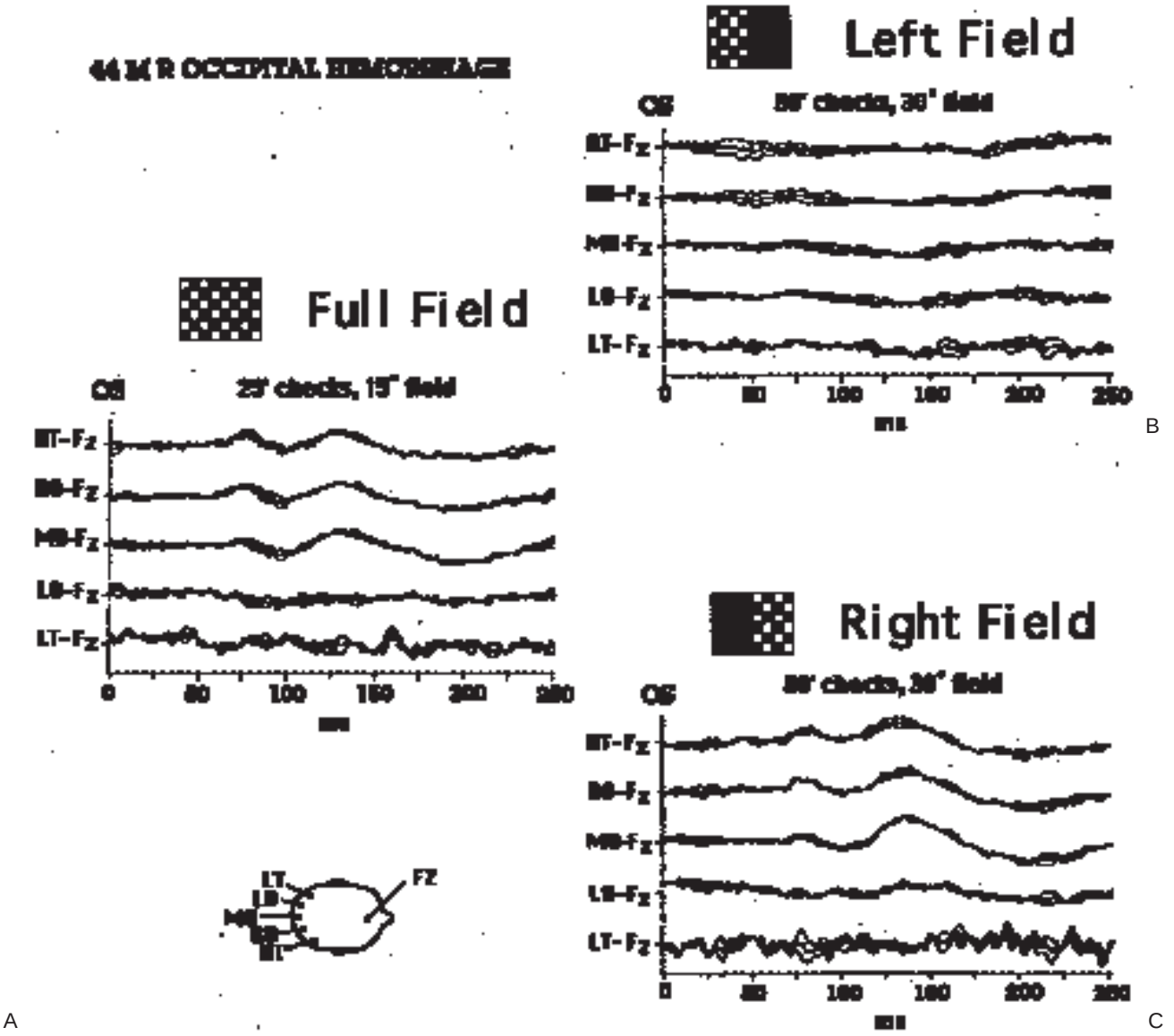

FIG. 27.20. Abnormal pattern visual evoked potentials (PVEPs) in a patient with complete left homonymous hemianopia after a right occipital lobe hemorrhage from an arteriovenous malformation. **A:** The full-field response demonstrates a "paradoxical" asymmetry with the $\overline{P100}$ lateralized to the right of midline. **B:** Selective stimulation of the left hemifield elicits no discernible response. **C:** Stimulation of the intact right hemifield elicits a normal response, which is virtually identical to the PVEP after full-field stimulation. (Figure courtesy of T. A. Pedley.)

achieve the precise localization routinely obtained with skilled perimetry and neuro-ophthalmologic examination. Conventional PVEPs do not reliably detect changes involving much less than one hemifield or identify anatomical landmarks such as partial incongruity, Wilbrand's knee, and the loop of Meyer.

Steady-state VEP perimetry has been applied in the visually evoked spectral array (12,38), which delivers stimuli to all quadrants of the retina at slightly different frequencies. Unfortunately, the accuracy of testing with the visual evoked spectral array is restricted by the same factors that confound attempts at perimetry with transient VEPs. In cooperative and communicative patients, it cannot replace conventional visual field testing. In patients who cannot cooperate, results have limited clinical value.

FLASH VISUAL EVOKED POTENTIALS

FVEPs are familiar to electroencephalographers as the photic following (or "driving") response. Averaged FVEPs were studied for many years before evoked potentials came into use as a common clinical test. However, the anatomy, physiological features, and applications of FVEPs are quite different from those of the pattern-shift techniques that have largely superseded them.

The cortical response to flash stimuli is much more widespread, complex, and variable than that resulting from pattern shift. Comprehensive rules for interpretation have been difficult to formulate despite extensive studies (1,89), and none are offered here. The greater topographic complexity of FVEPs may be attributable, in part, to the effects of activating additional cortical projection systems. Before reaching the thalamus, one group of retinal axons leaves the optic tract and courses to the midbrain, synapsing in the pretectal area and superior colliculus. These fibers mediate the pupillary response to light, and they also generate an independent retinotopic field in the superior colliculus. Axons from the superior colliculus project to the pulvinar, which in turn projects to nonstriate areas of the occipital and parietal lobes. "Far-field" VEPs arising from the subcortical pathways have been much more difficult to record than the corresponding short-latency potentials for auditory and somatosensory systems. However, a few investigators using flash stimuli have identified an early oscillatory potential that appears to arise subcortically (46,133).

The great variability of FVEPs limits their utility, because it complicates the task of separating normal responses from abnormal ones. An apparently robust FVEP may occur even with cortical blindness (56). Thus, the ACNS Guidelines (3) advise that only the total absence of a flash response can be considered definitely abnormal. Although some authorities consider this recommendation excessively conservative, the difficulty in interpreting FVEPs generally confines their clinical use to situations in which pattern stimulation is not feasible.

Applications

The FVEP can be recorded easily through closed eyelids and through all but the most dense ocular opacities (Fig. 27.21). It is unaffected by refractive errors. These properties make it useful in assessing function of the optic

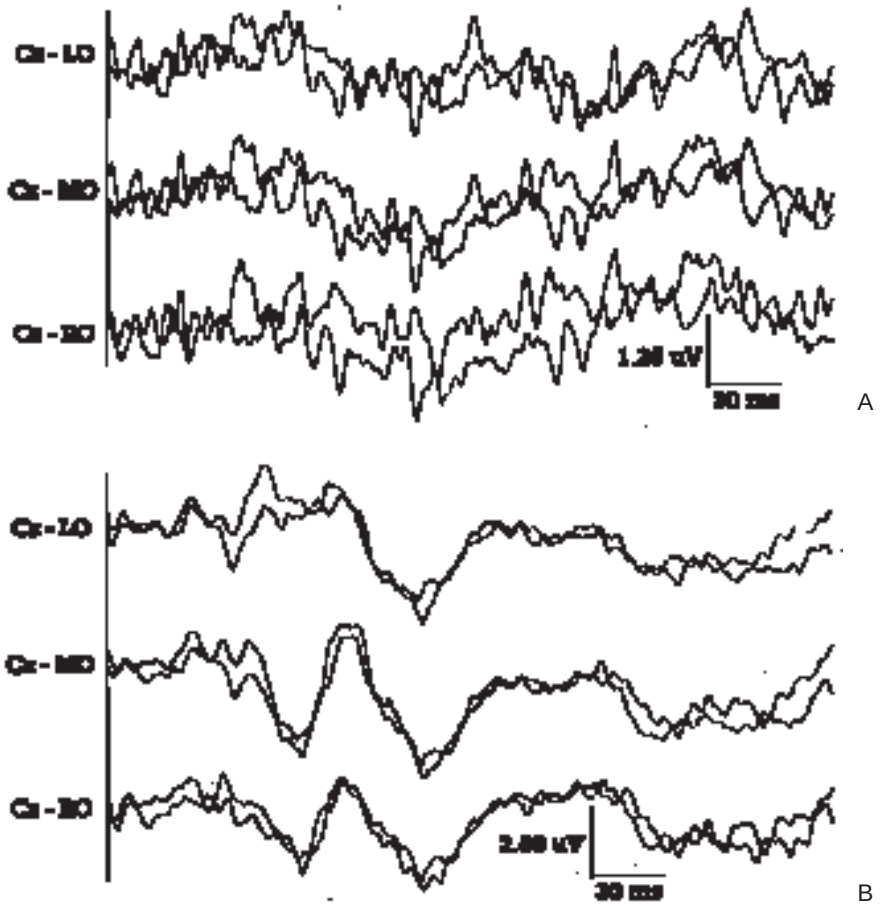

FIG. 27.21. Pattern visual evoked potential (PVEP) in a 68-year-old woman with dense cataracts. **A:** The PVEP is essentially absent, even with 1-degree checks. **B:** The flash visual evoked potential is robust and complex.

nerve and central visual pathways in patients with ocular scarring or hemorrhage. Preservation of a well-defined FVEP in these situations suggests that the visual pathways are at least partially intact, whereas its absence usually indicates that no useful visual function can be salvaged. Note, however, that stroboscopic flash units often produce an audible click with each flash; to prevent auditory evoked potentials from contaminating the FVEP, the subject may have to wear earphones that provide sound attenuation or white noise.

The wide topographic distribution of FVEPs has led to their use with computerized "brain mapping" systems, in which they are preferred over the spatially restricted PVEP. Topographic evoked potential analysis depends primarily on asymmetries between hemispheres, and such asymmetries have been shown to occur at the sites of brain tumors and other structural lesions (48). Amplitudes of FVEPs are increased focally in some children with benign rolandic epilepsy (48). Appropriately localized abnormalities were reported in almost 50% of patients with intractable focal seizures (122). However, such sophisticated computer analyses require at least as much skill as conventional EEG and evoked potentials; they have not gained wide acceptance in clinical medicine.

PATHOPHYSIOLOGY OF LATENCY PROLONGATION IN VISUAL EVOKED POTENTIALS

Because VEPs are sensitive to disorders of myelin, and because damage to the myelin sheath produces slowing of transmission, a decrease in optic nerve conduction velocity is commonly invoked as the cause of VEP latency prolongation in neurological disease. Quantitative calculations support the plausibility of this explanation (106). However, as noted previously, conduction through the optic nerve accounts for only a small fraction of the latency from stimulus onset to the peak of P$\overline{100}$; therefore, other possible mechanisms of latency prolongation must be considered as well. A fall in luminance increases the interpeak interval from P$\overline{50}$ to P$\overline{100}$, although both peaks appear to arise from the cortex (29). Simple refractive errors produce substantial delays with small pattern elements (159), presumably at a retinal level. The retinal response to pattern reversal may be delayed through damage to dopaminergic systems (24,64). Paracentral scotomata may displace the lateral PNP complex into the occipital midline, where P$\overline{135}$ has the appearance of a delayed P$\overline{100}$ (58,173). Retrochiasmatic demyelination may produce true half-field delays (144), although this mechanism has been more difficult to document rigorously. Thus, an apparent latency prolongation may occur at several different sites along the visual pathways. There remains a strong empirical correlation between optic nerve disease and a delayed P$\overline{100}$, but the interpreter must consider the localization, mechanism, and cause of VEP abnormalities separately in every case.

SUMMARY

Full-field PVEPs are exquisitely sensitive to lesions of the optic nerve and anterior chiasm. However, they may also be affected by a wide variety of other ophthalmological and neurological disorders, by patient factors, and by the choice of test conditions. The major benchmark of PVEP interpretation is the latency of P$\overline{100}$ at the occipital midline; normal values for this and other measurements must generally be established independently by each laboratory. Although check sizes of less than 30 minutes of arc may increase the sensitivity of the PVEP in some situations, a size between 30 and 50 minutes lessens the influence of confounding factors and simplifies the collection of normative data.

Retrochiasmatic lesions of the visual system are often not detected by full-field PVEP testing. Hemifield techniques increase the sensitivity of PVEPs to retrochiasmatic lesions, but their interpretation is more difficult and their precision does not match that of conventional visual field assessment.

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Chapter 28

Brainstem Auditory Evoked Potentials

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Brainstem Auditory Evoked Potentials
Acoustic Stimulation
Recording Strategies
Conducting a Brainstem Auditory Evoked Potential Study
The Normal Brainstem Auditory Evoked Potential
The Abnormal Brainstem Auditory Evoked Potential
Clinical Correlations
References

Potentials elicited from stimulation of the auditory system are called auditory evoked potentials. They are categorized by their latency from stimulus onset and their neural origin. The short-latency auditory evoked potentials are those arising within the first 15 milliseconds after appropriate acoustic stimulation in normal subjects. By neural origin, short-latency auditory evoked potentials are subdivided into the electrocochleogram and the brainstem auditory evoked potentials (BAEPs). BAEPs are widely used in clinical neurology, in contrast to middle-latency auditory evoked potentials and long-latency auditory evoked potentials. The latter two responses are not yet widely used for diagnostic or monitoring applications.

Clinical applications of BAEPs for hearing assessments are particularly useful for patients who are unable to cooperate sufficiently for typical audiological assessment techniques. BAEP testing is common in infants and cognitively impaired older patients. Although usually the domain of audiology, hearing deficits caused by either abnormalities of sound conduction to the inner ear or neurosensory abnormalities of the cochlea and/or acoustic nerve may alter potentials generated in the brainstem. Because of the interpretative problems caused by auditory impairments, this chapter also touches on the effects of audiological deficits on BAEPs and electrophysiological methods of assessing such impairments.

BAEP techniques are useful partly because they are sensitive to the degree that the brainstem auditory pathway can be grossly abnormal without detectable clinical manifestations. This is true both of disorders within the brainstem, such as demyelination, and of extrinsic pathological processes, such as some tumors.

BRAINSTEM AUDITORY EVOKED POTENTIALS

Acoustic Stimulation

Stimulus Types and Applications

The stimulus type selected is determined by the diagnostic application.

Sine Waves

Pure tone audiometry involves the use of sine waves of a specific frequency and relies on behavioral criteria of stimulus detection. The tones last approximately 1 second. There is an interaction between sound intensity and duration for threshold detection. Sine waves are not used to elicit BAEPs.

Clicks

BAEPs are elicited by brief acoustic stimuli that sound like clicks. The acoustic click is usually generated by a 100-microsecond rectangular pulse delivered to a headphone, resulting in an initial deflection of the headphone diaphragm, followed by several rapidly decaying oscillations lasting a few milliseconds. The frequencies of the oscillations are dependent on damping, the natural resonant frequency of the particular headphone, and its housing, and they differ markedly between different makes of headphones. Frequency analysis of oscillations produced by the rectangular wave input reveals a spectrum of frequencies ranging from 500 to 6,000 Hz; the major power is approximately 3,000 Hz (238). The term *broad-band-click* is used to describe BAEP stimuli.

For longer latency auditory evoked potentials, tone pips, which are a series of sine waves of constant frequency lasting approximately 1 second, are used for stimulation. Onset and offset of a tone pip would also generate a click if it were not for a gradual onset and offset (ramp) each lasting approximately 25% of the steady sine-wave duration.

Stimulus Delivery Methods

In animal studies of auditory evoked potentials, researchers often use loudspeakers with open-field stimulation. In adult human clinical studies, open-field stimulation has few applications because of the usual need to assess left- and right-sided responses separately. Neonatal acoustic perception evaluations have been done with open-field stimulation.

Clinical diagnostic BAEP studies are often conducted with audiological grade transducers housed in headphones to provided shielding from environmental noise. Currents flowing in the coils of the transducer generate magnetic fields that cut across the ear electrode and attached lead, which functions like the secondary winding of a transformer. Thus, there is induction of currents into the recording electrodes. The artifact is directly related to the power delivered to the headphones. A linear increase in decibels (dB) requires a logarithmic increase in power (wattage) because 1 dB is 10 times the logarithm of the before-and-after power ratio (1 dB = 10 log P1/P2). Thus, boosting the sound level by 10 dB requires increased power by a factor of 10; boosting sound by 20 dB requires a power factor increase of 100; and a 30-dB increase requires a power factor increase of 1,000. Artifacts from clicks at 70 decibels above hearing level (dBHL) may be acceptable, but at 90 dBHL, the response may be unacceptably distorted when monophasic clicks are used.

More recently, ear insert devices for sound stimulation have come into common use. There are ear inserts that contain the transducer coil. Although they provide less mechanical interference during surgery than do audiological acoustically shielded headphones, they do produce similar amounts of stimulus artifact with no stimulus delay. Ear insert devices that produce little or no artifact are those with a remote transducer connected by a standard length of tubing to the ear canal. The transducer is usually near the clavicle with flexible tubing connecting the source of sound generation to the ear cannel. The usual length of tubing produces a delay of approximately 0.9 milliseconds. Occlusion of the tube from fluids or crimping can be an obscure cause of improper stimulation.

Sound Intensity Methods

In pure tone audiometry, calibrated sine waves of specific frequency are used, with the intensity of sound measured in decibels. Behaviorally, 0 dB is the average threshold of perception for humans with normal hearing. This has been defined to an objective standard of a force of 40 μPa per square centimeter. An "artificial ear" (calibration system) is used to assess an audiometric headphone by measuring the decibel sound pressure level (dBSPL) output of a headphone in response to a sustained sine wave input. Because sound perception requires both physiological and psychological functions, normal thresholds range from −10 to 20 dBSPL at frequencies between 0.5 and 8 kHz.

The calibration of broad-band clicks is different from sustained sine waves because the duration of the click is too short for the electronics of an artificial ear to respond. Behavioral thresholds are often used. The term *decibel sensation level* (dBSL) is used when the zero thresholds have been determined for the person being tested. Thus, if a person has a threshold of 10 dB for the left ear and 20 dB for the right ear, both ears could be tested at 70 dBSL with machine settings of 80 and 90 dB, respectively.

The term *decibel hearing level* is used when the zero thresholds has been determined from a group of persons with normal pure tone audiometry. This

level is often 5 to 10 dB higher in a neurophysiology laboratory than in a sound-attenuated audiometric chamber because of masking by low-frequency building noises. Thus, if the mean perceptual threshold were 5 dB, subjects would be tested at 70 dBHL with machine settings of 75 dB. The terms *decibel hearing level* and *decibel normal hearing level* are interchangeable.

Although widely used, both dBHL and dBSL are subjective measures. Audiological applications may require a more objective measure such as decibel peak equivalent sound pressure level (dBpeSPL). With this technique, the amplitude of the initial component of a headphone's acoustic response to the electrical input is displayed and measured on an oscilloscope. The amplitude is matched to a steady sine wave of known decibel intensity and the term *peak equivalent* is used. Although the sine wave and the transient click are of the same amplitude, they evoked different behavioral responses because of their different duration. The measure dBpeSPL is approximately 30 dB higher than dBSL or dBHL.

Stimulus Polarity

When the initial movement of the transducer diaphragm is toward the tympanic membrane, the click acoustic polarity is called *condensation.* When the initial movement is away from the tympanic membrane, the click acoustic polarity is called *rarefaction.* When successive clicks are of opposite polarity, they are called *alternating* (used for stimulus artifact suppression). The electrical impulse delivered to the transducer can be only negative or positive, but there is no industry standard about which electrical polarity should produce which acoustic click polarity. Subjectively, rarefaction and condensation clicks sound identical, and test devices are required to determine click polarity. As noted later in this chapter, there are replicable differences in BAEP responses produced by different click polarities.

Masking

Stimuli from monaural stimulation strike not only the ipsilateral tympanic membrane but continue through the cranium to reach the contralateral cochlea. Transcranial attenuation is approximately 30 to 40 dB. Therefore, if 90-dBHL clicks are delivered to a totally nonfunctional cochlea, about 50- to 60-dBHL clicks pass through the skull and brain to stimulate the opposite cochlea, which if normal will produce normal BAEP responses. This produces confusing responses that can be avoided by delivering noise (e.g., white, pink) to the opposite, nonstimulated ear. The *American Electroencephalographic Society Guidelines in Electroencephalography, Evoked Potentials, and Polysomnography* (6) (referred to henceforth as the *Guidelines*) recommend masking at 60 dBpeSPL.

Recording Strategies

Patient Variables and Recording Strategies

Two important subject or patient variables for the recording of high-quality studies are arousal level and body position. One of the most common impediments to obtaining acceptable BAEP recordings is low-level tonic electromyographic (EMG) activity, found in 30% to 50% of subjects. Sleep, whether spontaneous or induced by medication, greatly reduces such tonic EMG contaminants. Benzodiazepines are frequently used for their combined anxiolytic, myorelaxant, and hypnotic effects with no measurable effects on BAEP latency, amplitude, or morphological pattern. High-amplitude, phasic events are excluded from the average by automatic artifact rejection features found on all modern instruments.

A comfortable bed or reclining chair promotes the likelihood of sleep while relaxing the cervical extensor muscles, which contribute to the postauricular myogenic response. This artifact develops between 10 and 15 milliseconds after presentation of a stimulus.

Electrode Placement

Three recording electrodes are typically used: one at the vertex and one at each of the mastoid/ear locations. The later BAEP components (waves II to VII) are of brainstem, far-field origin and have a widespread distribution over the vertex. Indeed, a Cz-Fz derivation would be expected to be virtually isopotential because of in-phase cancellation. Wave I is both near-field (negative near the ear) and far-field (positive projections to the opposite ear and vertex). On occasion, particularly in neonates, a noncephalic reference is useful because in-phase cancellation can markedly attenuate some components of the BAEP response. All BAEP components can be recorded from both ear electrode locations. With noncephalic recording, it is possible to show all waveforms of the BAEP with different

topographies at the three electrode recording sites, and apparent absence of responses from standard bipolar montages can be seen. Distant bone locations such as the patella or medial malleolus are suitable as sites for a noncephalic reference (Fig. 28.1). An increased (often double) number of stimuli are needed to reduce the increased artifact.

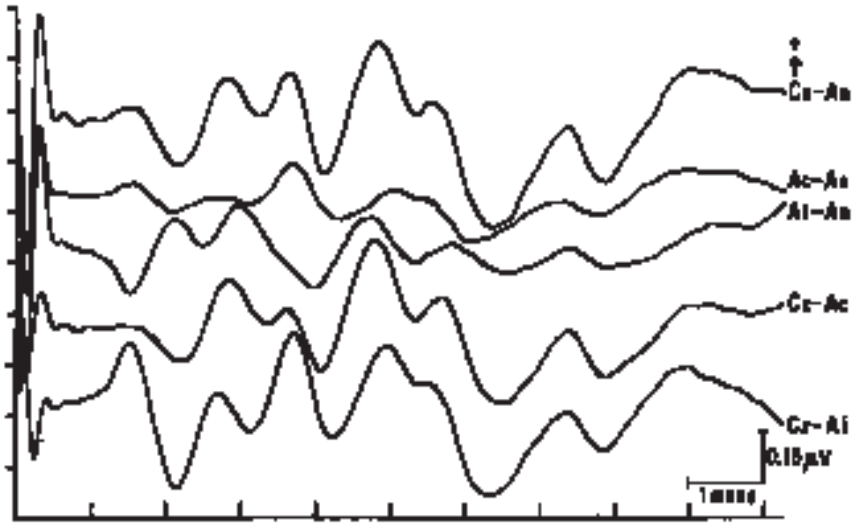


FIG. 28.1. Group BAEP data from five normal subjects (responses from independent stimulation of both ears) is presented. All subject's responses were normal with presence of waves I through V. Stimulation produced by standard TDL 49 audiometric headphones. The bottom two traces are standard bipolar derivations with Cz (vertex) to Ai (ipsilateral ear lobe) and Ac (contralateral ear lobe). This montage caused a positive event at the first named electrode to have an upward deflection. Conversely, a positive event at the second named electrode caused a downward deflection. The top three channels show Cz, Ac, and Ai referenced to An (medial malleolus of the ankle) to provide a distant, relatively uninvolved reference. These three derivations show the unique contributions of responses at each electrode site to the bipolar derivations. There are deflections at each of the three sites for all of the major BAEP components, with the exception of an absent wave III at Ai. (Unless noted otherwise, in Figs. 28.1 to 28.9*B,* BAEP data was recorded with the following stimulation and recording parameters: rate, 11.1 per second; masking of the nonstimulated ear with white noise at 20 dB less than the click level to the stimulated ear; horizontal resolution of 10 microseconds between samples; low-frequency setting, 150 Hz; high-frequency setting, 3,000 Hz; ear insert transducers causing a 0.9-millisecond delay.)

Because BAEP components have different topographies at Ai, Ac, and Cz, this leads to varying degrees of potentiation, attenuation, and apparent latency shift of the individual waves. Wave identification can proceed logically through an understanding of the topographic differences between the ipsilateral and contralateral channels. See the section on waveform identification.

Polarity Conventions

Polarity conventions for electroencephalography (EEG), visual evoked potentials, and somatosensory evoked potentials are the same; a negative event at the first named electrode of a derivation causes an upward deflection. BAEP polarity convention is the opposite. Wave I has a near-field negative field and a far-field positive field with broad projections to Ac and Cz. The near-field, negative component of wave I, when recorded by an Ai electrode connected to negative input, causes an upward deflection. The positive, far-field component, when recorded by the Cz electrode connected to positive input, also causes an upward defection. Thus, all BAEP components are displayed upward, but wave I is negative at the ear and positive at the Cz, whereas waves II to VII are primarily positive at Cz.

Naming of Brainstem Auditory Evoked Potential Components

The up-going, positive peaks of major BAEP components recorded in the ipsilateral Cz-Ai derivation are named waves I, II, III, IV, V, VI, and VII. The down-going negative valleys recorded in this derivation were named I_N, II_N, III_N, IV_N, V_N, VI_N, and VII_N by Stockard et al. (217). The up-going, positive waves recorded in the contralateral (Cz-Ac) derivation are called I_C, II_C, III_C, IV_C, V_C, VI_C, and VII_C; and the down-going negative valleys are called I_{NC}, II_{NC}, III_{NC}, IV_{NC}, V_{NC}, VI_{NC}, and VII_{NC} (Fig. 28.2).

Stimulus Rate and Polarity

Use of stimulus rates of 5 to 90 Hz (and higher) have been reported. A rate of approximately 10 Hz is most common, but many clinical laboratories use approximately 50 Hz for an initial rate. To avoid time locking to 60-Hz artifact, exact multiples of 60 are avoided. Rates faster than 10 per second cause a progressive reduction of amplitude, a broadening of all waves, and a lengthening of all interpeak latencies. Because of this latter factor, sepa-

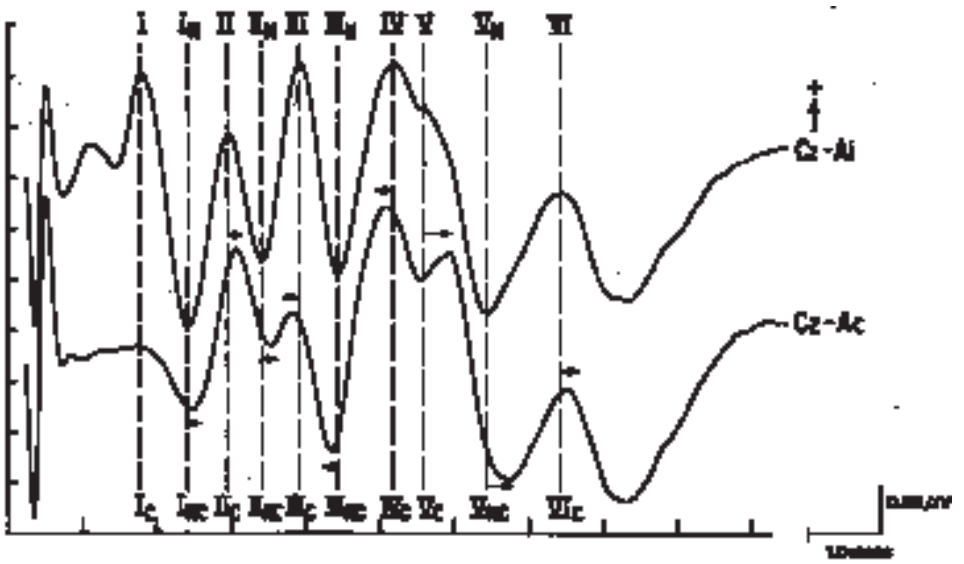


FIG. 28.2. Group BAEP data as in Fig. 28.1, a component-naming method, and apparent latency differences of various peaks as recorded in standard derivations. These latency shifts are useful in waveform identification, particularly when there are missing or redundant peaks or valleys. In the Cz-Ai (ipsilateral) derivation, the up-going peaks are labeled with Roman numerals I through VI. The down-going valleys of this derivation are labeled with Roman numerals followed by a subscripted "N" because they have a negative polarity, with the exception of wave I_N. In the Cz-Ac (contralateral) derivation, the up-going peaks are labeled with Roman numerals followed by a subscripted "C," and the downgoing valleys are labeled with Roman numerals followed by a subscripted "NC." (See legend for Fig. 28.1 for stimulation and recording parameters.)

rate normative values are needed for interpretation of data elicited by different rates of stimulation.

Filtering

Recommended filter settings for BAEPs in adults are 10 to 3000 Hz (6). In the past, the majority of clinical studies were done with low-filter settings of 150 Hz. Lowering the passband has surprisingly little impact on data acquisition (no increase in artifact rejection rate) but produces obvious changes in the morphological pattern of the response. Separate normative data for such filter settings are required for both latency and amplitude criteria of abnormality.

Averaging: Artifact Suppression and Horizontal and Vertical Resolution

The number of responses required to produce relatively artifact-free responses varies between values of 1,000 and 4,000, depending on the signal-to-noise ratio. When responses are large (greater than 0.2 μV) and noise is relatively low in amplitude, fewer responses are required. When low-amplitude responses are present (common in pathological conditions) and/or noise components are relatively high in amplitude, there may be significant residual noise despite 4,000 or more responses. Increasing the intensity of stimulation increases the amplitude of the response, particularly wave I. Attention to electrode impedance and adequate sedation can significantly reduce environmental artifact and EMG (Fig. 28.3).

Horizontal resolution depends on sweep time and the amount of memory allocated to data. Current commercial systems have adequate horizontal resolution, and responses are usually oversampled. When a 15-millisecond sweep is used with 512 horizontal data points, the intersample interval, or dwell time, is 0.03 millisecond for an effective sampling rate of 33 kHz. This well exceeds the Nyquist number and samples the fastest waveforms adequately (3 kHz is the recommended setting of the high-frequency analog filter).

Vertical resolution is a function of the size of the analog-to-digital (AD) converter, the amplifier sensitivity, and the number of sweeps (stimuli). Even with a minimal 8-bit AD converter. there is overkill of vertical resolution with sweep values as low as 500. Whether such a relatively low number of sweeps is sufficient to adequately reduce noise is a separate issue, but with a full-scale sensitivity of 20 μV, the vertical resolution is 0.00016 μV (20 μV/256/500). Most AD converters are 12-bit, which with full scale sensitivity of 20 μV and 2,000 stimuli produces a vertical resolution of 0.000002 μV (20 μV/4,096/2,000).

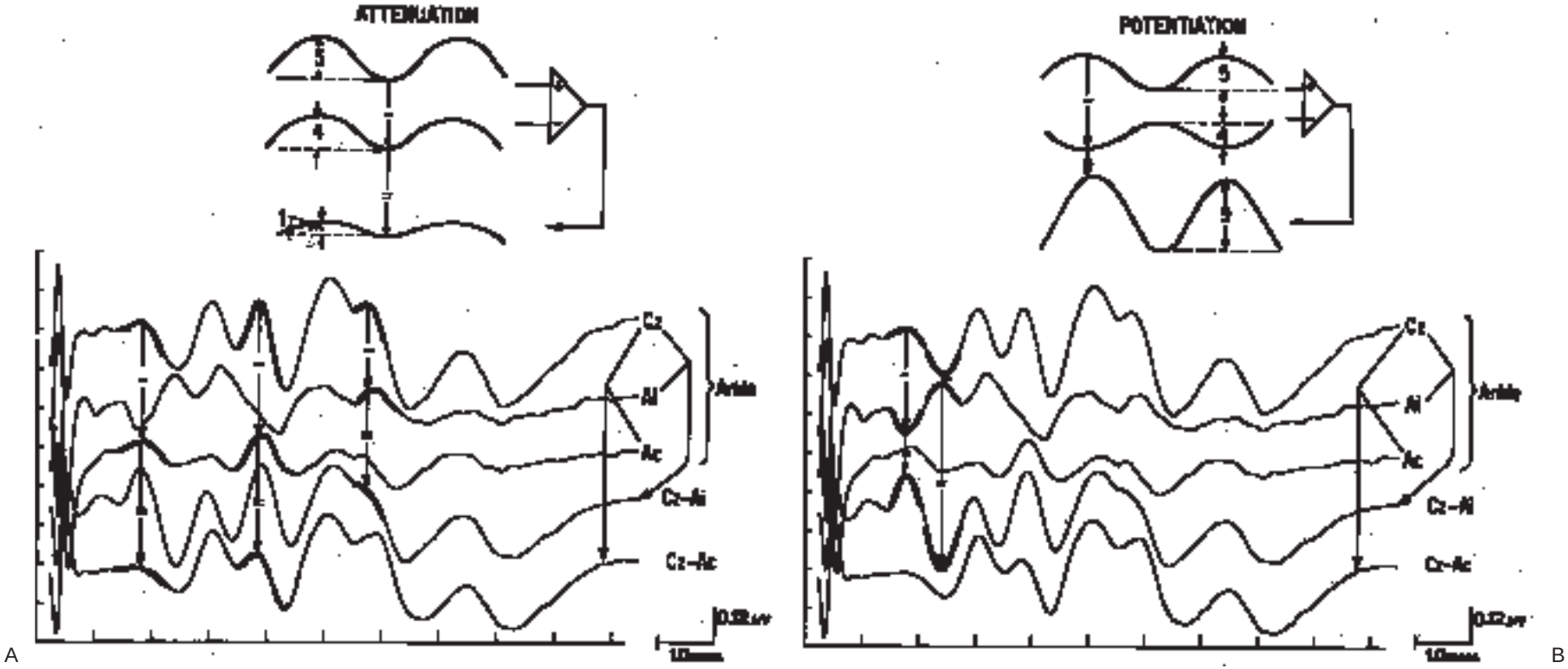


FIG. 28.3. A: Potentiation of waves I and I_N in the Cz-Ai derivation. Wave I is negative as recorded from Ai and projects as a positive event (dipole) at both Cz and Ai (usually larger at Cz). Opposite polarities, when connected to a deferential amplifier, cause additive (potentiating) effects. **B:** Relative attenuation of waves I and III in the Cz-Ac derivation and wave V in the Cz-Ai derivation. It is an example of in-phase cancellation. (See legend for Fig. 28.1 for stimulation and recording parameters.)

Conducting a Brainstem Auditory Evoked Potential Study

Medical History

Before performing the BAEP test, the technologist should obtain a relevant medical history, which may help with interpretation. A directed history should include the symptoms for which the test is being performed, their duration, and coexisting medical conditions. Neurological examination findings, especially those pertaining to cranial nerves, should be noted. Results of prior neuroimaging and audiological tests are particularly helpful. This historical information is used by the interpreter to suggest clinical relevance to the BAEP findings.

Explanation of the Test to the Patient

Patients undergoing central nervous system evaluations are often understandably anxious. Successful attempts to allay fears about the pending study allow the patient to relax, producing a shorter study with higher quality data. Explanations should be as simple as possible, tailored to the

patient's level of medical sophistication. It is better to err on the side of using too simple a language than too complex. The laboratory director, to ensure consistency of the message, should review a written outline of the explanation content.

Sedation

Good-quality BAEPs can be obtained in approximately 60% of unsedated, awake adults (authors' unpublished experience). In patients with varying degrees of anxiety or pain, which causes increased tonic EMG, recording may be more difficult. The authors routinely sedate all adults with orally administered diazepam (usually 10 mg) at the beginning of a BAEP study because it has combined anxiolytic, myorelaxant, and hypnotic qualities. Spectral analysis of scalp surface potentials with an analog passband of 150 to 3,000 Hz taken in an awake state and a sleep state reveals a band of activity from 200 to 500 Hz that is suppressed during sleep (authors' unpublished data). The suppression of this activity probably explains the improvement in data recorded when the patient is sedated.

Electrode Applications

Surface electrodes are preferred because of lower noise characteristics in comparison with needle electrodes. One electrode is placed at the vertex (Cz), and one electrode is placed at each of the two ears (A1 and A2). The ear electrodes are usually designated as Ai and Ac, which indicates the ear ipsilateral and the ear contralateral to stimulation. One study (217) showed a higher amplitude wave I when the ear electrode is placed on the mesial surface of the ear lobe. Comparisons were made between this location and the mastoid or lateral pinna locations. A fourth electrode is required for grounding purposes and can be placed anywhere on the body. A frontal scalp location is commonly used because of the ease of application; however, such a practice could lead to a "ground recording."

Determination of Hearing Threshold for Click Perception

As described in a previous section, determination of the hearing threshold for click perception is needed when dBSL stimulus descriptors are used. To stimulate at 70 dBSL, 70 dB is added to the perception threshold for the person's left and right ears. This technique is used infrequently for two reasons. First, it is inappropriate for a significant number of subjects because of their inability to cooperate (as a result of age, cognitive level, coma, anesthesia); and second, for persons with frequency-specific deficits, the frequency of the broad-band click that is useful for testing hearing may not be the same frequency that elicits various components of the BAEP response.

Usual Parameters for Obtaining Brainstem Auditory Evoked Potential Recordings

The usual parameters for BAEP recording technique (see Guidelines [6]) differ to some degree with the age of the subject and the setting of the study. Thus, a 10-millisecond sweep time is common for diagnostic studies in adults, whereas a 15-millisecond sweep time is common for infants and during intraoperative monitoring because of the distinct possibility that wave V will occur or move later than 10 milliseconds.

Other parameters are common to all studies. Amplifier sensitivity is set to produce an artifact rejection rate of about 15%, which usually translates to a full-scale sensitivity of 10 to 20 μV. Two replications are superimposed, each containing 1,500 to 4,000 responses. The most common is 2,000, but more may be needed when there is a high noise level or when response amplitude is lower than usual. A stimulus level of 60 to 70 dBHL is used initially and adjusted upward to 100 dBHL if no wave I is recorded. The adjustment is in 10-dB increments. Higher intensities shorten the absolute latency of all components of the response but do not affect interpeak latencies (see the Guidelines [6]). Masking of the nonstimulated ear at a level 60 dBSPL reduces the likelihood of significant stimulation of the ear contralateral to stimulation.

Troubleshooting

The four most common technical causes of recording no response and methods of troubleshooting are as follows:

1. Inadequate stimulation, which the technologist can detect by putting on the headset or ear inserts and listening for the presence of adequately loud clicks.
2. A defective amplifier, AD converter, or their connections, which the technologist may detect by viewing the data input rather than the average. Input data is best viewed by extending the sweep to 1 second, decreasing the sensitivity, and touching one or more electrodes, producing an obvious artifact.

3. Improper filters, as from a previous visual evoked potential (1 to 100 Hz) that will essentially eliminate all BAEP responses. The technologist can detect this condition by inspecting the filter controls or settings files.
4. Improper triggering, which prevents averaging of a response. The technologist can detect this condition by slowing the stimulation rate to one per second, viewing the input, and visually confirming that a sweep initiates with each click.

The Normal Brainstem Auditory Evoked Potential

Anatomy and Physiology of the Auditory Pathways

Auditory pathways start in the cochlea. The cochlea coils two and a half times and tapers toward its termination, known as the apex. Two membranes, the vestibular and basilar membranes, separate this coil into three cavities: the scala vestibuli, scala media, and scala tympani. All three are fluid filled; the scala vestibuli and tympani contain perilymph, which communicates with cerebrospinal fluid, and the scala media contains endolymph. The auditory transducer is known as the organ of Corti, which is attached to the basilar membrane throughout its length and lies within the scala media. It contains four rows of hair cells and is stimulated by changes in the hydrostatic pressure of the endolymph. Hydrostatic pressure changes are a result of sound waves that are transmitted to the cochlea through the outer and middle ears. The frequency of the acoustic stimulus determines the precise location on the basilar membrane where the organ of Corti is stimulated; low frequencies stimulate the apex, and high frequencies stimulate the base of the cochlea.

Hair cells of the organ of Corti communicate with processes of bipolar cells, also known as first-order auditory neurons. Bipolar cells have cell bodies located within the cochlea and form the cochlear part of the vestibulocochlear nerve. The vestibulocochlear nerve, after traveling through the petrous bone and the subarachnoid space, enters the brainstem at the pontomedullary junction. Fibers of the cochlear part of the vestibulocochlear nerve terminate in either the ventral or dorsal cochlear nucleus. These nuclei are located along the lateral aspect of the rostrum of the medulla.

The remainder of the auditory pathway from the cochlear nuclei to the auditory cortex is not clearly understood. Although numerous pathways of impulse transmission probably exist, only the one best known and relevant to the discussion of auditory evoked potentials is described here. The cochlear nuclei give rise to second-order auditory neurons, most of which cross to the contralateral side; the ones arising from the ventral cochlear nucleus form the trapezoid body. Most second-order auditory neurons synapse in the superior olivary nucleus, either contralaterally or ipsilaterally. Third-order auditory neurons arise from the superior olivary nuclei and ascend in the lateral lemniscus in the tegmentum of the pons and midbrain to terminate in the inferior colliculus. From the inferior colliculus arise fourth-order auditory neurons that ascend through the inferior brachium to the medial geniculate body of the thalamus. Fifth-order auditory neurons arise in the thalamus and terminate in Heschl's gyri. Auditory perception takes place in Heschl's gyri. Thus, unilateral auditory input is perceived bilaterally.

Generators of Waveforms

BAEPs usually consist of five waveforms, labeled waves I to V (see Fig. 28.2). In addition, two additional waves (VI and VII) are sometimes identified in many, but not all, normal adult humans. Much of the work on waveform generators has been done with animals; the human auditory system is significantly more complex (102), and transspecies correlations require caution.

Results of initial experiments with implanted macroelectrodes in cats suggested discrete synaptic generators for the various BAEP waveforms (96). Wave I was thought to arise from the acoustic nerve, wave II from the cochlear nucleus, wave III from the superior olivary complex, wave IV from the lateral lemniscus, and wave V from the inferior colliculus. Other investigators studied the auditory pathway with different techniques and arrived at comparable results (83,211).

However, other experiments have revealed conflicting findings regarding presumed waveform generators. Whereas there is general agreement that wave I arises in the part of the cochlear nerve closest to the cochlea (35,51,68), there is considerable debate about the generator of wave II. Data have suggested that, instead of arising from the cochlear nucleus, wave II probably originates from the proximal vestibulocochlear nerve (63,140). Additional support for this assertion is provided by studies that demonstrate presence of both waves I and II in patients with brain death, which suggests that these waves arise from the cochlear nerve (68,218). There have been disagreements about the generator of wave III as well. Chiappa (26) suggested that the superior olivary complex generates wave III, whereas other researchers believe that the cochlear nucleus is responsible for this waveform (138,140,194).

The generators of waves IV and V are even more ambiguous. In rat auditory pathway ablation experiments, researchers noted that lesions of

the lateral lemniscus had inconsistent effects on waves IV and V, and lesions of the inferior colliculus had no significant effects on these waveforms (25). There is some agreement among many investigators that wave IV arises from the area of the superior olivary nucleus (83,135–137). However, there is much disagreement as to whether the waveform is generated ipsilateral or contralateral to the side of stimulation. Ponton et al. (172) and Moore et al. (142) suggested that wave IV arises from contralateral auditory fibers that do not synapse in the superior olivary complex but run near it. Curio and Oppel (41) suggested that the ipsilateral superior olivary complex produces wave IV with some contribution from contralateral nonsynaptic cochleocollicular fibers. Clinical human data has suggested that lesions in the middle and upper pons cause ipsilateral loss of waves IV and V (15,20,201,211). The exact generator of wave V remains equally uncertain. The contralateral superior olivary complex (41, 142,172,236,237), the contralateral lateral lemniscus (115,137,139,140), and the contralateral inferior colliculus (47,83) have all been proposed as possible generators for wave V. Waves VI and VII are thought to arise from the medial geniculate body and auditory radiations, respectively (28). However, because these waveforms are extremely variable, they are unreliable and are not used in clinical interpretation.

Since the initial attempts at identification of specific neural generators for BAEP waveforms, most investigators have come to believe that each of the waveforms have multiple generators and the various structures along the auditory pathway contribute to more than one peak (2,19,181). Malhotra (119) concluded that waves I and II originate from the acoustic nerve and waves III, IV, and V have multiple generators in the auditory pathway up to the lemniscal level. Chiappa (28) summarized by suggesting that wave I is generated by the distal vestibulocochlear nerve; wave II, by the proximal vestibulocochlear nerve or cochlear nucleus; wave III, by the lower pons (possibly superior olivary complex); wave IV, by the middle or upper pons (possibly lateral lemniscus); and wave V, by the upper pons or inferior colliculus. Although a majority of fibers of the auditory pathway ascend contralaterally, waves I to IV are probably generated ipsilaterally, whereas wave V may be generated contralaterally (28). Markand et al. (121) noted that in patients with unilateral brainstem pathology seen on magnetic resonance imaging (MRI), BAEP abnormalities are elicited from stimulation of the ear ipsilateral to the side of disease. Either the BAEPs elicited by contralateral ear stimulation are normal or the abnormality is not as marked as the ipsilateral abnormality. Markand et al. noted, however, that mesencephalic lesions are more likely to produce bilateral abnormalities.

Variability of Brainstem Auditory Evoked Potentials from Nonpathological Factors: Patient Variables

Age

The effects of age on BAEP are most remarkable in premature infants and neonates. Normal premature infants younger than 30 weeks of conceptional age may not have recordable BAEPs (226). BAEPs recorded in premature infants and neonates are often of higher amplitude than those seen in adults (217); this is presumably because of smaller head size, thinner skull bones, and greater proximity of electrodes to the neural generators of the waveforms. The wave I amplitude is larger than that seen in adults; therefore, the ratio of wave V amplitude to wave I amplitude is smaller (187). Waves II and IV are often difficult to identify in this age group (110). Stimulation rates of ten per second worsened the morphological appearance of waveforms in comparison with a rate of five per second (188) and cause prolongation of wave V (59,112). Waveforms comparable with those seen in adults can be identified by the age of 3 to 6 months (88,132).

Absolute and interpeak latencies undergo remarkable changes as premature infants and neonates mature. The interpeak latency (IPL) from wave I to wave V (I-V IPL) changes at a rate of 0.45 milliseconds per week between the ages of 32 and 34 weeks of conceptional age; the change slows to 0.1 milliseconds per week closer to term (39,162). The change in wave V absolute latency is about 0.2 milliseconds per week between the ages of 26 and 40 weeks of conceptional age (88,189,209). At term, the I-V IPL is 0.8 to 1 millisecond longer than that of adults. Adult values are reached at the ages of about 1 to 2 years (60,132,155). BAEP changes in the early weeks of life have been thought to result from progressive myelination, increase in fiber diameter, and increased synaptic efficiency (86,209). Because of the remarkable latency changes in premature and young infants, Chiappa (28) recommended that age-specific norms be obtained for every 2-week age change before term, at birth, at 3 weeks, at 6 weeks, at 3 months, at 6 months and at 1 year. Of importance, however, is that BAEPs are not affected by prematurity; maturation follows the conceptional age rather than legal age (48).

Beyond childhood, age has variable effects on the BAEP. Although some investigators have noted increases in absolute and interpeak latencies of the waveforms (106,182,185,225), others have found no such effect (12). Malhotra (119) noted that, whereas the latency of wave I does not change with age, the amplitude does. He noted that mean amplitude was 0.21 μV in subjects younger than 40 years and 0.13 μV in those older than 40. Sim-

ilarly, whereas some researchers have found these latency changes in both genders (182,185), others have found them to be significant in boys and men only (106,119). Chiappa (28) summarized these findings and noted that these latency differences are too small to have an impact in clinical interpretation.

Gender

Girls and women have shorter BAEP absolute and inter peak latencies (3,5,12,95,106,119,128,131,155,225). The wave V latency has been noted to be 0.12 to 0.3 millisecond shorter in girls and women (107,128,168,220). These gender-based differences were seen in children as young as 8 years of age (155). It has been postulated that these shorter latencies resulted from smaller head size (3,8). Mitchell et al. (131) found a correlation between head diameter and the latency of wave V and the I-V IPL. However, Trune et al. (229) controlled for head size and found that girls and women consistently had shorter peak latencies, which thus suggests that factors other than brain size were responsible for the gender differences. Some investigators (128) have attributed shorter waveform latencies in girls and women to hormonal effects. Elevation in progesterone level has been thought to be the cause of these differences (42). Picton et al. (167) noted I-V IPL variability in the menstrual cycle, being a mean of 3.81 milliseconds between days 12 and 26 of the cycle (when the levels of progesterone are the highest) and 3.92 milliseconds on other days. These investigators, as well as others (210), have concluded that shorter latencies in girls and women are caused by their higher core body temperatures.

Temperature

Temperature changes have an effect on both absolute and inter peak latencies; these increase with decreases in body temperature (72,219). Temperature correction factors range from 0.17 to 0.20 millisecond prolongation in wave V latency per degree centigrade below 37 degrees (75,167). Below 27 degrees, centigrade waveforms disappear (43,98). Although decreases in temperature can have significant effect on BAEP absolute and interpeak latencies, most patients undergoing routine BAEP studies do not need their temperatures checked (75). Rather, those at greatest risk for hypothermia (i.e., those acutely ill or with severe head trauma) benefit from temperature determination and latency adjustments (40,75,78). The effects of hyperthermia have been less clearly studied. Hall (75) found a decrease of 0.50 to 0.60 msec in the I-V IPL in patients with temperatures ranging from 38° to 42°C. He suggested a 0.15-millisecond-per-degree correction for patients who are hyperthermic.

Sleep

Numerous investigators have noted the lack of effects of sleep on BAEP waveform latency and amplitude (5,157,167,202). BAEP waveforms also do not appear to be affected by the level of attention during testing (111,116,165,166,196). Certain pathological states that produce sleep and sedation, such as narcolepsy and metabolic coma, also do not have significant effects on BAEPs (76,89,207,221). The lack of effects of sleep on BAEPs is of particular importance because sleep deprivation and sedation is often employed so that the patient is more relaxed during the procedure. This, in turn, serves to decrease electromyographic artifact that can otherwise degrade the quality of the study.

Drug Effects

BAEP waveforms are not affected by central nervous system depressants in therapeutic doses. This property makes BAEPs a robust evoked potential modality to monitor in operative procedures. Phenobarbital, diazepam, and chloral hydrate do not affect BAEP waveforms in therapeutic doses (134,161,212). However, overdose with phenobarbital and nitrazepam can cause minor BAEP IPL changes (186).

Numerous anesthetics, including thiopental, pentobarbital, etomidate, ketamine, halothane, isoflurane, fentanyl, and nitrous oxide, have minimal to no significant effects on BAEPs (38,73,75,123,191,213). A number of other agents, however, do affect BAEP waveform latencies and morphological features. Methohexital prolongs wave V latency without affecting waves I and III; therefore, it can cause a prolongation of IPLs (75). Thiopental in very high doses has been shown to cause prolongation of IPL and decrease in amplitude (44,67). Enflurane causes a linear increase in IPLs as a function of concentration (45,227).

The effects of alcohol on BAEPs have been extensively studied. Acute intoxication with alcohol has been shown to cause latency prolongations of absolute and inter peak latencies without significant change in amplitude (32,33,173,204,205). Whereas some authorities have contended that these effects result from hypothermia induced by the alcohol (97,215), others have maintained that these changes are temperature independent (204). Lee et al. (113) suggested that the changes depend on how fast the

alcohol concentration in blood rises. With chronic use, the latencies remain prolonged (13,32). With discontinuation of alcohol use, there is disagreement as to the changes in BAEP waveforms. Some authorities have argued that during withdrawal, latencies are shorter than usual with higher amplitudes (32), whereas others have argued that even with discontinuation, the latencies remain prolonged, possibly because of demyelination or edema (13).

Aminoglycoside antibiotics are an important class of drugs that may have significant effects on BAEPs because of their ototoxicity. The incidence of ototoxicity ranges between 3% and 25% (46,148,231). Rapid intravenous infusion has been found to result in reduced amplitudes of the waveforms and prolongation of wave I latency; after continued infusion, these effects gradually return to baseline (71,197). Oral administration of these agents results in the same effects, although of smaller magnitude; the effects resolve with discontinuation of medication. Aminoglycosides are proposed to produce these effects on BAEPs by causing destruction of the organ of Corti and loss of microvasculature in the basilar membrane (9).

Other drugs such as salicylates have similar effects on the BAEP, presumably because they too have ototoxic properties. Platinum-containing antineoplastic agents, such as cisplatin and carboplatin, cause a delay in absolute latencies of all waveforms and increase the threshold at which BAEPs are elicited (104,159,222). Depolarizing and nondepolarizing neuromuscular blocking agents have not been found to alter BAEP waveform morphological features and latency (74,82,103,200). The antiepileptic drugs phenytoin and carbamazepine cause a prolongation of absolute and interpeak latencies (24,70,94,163,212,245). In contrast, similar effects have not been noted with valproic acid (245). Electrically induced seizures (electroconvulsive therapy) do not affect BAEPs (239).

Hearing Disorders

Hearing disorders can result from problems with the external or middle ear (conductive hearing loss), the cochlea or vestibulocochlear nerve (sensorineural hearing loss), or a mixture of these (mixed hearing loss). All types of hearing loss cause prolongation of the absolute latencies of the BAEP waveforms (75); however, this does not preclude accurate interpretation relevant to central conduction. Numerous investigators have established that IPLs remain normal in conductive, sensorineural, and mixed types of hearing loss (29,31,50,129,183,203). Some studies have suggested that the prolongation of wave V in sensorineural hearing loss is not as great as that of wave I; hence, the I-V IPL is shorter than would be expected (36,37) (Fig. 28.4). Keith and Greville (101) found similar shortening of the I-V IPL in patients with conductive hearing loss.

The effects of hearing loss on the latency/intensity series and the behavioral audiogram are more remarkable. Hecox and Galambos (88) discussed these changes in detail. In patients with conductive hearing loss, the curve of the latency/intensity series has the same slope as that of normal persons but is displaced to a higher hearing intensity. Patients with sensorineural hearing loss, on the other hand, have peak latencies that are comparable with those of normal persons at high stimulation intensities. At lower intensities, however, the latencies are significantly prolonged. This is an electrophysiological correlate of the behavioral phenomenon of recruitment typically present in patients with sensorineural hearing losses.

The Abnormal Brainstem Auditory Evoked Potential

Statistical Considerations of Brainstem Auditory Evoked Potential Abnormality

To consider a given finding abnormal, the finding must be shown to occur rarely if ever in a normal person, and it must be seen in persons with recognizable disease conditions (pathological correlates).

The criteria (latency or amplitude) values, above or below which abnormality is implied, are determined by studying a population sample that can be independently determined to be normal according to history and examination. From these data, statistics of central tendency (mean) and dispersion characteristics (standard deviation) are computed. A criterion value is then selected, usually by adding some fixed multiple of standard deviations (SD) to the mean. The expression "X + 3 SD" is a shorthand notation to indicate that three times the standard deviation has been added to the mean. Statistical theory predicts that X ± 3 SD will include values from 99.72% of the population. There is no fixed rule that 3 SD must be added to the mean; the literature contains examples in which 2 or 2.5 SD were added. The amounts of the population contained would be 95.46% and 98.75%, respectively.

The mean BAEP I-V IPL is usually close to 4.0 milliseconds, and the standard deviation of the mean is approximately 0.2 milliseconds. A decision to make the mean plus 2.5 SD the upper limit of normal would yield an upper limit of 4.5 milliseconds. Using 3 SD increases the upper limit to 4.6 milliseconds. The test becomes more specific but less sensitive with 3

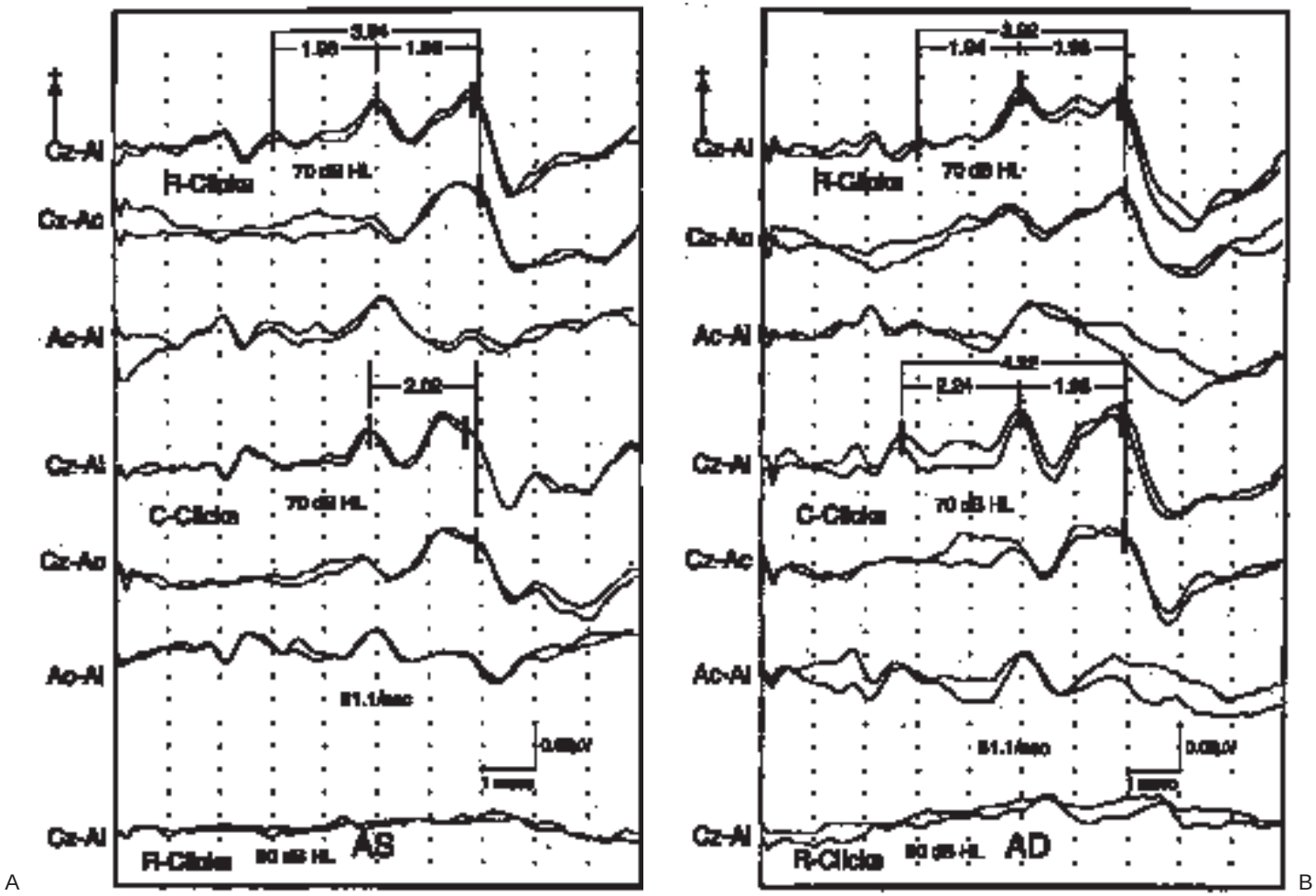


FIG. 28.4. A&B: BAEP in an 83-year-old man with worsening hearing loss. The BAEP shows changes related to a neurosensory, high-frequency auditory loss, which resulted in a late and absent to low-amplitude wave I, shortened I-V IPLs, and abnormal latency/intensity testing. It also highlights potential problems in identification of wave I. In this study, waves I are identified as occurring at a delayed absolute latency of ±3.0 milliseconds (0.9-millisecond delay for ear-insert transducers). An up-going event occurs at 2.07 milliseconds, preceding the identified wave I. There are two reasons why this larger event is a cochlear microphonic (CM) rather than a wave I: First, it is too early to be a valid wave I. Subtracting for the ear-insert delay, its absolute latency would be 1.17 milliseconds, which is appropriate for a CM. Second, the polarity of the event reverses when click polarity is changed from rarefaction to condensation clicks, which is to be expected for a CM but not for a wave I. Persons with normal audition have recordable waves V at 30-dBHL (decibel hearing level) of stimulation. In this patient, responses are essentially lost at 50 dBHL. The stimulation rate of 51.1 per second would be expected to produce an average interpeak latency (IPL) from wave I to wave V of 4.2 msec. The shortened IPLs seen in this study are the result of the differential effects of high frequency loss on wave I (smaller and later) and minimal to no change to wave V. (See legend for Fig. 28.1 for stimulation and recording parameters.)

SD added to the mean; there are fewer false-positive results but more false-negative interpretations. Using 2.5 SD does the opposite; the test is less specific but more sensitive, with more false-positive results and fewer false-negative interpretations.

Tolerance Limits

The Guidelines (6) correctly state that addition of a specific number of standard deviations to the mean is not the most appropriate statistical method. The Guidelines (6) indicate that such an application may be correct for dealing with the question "What is the likelihood that two samples were drawn from the same population?"—that is, whether they are different. A more specific example of this type of question is whether a patient group is different from a normal group. Standard deviations were not designed to answer the question of whether a specific value (latency of a person's evoked potential study) is normal or abnormal. To answer this different question, the tolerance limit statistic is suggested. The reader is referred to the Guidelines (6) for a complete discussion of the subtle differences between these two different statistical techniques.

The ultimate goal of the statistical applications is to maximize sensitivity and specificity (in view of the inverse relationship of these concepts), so as to make a clinically relevant interpretation. A BAEP diagnostic study should not be expected to lead to an etiologically specific diagnosis. The BAEP procedure evaluates the physiological integrity of some aspects of the auditory system. Etiologically disparate disorders can produce identical physiological disturbances and identical BAEP abnormalities. The physiological disturbance identified by BAEP abnormality may or may not disturb clinical function. Indeed, a major strength of the study is its ability to demonstrate subclinical disturbance.

Interpretative Criteria of Brainstem Auditory Evoked Potential Abnormality

Obligate Wave Absence

Obligate waves are those that are present in essentially all audiologically and neurologically normal control subjects. The obligate BAEP waves are I, III, and V. Waves II, IV, VI, and VII are known to be absent in some normal subjects, and therefore pathological processes should not be thought to account for their absence. Absence or virtual absence is an amplitude criterion. Absence of any obligate wave indicates abnormality (Fig. 28.5). The obligate wave most commonly absent is wave I, usually as a result of end-organ (cochlear) or conductive deficits; however, retrocochlear (acoustic nerve) dysfunction can also lead to absence of wave I.

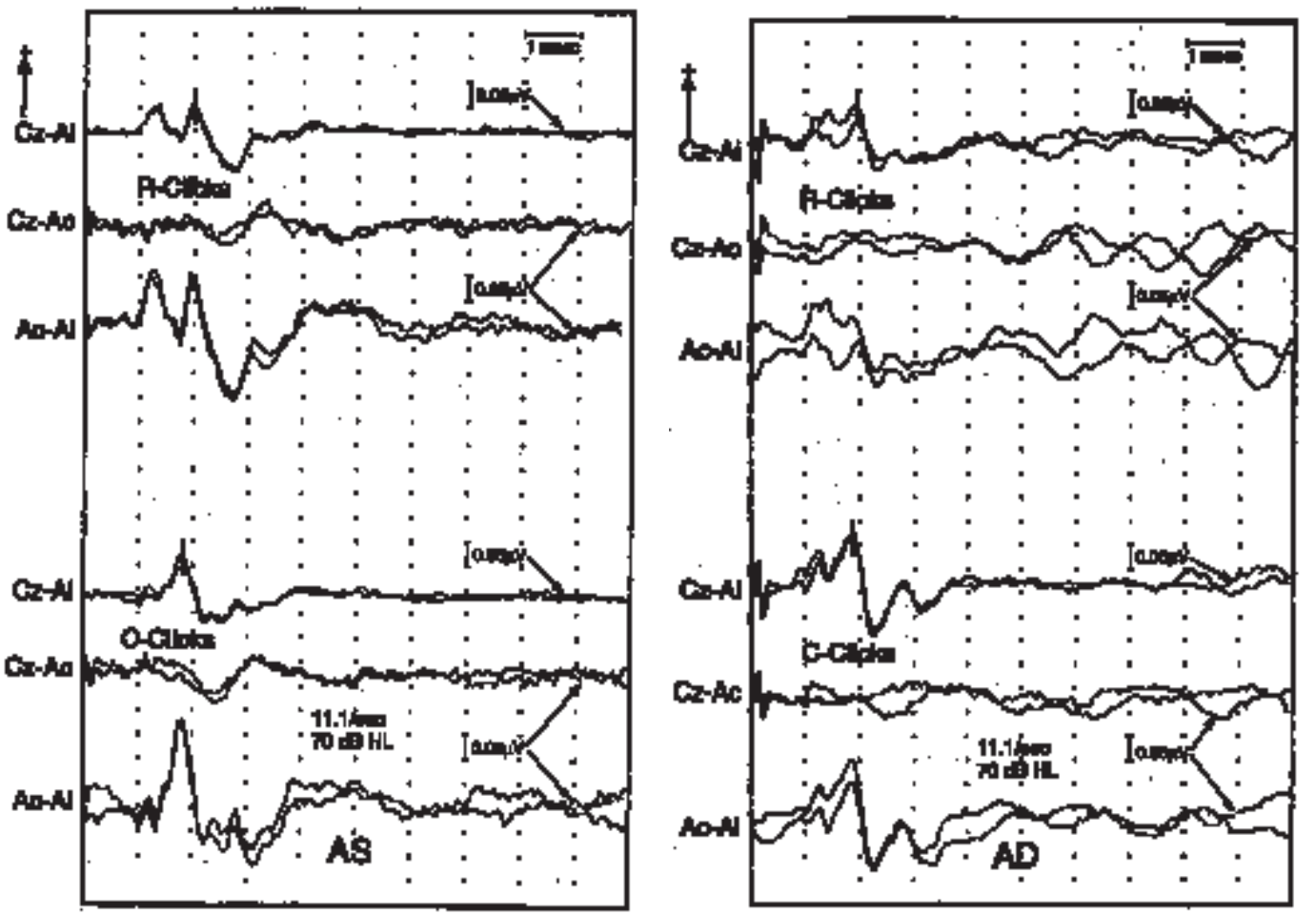
Absolute Latency

Prolongation of absolute latency beyond upper limits is a reliable criterion of abnormality. It is common in conductive and neurosensory disturbances. When audiological evaluation indicates no hearing loss, retrocochlear involvement should be considered. Malfunctioning stimulators, transducers, and displaced transducers can indicate absolute latency prolongations.

Interpeak Latency

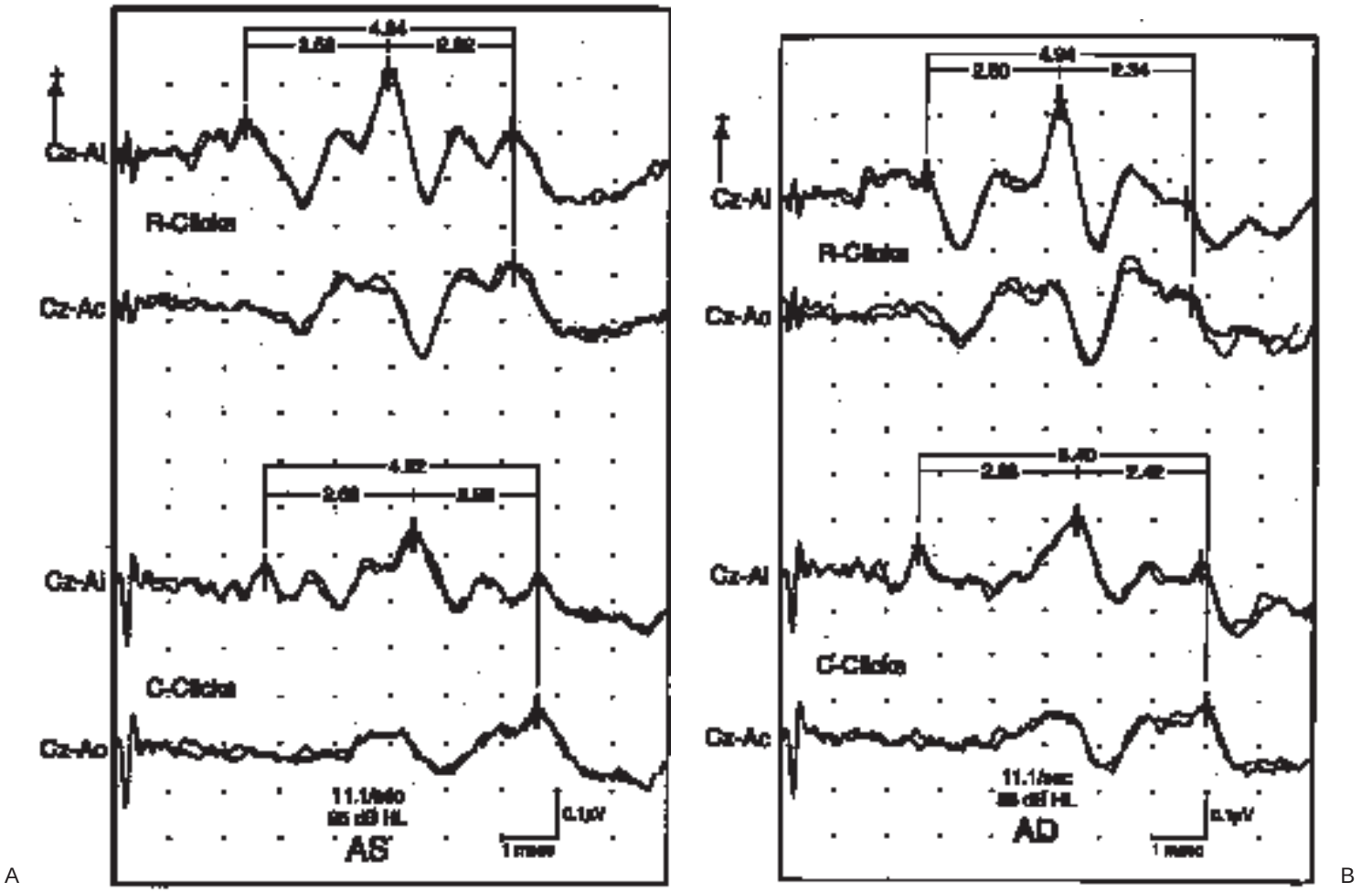
The I-V IPL is a measure of central brainstem conduction time from the generators of these two waves, generally held to be the distal acoustic nerve to caudal midbrain. Three laboratories independently collecting normative data found remarkable consistency for the I-V IPL when similar ages, genders, stimulation rates, and filter settings were held relatively constant (185). Any IPL can be measured and evaluated, but excessive reliance on IPL is inappropriate on statistical grounds and may lead to excessive false-positive test results. The I-V IPL recorded from stimulation of each ear is usually compared to the upper limits derived from study of normal controls (in the range of 4.6 milliseconds). In addition, a side-to-side comparison is made, whereby asymmetries exceeding 0.4 milliseconds in the interaural I-V IPL are considered abnormal. When the two waves I are relatively symmetrical and the asymmetry is caused by the waves V, the abnormality is that of central conduction. When the waves V are relatively symmetrical and waves I are not, the abnormality is usually caused by a peripheral disturbance. Once an abnormality has been identified, other IPLs (I-III and III-V) may be considered to assess what region of the brainstem may show the major disturbance (Figs. 28.6 and 28.7).

No neuropathological process leads to a shortening of absolute or interpeak latencies. A high-frequency audiological disturbance can shorten I-V IPL by selectively lengthening wave I, which is generated primarily by the high-frequency components of the broad-band click stimuli, and leave the wave V at a normal absolute latency.



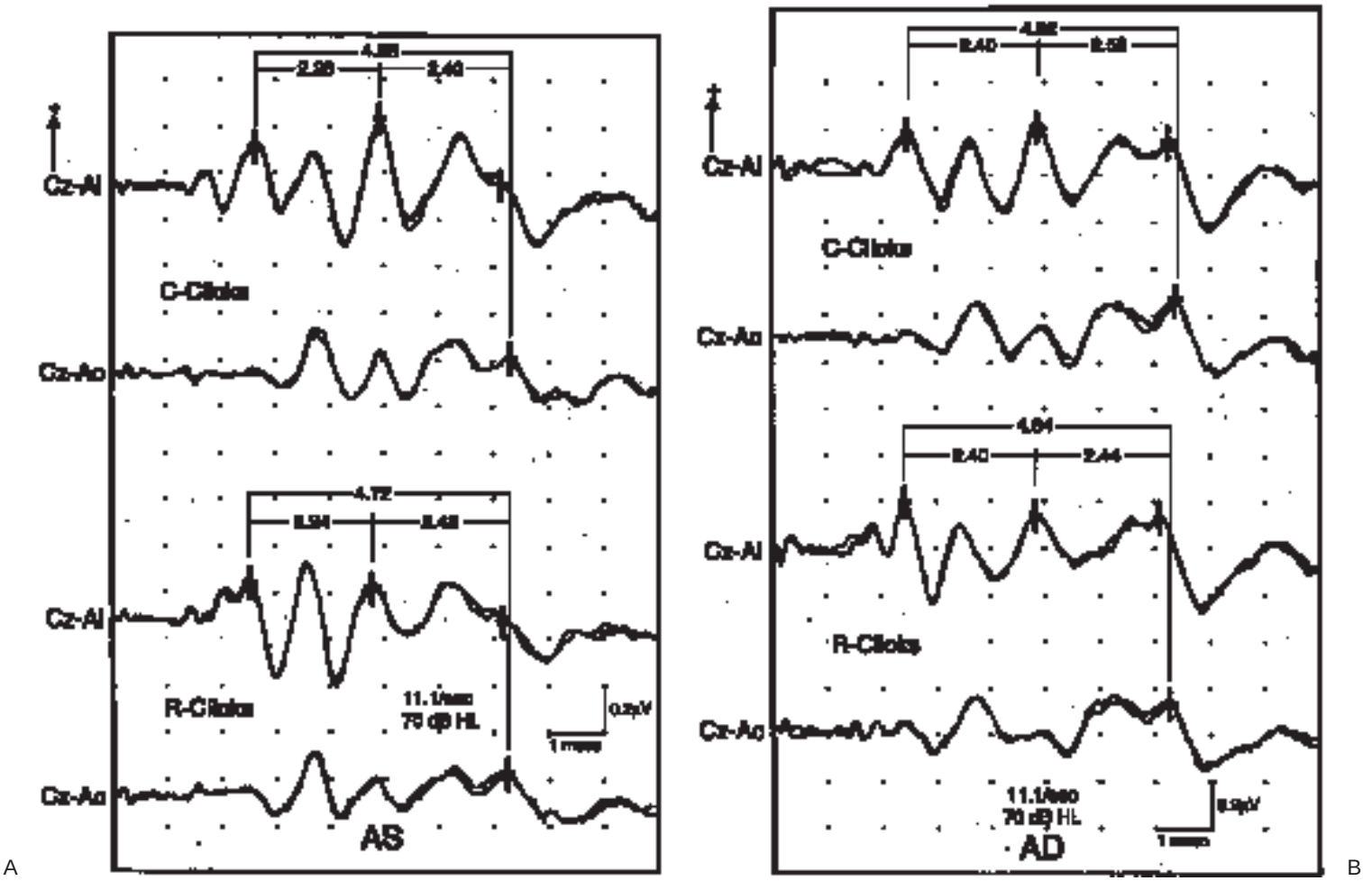
A B

FIG. 28.5. A&B: Magnetic resonance imaging shows extensive white matter changes in the cerebral hemispheres and the brainstem of a 1-year-old girl with Krabbe's disease. The BAEP is very abnormal as a result of virtual absence of all waves after wave I_N. This finding indicates severe dysfunction of brainstem structures rostral to the acoustic nerve and is etiologically nonspecific. Whether this represents a block in conduction or marked temporal dispersion cannot be determined from the BAEP data. There is a small stimulus artifact at the beginning of the traces caused by the magnetic fields generated by the transducer near the clavicle. A cochlear microphonic is the first prominent up-going peak, followed by waves I and I_N. There is virtually no activity in the Cz-Ac channels because of in-phase cancellation. (See legend for Fig. 28.1 for stimulation and recording parameters.)



A B

FIG. 28.6. A&B: Magnetic resonance imaging shows T2 hyperintensity in the medulla of an 80-year-old woman with progressive ataxia. The BAEP shows bilaterally prolonged interpeak latencies (IPLs) from wave I to wave V_C to both rarefaction (R) and condensation (C) clicks. The interpeak latency (IPL) from wave I to wave III shows greater bilateral prolongation than the IPL from wave III to wave V, which suggests a greater involvement of the pontine portions of the brainstem. Right ear C clicks produce IPLs from wave I to wave V_C that are 0.46 millisecond longer than those of R clicks because wave I is 0.14 millisecond earlier and wave V is 0.32 millisecond later than those produced by R clicks. Such click polarity discrepancies are often due to cochlear disturbances of neurosensory function, as revealed in the audiogram. (See legend for Fig. 28.1 for stimulation and recording parameters.)



A B

FIG. 28.7. A&B: Magnetic resonance imaging revealed hamartomas in the globus pallidi and upper pons bilaterally in a 10-year-old boy with neurofibromatosis I. The BAEP shows interpeak latencies (IPLs) from wave I to wave V that are well above the upper limits of normal for the laboratory (4.6 milliseconds, rate and age adjusted) bilaterally. The IPL from wave III to wave V shows a greater prolongation than the IPL from wave I to wave III, which is suggestive of greater involvement in the pontomesenphalic region of the brainstem. (See legend for Fig. 28.1 for stimulation and recording parameters.)

Amplitude

The most extreme amplitude abnormality is absence of an obligate wave (see Fig. 28.5). Because of the wide range of amplitudes encountered in the normal population, lesser degrees of absolute low amplitude cannot be assessed; this would lead to excessive variance. Comparing the amplitude of a wave in reference to another wave can partially avoid such problems. When the amplitude ratio of waves IV and V to wave I is less than 0.5, wave V is abnormally small. This criterion is relatively specific because audiological disturbances cause a lowering of wave I amplitude, which in turn cause the amplitude ratio of waves IV and V to wave I to be greater. This ratio, like all ratios, is not normally distributed and must be transformed (usually a by logarithmic transform) before statistics are computed (127).

Latency/Intensity Functions

See Hearing Disorders section (p. 874).

Clinical Correlations

Cerebellopontine Angle Tumors

Acoustic neuromas and meningiomas are the most frequent types of tumors found in the cerebellopontine angle (CPA). These tumors most often produce hearing loss by compression of the vestibulocochlear nerve. About 75% of the nerve fibers need to be involved before pure tone hearing thresholds are affected (195). Acoustic neuromas, by virtue of their attachment to the vestibulocochlear nerve, produce hearing deficits earlier than do other CPA tumors.

The following are the abnormalities noted most often in CPA tumors ipsilaterally (141,164,247):

1. Absence of all waveforms.
2. Absence of all waveforms after wave I.
3. Absence of all waveforms after waves I and II.
4. Absence of all waveforms after waves I, II, and III.
5. Absence of wave I and prolongation of wave V latency.
6. Prolongation of I-III IPL.7. Prolongation of III-V IPL.
7. Prolongation of I-V IPL.

Because many patients with CPA tumors have associated hearing loss, Selters and Brackmann (199) recommended that a correction factor be used if wave I could not be identified and wave V was prolonged. They proposed to use the factor to correct wave V latency for the hearing loss before concluding that the delay in latency was caused by a CPA tumor by subtracting 0.1 millisecond for every 10 dB or fraction thereof of loss of 4-kHz pure-tone threshold over 50 dB. Hyde and Blair (92) recommended subtracting 0.1 millisecond per 5 dB of hearing loss over 55 dB. Because of these problems with absolute latencies, numerous investigators have noted that IPLs are a better measure of abnormality because they are not affected by hearing loss (49,164,190,246). However, even though IPLs are a more definite indicator of abnormality, wave I in many patients with CPA tumors is not recordable by conventional methods (92). For these patients, additional effort should be expended to determine the presence and location of wave I by increasing the stimulation level to the maximum output necessary to elicit wave I. In addition, ear canal electrodes may be used to advantage in recording wave I. These extra efforts may reveal the wave I, making determination of IPLs possible (30,35,51).

CPA tumors can also produce contralateral BAEP abnormalities by distortion and cross-compression of brainstem structures (133,199,213,246). The abnormality most often seen is prolongation of ipsilateral or contralateral III-V IPL (17,133,147); however, investigators have noted I-III IPL prolongation; absence of all waves except wave I; absence of all waves except waves I and II; and absence of all waves except waves I, II, and III (164,199,240). These abnormalities regress with tumor removal (164).

Although large CPA tumors have a higher likelihood of causing contralateral BAEP abnormalities (17,147), severity of ipsilateral abnormalities is related to factors other than size. In their series of 61 tumors, all nearly the same size, Musiek et al. (146) demonstrated that abnormalities ranged from absence of all waves to presence of all waves. Acoustic neuromas limited to the internal acoustic canal produce symptoms early and tend to cause more destructive effects on the vestibulocochlear nerve and to produce abnormalities of the ipsilateral BAEP earlier; they usually do not affect contralateral BAEPs. In contrast, CPA tumors more proximal to the brainstem often produce symptoms later. When they are large enough to affect the ipsilateral vestibulocochlear nerve, they often cause brainstem and contralateral BAEP abnormalities. Malhotra (119) proposed that the following processes may be responsible for producing BAEP abnormalities in patients with CPA tumors: (a) pressure on the vestibulocochlear nerve, which causes asynchrony in neuronal firing; (b) tumors in the CPA, which can cause pressure effects on contiguous brainstem areas; and (c) compression of blood supply to the cochlea, which causes cochlear ischemia.

The sensitivity of BAEPs in detecting CPA tumors has ranged from 93% to 100% in some studies (10,11,34,66) and has been as low as 75% to 76% in others (17,65,232). Faster rates of stimulation have been shown to increase the sensitivity of BAEPs in detecting CPA tumors (223). In comparison to computed tomographic scanning, BAEPs were more sensitive (11,66,164). Before the availability of MRI, BAEPs became the screening study of choice for evaluating for CPA tumors. However, MRI has been shown more recently to be more sensitive than BAEP in evaluation of small tumors (56,149). Wilson et al. (241) demonstrated that BAEP detected only five of 15 small intracanalicular tumors, whereas MRI detected all 15. Because of the significantly higher expense of MRI, Chiappa (28), however, recommended that if the BAEP I-III IPL is normal and there is no other strong evidence of acoustic neuromas, no further testing needs to be performed.

Other Brain Tumors

The results of BAEPs in patients with a variety of intrinsic brainstem tumors have been reported. Brainstem gliomas (20,26,150), fourth ventricle ependymomas (216), cerebellar tumors (117,216), pinealomas, thalamic gliomas (69), and brainstem metastatic tumors (150,156) produce prolongations of absolute and interpeak latencies (Fig. 28.8; see Fig. 28.5). It is widely believed that virtually all intrinsic brainstem tumors produce BAEP abnormalities.

Coma and Brain Death

BAEP is used to evaluate the auditory pathways in the brainstem between the lower pons and the midbrain. Thus, if the cause of coma does not directly affect these pathways, the BAEPs are normal. Coma caused by metabolic dysfunction has little effect on the BAEPs (208,211). Similarly, central nervous system depressant medications do not affect the BAEP significantly (186,218). Support of this observation also comes from studies on patients in persistent vegetative state; these patients have been found to have normal BAEPs (81,99,208), presumably because the site of primary involvement is rostral to the thalamus (233). However, if supratentorial causes of coma cause distortion or pressure on the brainstem, BAEP abnormalities are noted

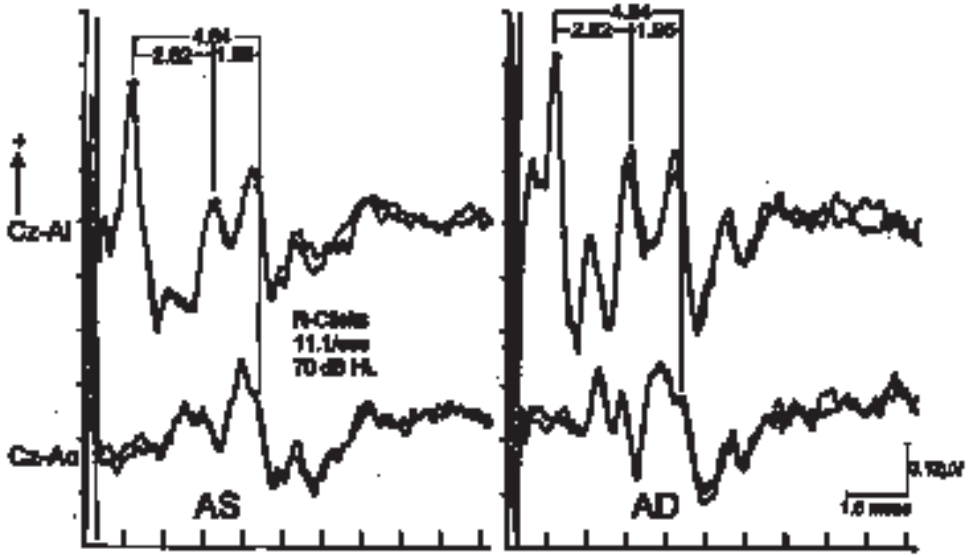


FIG. 28.8. Lower pontine glioma in a 63-year-old man. Brainstem auditory evoked potentials demonstrated prolongedinterpeak latencies from wave I to wave V_C and from wave I to wave III, which are consistent with the lower brainstem lesion. (See legend for Fig. 28.1 for stimulation and recording parameters.)

(28). BAEP abnormalities have also been noted with herniation syndromes and lessen with clinical improvement (55,68,108,207). In such cases, there is gradual disappearance of waves V to II, in a rostrocaudal manner (108,207). Abnormal BAEPs after head injury have been correlated with poor prognosis (99,198).

BAEPs have been shown to be useful for prognosis of patients in coma (7,77,158,192). Elwany (52) correlated BAEPs with neurological outcome. The presence of only wave I or absence of all waves was correlated with a poor outcome. In contrast, 60% of patients with normal BAEPs had a favorable outcome. Presence of wave V, even on only one side, is suggestive of a good outcome (1). BAEPs are most useful prognostically if wave I is completely absent or only wave I is present; this finding is suggestive of a poor outcome. Similar results have been found in children with traumatic coma, in whom absence of BAEPs is suggestive of a poor outcome (16,21).

In patients with brain death, BAEPs are remarkably abnormal; either all waves are completely absent or only wave I is present (68,108). Barbiturates in anesthetic doses sufficient to cause an isoelectric EEG do not affect the BAEP (191,212,218). Thus, BAEPs are useful in confirming brain death in patients being treated with high doses of barbiturates or anesthetics. Before concluding that absence of BAEP waveforms is consistent with brain death, the clinician must rule out preexisting hearing loss and technical problems that may be precluding appropriate stimulation or recording.

Vascular Diseases

Vascular lesions of the brainstem produce BAEP abnormalities only if the auditory pathways are involved. If lesions are below the level of the pontomedullary junction, the BAEP is usually normal (20). This has been demonstrated by the presence of normal BAEPs in patients with locked-in syndrome caused by lesions in the medulla (20,79,228). Various stroke syndromes with lesions above the pontomedullary junction result in BAEP abnormalities (145,156,178,211). There is disagreement about the effect of transient ischemic attacks on BAEPs. Whereas some authors have demonstrated that even brainstem transient ischemic attacks result in BAEP abnormalities (54,184), others have not found this to be the case (105). Rao and Libman (179) noted abnormal BAEPs in patients with isolated vertigo that later progressed to an anterior inferior cerebellar artery stroke. They recommended using BAEPs to differentiate vertigo caused by labyrinthine disease from that caused by vertebrobasilar ischemia.

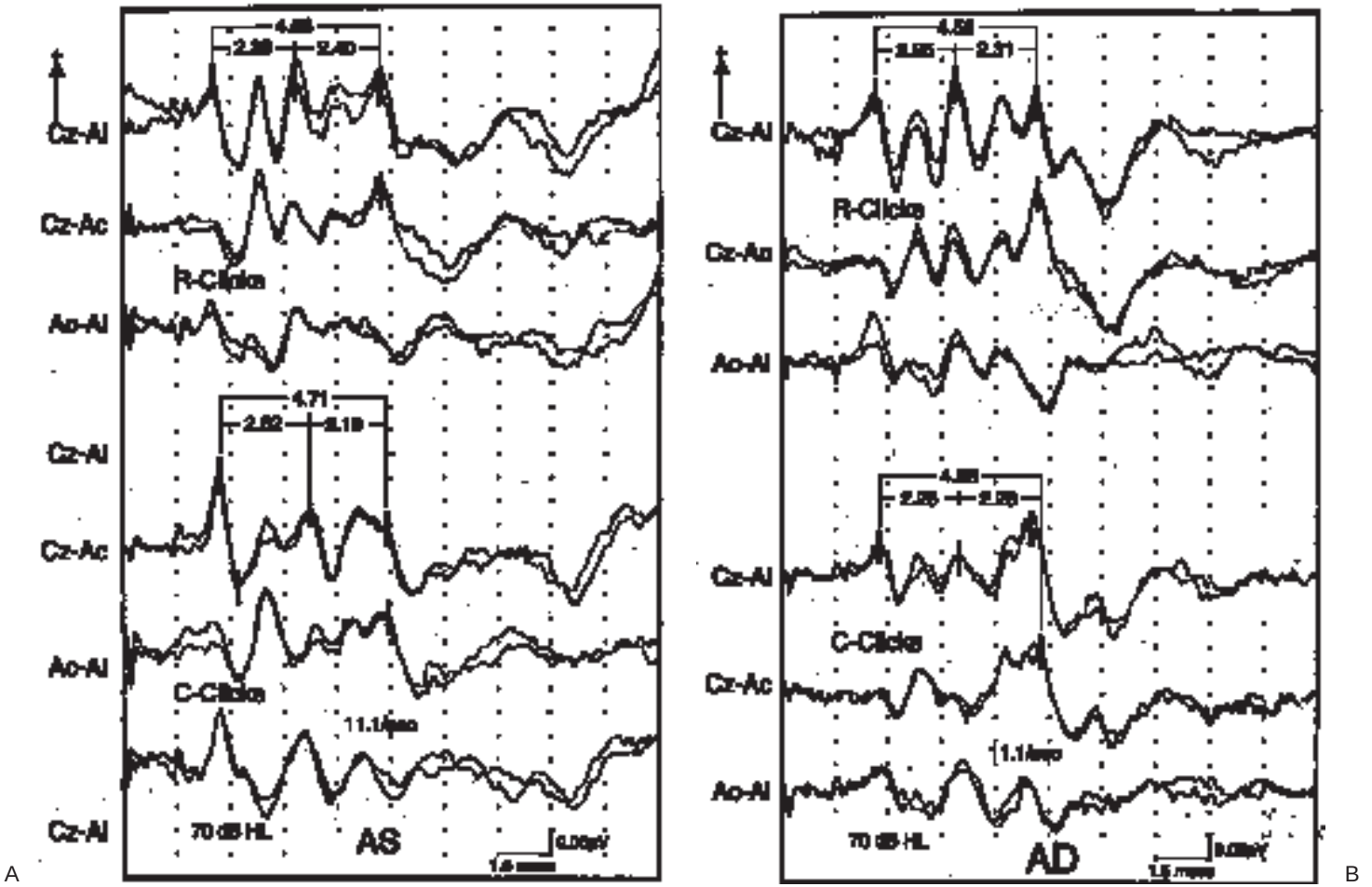
Brainstem hemorrhages much like ischemic lesions (20,26,55,80). Stockard and Rossiter (211) noted that lower pontine lesions affect wave III and the I-III IPL, whereas higher lesions leave wave III intact. BAEPs have also been shown to be helpful in prognosticating outcome after infratentorial hemorrhages and primary subarachnoid hemorrhages; normal evoked potentials imply good prognosis, whereas absence of waveforms implies poor outcome (84,85). Faster stimulation rates (beyond 50 Hz) have been shown to demonstrate abnormalities more often in patients with vascular brainstem dysfunction (14,58). This is thought to occur because the sites most vulnerable to increased rates of stimulation, the synapses, are the same sites that are most vulnerable to ischemia (176).

Multiple Sclerosis

BAEPs, like other modalities of evoked potentials, are useful in the evaluation of multiple sclerosis. Abnormalities are seen in declining incidence in patients grouped as having definite, probable, and possible multiple sclerosis. BAEP abnormalities have been noted in 39% to 90% of patients with definite multiple sclerosis (160,174,175); 33% to 77% of patients with probable multiple sclerosis (57,100,118,153,174,175,180,216); and 19% to 67% of patient with possible multiple sclerosis (118,174,175) (Fig. 28.9). Chiappa (28) reviewed a number of studies that included all classes of patients with multiple sclerosis. Of the 1,006 patients in these studies, 466 (46%) had abnormal BAEPs. When divided into different classes, 67% of patients with definite multiple sclerosis, 41% with probable multiple sclerosis, and 30% with possible multiple sclerosis had BAEP abnormalities. Most important, 38% of patients without brainstem symptoms or signs had BAEP abnormalities.

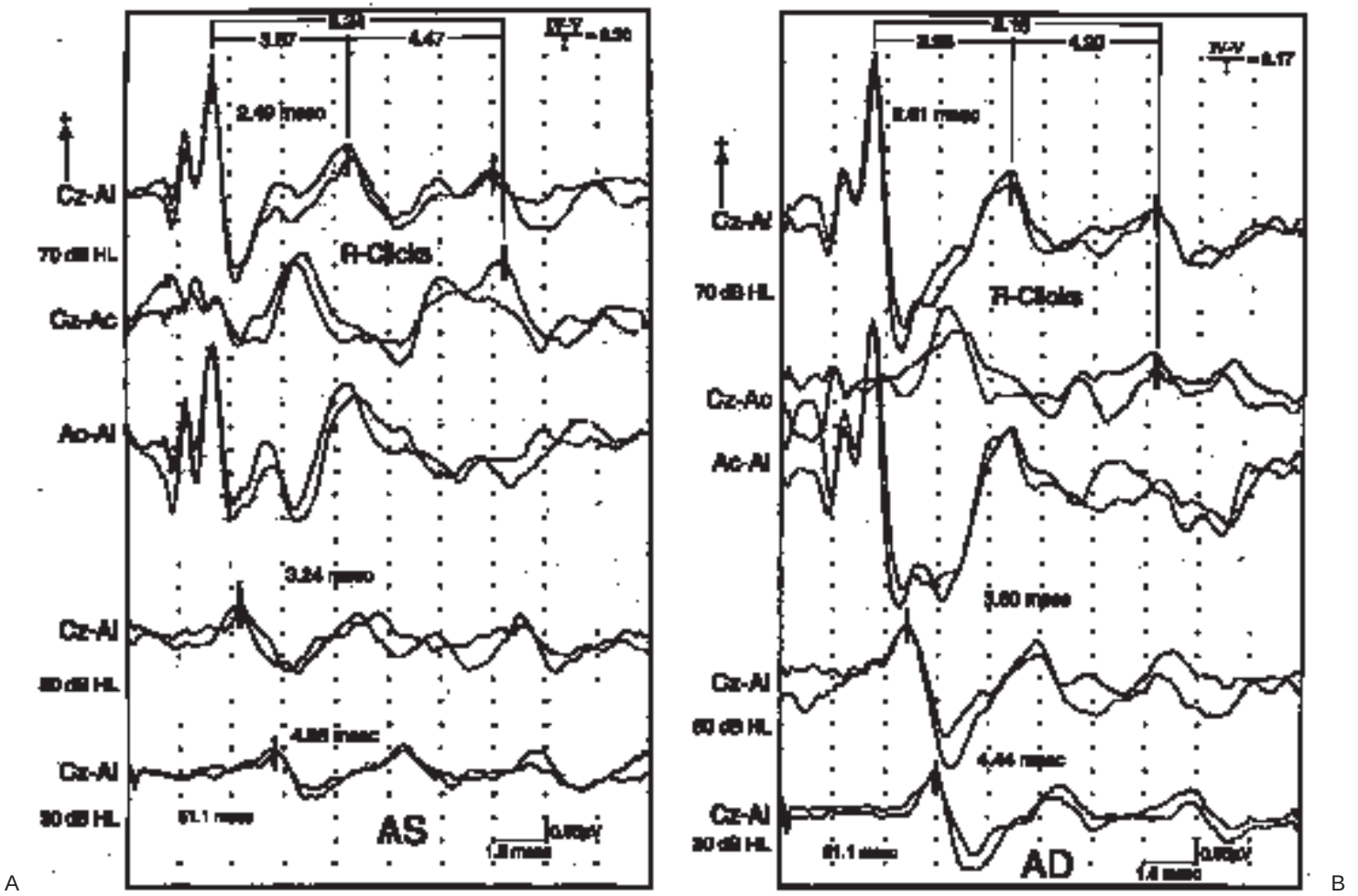
The BAEP abnormalities seen most commonly in multiple sclerosis include delay in wave V latency, wave V amplitude abnormalities, and III-V IPL prolongation (29,100,174,175). I-III IPL abnormalities are less common. Fast rates of stimulation have been noted to increase the frequency with which abnormalities are detected.

Other demyelinating and dysmyelinating conditions have been associated with abnormal BAEPs. In leukodystrophy (64,114,120,122,154) and Alpers' syndrome (124), IPL prolongations and absence of waves after wave I have been demonstrated (Fig. 28.10; see Fig. 28.5).



A B

FIG. 28.9. A&B: Magnetic resonance imaging (MRI) of the brain of a 50-year-old man with a 5-year history of left lower extremity weakness revealed multiple white matter plaques in the cerebral hemispheres but none in the brainstem. The BAEP revealed prolonged interpeak latencies from wave I to wave V after left ear stimulation that exceed 4.60 milliseconds. The responses from right ear stimulation are just below 4.6 milliseconds. Neither the wave I–wave III nor wave III–wave V segment is prolonged, which suggests that the disturbance is diffuse, from the pontomedullary junction to the caudal midbrain with greater physiological disturbance on the left. This study supports the diagnosis of multiple sclerosis by suggesting yet another site of possible demyelination in the brain stem not seen by MRI. (See legend for Fig. 28.1 for stimulation and recording parameters.)



A B

FIG. 28.10 A&B: Magnetic resonance imaging revealed diffuse T2 hyperintensity in the subcortical white matter and brainstem of a 5-month-old girl with Krabbe's disease. The BAEP showed markedly prolonged interpeak latencies from wave I to wave V_C of 8.34 milliseconds AS and 8.16 milliseconds AD. The ear insert transducers produce essentially no stimulus artifact and delay the stimulus onset by 0.9 millisecond, producing wave I responses of 2.49 and 2.61 milliseconds after left and right ear stimulation, respectively. Wave I is preceded by a cochlear microphonic response that is more prominent than usual. Waves V and V_C are both prolonged and attenuated, as evidenced by the low amplitude ratios of wave IV or wave V to wave I bilaterally. The latency/intensity series with stimulation at 70, 50, and 30 dBHL (decibel hearing level) shows appropriate time displacements for wave I. Wave V is usually more robust at lower levels of stimulation, but in this instance, wave I is the more robust, confirming the pathological attenuation of wave V at 70 dBHL.

Miscellaneous Disorders

Myelomeningocele and Arnold-Chiari Malformation

BAEPs have been shown to be useful in predicting which patients with myelomeningocele will ultimately have brainstem dysfunction. Children without brainstem symptoms at birth or shortly thereafter and abnormal BAEPs are more likely to become symptomatic than are those with normal BAEPs (224,242). The most common abnormality in this group of children was fusion of waves III, IV, and V, caused in part by the absence of wave III_N (242). The average I-V IPL was also greater in those that later developed symptoms. Others have noted that in natural progression of Arnold-Chiari malformation there is gradual shortening of the III-V IPL and prolongation of I-III IPL (143,151) (Fig. 28.11). Those authors postulate that this is caused by gradual myelination of the brainstem with age. On the other hand, stretching and prolongation of the abnormally placed lower cranial nerves with growth leads to prolongation of the I-III IPL.

Alcoholism

Acute intoxication causes a prolongation in the I-V IPL (204,205,215); these changes do not disappear with discontinuation of alcohol (13).

BAEP abnormalities have also been reported in Wernicke-Korsakoff syndrome (23).

Sleep Disorders

As may be expected, patients with central sleep apnea have been noted to have BAEP abnormalities (214); however, patients with obstructive and mixed apneas often have normal findings (144,214,235). The exception to this observation came from Kotterba and Rasche (109), who found prolongation of IPLs in 12 of 20 patients with obstructive sleep apnea; interestingly, nine of these patients had demonstrable brainstem lesions. In narcolepsy, although a site of pathophysiological abnormality is thought to be the brainstem, BAEPs are normal (89,125).

Neurodegenerative and Other Progressive Neurological Disorders

Although many neurodegenerative disorders have been studied with BAEPs, the number of patients in each group has been small, and the results are thus inconclusive. This is demonstrated by the variability of findings reported in Friedreich's ataxia. Patients with this condition have been reported to exhibit BAEPs with central conduction abnormalities (87,93), only periph-

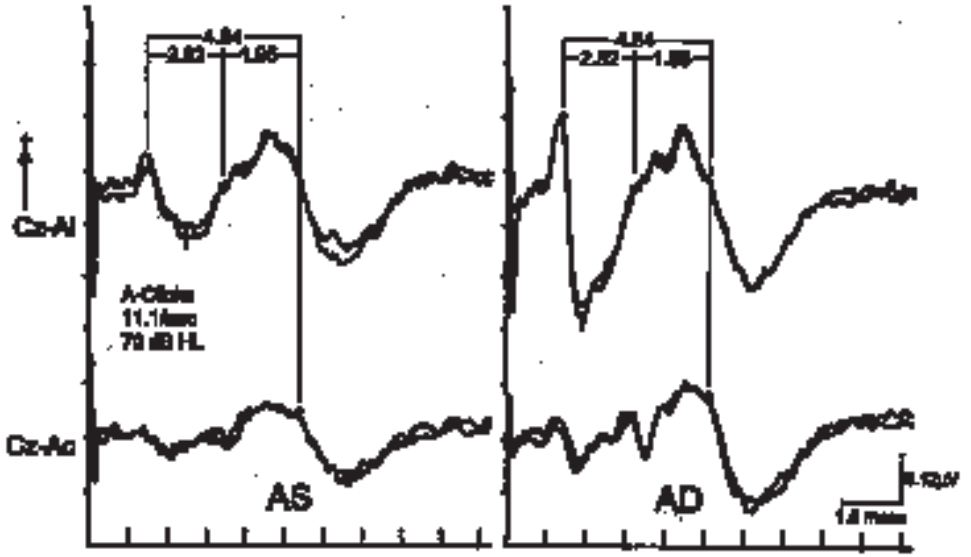


FIG. 28.11. Chiari malformation in a 4-year-old girl. The BAEP showed prolongation of the interpeak latencies from wave I to wave V_C and from wave I to wave III bilaterally, which suggests lower brainstem dysfunction. In addition, fusion of waves III, IV, and V is present bilaterally, forming the typical mitten-shaped waveform.

eral conduction abnormalities (193), and normal findings (152). In numerous other neurodegenerative conditions, including Parkinson's disease (230), Huntington's disease (170), and amyotrophic lateral sclerosis (22), normal BAEPs have been demonstrated. In Creutzfeldt-Jakob disease, there is progressive deterioration of the BAEPs as disease severity increases (171).

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Chapter 29

Somatosensory Evoked Potentials

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Origins of Surface-Recorded SSEPs
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Contributions from Gray Matter Structures
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Stimulation of peripheral nerves results in generation of electrical signals that are recordable over the spine and scalp. Potentials evoked in this manner reflect activity within the large fiber sensory systems. Abnormalities of somatosensory evoked potentials (SSEPs) occur in a wide variety of pathological conditions:

Focal lesion affecting the somatosensory pathways: tumors, strokes, and spinal cord compression (16,21,39,107)
Demyelinating diseases: multiple sclerosis (15), adrenoleukodystrophy and adrenomyeloneuropathy (26,48,71,146), metachromatic leukodystrophy (140,160), and Pelizaeus-Merzbacher disease (97)

In adrenoleukodystrophy and adrenomyeloneuropathy, even asymptomatic heterozygotes manifest SSEP abnormalities (48,146).
Diseases that affect the nervous system diffusely: hereditary system degenerations (110), subacute combined degeneration (65), vitamin E deficiency (12, 70), human immunodeficiency virus encephalopathy (61,106), amyotrophic lateral sclerosis (49,167), myotonic dystrophy (55,142), diabetes (44,95)
Brain death (54)

Lesions generally alter SSEPs by prolonging interpeak latencies, reflecting delayed conduction, or attenuating or abolishing component waveforms,

indicating conduction block or dysfunction of the responsible generator(s). An exception is cortical reflex myoclonus, in which high-voltage SSEPs reflect enhanced excitability of sensory cortex (57,68).

SSEPs are best utilized as an extension of the neurological examination. They help to document lesions of the nervous system and often suggest their location. SSEPs are therefore most useful when they detect clinically occult abnormalities that might otherwise be unrecognized. They also often assist in resolving clinically vague symptoms or ambiguous sensory findings on examination. Increasing, SSEPs are being used intraoperatively, both to identify specific structures and to detect injury to neural structures while it is still reversible.

ORIGINS OF SURFACE-RECORDED SSEPS

Although Dawson (24) first recorded SSEPs over 40 years ago, there is still considerable uncertainty about their neural generators. The present level of understanding provides an adequate basis for many clinical purposes; however, improved interpretation of complex abnormalities, as well as precise localization of lesions, requires additional detailed knowledge of generator sources.

An appreciation of the basis for uncertainties about the origins of SSEPs can be gained by considering the criteria that must be met to establish a causal relation between activity in a neural structure and a scalp-recorded potential (2):

1. The neural event and the surface potential must occur simultaneously.
2. There must be evidence that the neural event produces a signal that can be recorded beyond the bounds of the active structure.
3. No other simultaneous neural activity must exist that could explain or substantially contribute to the scalp recording.

These criteria are virtually impossible to fulfill in humans. On a few occasions, temporal coincidence has been demonstrated between (a) neural activity occurring at likely generator sites and (b) surface recordings. However, even when intracranial or spinal recordings are made, it is almost never possible to track a potential from its origin to the surface, which makes it difficult to prove a direct relation (2,4). Therefore, the present conclusions about the origins of SSEP components are derived largely from indirect evidence, including (a) analysis of surface distributions of waveforms; (b) inferences about probable anatomical sites from calculations measured in peripheral nerves with adjustment for fiber size, tract length, and synaptic delays; and (c) the effects of lesions.

At least two distinct classes of neural events contribute to brain electrical activity recorded at the scalp: (i) synaptic potentials arising in gray matter and (ii) propagated action potentials generated in white matter fiber tracts. The following discussion reflects our own beliefs and prejudices; nonetheless, we believe it is a reasonable synthesis based on the current evidence.

Contributions from White Matter Structures

White matter fiber tracts generate propagated compounded action potentials. An overlying electrode records these as triphasic, positive–negative–positive waveforms representing, respectively, outward current flow in advance of the active region of depolarization, inward current flow in the actively depolarized area, and then outward current flow as a depolarization passes and repolarization occurs (Fig. 29.1) (11). Such signals can be recorded ordinarily only in the vicinity of the fiber tract itself and have been termed *near-field potentials* (NFPs). Because current density gradients are steep in the vicinity of a localized area of depolarization, the voltage of NFPs is highly dependent on the position of the recording electrode. Small changes in electrode position produce large changes in voltage. Another important characteristic of NFPs is that, when recorded from an array of electrodes along the course of a fiber tract, NFPs increase in latency at recording sites progressively more distant from the point of stimulation.

White matter fiber tracts also generate another class of signals, known as *far-field potentials* (FFPs). These are unlike NFPs in that they are widely distributed and their latency is independent of electrode position (i.e., they are stationary). Their amplitude and morphology also remain relatively constant despite substantial changes in position of the recording electrode (10,62). FFPs are generated when a propagated action potential reaches or traverses certain fixed points along the course of a nerve or fiber tract. In classical neurophysiology, FFPs were recognized only as positive signals that reflected the moving front of an approaching volley recorded from a point beyond the termination of active fibers (159). A theoretical model involving an exploring electrode situated at a distance from an active neural element in a uniform volume conductor supports this view, as does an experimental model in which a recording electrode was placed beyond the crushed end of a nerve in a saline bath (91,159).

More recently, investigators recognized that FFPs also are generated under other conditions (40,75,76,92,108). Kimura and colleagues (72,73,75, 164) demonstrated in humans that FFPs are generated at specific sites along a peripheral nerve where physical boundaries are crossed. These potentials, which Kimura et al. labeled "junctional" or "intercompartmental" potentials, are typically diphasic but may appear predominantly either negative or positive. Far-field signals also may be generated at points where nerve trunks bend or branch (34).

Nakanishi (108,109) presented an experimental model that showed that FFPs could be generated at points along the course of a nerve where the impedance of the surrounding tissue changed abruptly. He passed a nerve through a series of chambers separated by slotted partitions sealed with petroleum jelly. Each chamber was filled with Ringer's solution and contained a recording electrode so as to become a fluid electrode surrounding the portion of the nerve coursing through it. The sealed partitions constituted high-impedance boundaries between fluid electrode chambers. Nakanishi recorded a potential between two adjacent chambers at the moment the volley reached the separating partition and the recorded potential reversed polarity as the volley crossed the partition (Fig. 29.2.). Recordings across multiple partitions produced a multipeaked waveform, with the number of peaks equaling the number of partitions crossed by the nerve (Fig. 29.3).

Generation of junctional FFPs seems to depend on a change in current density in tissues surrounding a nerve, caused by abrupt alteration in either their geometry (75,76) or conductive properties (93,108; see also ref. 121). Kimura et al. (72) hypothesized that tissue on either side of a boundary approximates a volume conductor acting as a lead connecting all points within an anatomical compartment to the voltage source at the boundary. This is consistent with Nakanishi's model (108) and suggests that there may be no inactive site on the body for junctional FFPs.

Other factors may influence the distribution of a FFP within a compartment, including the direction of the volley crossing the partition (33,69). A model based on a moving quadrupole in a cylindrical volume conductor, in which FFPs result from asymmetries between leading and trailing dipoles, has been proposed (34).

Figure 29.4 illustrates the generation of junctional FFPs ($N\overline{3}$, $N\overline{6}$, and $N\overline{9}$) as the median nerve afferent volley crosses borders between anatomically distinct compartments. This figure also illustrates the use of bipolar and referential derivations to emphasize near-field and far-field components selectively. Sequential bipolar recordings from a chain of electrodes overlying the course of the median nerve depict only the propagated near-field volley. Referential recordings from the same electrodes also detect the more widely distributed far-field stationary signals that are generated as the volley enters the brachioradialis muscle, enters the distal end of the deltoid, and crosses the boundary between arm and body. These far-field signals in phase cancel in the bipolar recordings (164).

Yamada et al. (164) further demonstrated that the $N\overline{3}$, $N\overline{6}$, and $N\overline{9}$ potentials could be recorded from distant electrodes and were therefore, by definition, FFPs. Three subjects were electrically connected at the forearm. Fol-

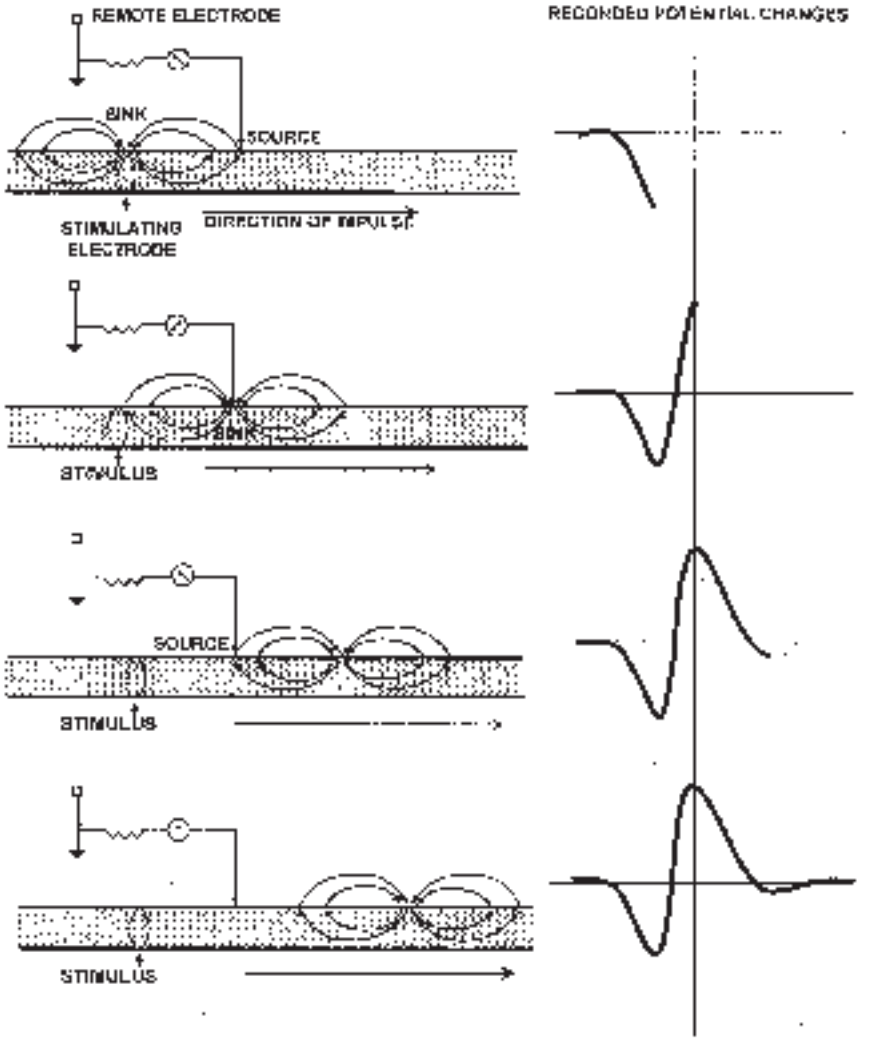


FIG. 29.1. Generation of the classical triphasic, positive–negative–positive signal by a propagated action potential. (From Brazier MAB. *Electrical activity of the nervous system*. Baltimore: Williams & Wilkins, 1977:68, with permission.)

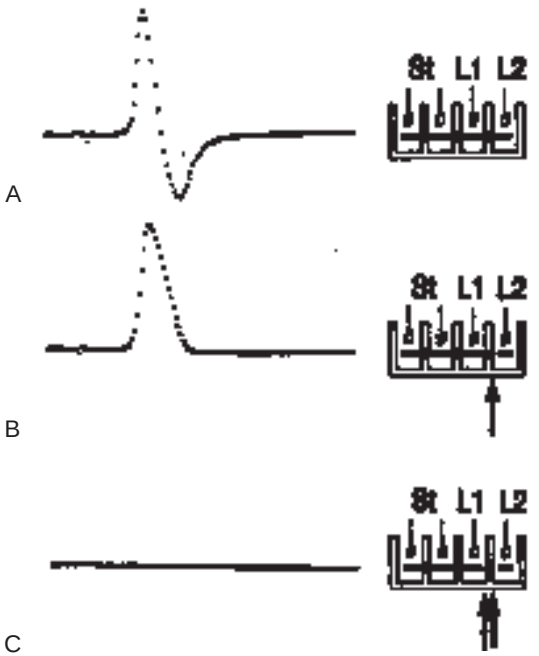


FIG. 29.2. Action potential recorded differentially between adjacent fluid electrodes, L1 and L2, following stimulation at electrode S1. **A:** With the nerve intact, a biphasic signal is recorded. **B:** When the nerve is severed at its point of exit from the partition between L1 and L2, only a monophasic signal is recorded. **C:** When the nerve is cut prior to entering the partition, no signal is recorded. (From Nakanishi T, Tamaki M, Arasaki K, et al. Origins of the scalp-recorded far field potentials in man and cat. *Electroencephalogr Clin Neurophysiol Suppl* 1982;36:336–348, with permission.)

lowing stimulation of the median nerve of the middle subject, this series of negativities, recordable as stationary potentials over the stimulated forearm, was conducted to the nonstimulated subject on either side. Yamada et al. (164) observed that the $N\bar{9}$ stationary potential was precisely coincident with the scalp-recorded $P\bar{9}$ FFP, and found evidence that N6 had a positive counterpart over the lower third of the body. Although unable to identify a corresponding positivity for $N\bar{3}$, they suggested that a negative stationary potential may be necessary for the occurrence of the familiar positive FFP. It is now clear, however, that junctional FFPs can be recorded as either predominantly negative or positive, or as diphasic potentials.

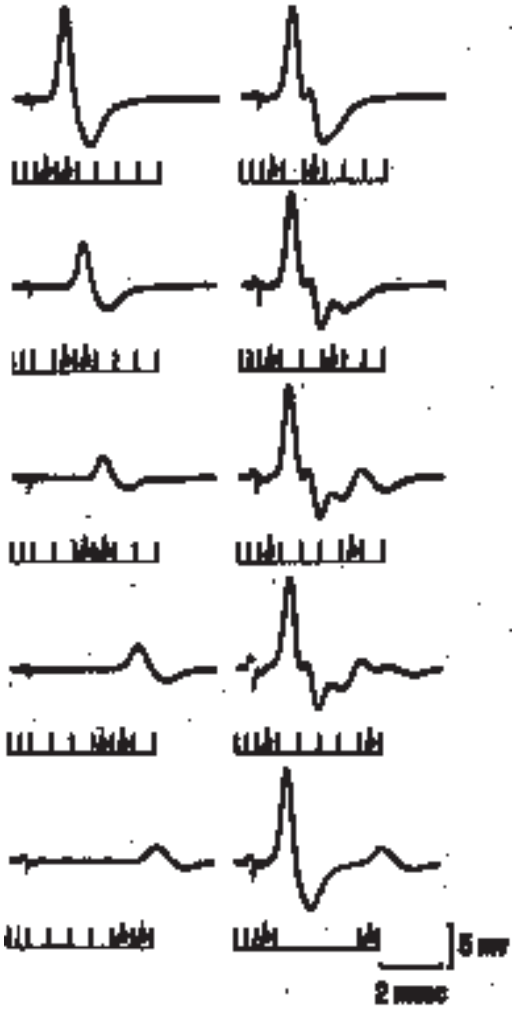


FIG. 29.3. Action potentials recorded differentially between fluid electrodes separated by a variable number of partitions. (From Nakanishi T. Action potentials recorded by fluid electrodes. *Electroencephalogr Clin Neurophysiol* 1982;53: 343–346, with permission.)

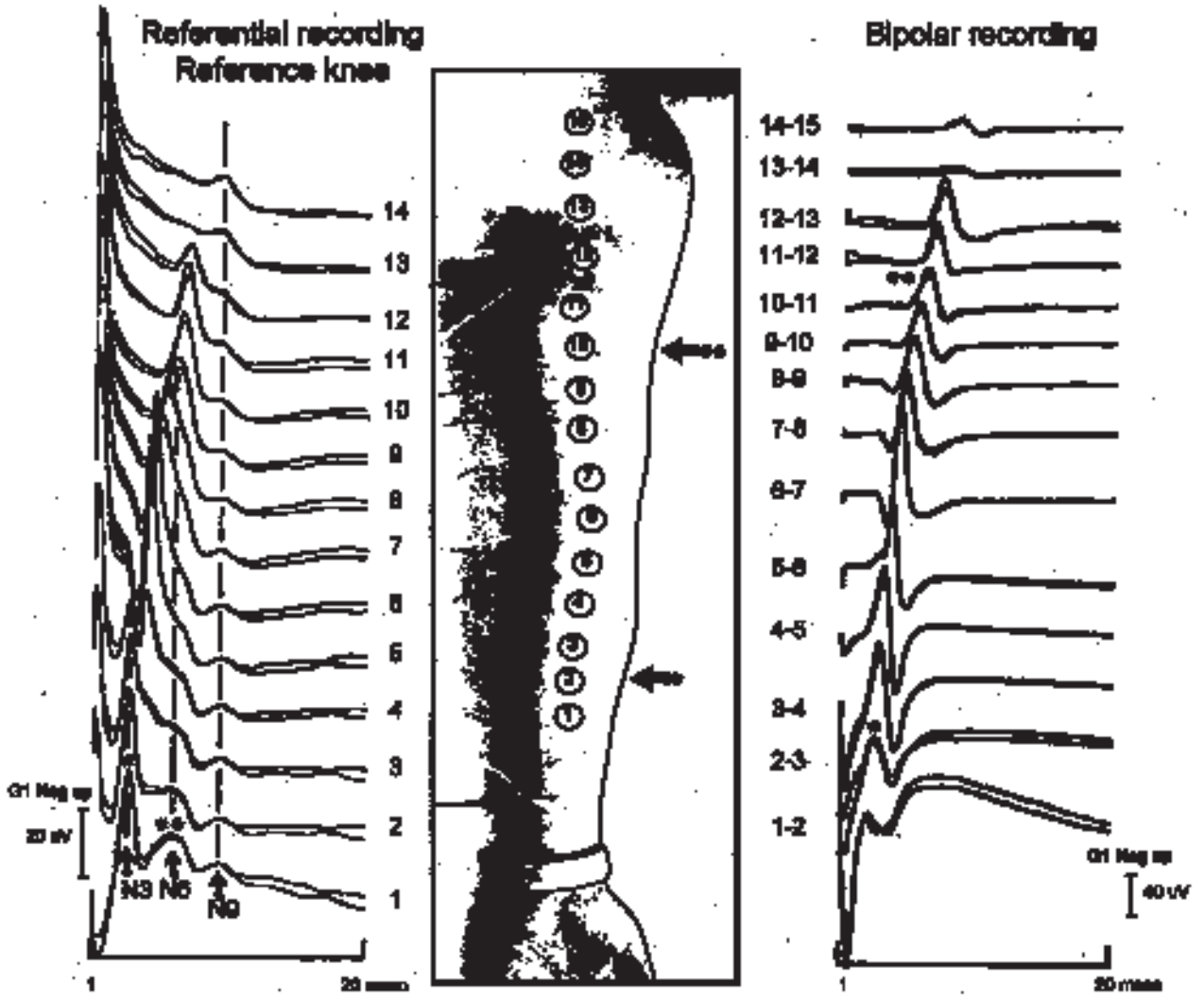


FIG. 29.4. Near-field and far-field potentials generated in the arm and shoulder following stimulation of the median nerve at the wrist. *Right:* A series of bipolar recordings from sequential pairs of electrodes over the course of the median nerve show near-field signals corresponding to the afferent volley. *Left:* Referential recordings from the same electrodes to a knee reference show both near-field (propagated) and far-field (stationary) signals. Far-field signals are generated when the afferent volley enters the brachioradialis (*) and deltoid (**) muscles, and crosses the boundary between the arm and the trunk. (Modified from Yamada T, Machida M, Oishi M, et al. Stationary negative potentials near the source vs. positive far-field potentials at a distance. *Electroencephalogr Clin Neurophysiol* 1985;60:509–524.)

Contributions from Gray Matter Structures

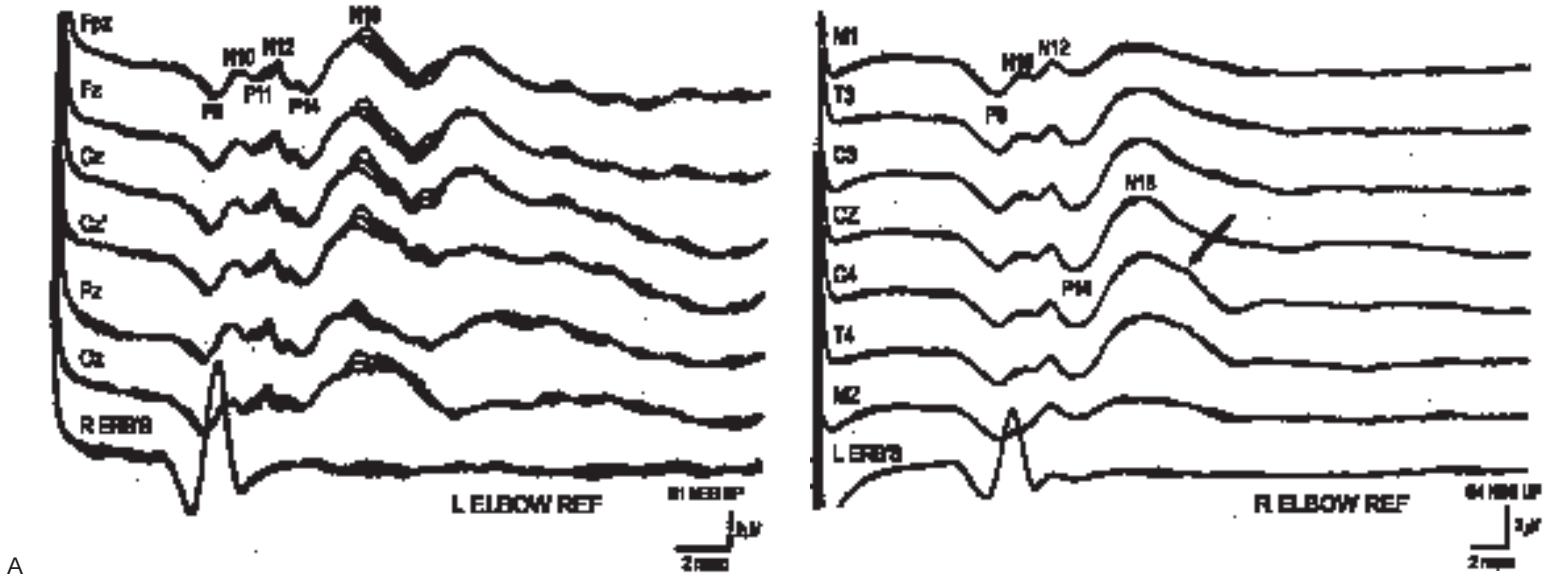
Graded postsynaptic potentials (PSPs) generated in gray matter structures also contribute to surface-recorded evoked potentials. The scalp-recorded electroencephalogram primarily reflects extracellular current flow resulting from summated excitatory and inhibitory PSPs generated in the parallel, vertically oriented pyramidal cells and their dendrites (35,78,147,164). Similar postsynaptic activity is probably responsible for the primary and subsequent cortical components of median nerve and posterior tibial nerve (PTN) SSEPs.

Although many subcortical nuclei are considered "closed-field" systems because their internal geometries are not conducive to producing current flow much beyond their boundaries (6,78,90), some subcortical nuclear structures do generate surface-recordable evoked potentials ("open-field" system). Examples include (a) central gray matter of the cervical (29,40,93) and lumbar spinal cord (125) and (b) the cochlear nuclear complex (85).

The terms *near field* and *far field* are also used to classify evoked potentials generated predominantly by PSPs. However, the distinction between the two is not always clear in this setting, and, in fact, a continuum probably exists. Furthermore, when applied to synaptically generated potentials, the terms do not necessarily imply a difference in generator mechanisms—in contrast to their use with potentials reflecting propagated volleys in white matter. Close to the region of depolarization, current gradients are steep, causing the voltage to vary substantially with changes in electrode position; evoked potentials recorded close to their generators appear as near-field potentials. In contrast, evoked potential signals recorded far from their generators are much less affected by alterations in electrode position, and hence appear as far-field signals (10).

COMPONENTS OF THE MEDIAN NERVE SSEP

For 18 milliseconds following electrical stimulation of the median nerve at the wrist, electrodes distributed widely over the scalp record similar waveforms (Fig. 29.5). Using an elbow reference, these consist of an initial positivity occurring at approximately 9 milliseconds ($P\bar{9}$), followed first by a



A B

FIG. 29.5. Median-nerve SSEPs recorded in midsagittal (**A**) and coronal (**B**) planes using elbow references in two different normal individuals. In this and subsequent figures, amplifier passband settings are 30–3,000 Hz (–6 dB) unless noted. Upward deflections correspond to a relative negative voltage at the noninverting amplifier input.

series of small oscillations and then by a large-amplitude negative deflection of relatively long duration. The homogeneity of the recordings from virtually all scalp locations suggests that these components correspond to FFPs generated by relatively remote subcortical structures. After 18 milliseconds, differences appear in recordings from different scalp regions that reflect localized near-field activity (arrow, Fig. 29.5B).

Scalp-recorded activity following P$\overline{9}$ is customarily described as a series of two or more positive waves (5,6,19,20,28–30,64,79,93,99,109,148,157, 163). This view is consistent with, and may have been influenced by, the traditional concept that FFPs "should" be positive. It is clear from the foregoing section, however, that mechanisms of FFP generation are complex and that FFPs can appear either positive or negative.

Electrodes placed over the neck allow identification of signals corresponding to passage of the afferent volley through the proximal brachial plexus and the cuneate tract of the cervical spinal cord. Comparison of these measurements with simultaneous scalp recording provides important clues to the origins of the scalp-recorded FFPs. In addition to activity in ascending long tracts, neck electrodes register a distinct, localized stationary potential most likely generated in the gray matter of the cervical cord.

Brachial Plexus Volley

The scalp P$\overline{9}$ potential corresponds to the afferent volley in the brachial plexus (93,99,109,148,157,163) and occurs after the onset of afferent depolarization at the axilla but prior to arrival of the volley at Erb's point (28,163). The exact latency of P$\overline{9}$ can be influenced by changes in shoulder position (33).

Activity in Proximal Brachial Plexus and Cervical Roots

A vertical array of electrodes placed laterally over the anterior border of the sternocleidomastoid muscle, ipsilateral to the stimulated nerve, records a propagating wave that begins immediately after the afferent volley passes beneath Erb's point. No similar wave occurs contralaterally. The timing and topography of this potential indicate that it must represent activity in the brachial plexus or cervical spinal roots proximal to Erb's point. As illustrated in Fig. 29.6, the N$\overline{10}$ scalp FFP coincides with passage of this proximal plexus volley (PPV) through the neck. Although N$\overline{10}$ is widely distributed over the scalp, it is not identical at all electrode sites. It is maximal at the auricular electrode ipsilateral to the stimulus and is of significantly lower voltage contralaterally (Fig. 29.6). The exact point along the brachial plexus at which the N$\overline{10}$ FFP is generated is not known. There is considerable inter-

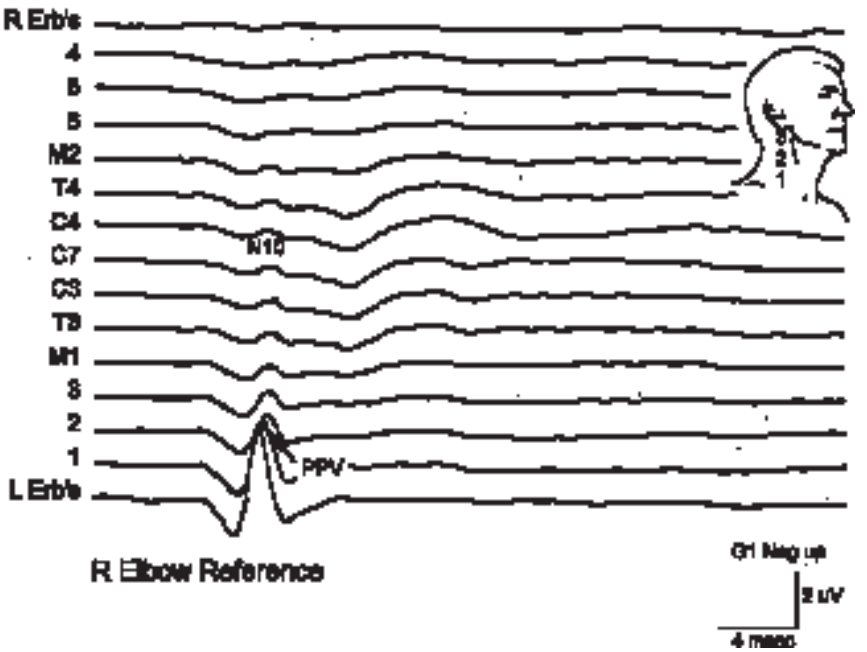


FIG. 29.6. Scalp topography of the N$\overline{10}$ potential in the coronal plane following left median nerve stimulation. Amplifier passband is 1–3,000 Hz.

subject variation in the position over the lateral neck where the negative peak of PPV becomes coincident with the scalp N$\overline{10}$ potential. It is likely that the relation of activity in the brachial plexus both to the propagating wave recorded over the neck and to its far-field counterpart on the scalp is determined by individual considerations of neck geometry and the electrical properties of intervening structures.

Dorsal Column Volley

Approximately 2 milliseconds after N$\overline{10}$, a second negative deflection, N$\overline{12}$, appears at scalp electrodes (see Fig. 29.5). This corresponds to another propagated volley that can be recorded directly from an ascending series of electrodes placed over the dorsal aspect of the neck (Fig. 29.7). Its characteristics are compatible with the sensory signal ascending the cuneate tract, and we have accordingly designated this the "dorsal column volley" (DCV). The scalp N$\overline{12}$ FFP occurs simultaneously with arrival of the DCV at the first cer-

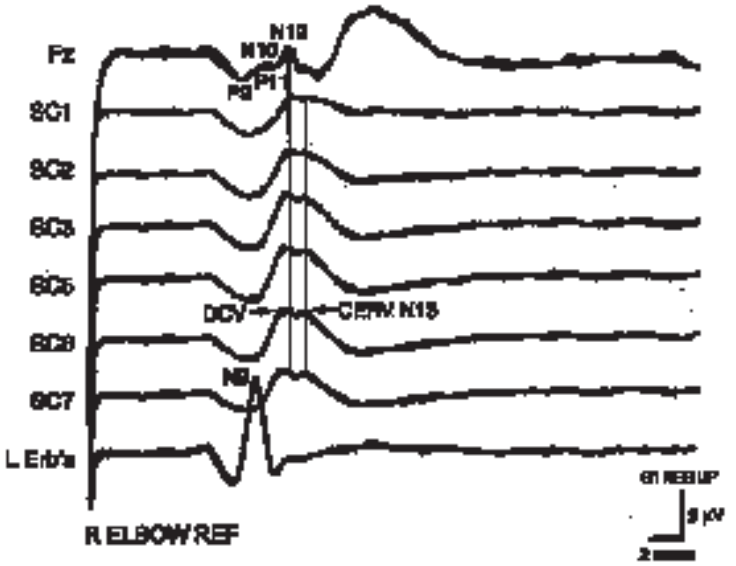


FIG. 29.7. Median nerve SSEPs recorded from a series of ascending cervical electrodes and from FZ using a noncephalic common reference.

vical level, SC1 (Fig. 29.7). This relationship suggests that the N12 potential is generated at or before termination of the cuneate tract at the cuneate nucleus, perhaps because of changes in current density occurring as the afferent volley passes the boundary between spinal and cranial compartments.

Postsynaptic Activity in the Cervical Cord

Desmedt and Cheron (30) and Lueders et al. (93) provided evidence for a fixed generator of NFPs in the cervical spinal cord. Figure 29.7 demonstrates that a negativity (Cerv N13) follows the DCV over the posterior neck. The Cerv N13 potential is stationary in time (i.e., its latency does not change with rostral–caudal movement of the recording electrode), and its voltage is maximal over the low to middle cervical region. Desmedt and Cheron (30) used electrodes placed within the esophagus to identify a stationary positivity that was synchronous with the simultaneously recorded fixed dorsal negativity. We confirmed this observation using a ring of electrodes around the neck at the level of the fifth cervical spine (SC5) posteriorly and the superior border of the thyroid cartilage anteriorly (40). As illustrated in Figure 29.8, this stationary cervical potential attenuates laterally, passes through a null point, and becomes positive over the anterolateral neck, reaching maximal positivity in the anterior midline (Cerv P13). It is not uncommon for the Cerv N13 potential to mask the DCV. In these subjects, placement of lateral neck electrodes, where the stationary potential is near its null point, permits separation of the DCV from the Cerv N13 potential.

It is most probable that the Cerv N13/P13 complex reflects postsynaptic activity in the central gray matter of the cervical spinal cord generated in response to input from axon collaterals. This conclusion is supported by direct intramedullary recordings in cats (7,17,43) and monkeys (7,8) that demonstrated potentials that reversed polarity between dorsal and ventral horns of the spinal cord gray matter. A contribution to Cerv N13 from the cuneate nucleus has also been proposed (127).

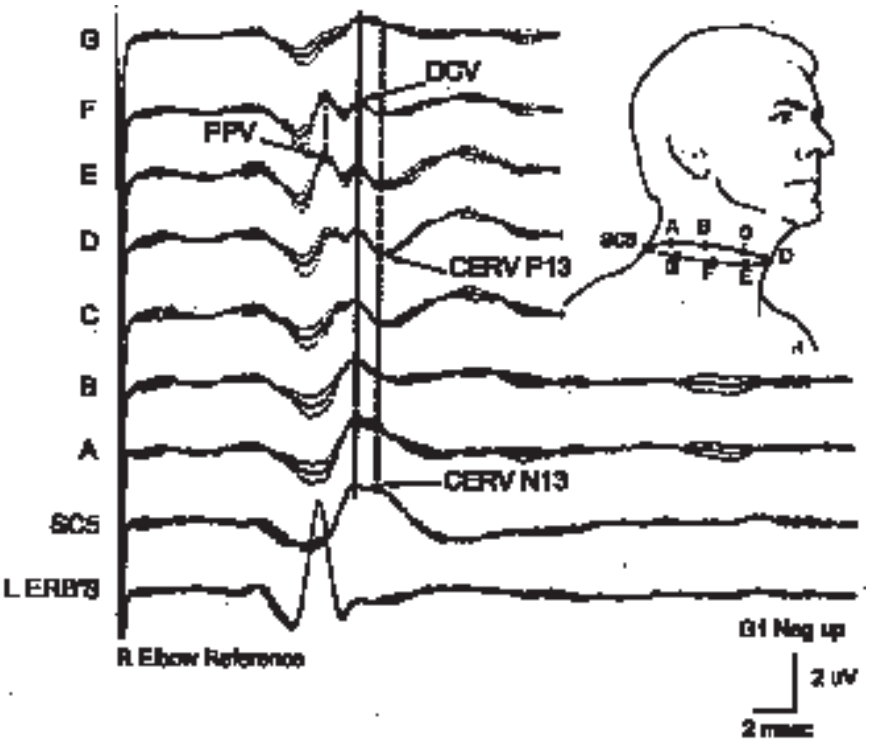


FIG. 29.8. Median nerve SSEPs recorded from a ring of electrodes about the neck using a noncephalic site.

Between N10 and N12, a downward deflection is present that has been designated P11 (see Fig. 29.5). Desmedt and Cheron (28) concluded, by extrapolating from measurements of the velocity of the approaching volley in peripheral nerve, that P11 onset coincided with the spinal entry of the afferent signal. Similarly, Lueders et al. (93) observed intraoperatively that the peak latency of the afferent volley at the C6 posterior rootlet corresponded to P11 latency.

The P14 Complex

Following N12, a clearly demarcated positive deflection, P14, is seen at all scalp electrodes (see Fig. 29.5). P14 often appears as a single positive wave (see Fig. 29.5*B*), although frequently one or more inflections appear superimposed on it (see Fig. 29.5*A*) (6,28,38,60,93,163).

Although the exact origin of the P14 potential is debated, based on observations in normal subjects (28–30), patients (100,143,161), and experimental animals (2,6), it is generally agreed that P14 reflects activity in the medial lemniscus in the caudal brainstem. A presynaptic contribution from the upper cervical cord has also been suggested (66,119,120). Figure 29.9 is the median nerve SSEP of a 70-year-old woman with locked-in syndrome secondary to basilar artery occlusion. She had sudden onset of quadriparesis and a right hemisensory deficit that included the face. Pupillary reflexes and vertical eye movements were intact, but horizontal eye movements were absent. Although an autopsy was not permitted, the clinical picture indicated a bilateral lesion affecting the ventral portion of the midpons. Additionally, the right hemisensory deficit suggested that the lesion had sufficient dorsal extension to affect lemniscal fibers in the left pontine tegmentum. The SSEP in response to right median nerve stimulation revealed a normal P14 complex, but N18 was absent (see below). Preservation of P14 in this patient is consistent with a generator site in the caudal medial lemniscus, below the midpons. A patient with a right pontine arteriovenous malformation showed similar findings (Fig. 29.10). Additionally, intraoperative recordings have demonstrated activity in the caudal medulla that is coincident with the scalp-recorded P14 complex (Fig. 29.11).

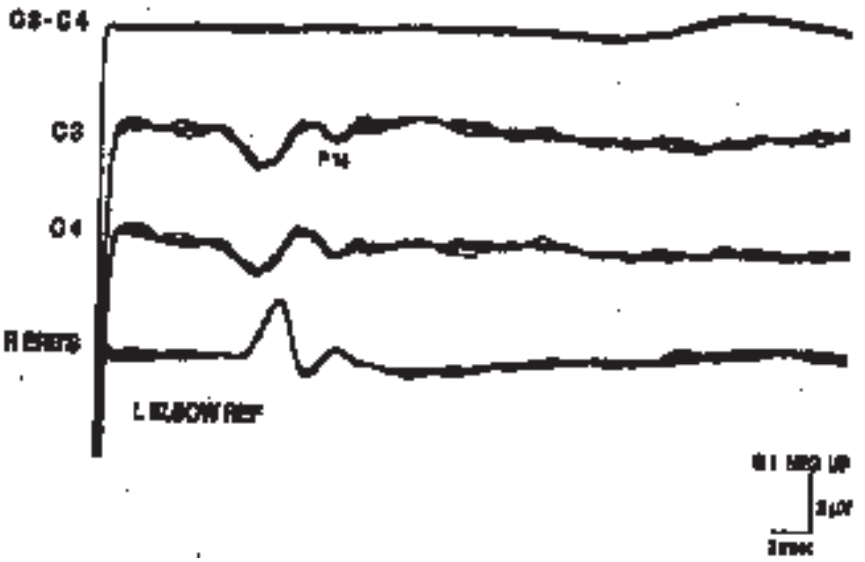


FIG. 29.9. Median nerve SSEP of a patient with locked-in syndrome as a result of basilar artery occlusion. P14 is preserved, but subsequent short-latency potentials are lost.

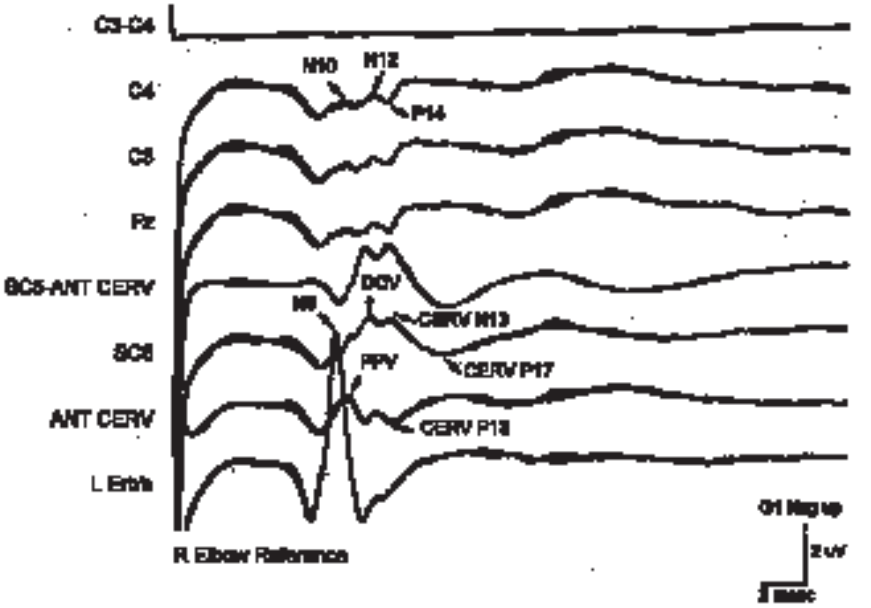


FIG. 29.10. Loss of potentials following P14 in a patient with a pontine arteriovenous malformation.

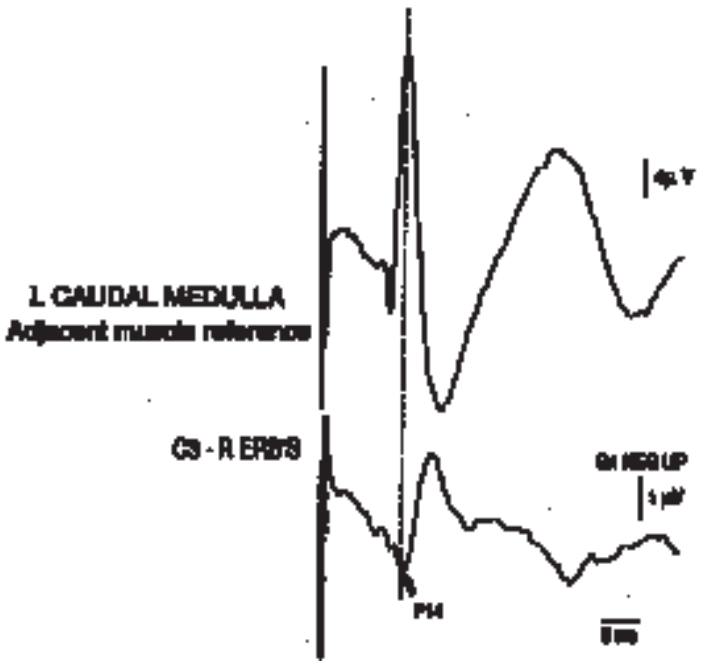


FIG. 29.11. Intraoperative recording demonstrating coincidence of the scalp-recorded P14 potential with activity in the caudal medulla.

The morphology of P14 varies considerably among individuals, although it is remarkably stable for individual subjects on repeat testing (134). Among 62 normal subjects, Sonoo et al. observed that P14 consisted of one, two, and three distinct peaks in 22, 35, and 5 subjects, respectively. Based on the timing of these peaks with respect to the onset of P14, they proposed that P14 is a composite of three components (P14a, P14b, and P14c[1] Figure 29.12), that are variably expressed among normal subjects (134,136).

Sonoo suggested that, whereas components P14a and P14b are most likely generated in the caudal medial lemniscus, P14c may originate more rostrally (134). Figure 29.13 illustrates the unilateral loss of P14c (and N20), but preservation of P14a and P14b, in a patient with a midpontine tumor. In contrast to the symmetrically distributed P14a and P14b, P14c is of greatest voltage over the central scalp region opposite the stimulated median nerve.

[1]P14a, P14b, and P14c, in this discussion, correspond to Sonoo's P13, P14a, and P14b (134).

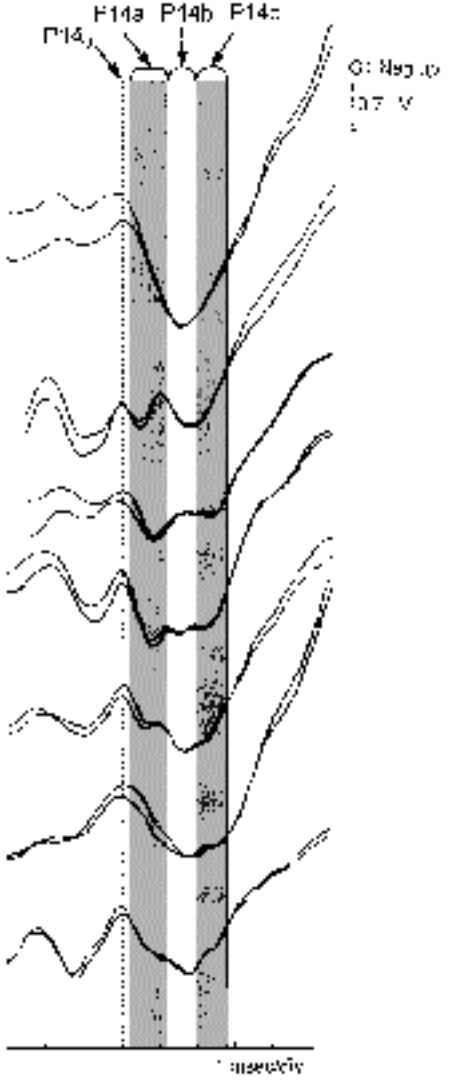


FIG. 29.12. Scalp-to-noncephalic recording following median nerve stimulation in seven normal subjects, illustrating the range of normal variability of the P14 complex. Tracings are aligned at the onset of P14 ($P14_o$), and subcomponents P14a, P14b, and P14c are identified. (Modified from Sonoo M, Kobayashi M, Genba-Shimizu K, et al. Detailed analysis of the latencies of median nerve somatosensory evoked potential components, 1: selection of the best standard parameters and the establishment of normal values. *Electroencephalogr Clin Neurophysiol* 1996;100:319–331.)

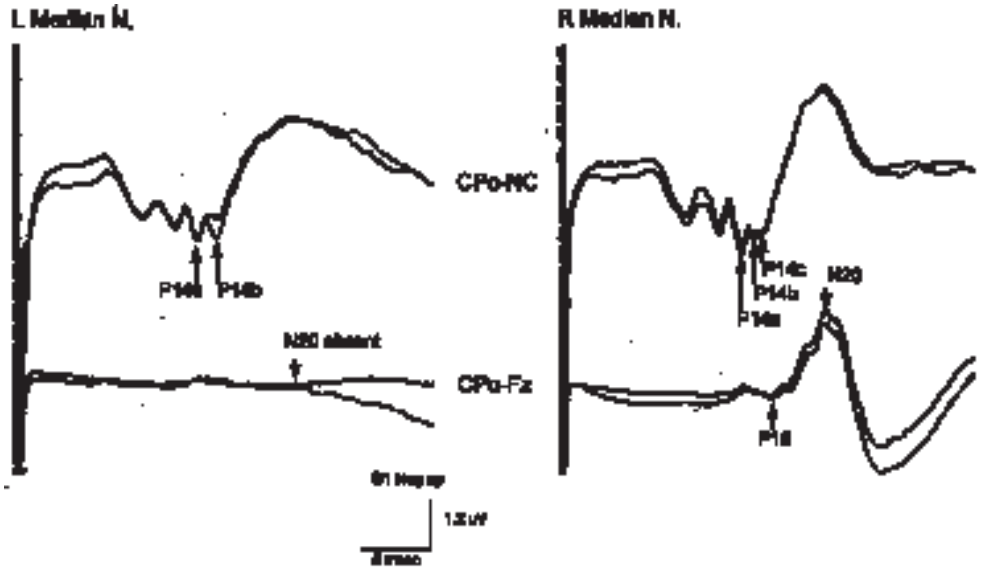


FIG. 29.13. Median nerve SSEP recorded in a patient with a low-grade astrocytoma in the midpons, in the vicinity of the right medial lemniscus. The right median nerve SSEP is normal, and components P14a, P14b, and P14c are identified. The left median nerve SSEP is abnormal, with loss of both N20 and P14c; P14a and P14b are preserved. (From Sonoo M, Kobayashi M, Genba-Shimizu K, et al. Detailed analysis of the latencies of median nerve somatosensory evoked potential components, 1: selection of the best standard parameters and the establishment of normal values. *Electroencephalogr Clin Neurophysiol* 1996; 100:319–331, with permission.)

P14c may be lost in patients with lesions of the brainstem and thalamus, and with long-standing lesions of cerebral cortex. For these reasons, Sonoo et al. suggested that P14c may originate in the thalamocor tical radiations (134). Intracranial recording in monk eys have also shown that the third of three positive far-field signals, which together appear to correspond to the human P14 complex, originates in the thalamocor tical radiations (6). Because of asymmetry of its scalp distrib ution, P14c most likely corresponds to the small positivity that is sometimes detectab le prior to the onset of N20 on bipolar scalp derivations (41).

Many clinical laboratories routinely utilize a recording montage that combines Cerv N13 with the scalp P14 FFP (e.g., SC5-Fpz). In contrast to this practice, we cannot overemphasize the importance of employing montages that preserve the distinct identities of the Cer v N13 and scalp P14 FFPs (39,105). As shown in Figure 29.14, a compressive cervical myelopathy produced a mark ed dissociation betw een these nor mally near-simultaneous components. Two distinct upw ard deflections are present in the SC5-Fpz derivation, but it is not possible to identify each. Separate referential recordings from SC5 and Fpz demonstrated that the f irst inflection is a nor mal-latency Cerv N13 potential; the second is a mark edly prolonged P14 complex. In Figure 29.15, from a patient with syringom yelia (152), there is no Cerv N13, but P14 is normal. In both of these cases, use of a SC5-Fpz derivation would have obscured the abnormality.

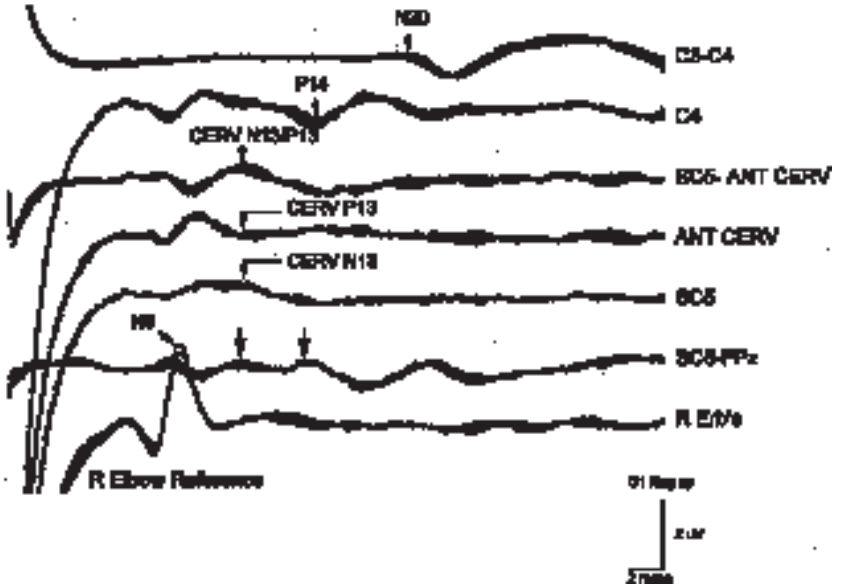


FIG. 29.14. Right median nerve SSEP in a patient with a compressive cervical myelopathy. Cerv N13 occurs at normal latency, but P14 is delayed. The potentials may be properly identified on separate referential derivations from SC5 and Fpz but not in the bipolar SC5-Fpz derivation.

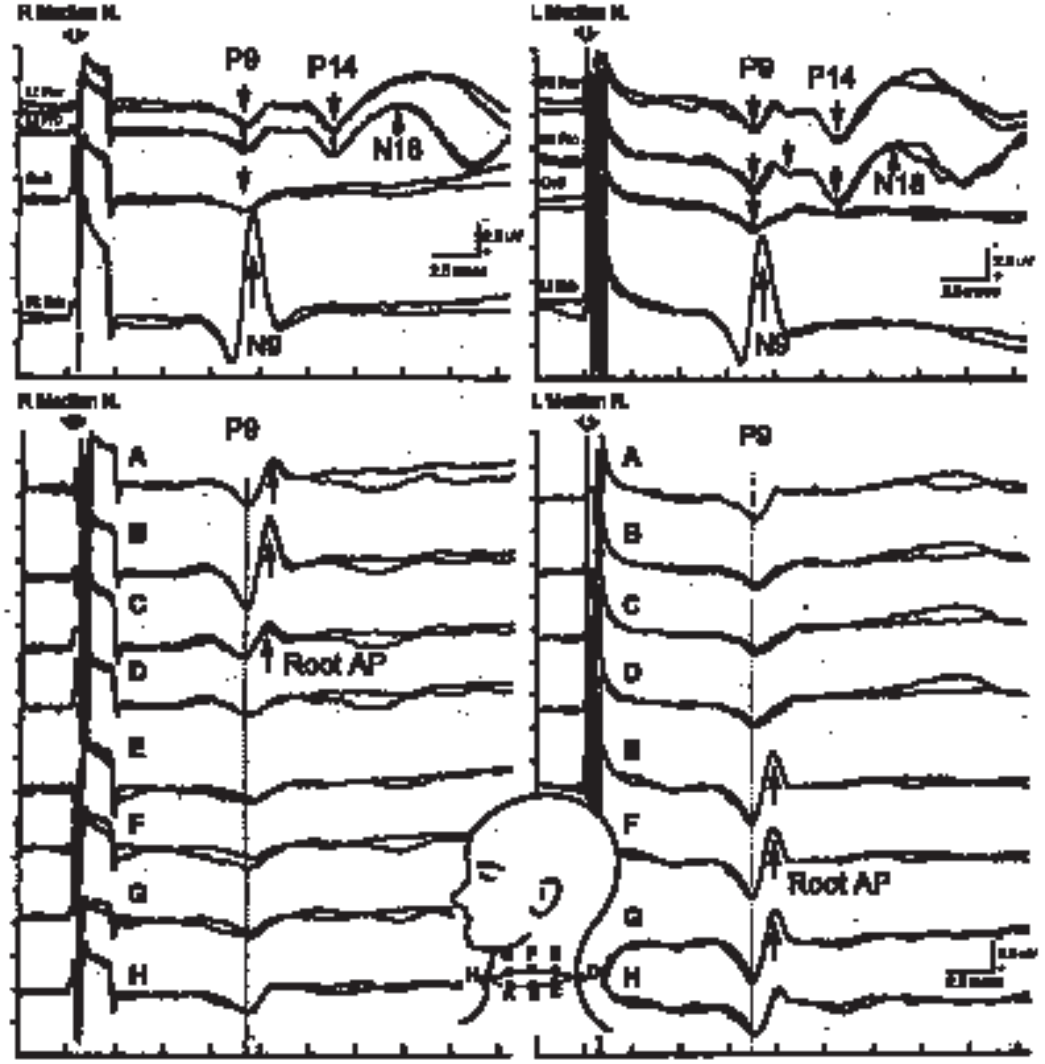


FIG. 29.15. Median nerve SSEPs in a patient with syringomyelia extending from C1 to T11. In all recordings, the reference electrode was at Erb's point on the side opposite the stimulated arm. Scalp-recorded components are preserved, but the cervical N13/P13 complex is abolished. (From Urasaki E, Wada S, Kadoya C, et al. Absence of spinal N13-P13 and normal scalp far-field P14 in a patient with syringomyelia. *Electroencephalogr Clin Neurophysiol* 1988;71:400–404, with permission.)

The N18 Potential

Following P14, a prolonged negative potential, N18, is recorded from all scalp electrodes. The distribution of N18 is illustrated in Figure 29.5. The initial part of the deflection is symmetrical, but a notch (arrow, Fig. 29.5B) at the contralateral parietal area indicates an additional negative component restricted to this region. Desmedt and Cheron (29) have carefully defined the characteristics of these two waves and designated them, respectively, N18 and N20. N20 may be separated from the underlying N18 potential by subtracting recordings made simultaneously from the ipsilateral and contralateral parietal electrodes (Fig. 29.16; see also "The N20 and Other Short-Latency Cortical Potentials" below).

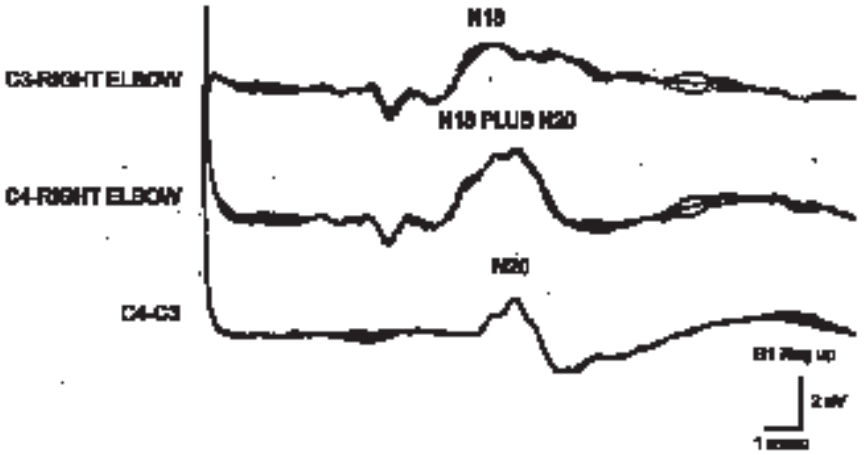


FIG. 29.16. Separation of N20 from the underlying N18. The lower channel was computed by subtracting the upper channel from the middle channel.

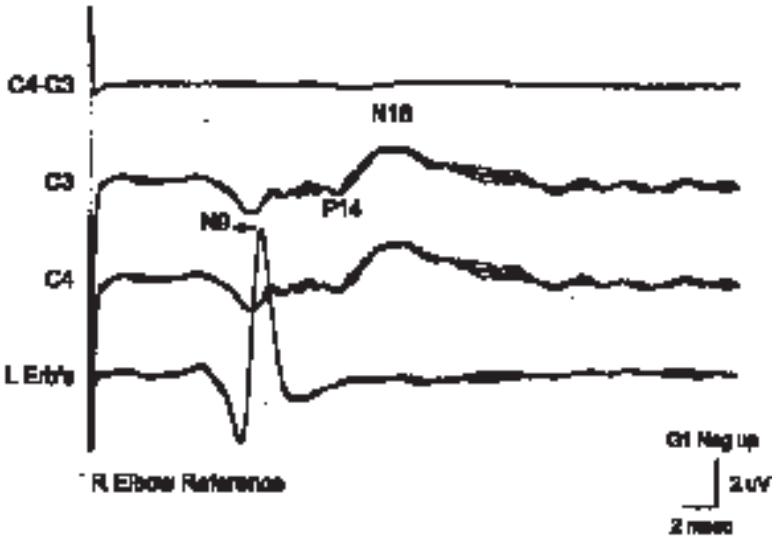


FIG. 29.17. Preservation of N18 with loss of N20 in a patient with a bilateral thalamic astrocytoma.

The widespread distribution of N18 is characteristic of a FFP and suggests a subcortical origin. Desmedt and Cheron (29) originally proposed that N18 reflected delayed activity within the thalamus or caudal portions of thalamocortical projection fibers. However, it was subsequently demonstrated that N18 is preserved with destructive lesions of the thalamus that cause the loss of later components of the median nerve SSEP (104) (Fig. 29.17). Although postsynaptically generated signals, coincident with the scalp N18, have been recorded from the Vim nucleus of the thalamus, they have been confined to that structure, demonstrating high-voltage gradients that are characteristic of closed-field systems (153). In contrast, direct brainstem recording from within the forth ventricle demonstrates a stationary peak, with shallow spatial voltage gradients, coincident with the scalp-recorded N18 potential, beginning above the level of the midpons (153). This observation is consistent with the view that N18 reflects postsynaptic activity in the upper brainstem gray matter structures, especially tectal and pretectal nuclei, that receive axon collaterals from the medial lemniscus (101,151,153,154). The organization of the tectum is compatible with an open-field system that could generate scalp-recordable far-field evoked potentials (101). Loss of N18 amplitude has been observed in patients with lesions of the pons and midbrain (154) (see Fig. 29.10). Conversely, reports of patients with largely intact N18 despite pontine and rostral medullary lesions suggest that postsynaptic activity in the cuneate nuclei may contribute to the N18 potential (118,135).

N18 has a long duration (up to 19 milliseconds), which supports postsynaptic (rather than axonal) activity as a major contributor to scalp-recorded FFPs (104). Careful inspection of the N18 potential often reveals small, superimposed inflections that persist even when hemispherectomy has removed the possibility of cortical near-field contamination (2,101) (Fig. 29.18). These inflections plus its long duration suggest that N18 is a complex wave with multiple, possibly sequentially activated, brainstem generators (101).

The N20 and Other Short-Latency Cortical Potentials

The earliest localized scalp potential is the N20 potential. It is recorded only over parietal regions contralateral to the stimulated side, where it is superimposed on N18 and represents the initial cortical response to the sensory volley (1,2,29,60,103). Loss of the N20 potential, with preservation of the underlying N18 potential, can be seen in patients with small lesions of the parietal cortex that produce severe astereognosis and loss of graphesthesia but do not disturb perception of intact touch, pain, temperature, position, and vibration. Like earlier components, N20 often has several small inflections superimposed on it (see Figs. 29.16 and 29.23), suggesting that it may result from activity within multiple generators (1,2,29,60,103,104). The view of N20 as a

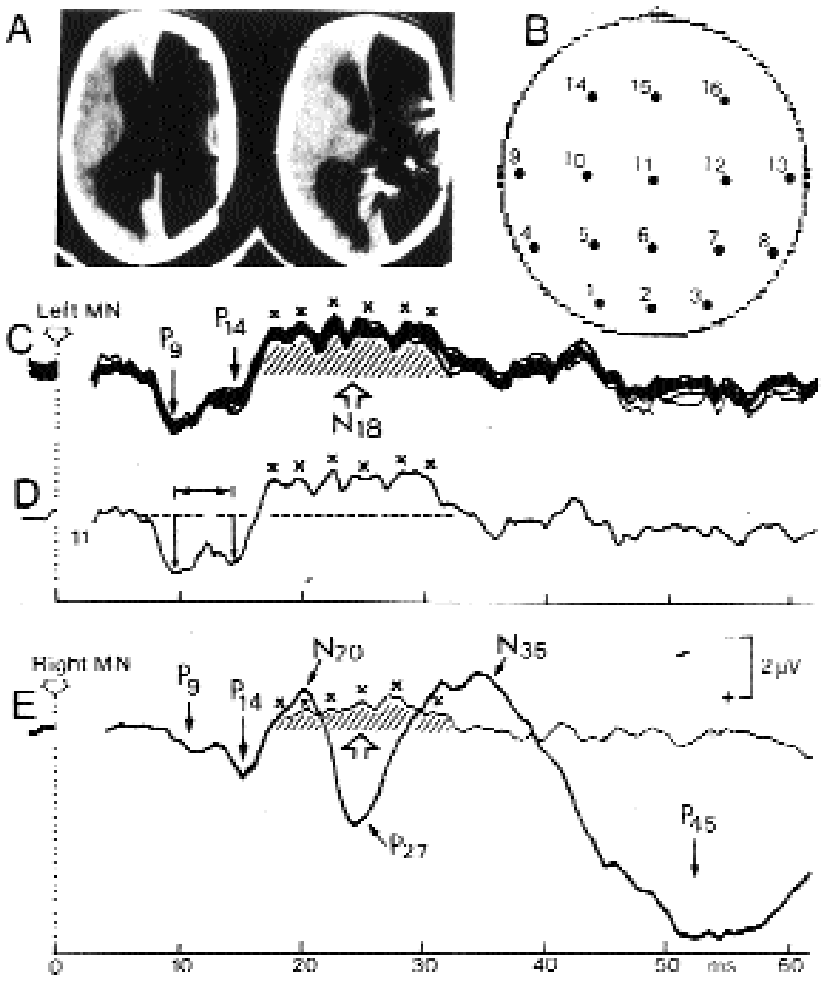


FIG. 29.18. Median SEPs recorded from a patient with a long-standing right hemispherectomy performed for intractable epilepsy. **A:** Computed tomography scans. **B:** Electrode placements. For all recordings, the reference electrode was on the shoulder opposite the stimulated arm. **C:** Left median nerve SSEP, with all 16 channels superimposed. Responses are essentially identical in all channels. **D:** Left median nerve SSEP, recorded from electrode 11. **E:** Right median nerve SSEP, showing superimposed recordings from electrodes 5 (thicker line) and 7. In **B** and **D**, N18 is shown as the *hatched area*. (From Mauguière F, Desmedt JE. Bilateral somatosensory evoked potentials in four patients with long-standing surgical hemispherectomy. *Ann Neurol* 1989;26: 724–731, with permission.)

composite waveform is supported by (a) recordings from subdural electrodes (92); (b) studies of state-dependent effects (42,162); and (c) changes in N20 topography produced by selective stimulation of muscle and cutaneous afferents in the median nerve using intrafascicular microelectrodes (45).

Recorded from a subdural strip electrode perpendicular to the central fissure, the earliest cortical response is a negativity beginning at approximately 18 milliseconds and peaking at about 20 milliseconds following median nerve stimulation (93). This signal, which corresponds to the scalp-recorded N20 potential, is maximal in voltage just posterior to the central fissure, and is accompanied by a simultaneous, nearly mirror-image positivity occurring anterior to the central sulcus (Fig. 29.19). This postcentral negativity and the corresponding precentral positivity are thought be volume conducted from a tangentially oriented "dipole" in the posterior wall of the central sulcus, generated by activation of area 3b, with possible contributions from area 3a (Fig. 29.20.) (6,92,115,155).

In scalp recordings, the parietal N20 potential is accompanied by a frontal positivity, the P22 potential, which usually peaks slightly later. P22 is generated separately from N20. It does not share a common generator with N20 in the posterior wall of the central sulcus, as was previously thought (1,13). N20 and P22 have different peak and onset latencies (25,28,32,122). They respond differently to changes in stimulation rate, to anesthetic drugs, and to ischemia (122). They can be affected separately by focal internal capsular lesions (Figs. 29.21 and 29.22) (81,85). Anatomical and physiological studies have previously established independent thalamocortical projections to the crown of the postcentral gyrus and to anterior and posterior banks of the central sulcus (63,98,112). Mauguière and Desmedt suggested that, whereas activation of the posterior bank of the central sulcus following input from VPL_c is responsible for generation of the N20 potential, depolarization of motor area 4 on the opposing anterior bank, in response to independent input from VPL_o, results in generation of the P22 potential (102).

Over the central-parietal scalp, N20 is followed by a positivity, P27, that likely reflects activation of area 1 on the crown of the postcentral gyrus (102). Over the frontal scalp, P22 is followed by a negativity, N30, thought to be generated by supplementary motor and premotor cortex (102). Although the electrical fields of P22 and N30 extend bilaterally, recordings following hemispherectomy indicate that these signal are generated only by the hemisphere opposite the stimulated side (101).

Most studies of SSEPs in humans have been conducted with subjects or patients relaxed and often asleep, frequently with the aid of sedative drugs. By recording median nerve SSEPs with subjects both fully alert and in stage 2 sleep, we demonstrated that the multiple inflections superimposed on the

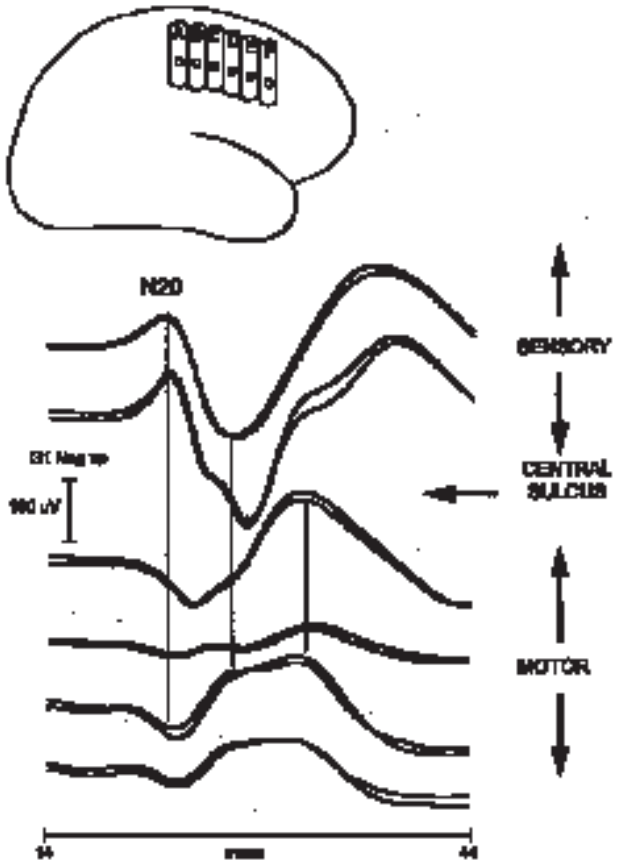


FIG. 29.19. Cortical surface recordings of a median nerve SSEP made from a subdural electrode grid crossing the central sulcus. Motor potentials were elicited by electrical stimulation at electrode locations shown as *black circles*. (Modified from Lueders H, Lesser RP, Hahn J, et al. Cortical somatosensory evoked potentials in response to hand stimulation. *J Neurosurg* 1983;58:885–894.)

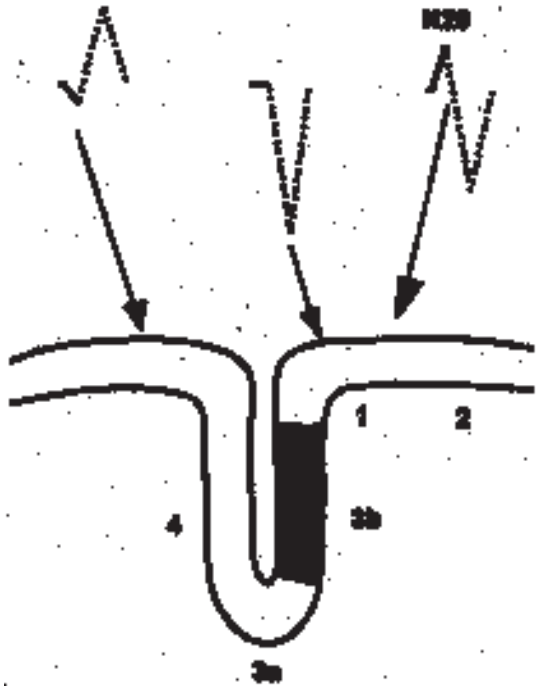


FIG. 29.20. Model proposed to explain the generation of N$\overline{20}$. Waveforms corresponding to the median nerve SSEP in immediate pre- and postcentral regions are illustrated. Depolarization of area 3b is responsible for the solid portion of the waveform. Subsequent depolarization of adjacent cortical regions contributes to subsequent dotted portions of the waveform. (Modified from Lueders H, Lesser RP, Hahn J, et al. Cortical somatosensory evoked potentials in response to hand stimulation. *J Neurosurg* 1983;58:885–894.)

initial upstroke of the N$\overline{20}$ potential are state dependent: They are prominent during wakefulness but attenuate or disappear during sleep (42). Yamada et al. (162) have confirmed this. Stage 2 sleep also prolongs N$\overline{20}$ peak latency by 0.2–0.9 millisecond (mean 0.6 millisecond) (F ig. 29.23) (42,130). We have speculated that loss of the inflections, along with the associated shift in N$\overline{20}$ peak latency, reflects selective downward modulation (during sleep) of specific thalamocortical projection systems that contribute to the composite N$\overline{20}$ waveform (42,46,47,138).

In fully alert subjects, N$\overline{20}$ is often preceded by a small positivity (mean latency 15.4 milliseconds; n = 10), P$\overline{15}$, which has a similar scalp topo graphy (see Fig. 29.23) (41). P$\overline{15}$, recorded using a bipolar scalp deri vation, is nearly coincident with P$\overline{14}$ c on referential scalp deri vations, and is most likely generated in the thalamocor tical radiations (134).

Although the caudal–rostral or ganization of the lar ge-fiber sensory system might suggest serial processing of sensor y signals, examples of selective loss of subcor tical SSEP components with preser vation of the cor tical

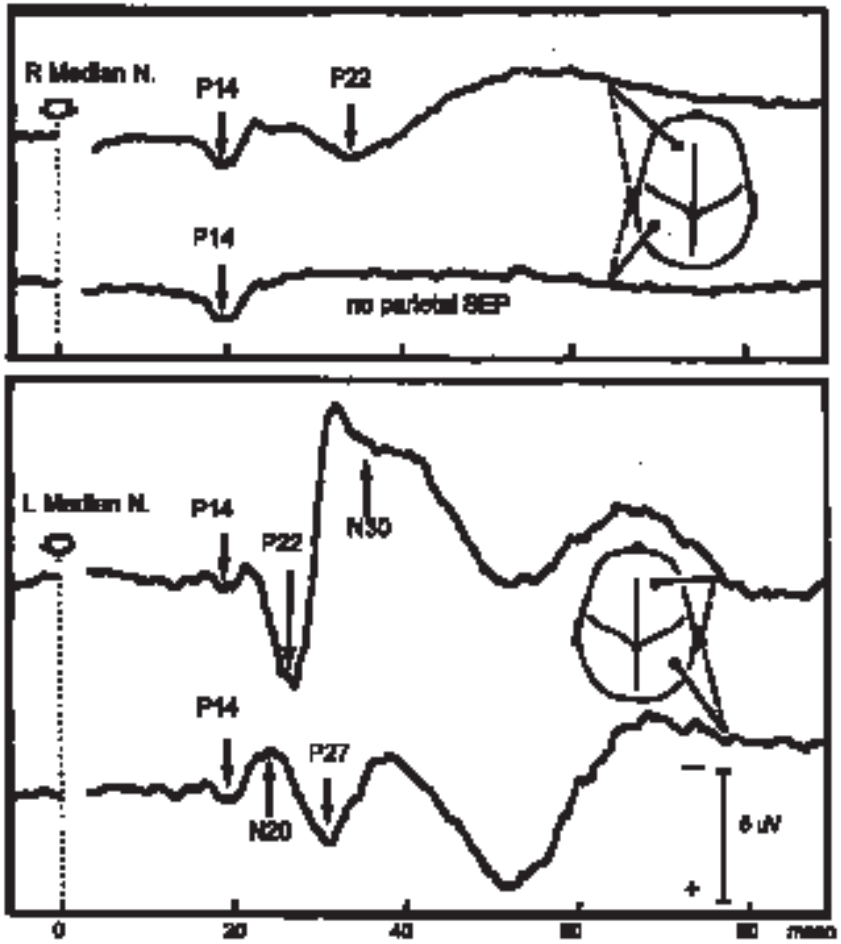


FIG. 29.21. Median nerve SSEPs from a patient with a small left internal capsular hematoma, presenting with severe right-sided motor and sensory deficits. The right median SSEP shows complete absence of the N20 potential, and the P22 potential, although present, is delayed and of lower voltage when compared with the normal response obtained to left-sided stimulation. (From Mauguière F, Desmedt JE. Focal capsular vascular lesions can selectively deafferent the prerolandic of the parietal cortex: somatosensory evoked potentials evidence. *Ann Neurol* 1991;30:71–75, with permission.)

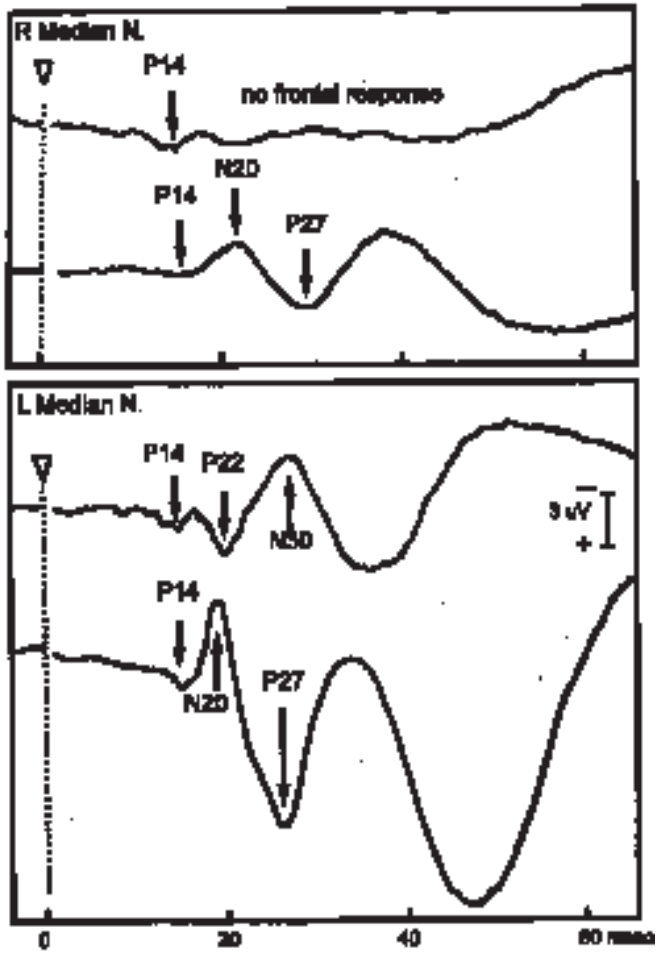


FIG. 29.22. Median nerve SSEPs from a patient with a left internal capsular hematoma, presenting with right hemiplegia and partially preserved touch, point position, pain, and temperature sensation on the right. The right median nerve SSEP shows loss of the frontal P22 potential. The parietal N20 potential is present, but delayed and lower in voltage than that obtained following stimulation of the normal left side. (From Mauguière F, Desmedt JE. Focal capsular vascular lesions can selectively deafferent the prerolandic of the parietal cortex: somatosensory evoked potentials evidence. *Ann Neurol* 1991;30:71–75, with permission.)

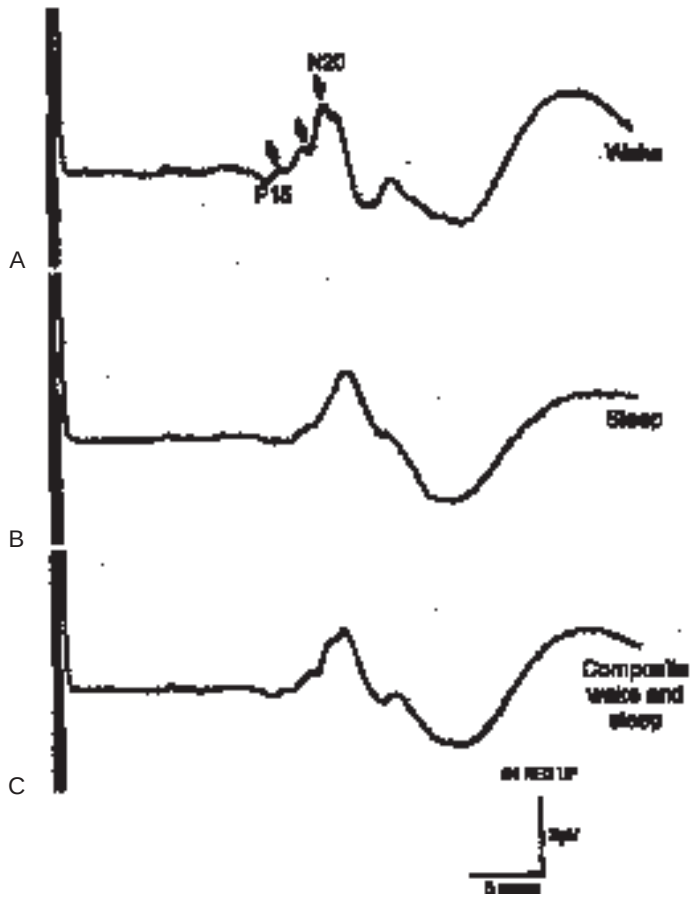


FIG. 29.23. State-dependent changes in N20. **A:** Changes in N20 during transition from wakefulness to sleep are depicted using a two-dimensional filtering technique. Each line represents the average of 32 sequential trials; sequential sets are stacked vertically. (**A** from Sgro JA, Emerson RG, Pedley TA. Real-time reconstruction of evoked potentials using a new two dimensional filter method. *Electroencephalogr Clin Neurophysiol* 1985;62:372–380, with permission.) **B:** N20 recorded with the subject awake. **C:** N20 recorded with the subject asleep after oral diazepam. **D:** "Composite" N20 including responses obtained during wakefulness, drowsiness, and sleep. Note that both morphology and peak latency are intermediate between waking and sleep N20 potentials. (**B–D** from Emerson RG, Sgro JA, Pedley TA, et al. State-dependent changes in the N20 component of the median nerve somatosensory evoked potential. *Neurology* 1988;38:64–68, with permission.)

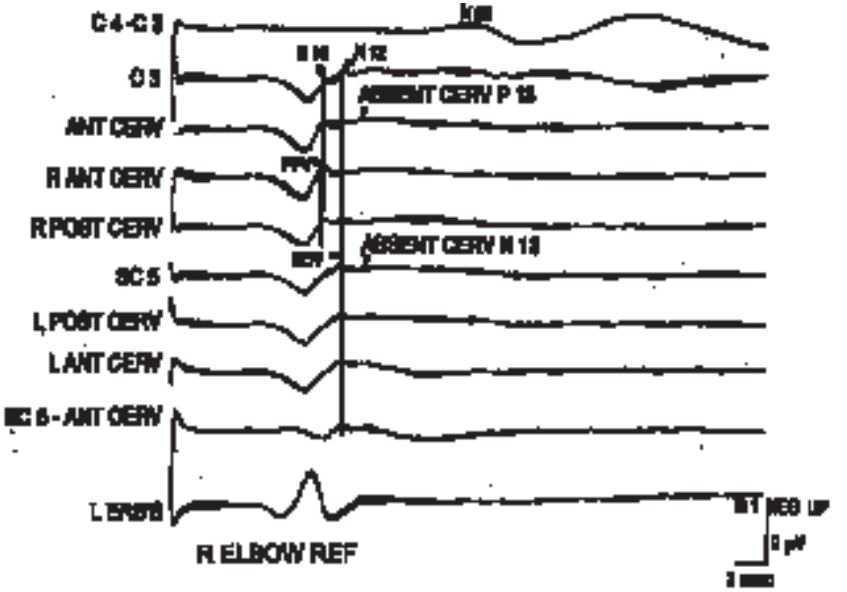


FIG. 29.24. Left median nerve SSEP record from a patient with multiple sclerosis, demonstrating loss of Cerv N13/P13, P14, and N18 with preservation of a normal N20 potential.

response are occasionally encountered (15,133). Figure 29.24 depicts the left median nerve SSEP recorded in a patient with multiple sclerosis. Although Cerv N13/P13, P14, and N18 are absent, N20 is normal. The relative independence of subcortical and cortical SSEPs may be explained either by nonserial linkage of at least some component generators or by central amplification of abnormally weak input signals (36,39).

COMPONENTS OF THE PTN SSEP

SSEPs recorded following PTN stimulation are, in part, analogous to responses evoked by median nerve stimulation. The afferent signals that produce the PTN SSEP traverse the dorsal columns (23,53), although signals mediated by other pathways, (e.g., the dorsolateral funiculus) may also play a role (14,50,139). Some laboratories routinely use common peroneal nerve stimulation for lower-limb SSEPs. However, common peroneal nerve SSEPs show a greater degree of intersubject variability than PTN SSEPs (113), and the latter are therefore preferred for routine clinical use.

Following PTN stimulation, electrodes over the lumbar spine record both a propagated volley and a stationary potential that are analogs of the DCV and Cerv N13 potentials seen after median nerve stimulation. Scalp electrodes initially record widely distributed potentials reflecting subcortical activity, and then register lateralized activity that represents the early cortical response.

Spinal Components

Electrodes positioned over the lower spine record two distinct components (Fig. 29.25) (125). The potential labeled N22 is of maximal amplitude between T10 and L1 (37) and has properties identical to the Cerv N13 potential. Its amplitude attenuates, but its latency remains fixed, in electrodes rostral and caudal to the point of maximal voltage. It reverses phase from dorsal to ventral, and electrodes over the abdominal wall record a positivity, P22 (Fig. 29.26). The N22/P22 complex most likely represents postsynaptic activity in the lumbar enlargement of the spinal cord.

Electrodes over the lumbosacral spine record a second waveform that occurs just before the N22 potential. The latency of this potential increases at progressively more rostral electrode sites (see Fig. 29.25). This potential arises from the propagated volley (PV), occurring first in the spinal roots of the cauda equina and subsequently in the gracile tract. Because its latency changes depending on recording electrode position, its timing in relation to N22 is variable. Thus PV precedes N22 over the lumbosacral spine but occurs with, or just following, N22 over the thoracic spine.

As already mentioned, N22 is normally of maximum voltage over the lower thoracic spine, at the level of the spinal cord's lumbar enlargement just

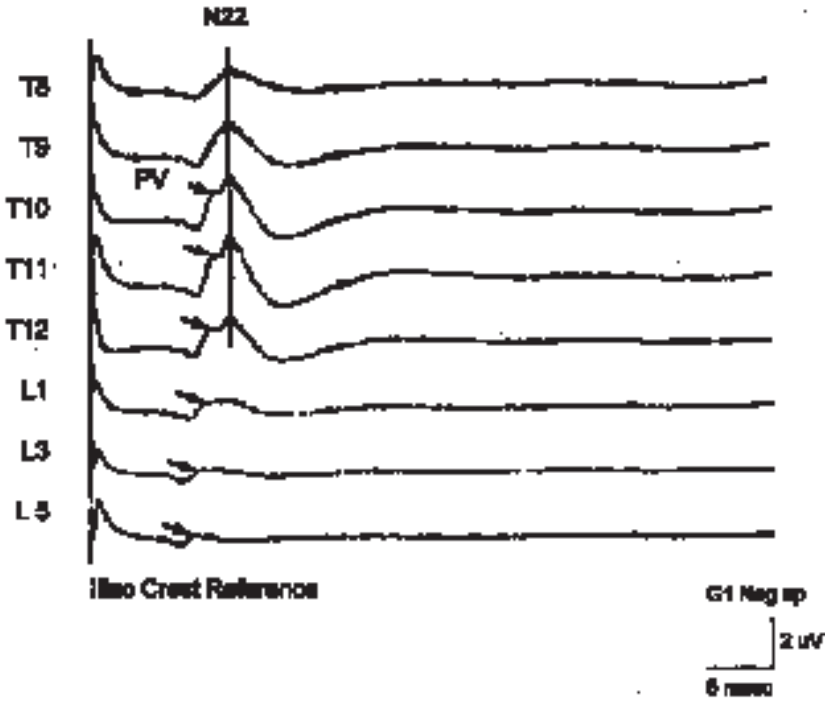


FIG. 29.25. Left PTN SSEP recorded over the lower thoracic and lumbar spine using a reference electrode on the right iliac crest. The thoracolumbar response consists of two distinct signals: a propagated volley (PV) that increases in latency at more rostral electrodes, and a stationary potential (N22) whose voltage is maximal between T10 and L1.

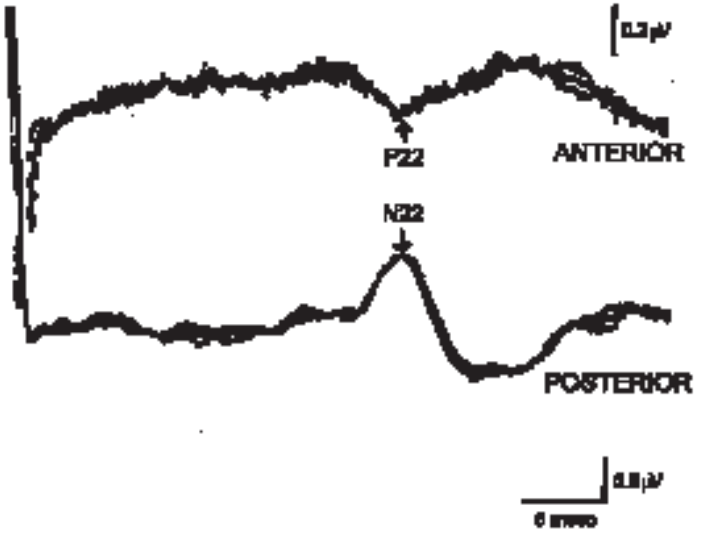


FIG. 29.26. PTN SSEP recorded simultaneously from a lumbar electrode 10 cm rostral to the L4 spinous process (*lower tracing*) and an electrode over the abdomen at the same level (*upper tracing*). The reference electrode was on the elbow opposite the site of stimulation. (From Seyal M, Gabor AJ. The human posterior tibial somatosensory evoked potential: synapse dependent and synapse independent spinal components. *Electroencephalogr Clin Neurophysiol* 1985;62: 323–331, with permission.)

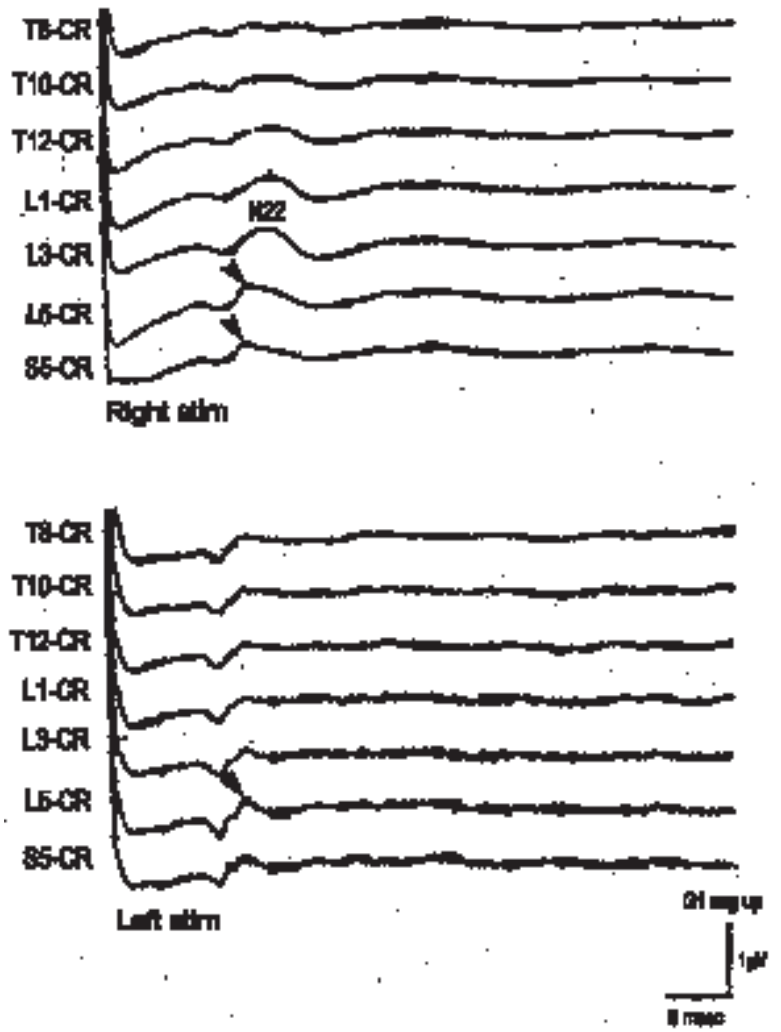


FIG. 29.27. PTN SSEP recorded in a 7-year-old boy with a lumbosacral lipoma and tethering of the spinal cord. Reference electrode was on the contralateral iliac crest. **Upper panel:** Right PTN stimulation reveals caudal displacement of N22. **Lower panel:** Following left PTN stimulation, N22 is absent, and only the PV (*arrowhead*) component of the lumbar response is seen.

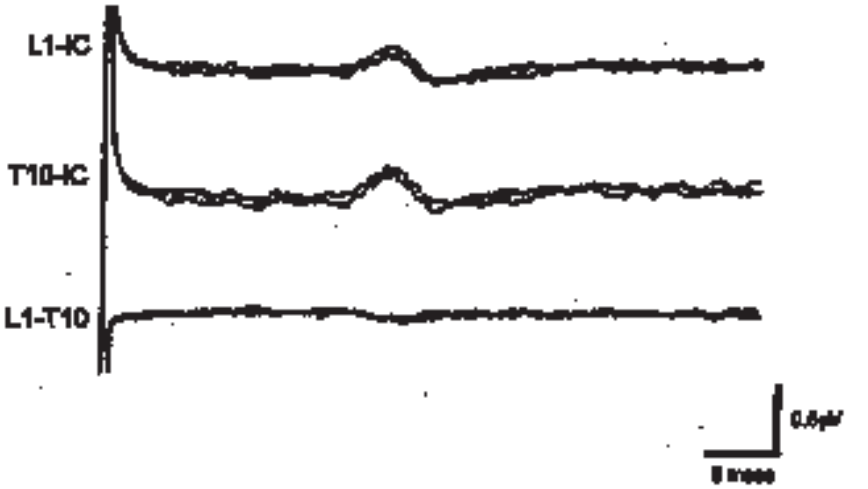


FIG. 29.28. Comparison of bipolar and referential techniques for recording the lumbar response to PTN stimulation. N22 is well delineated using the iliac crest (IC) reference, but it is virtually absent on the L1-T10 bipolar derivation because of in-phase cancellation.

rostral to the termination of the conus medullaris at L1 or L2 (8). In patients with tethered cord syndrome, the N22 potential, if preserved, is displaced caudally, corresponding to the abnormally low position of the terminal spinal cord (Fig. 29.27) (37).

The most prominent evoked potential component recorded over the lower thoracic and upper lumbar spine following PTN stimulation is N22, not the afferent volley. Indeed, in many recordings, N22 is the only spinal component identifiable. Because N22 is widely distributed over the lower spine, bipolar spinal recordings frequently result in in-phase cancellation. Referential recording (e.g., T12 to iliac crest) (Fig. 29.28) allows clear characterization of N22 and also allows distinction between N22 and the more variable PV (87). Over the upper cervical spine, a second low-amplitude stationary potential can be recorded following PTN stimulation, which may reflect postsynaptic activity in the gracile nucleus (126).

Subcortical Components

Scalp recordings using a non

cephalic reference (shoulder or lower cervical spine) initially demonstrate a series of widespread waves representing FFPs arising at subcortical sites. The most consistent of these are a small positive deflection, P31, and a following negative potential of larger amplitude and longer duration, N34 (Fig. 29.29). Sometimes another positive component, P28, precedes P31. At sites away from the vertex, N34 shows a gradual return to baseline approximately 40 milliseconds after the stimulus (124).

The best information about the origin of the subcortical components of the PTN SSEP comes from analogies to the more extensively studied median nerve SSEP (74,150). P31 is strikingly similar to P14 recorded after median

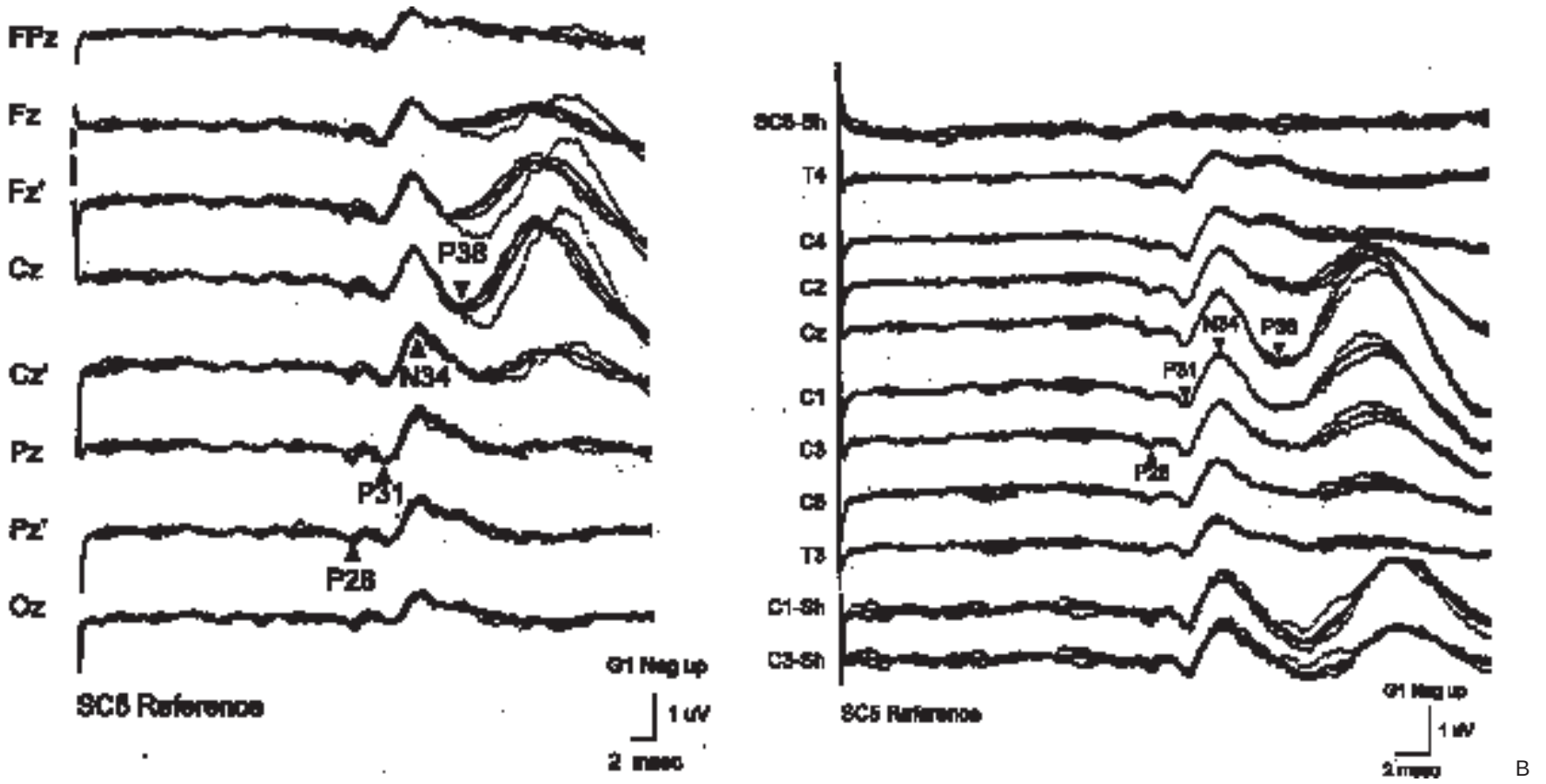


FIG. 29.29. A: Left PTN SSEP recorded in the coronal plane through Cz, with electrodes in channels 2–9 referred to an electrode on the spinous process of the fifth cervical vertebra (SC5). Responses are nearly identical if a contralateral shoulder reference (sh) is used for comparison (*bottom two tracings*). There is no detectable response in the SC5-sh derivation confirming the relative inactivity of SC5. **B:** Left PTN SSEP recorded in the midsagittal plane using a SC5 reference. Note that Fpz is relatively inactive for events occurring after the N34 potential.

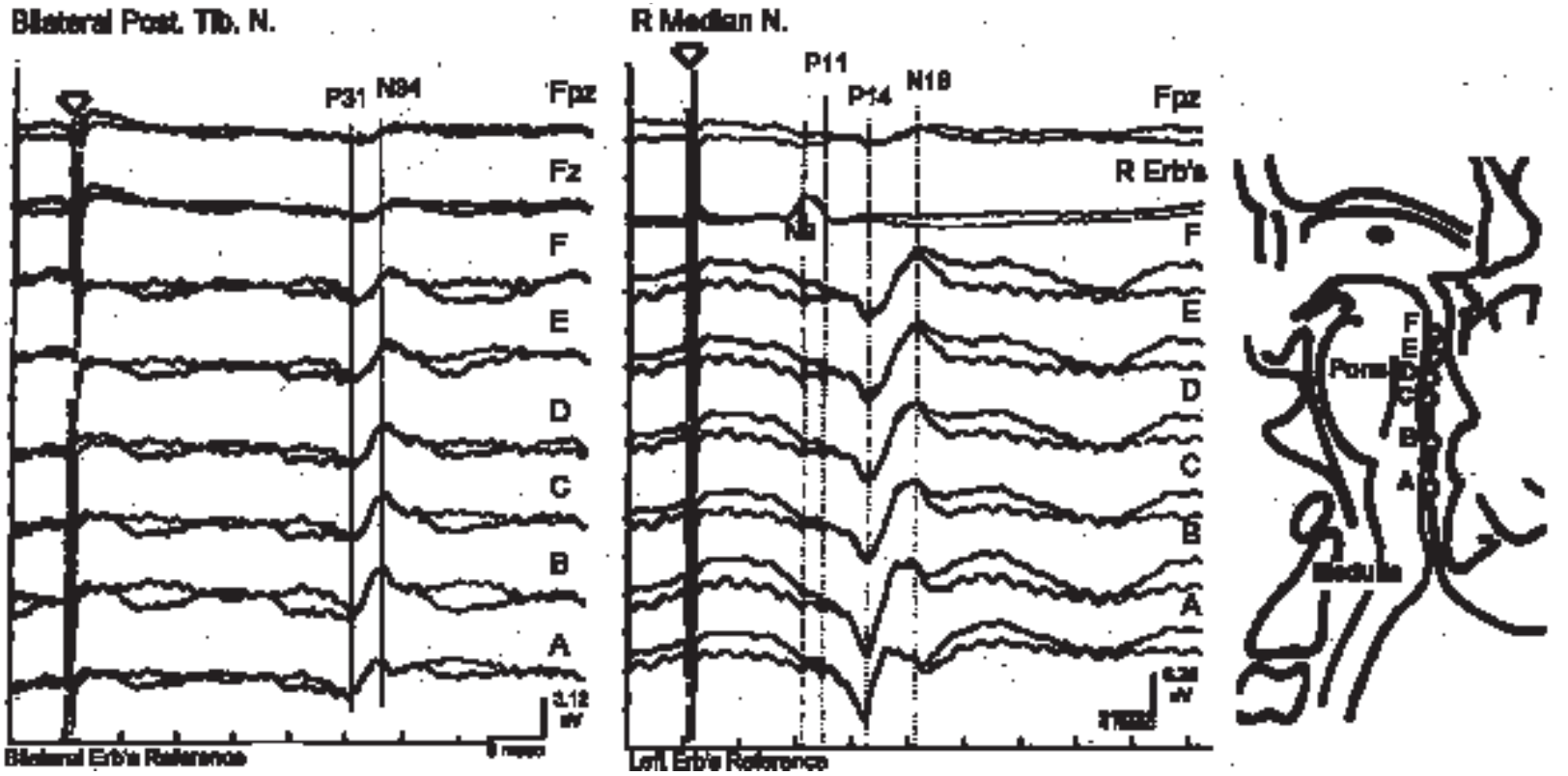


FIG. 29.30. PTN and median nerve SSEPs recorded referentially from both scalp and intracranial electrodes. Electrode positions are illustrated in the accompanying diagram. The analogy of the P31 and N34 following PTN stimulation to P14 and N18 following median nerve stimulation is clear. (From Urasaki E, Tokimura T, Yasukouchi H, et al. P30 and N33 of posterior tibial nerve SSEPs are analogous to P14 and N18 of median nerve SSEPs. *Electroencephalogr Clin Neurophysiology* 1993;88:525–529, with permission.)

nerve stimulation in terms of polarity, distribution, and morphology, and N34 closely resembles N18. These similarities are illustrated in Figure 29.30, which shows PTN and median nerve SSEPs recorded referentially both from Fpz and from within the fourth ventricle. Electrodes along the dorsal surface of the medulla and pons record stationary positivities that coincide with scalp-recorded P14 and P31, and electrodes over the mid- and upper pons record stationary negativities that correspond to N18 and N14 (150). Accordingly, P31 most likely is generated in the medial lemniscus, and N34 probably arises from multiple brainstem nuclear generators (29,104,150).

The effects of clinical lesions on the subcortical components of both PTN and median nerve SSEPs also support this relationship. For example, Figure 29.31 illustrates absent upper and lower extremity far-field SSEPs that returned following removal of a cervical chondrosarcoma (143).

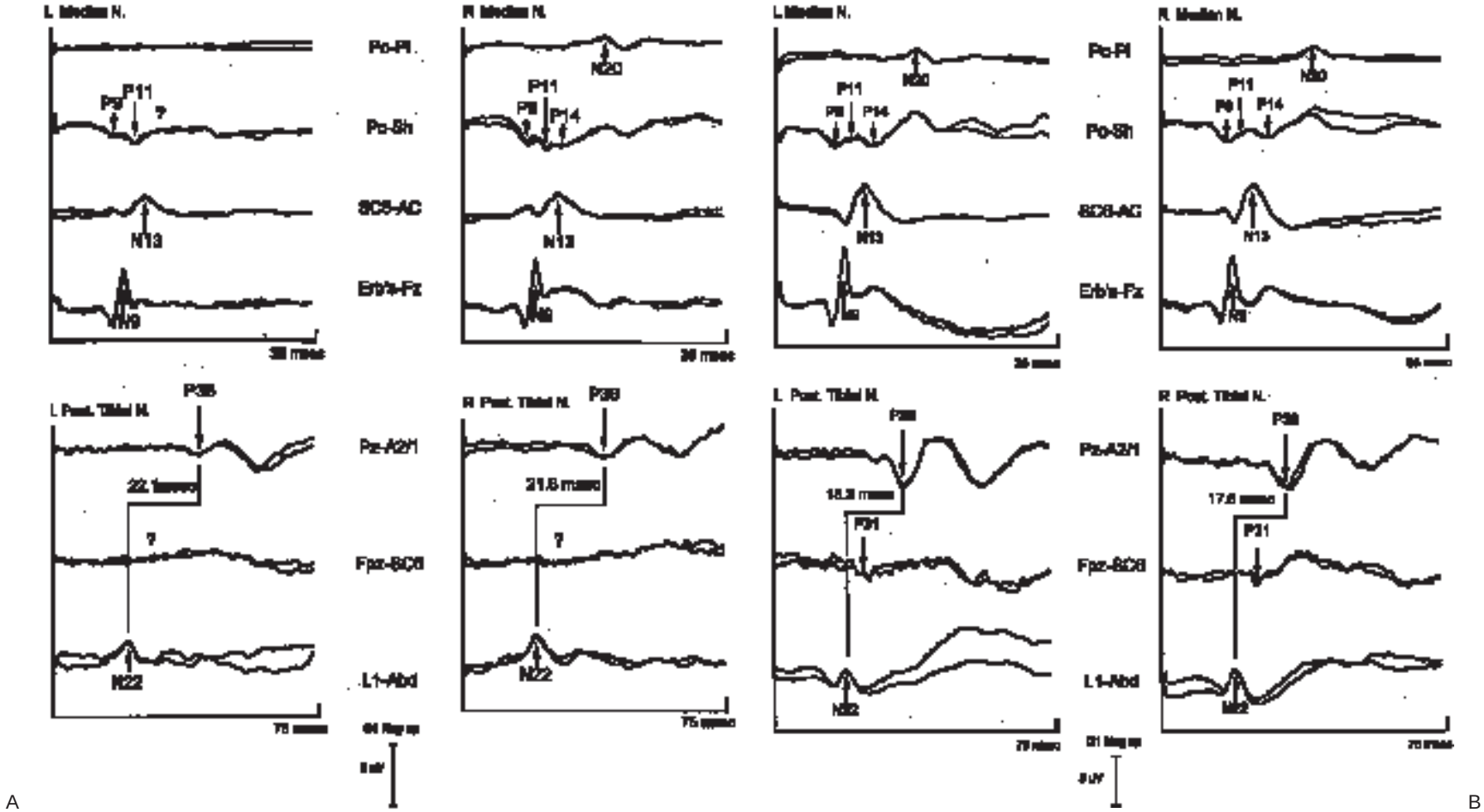


FIG. 29.31. Pre- and postoperative SSEPs in a patient with a C2-C4 chondrosarcoma. **A:** Preoperative median nerve SSEPs demonstrate loss of P14 and subsequent waves in response to left-sided stimulation and attenuation of P14 in response to right-sided stimulation. PTN SSEPs show delay of the P38 potential and loss of subcortical P31 and N38 signal bilaterally. **B:** Seven months postoperatively, both median nerve and PTN SSEPs are normal. Note that a bipolar SC6–anterior cervical electrode derivation is used to record the stationary cervical N13 potential, and similarly an L1-abdominal electrode derivation is used to record N22. (From Tinazzi M, Zanette G, Bonato C, et al. Neural generators of tibial nerve P30 somatosensory evoked potential studied in patients with a focal lesion of the cervicomedullary junction. *Muscle Nerve* 1996;19:1538–1548, with permission.)

The P38 Potential

At Cz and adjacent scalp areas ipsilateral to the stimulus, the N34 deflection terminates with the onset of a large positive wave, P38 (see Fig. 29.29). Unlike earlier far-field subcortical components, P38 has a restricted field involving mainly the central parasagittal region. Because Fpz is virtually inactive with respect to potentials occurring after 34 milliseconds, it is a useful reference electrode for selectively recording P38 and other localized scalp activity. Figure 29.32*A* shows the nearly complete in-phase cancellation of the widespread early potentials in scalp Fpz recordings, with preservation of localized activity near Cz.

P38 is the first localized wave in the scalp-recorded PTN SSEP. It is asymmetrically distributed about Cz with consistently greater involvement of areas ipsilateral to the stimulated PTN. P38 topography is somewhat variable from subject to subject, and the maximal positivity can occur either at Cz or in the lateral parasagittal region ipsilateral to the stimulated leg (compare Fig. 29.32*A* with Fig. 29.32*B*). In the midsagittal plane, P38 is of greatest voltage just posterior to Cz. In most subjects, an approximately simultaneous signal, N38, can be recorded over the contralateral frontocentral scalp (144). N38 amplitude is usually lower than that of P38, although in some subjects the two components are of nearly equal voltage (22,67,124,144).

The apparently "paradoxical" localization of P38 to scalp areas ipsilateral to the stimulated leg is best explained by considering the location of the primary sensory areas for the leg and foot on the mesial aspect of the postcentral gyrus within the interhemispheric fissure. PTN stimulation

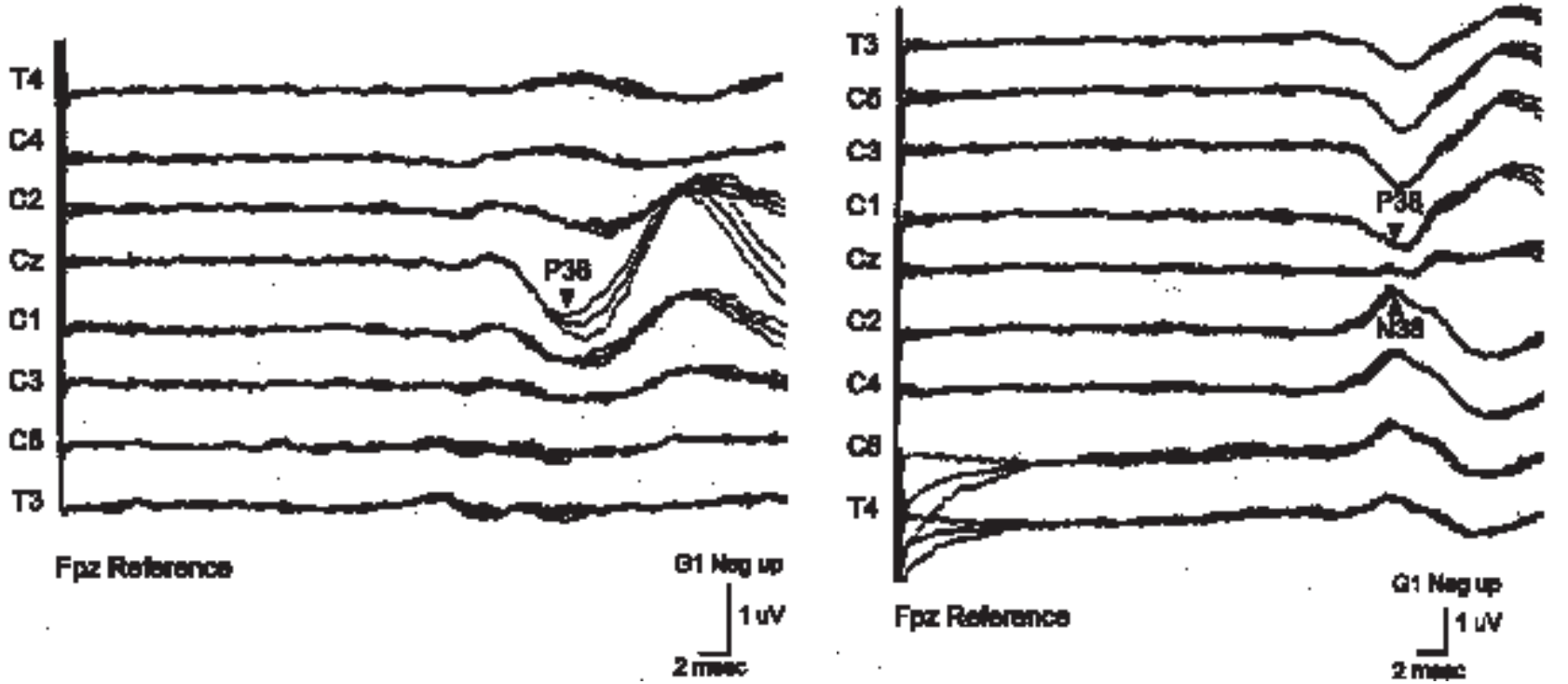


FIG. 29.32. Left PTN SSEPs recorded in two different subjects (**A** and **B**), illustrating the wide range of normal variability in scalp topography of the responses.

results in depolarization of layer IV pyramidal cells of the cortical receiving area, with a corresponding passive source located at the cortical surface (52). The cortical surface positivity projects ipsilateral to the simulated side, and the negative end of this "dipole" projects contralaterally (22,89,124). Intraoperative cortical surface recordings have supported this explanation by demonstrating a localized positivity on the contralateral mesial cortical surface coincident with the contralateral N38 and the ipsilateral P38 scalp-recorded signals (89).

Although this model for producing P38 based on a single dipole located within sensory cortex is appealing, it is an oversimplification. In many normal subjects, the P38 peak occurs following, rather than simultaneous with, the peak of N38. Furthermore, P38 is selectively sensitive to increases in stimulus rate and active and passive footmovement during stimulation (144,145). These observations are inconsistent with the single cortical generator model, and it is likely that there are contributions from multiple sources that modify the distribution and latency of the scalp-recorded response (67,89,103). As with the median nerve N20, the P38/N38 complex probably reflects nearly simultaneous activation of several regions within the primary sensory receiving areas for the lower extremity.

Intersubject differences in P38/N38 scalp topography probably reflect known anatomical variability in location of primary sensory cortex subserving the lower extremity (114). Location of the leg area near the superior edge of the interhemispheric fissure would cause vertical orientation of P38's cortical generator and result in scalp positivity that is maximal at or close to the midline. In contrast, location of the foot area deep within the interhemispheric fissure would cause the cortical generator to have a more horizontal orientation, with the P38 potential projecting to lateral parasagittal scalp leads (22,89,124). Consistent with this view and reflecting representation of the proximal leg close to the upper edge of the interhemispheric fissure or over the lateral convexity, Yamada et al. have shown that stimulation of the lateral femoral cutaneous nerve of the thigh produces a positivity with greater interindividual variability than the response to PTN, but generally lateralized to the hemisphere *contralateral* to stimulation (165).

Latencies of P38 and N38 are affected by alterations in a subject's level of arousal. In normal adults, stage 2 sleep can prolong P38 latency by more than 2 milliseconds and can prolong N38 latency by over 4 milliseconds (Fig. 29.33) (131). We speculate that P38 and N38, like N20, are composite waveforms reflecting activity from multiple cortical generators, and that, during sleep, downward modulation of selective components results in the observed latency shifts.

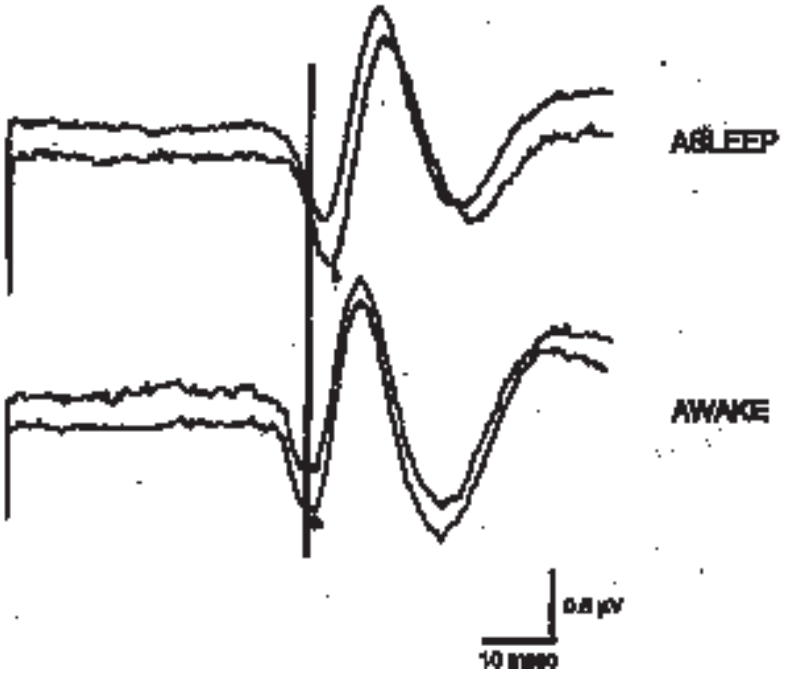


FIG. 29.33. PTN SSEP recorded from Cz-Fpz in a subject asleep (*upper tracing*) and immediately following arousal (*lower tracing*).

MATURATIONAL DEVELOPMENT OF SSEPS

There is less information available about SSEPs in children than in adults. Much of the available literature consists of studies performed using only limited scalp-to-scalp and neck-to-scalp bipolar derivations that, for reasons discussed in previous sections, are not adequate for detailed analysis of recorded potentials. Nonetheless, median nerve and PTN SSEPs may be recorded from earliest infancy. They are similar to responses obtained from adults in many ways, although important differences exist that largely reflect the degree of nervous system maturation.

Term neonates reliably demonstrate subcortical components following median nerve stimulation. The N20 potential (recorded from parietal scalp referred to a midfrontal electrode) is almost always present by 2 months of age, although some authors have observed it to be absent in as many as one-third of newborns (84,96,158).

Maturation of the median nerve SSEP is nonlinear. Central conduction time decreases dramatically prior to 40 weeks' postconceptional age (9) (Fig. 29.34), continues to fall rapidly during the first year, and declines more slowly thereafter, reaching adult values by 6–8 years of age (Fig. 29.35) (27,59,82,83,141). In children, as in adults, the N20 response is partially dependent on level of arousal (31,84,96), and the effect is most pronounced in infants and younger children. This state dependence may contribute to the apparent absence of N20 in many normal term babies.

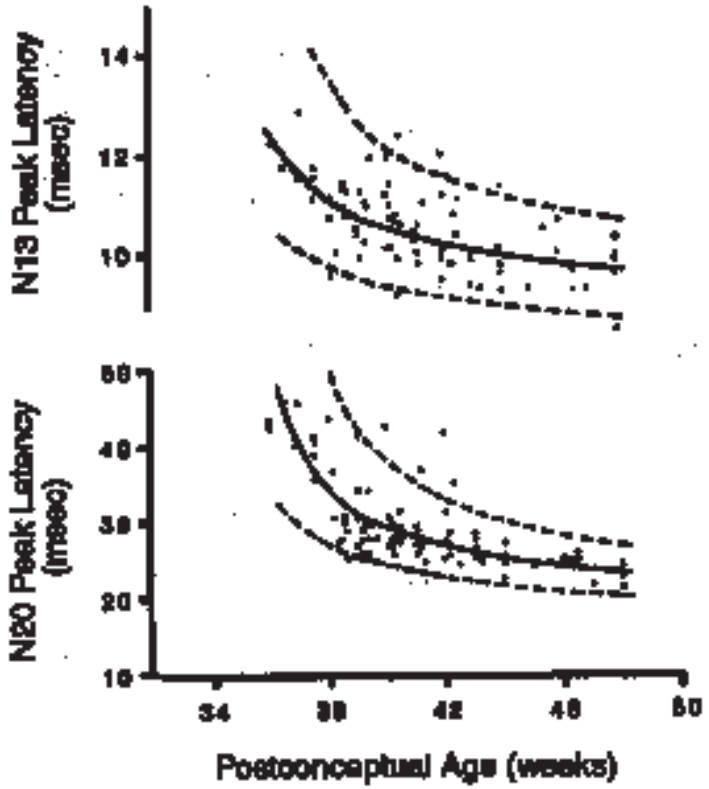


FIG. 29.34. Maturation of the median SSEP in the neonate. Between 36 and 48 weeks' postconceptional age, the N20 latency decreases dramatically compared with a more modest decrease in the N13 latency, producing a dramatic decrease in central conduction time. The N13 latency was measured using a bipolar SC2-Fpz derivation. (From Bongers-Schokking JJ, Colon EJ, Hoogland RA, et al. Somatosensory evoked potentials in term and preterm infants in relation to postconceptional age and birth weight. *Neuropediatrics* 1989;21:32–36, with permission.)

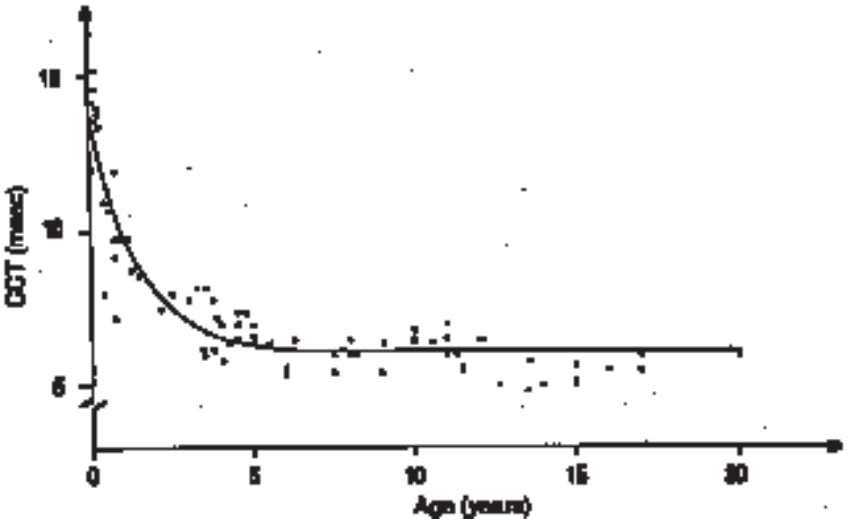


FIG. 29.35. Central conduction time (CTT) as a function of age. In this study, CTT was defined as the interpeak latency difference between N20 (recorded from C3 or C4 to Fz) and N14 (recorded from SC2 to Fz). (From Lauffer H, Wenzel D. Maturation of central somatosensory conduction time in infancy and childhood. *Neuropadiatrie* 1986;71:72–74, with permission.)

Spinal and subcortical components are readily recorded following PTN stimulation in infants and young children (18,51,59). Spinal conduction velocity increases from birth until about 5–7 years of age, when it reaches adult values (18,51,59). The P38 cortical response is reliably present in awake infants older than 1 year of age (18,51,59). Like N20, the P38 potential appears to be much more susceptible to the effects of level of arousal in infants and children. Indeed, by recording selectively during active sleep, Pike et al. were able to obtain reproducible cortical responses to PTN stimulation in each of 67 premature infants studied, ranging from 27 to 37 weeks' postconceptional age (mean 31 weeks) (116).

RECORDING TECHNIQUES AND INTERPRETIVE CONSIDERATIONS

Stimulation

Peripheral nerves are usually stimulated transcutaneously using electrodes placed on the skin over the selected nerve. Subdermal needle elec-

trodes also may be used, however. The cathode electrode should be placed 2–3 cm proximal to the anode to avoid anodal block. Either constant-voltage or constant-current stimulators can be used. Typical stimulus parameters include a pulse width of 100–300 microseconds, a stimulation rate of 3–5 per second (79,117,132), and a stimulus intensity adequate to produce a consistent, but comfortable muscle twitch. Lesser et al. (88) found that median nerve stimulation at the motor threshold produced SSEPs of submaximal amplitude, and that optimal responses required a stimulus intensity of motor plus sensory threshold. Tsuji et al. (149) recommended an intensity level three times the sensory threshold for PTN SSEPs.

Amplifier and Averager Settings

Most laboratories use a passband of approximately 30–3,000 Hz (−6 dB per octave), which is consistent with American Electroencephalographic Society guidelines (4). Although a wider passband—extending down to 1 Hz, for example—may be advantageous in recording long-duration signals (104), the additional low-frequency noise requires averaging a larger number of responses. Use of a 1- or 2-Hz high-pass filter setting has been reported to facilitate the recording of cortical SSEPs in young infants (9,116). More restrictive passbands are sometimes useful for examining selected SSEP components (36,94,162). When recording with restricted passbands, linear phase-shift digital filtering should be used to avoid distortions produced by analog filters (56).

Recording Montage

A minimum of four channels is necessary to record either median nerve or PTN SSEPs. For median nerve SSEPs, a minimal montage is as follows:

Channel 1: Erb's point–noncephalic (e.g., contralateral elbow or shoulder)
Channel 2: SC5-noncephalic
Channel 3: CPi-noncephalic
Channel 4: CPc-CPi

Channel 1 registers the afferent volley passing Erb's point. Channel 2 records activity in the cervical cord, principally CERV N$\overline{13}$. Channel 3 displays subcortical activity as FFPs, including P$\overline{14}$ and N$\overline{18}$. Channel 4 selectively records N$\overline{20}$.

If additional channels are available, other bipolar scalp derivations are useful (e.g., Pc-Pi) because of normal variation in the location of the maximal N$\overline{20}$ response (86). In cases of possible cervical spinal lesions, it is desirable to utilize an expanded montage including a ring about the neck (as in Figs. 29.8 and 29.15) to delineate cervical components optimally. Bipolar derivations using posterior and anterior cervical electrodes, or lumbar and abdominal electrodes, can be used to enhance cervical N$\overline{13}$/P$\overline{13}$ and lumbar N$\overline{22}$/P$\overline{22}$ potentials (see Fig. 29.31).

For PTN SSEPs, a minimal montage is as follows[2]:

Channel 1: T12–iliac crest
Channel 2: Fpz-SC5
Channel 3: CPi-Fpz
Channel 4: CPz-Fpz

Channel 1 records the stationary lumbar potential, and a relatively inactive distant reference should be used. Bipolar recordings using closely spaced lumbar electrodes are ill advised because of in-phase cancellation of the stationary lumbar response. Channel 2 records subcortical far-field activity (P$\overline{31}$ and N$\overline{34}$). SC5 is a reasonably inactive reference site and, in our experience, is usually subject to less artifactual contamination than shoulder or elbow placements. Channels 3 and 4 each record the P$\overline{38}$ cortical responses selectively by causing in-phase cancellation of widely distributed far-field activity. Reliable detection of P$\overline{38}$ requires use of at least two channels because of the normal interindividual variability in P$\overline{38}$ scalp topography (see Fig. 29.32).

Availability of additional channels permits recording of the afferent volley at the level of the popliteal fossa and the N$\overline{38}$ cortical response (CPi-Fpz). In additional, the topography of the lumbar stationary potential can be defined; this is useful in cases of spinal dysraphism.

Criteria of Abnormality

Clinical interpretation of SSEP recordings is based largely on identifying abnormal latency or absence of waveforms that are consistently present in normal individuals. Each laboratory should study at least 20 neurologically normal subjects who have no family history of neurological disease and should ensure that measurements in this control group are comparable to published values. Patient conduction times that are beyond 2.5 or 3 standard deviations from the mean for this control group are regarded as abnormal.

[2]The letters *i* and *c* denote, respectively, locations ipsilateral and contralateral to the stimulated limb. The designated CP locations are midway between standard central and parietal international 10-20 electrode placement locations. Similarly, CPz refers to scalp locations midway between Cz and Pz.

Statistical considerations and limitations of this approach are discussed in the American Electroencephalographic Society guidelines (4).

Interpeak latency measurements are used to minimize the effects of (a) peripheral conduction times and (b) differences in arm and leg lengths, and to evaluate segments of central sensory pathways separately. For median nerve SSEPs, the Erb's point–to-P14 and the P14-to-N20 interwave latencies provide measures of conduction between the brachial plexus and lower brainstem, and between lower brainstem and primary sensory cortex. For PTN SSEPs, similar information is provided by calculating the N22-to-P31 and P31-to-P38 latencies. Because amplitude of SSEP waveforms shows considerable normal variability, amplitude criteria alone generally are not used to interpret a response as abnormal. During intraoperative monitoring, however, when an amplitude baseline is established for each patient, a significant decrease in SSEP waveform amplitude is often the principal indicator of injury.

The P14-to-N20 and P31-to-P38 interpeak latencies are often regarded as measures of "central conduction time" (60) between the lower brainstem and sensory cortex. Although it is clinically useful, one must remember that this concept is an approximation. In all likelihood, each of these waveforms has more than a single, anatomically discrete generator (36,42,162). The latencies of peak amplitudes, therefore, do not correspond to occurrence of unitary physiological events, but rather to the maxima or minima of summated signals from several simultaneously active neural generators. For example, the model depicted in Figure 29.20 implies that, whereas the rising phase of N20 is generated by depolarization of area 3b, the peak latency of N20 is influenced by onset of subsequent positivity arising from activation of adjacent cortical areas. Although technically demanding, more accurate measures of central conduction time may be obtained using inter-onset rather than interpeak latency differences (111).

It has been generally assumed that short-latency evoked potentials are stable in a given individual, reproducible between testing sessions, and independent of effects of state or level of arousal (42,131,162). As already indicated, the peak latencies of N20 and P38 do, in fact, vary depending on the subject's level of arousal (42,131,162). This state effect is especially prominent for the P38 potential, whose latency may change by 2 milliseconds or more between the fully alert state and stage 2 sleep. Thus normative data for clinical testing should control for state. In the absence of such data, clinical interpretation of minor latency "abnormalities" should be appropriately cautious.

An evoked potential signal should only be reported as abnormal or absent if the technical quality of the recording is sufficient to permit that signal to have been adequately recorded. In some normal unsedated subjects, cortical SSEPs, recorded using scalp-to-scalp derivations, may be reliably recorded, whereas subcortical signals, recorded using noncephalic reference derivations, may be obscured by movement and muscle-related noise. For that reason, we favor the use of sedation for routine clinical SSEP testing.

STIMULATION OF OTHER PERIPHERAL NERVES

We have focused on SSEPs elicited by median nerve and PTN stimulation, because these nerves are used most commonly in clinical situations. However, stimulation of virtually any peripheral mixed or sensory nerve, including radial, ulnar, peroneal, sural, lateral femoral cutaneous, trigeminal, and pudendal nerves, gives rise to an SSEP (3,58,77,123,128,129,137, 156,165,166). To assess dorsal root integrity in patients with lumbar radiculopathy, Seyal et al. (129) compared stationary lumbar potentials evoked by stimulating saphenous, superficial peroneal, and sural nerves. Specific characteristics of the SSEP will vary, of course, depending on which nerve is stimulated. Allison et al. used SSEPs to stimulate median, posterior tibial, pudendal, and trigeminal nerves to map primary sensory and supplementary motor and sensory regions on the mesial cortex in patients undergoing evaluation for surgical treatment of epilepsy (3). Responses are influenced not only by the somatotropic representation of the structure(s) innervated by a nerve but also by the sensory elements within the nerve itself (e.g., relative amount of muscle and cutaneous afferents) (14,80,113).

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Chapter 30

Long-Latency Event-Related Potentials

Douglas S. Goodin

Event-Related Potentials
Effects of Age and Other Factors on the ERP
Clinical Utility of the ERP
Other Uses of the ERP
References

External stimuli produce changes of electrical potential within the nervous system that can be recorded using the technique of signal averaging (9). The nature of these so-called evoked potentials (EPs) depends, to a large extent, on the physical nature of the stimulus that is used to elicit them, and such potentials are commonly referred to as "exogenous" or "stimulus-related." These exogenous EPs include the brainstem auditory evoked potentials (BAEPs), the short-latency somatosensory evoked potentials (SSEPs), and visual evoked potentials (VEPs), all of which are in widespread clinical use. They also include the motor evoked potentials that are produced following transcranial electrical or magnetic stimulation of the brain. In general, these potentials do not depend on the subject's level of attention or interest in the task, and they often can be recorded when the subject is asleep or unconscious.

However, there is another type of EP, the so-called endogenous or event-related potential (ERP). Like exogenous EPs, these ERPs also can be recorded in response to an external stimulus (14,46,47,75,83,102). However, unlike exogenous EPs, these potential changes occur only when the subject is selectively attentive to the stimulus train and are elicited only when a subject is able to distinguish one stimulus or event (the target) from another group of stimuli (the nontargets). In addition, these potentials can be recorded in the circumstance (the event) where an anticipated stimulus is unexpectedly omitted (66, 92,96,103). ERPs are thus relatively independent of the physical nature of the stimulus, depending more importantly on the setting in which the target stimulus or event actually occurs.

As a result of experimental observations such as these, ERPs have been linked to a variety of cognitive processes thought to be associated with the task of distinguishing a target from a nontarget stimulus. Thus attempts even have been made to link different components of the ERP to particular stages of information processing, such as stimulus detection, stimulus classification, or response selection. The successful completion of these stages is often held to be a necessary prerequisite for a subject to respond selectively and accurately to a target stimulus (15,27,30,32,34,35,47,51,57,59,81,84,85, 106). As a result of this presumed relationship between these basic cognitive processes and the ERP, there has been considerable interest in the potential clinical role that the recording of these potentials might have in the evaluation of patients with impaired cognitive function.

EVENT-RELATED POTENTIALS

The usual experimental design used to elicit the ERP is the so-called oddball paradigm. In this design, a subject attends to a sequence of two different stimuli. One of these stimuli occurs quite often (the frequent stimulus) and thus is anticipated by the subject. The other stimulus occurs much less frequently (the rare stimulus), and it is this stimulus that evokes the endogenous components of the ERP. In order to ensure that the subject pays attention to the sequence of stimuli, he or she is typically required to count mentally or otherwise respond to one stimulus or the other.

The cerebral responses to the different stimuli are then recorded and averaged separately. The cerebral response to frequent stimuli consists of a series of waves that relate, to a large extent, to the sensory modality involved. Thus, following an auditory stimulus, this response has been divided into three sequential time periods. The early-latency response (occurring within the first 10 milliseconds after the stimulus) is the BAEP, and this reflects neural activity in auditory nerve and brainstem auditory structures such as the choclear nucleus, the superior olive, the lateral lemniscus, and the inferior colliculus (67). The midlatency response (10–50 milliseconds after the stimulus) is thought to reflect both reflex muscle activity and neural activity possibly arising in the thalamocortical radiations, the primary auditory cortex, and the early auditory association cortex (67). The long-latency response to the frequent stimulus (occurring more than 50 milliseconds after the stimulus) consists of a negative ($N\overline{1}$)–positive ($P\overline{2}$) complex that has been referred to as the vertex potential because it is of maximal amplitude in this scalp region (13). The neural basis for long-latency responses (including the vertex potential) is less well defined than it is for the earlier responses. Nevertheless, dipole localization methods using magnetoencephalography have generally localized the vertex potential to the superior temporal lobe (18,44,60,82,91). This vertex potential represents an obligate response of the nervous system to the external stimulus and can be recorded even when a subject is asleep (66). Therefore, like the early- and midlatency components, the vertex potential is an exogenous response.

In contrast to the long-latency response to the frequent tone, the response to the rare auditory stimulus consists not only of a negative ($N\overline{1}$)–positive (apparent $P\overline{2}$) complex but also of a following negative ($N\overline{2}$)–positive ($P\overline{3}$) complex (Fig. 30.1). The first positive wave in this sequence (apparent $P\overline{2}$) reflects the sum of the stimulus-related $P\overline{2}$ and the event-related $P\overline{165}$ (37). The amplitude and latency of this response are quite consistent for the same subject performing the same task (18,48,93). Although several other ERP components have been described in the literature (e.g., 22,37,43,50,58,75,100–102), most of the components other than this $N\overline{2}$-$P\overline{3}$ complex have not been studied widely in clinical contexts or are only elicited in special experimental circumstances. This $P\overline{3}$ response is a large wave of positive polarity that peaks in the midline central-parietal scalp approximately 300 milliseconds after an unexpected stimulus or event. An EP component with a scalp distribution similar to $P\overline{3}$ can be recorded in response to a stimulus of any sensory modality and, as mentioned earlier, can be recorded (in the absence of an associated vertex potential) even when an anticipated stimulus is unexpectedly omitted (66,68,92,96,103). The neural generators of this $P\overline{3}$ response are largely unknown, although a mesial cortical or subcortical location has been suggested by some authors (12,42,89,95,108,109).

The amplitude and latency of ERPs can be affected by several experimental manipulations that have little appreciable affect on exogenous EPs, and, conversely, other variables affect exogenous EPs without appreciable affect on ERPs. Thus the $P\overline{3}$ response is markedly influenced by the ease or difficulty with which targets are distinguished from nontargets (Fig. 30.2) (16,39), by the expectancy of the stimulus (21,73), or by the attention of the subject (see Fig. 30.1), whereas exogenous EPs are not (14,15,46,47, 66,67,75,83,102). By contrast, a change in the intensity of stimulation has relatively little effect on the $P\overline{3}$ component but a major influence on the associated exogenous EPs (14,46,47,66,67,75,83,102).

In order to record ERPs in a clinical setting, it is necessary to have a stimulator that is capable of delivering rare and frequent stimuli and recording the averaged EP in response to each stimulus separately. The stimuli need to be easily distinguished from each other in order to maximize the likelihood of eliciting robust ERPs. When two auditory stimuli are used (as is common in clinical practice), each stimulus is delivered binaurally. Typically, the stimuli used are 1000- and 2000-Hz tones (50–100 milliseconds in duration) delivered at an intensity of 65–75 decibels sensation level (dBSL). Because of the relatively long refractory period of the vertex potential, the interstimulus interval is usually more than 1 second. The amplitude of the $P\overline{3}$ response is typically 50–100 times the amplitude of the BAEP and, therefore, an average of only a few cerebral responses to rare tones is generally adequate to improve the signal-to-noise ratio to the point where the $P\overline{3}$ response can be seen easily (8). In fact, the $P\overline{3}$ amplitude is often large enough that this component often

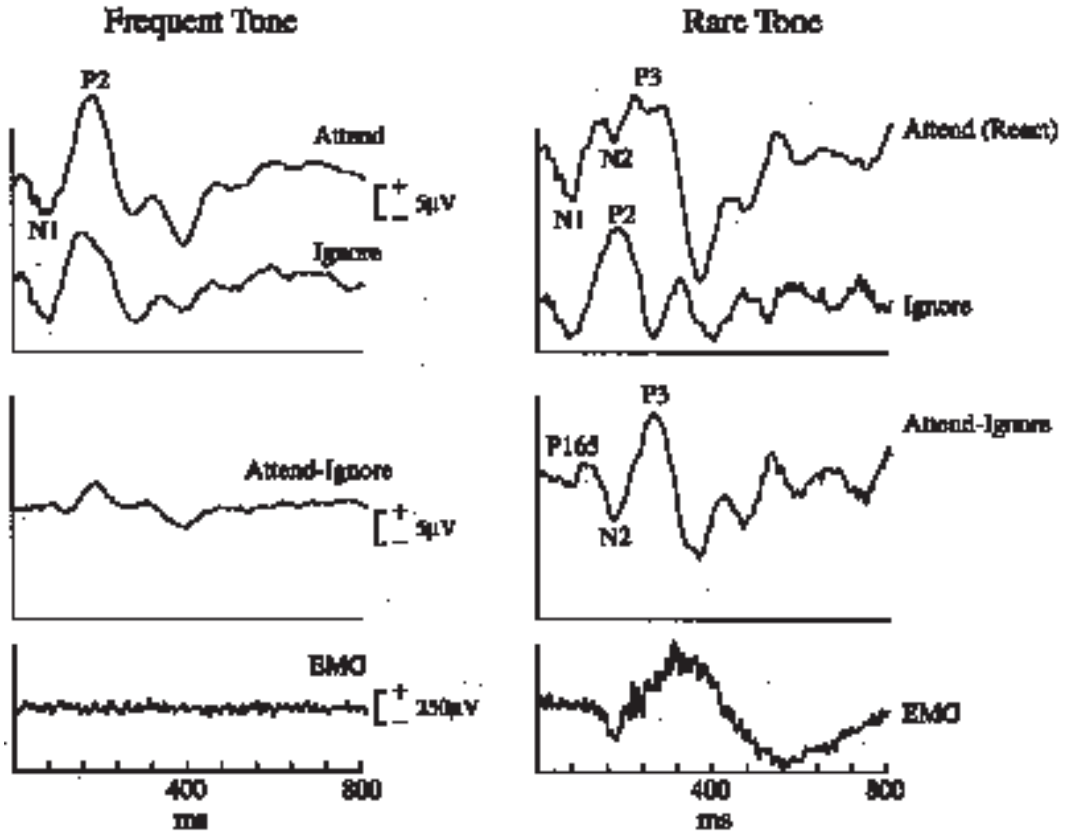

FIG. 30.1. Long-latency ERPs recorded from the vertex in a normal subject. Responses to the frequent stimulus are shown on the left and responses to the rare stimulus are shown on the right. Waveforms in the top row (react) were recorded when the subject listened to the stimuli and responded to each rare stimulus by extension of the right middle finger. Waveforms in the second row (ignore) are those recorded when the subject ignored the stimuli and read a book. Waveforms in the third row (react-ignore) represent difference waveforms obtained by digital subtraction of the ignore waveforms from the react waveforms. Compound muscle action potentials (CMAPs) from the right extensor digitorum communis muscle in the react condition are shown in the bottom row. (Modified from Goodin DS, Aminoff MJ. The relationship between the evoked potential and brain events in sensory discrimination and motor response. *Brain* 1984;107:241–251.)

can be identified in the response to a single stimulus. The ratio of rare to frequent tones is generally set at 20:80 or less. This allows approximately 50 responses to the rare tone per trial to be averaged in 10 minutes. At least two trials should be done to ensure that the responses are replicable.

Responses are recorded from Fz, Cz, and Pz electrode placements on the scalp (international 10-20 system) referenced to a common site such as linked mastoids. Eye movements should also be monitored to ensure that eye movement artifact has not contaminated the recordings, although it is possible with some recording systems either to reject contaminated trials automatically or to remove such artifacts from the recordings mathematically (54). Most of the electrical power present in ERPs is in the frequency band of less than 10 Hz, so that a high-frequency filter of 40 or 50 Hz is appropriate. The best low-frequency filter is controversial (17,31) because much of the power in ERP recordings is in the 1- to 4-Hz frequency band, and a marked distortion of the P3 amplitude begins to occur when low-frequency filters greater than this are used (31). As a result, high-pass filters of more than 1 Hz should be avoided. In addition, because high-pass analog filters will shift responses to earlier latencies, even at very low filter settings (31), it is important to ensure that both normal controls and clinical patients are recorded at an identical bandpass.

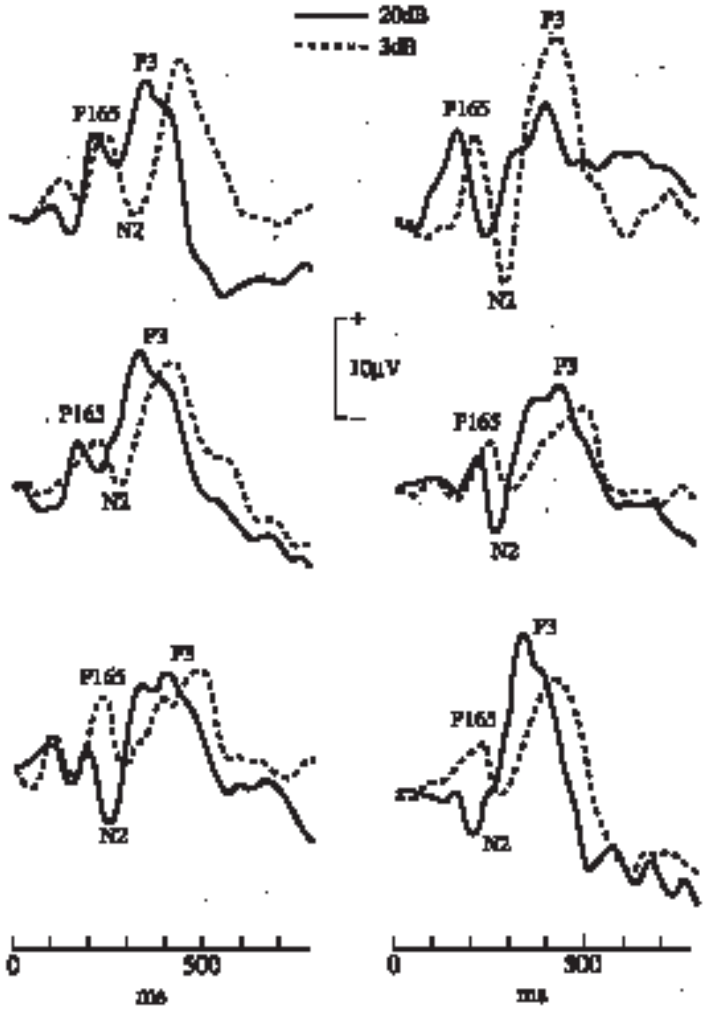

FIG. 30.2. Difference waveforms showing the ERPs in six subjects engaged in tasks of two different levels of difficulty. In the easy condition (*solid lines*), the frequent tone had an intensity of 40 decibels hearing level (dBHL), whereas the rare tone had an intensity of 60 dBHL. In the difficult condition (*dashed lines*), the rare tone was the same but the frequent tone had an intensity of 57 dBHL. The peak latencies of the ERP components are consistently longer in the difficult task compared to the easy one. (Modified from Goodin DS, Squires KC, Starr A. Variations in early and late event-related components of the auditory evoked potential with task difficulty. *Electroencephalogr Clin Neurophysiol* 1983;55:680–686.)

EFFECTS OF AGE AND OTHER FACTORS ON THE ERP

The long-latency ERP is strongly influenced by age (Fig. 30.3; Table 30.1). The exogenous N1 and P2 components seem to reach their adult latencies at the latest by the age of 5 or 6 years (10,36). By contrast, the N2 and P3 components are quite prolonged in young children and decrease in latency until reaching adult values in the mid- to late teenage years (10,36). Following this, the latency of both the stimulus-related (P2) and event-related (N2 and P3) components increases linearly with age (Fig. 30.3; Table 30.1). These findings have, in general, been confirmed by several studies (Table 30.2), although there has been some variation in the rate of change among reports (2,3,7,20, 36,41,63,68–70,76,80). A few groups have reported that the age–latency relationship for P3 is curvilinear, with an increased slope in elderly subjects compared to young controls (7,41). Picton and colleagues, however, specifically investigated this possibility and found no nonlinear trends on either trend analysis or formal testing for curvilinearity (68). As a result of these discrepancies, it is unclear whether nonlinear factors are important determinants of the P3 latency–age function. However, in two of the larger studies that have reported significant curvilinear effects (2,41), the incorporation of these effects into the model increased the explained variance by only a small amount, so that, from a practical standpoint, a linear approximation can be used to establish normal values for clinical purposes. In addition, because the changes in P3 latency that occur with maturation are so marked, separate normative data are necessary in children (10,36).

In addition to an increase in latency with age, there is also a decrease in the amplitude of both the stimulus-related and event-related components of the long-latency ERP (see Tables 30.1 and 30.2). Unlike the generally small intersubject variability of latency measurements, this variability of amplitude is large. Thus a single standard error around the regression line at age 60 years usually represents 60%–80% of the predicted amplitude of P3 (Table 30.2). This marked intersubject variability limits the clinical usefulness of measuring amplitude.

Medications can also affect the ERP. For example, metabolic encephalopathies (as might be caused by an overdose of many drugs) are known to affect the ERP (40). Of particular interest in the context of clinical ERP recordings are the medications used to treat depression or other psychiatric conditions, because these illnesses are often confused with dementia (24,49,107). The effect of these drugs taken in therapeutic dosages, however, has not been studied extensively. Baribeau-Braun and co-workers reported no difference in either P3 latency or amplitude between schizophrenic patients treated with high- and low-dose phenothiazines (4). In another

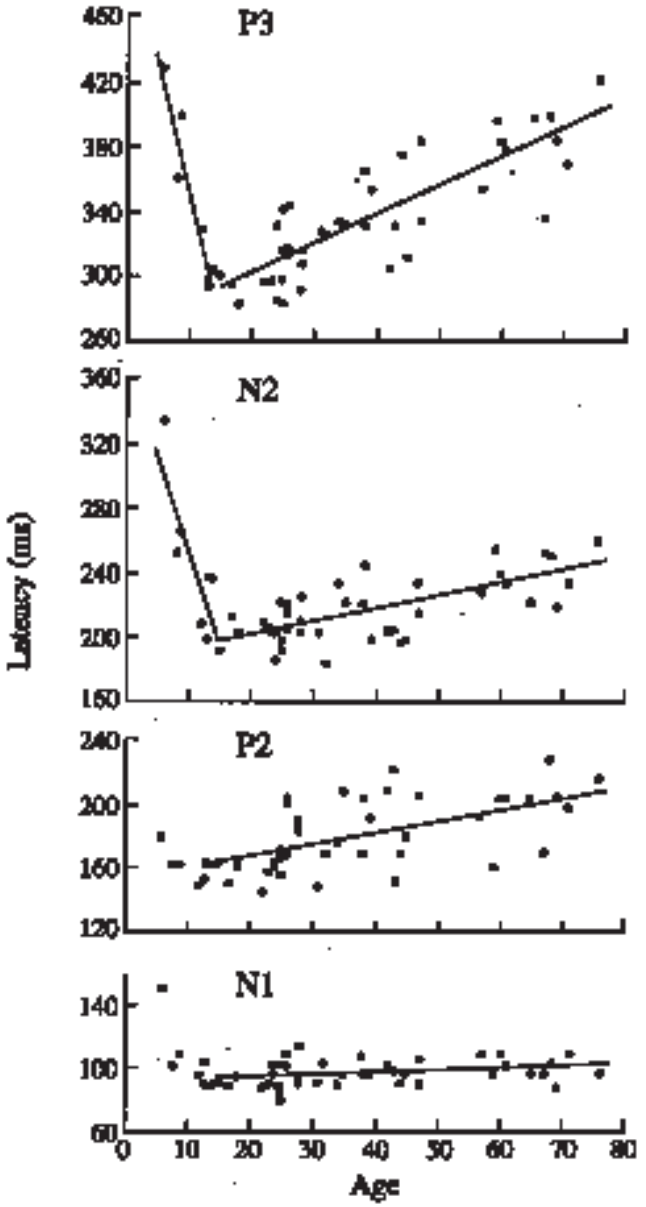

FIG. 30.3. Age–latency regression lines for the different long-latency ERP components. During maturation (age 6–15 years), the peak latency of the later N$\overline{2}$ and P$\overline{3}$ components becomes progressively shorter, reaching its shortest latency at approximately 15 years. Following this, each component increases in latency with age, although the rate of this change is faster for components that occur later in the sequence. (Modified from Goodin DS, Squires KC, Henderson BH, et al. Age-related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroencephalogr Clin Neurophysiol* 1978;44:447–458.)

study, Pfefferbaum and co-workers (65) studied 20 schizophrenic patients and found no difference in the P$\overline{3}$ response between treated and untreated patients. In depressed patients, by contrast, they found a P$\overline{3}$ amplitude reduction, but no latency difference, in the drug-free depressed patients compared with those receiving antidepressant medication. Therefore, from the available evidence, it seems that these psychiatric medications, at least when taken in therapeutic doses, do not have major effects on the ERP.

Certain other variables, such as how recently food has been consumed, body temperature, fitness, sleep deprivation, or time of day, also have been reported to affect the P$\overline{3}$ response (23,71). These findings still need to be confirmed, although, because the magnitude of the changes reported tends to be small, the relevance of these effects to clinical recordings is unclear.

Table 30.1. *Variation in the amplitude and latency of the auditory ERPs with age*

	Slope	SE[a]	Value at age 15 yr	Significance[b]
Latency				
N$\overline{1}$ component	0.1 msec/yr	8 msec	94 msec	NS
P$\overline{2}$ component	0.7 msec/yr	19 msec	168 msec	$p < 0$ 001
N$\overline{2}$ component	0.8 msec/yr	15 msec	199 msec	$p < 0.001$
P$\overline{3}$ component	1.6 msec/yr	21 msec	310 msec	$p < 0$ 001
Amplitude				
N$\overline{1}$-P$\overline{2}$	0.2 μV/yr	5.6 μV	15.6 μV	$p < 0.01$
N$\overline{2}$-P$\overline{3}$	0.2 μV/yr	7.9 μV	17.7 μV	$p < 0.05$

[a]Standard error of the estimate around the regression line.

[b]NS indicates that the regression slope is not significantly different from zero.

Data from Goodin DS, Squires KC, Henderson BH, et al. Age-related variations in evoked potentials to auditory stimuli in normal human subjects *Electroencephalogr Clin Neurophysiol* 1978;44:447–458.

Table 30.2. *Comparison of age-related changes in the auditory P3 amplitude and latency in different studies*

	Latency			Amplitude		
	Slope (msec/yr)	Intercept (msec)	SE (msec)	Slope (μV/yr)	Intercept (μV)	SE (μV)
Goodin et al. (36)	+1.64	285	21	–0.18	17.6	5.6
Picton et al. (68)	+1.71	294	25	–0.15	16.6	4.0
Syndulko et al. (104)	+1.07	297	22	*	*	*
Brown et al. (7)	+1.12	272	28	–0.15	*	*
Pfefferbaum et al. (63)	+0.94	*	51	–0.13	*	*
Emmerson et al. (20)	+1.46	*	*	*	*	*
Gordon et al. (41)	+0.91	*	31	*	*	*
Puce et al. (80)	+1.34	281	*	–0.28	23.0	*
Polich (69)	+0.92	304	32	*	*	*
Anderer et al. (2)	+0.92	327	33	–0.12	19.2	6.3

Asterisks indicate data are not included in the reports.

ERPs also may be difficult to interpret in certain situations. For example, unlike the interpretation of many clinically used EPs such as the BAEP, the VEP, and the SSEP, the complete absence of a P3 response should not be considered as an abnormality. On occasion, the P3 response may absent in alert, attentive, and cooperative nondemented subjects who are engaged in the task. Conversely, such a finding might simply reflect a subject's inattention to the task. Another difficulty is that occasionally the P3 peak consists of two distinct subcomponents, the so-called P3a and P3b, as initially described by Squires and co-workers (98). These authors found the P3a subcomponent in the averaged response to rare tones regardless of the subject's attention, whereas the P3b subcomponent was present only when subjects attended to the stimulus train. They therefore concluded that it was the P3b subcomponent that was sensitive to task requirements. Some authors have recommended separate measurement of these two subcomponents in order to improve the sensitivity of the test (72). In practice, however, the P3a and P3b subcomponents often are fused and cannot be identified separately. Even so, measuring a single P3 latency generally results in both small standard errors and high sensitivities (Tables 30.2 and 30.3).

Table 30.3. *Clinical experience with P3 latency in neurological and psychiatric patients*[a]

Study	Demented	Psychiatric	Nondemented
Squires et al. (97)	74% (58)	3% (33)	4% (51)
Brown et al. (6)	61% (18)	0% (7)	
Pfefferbaum et al. (65)	30% (37)	19% (54)	
Leppler and Greenberg (52)	73% (15)	0% (15)	
Slaets and Fortgens (94)	38% (8)	17% (6)	
St. Clair et al. (99)	7% (14)		
Gordon et al. (41)	80% (19)	12% (32)	
Polich et al. (74)	28% (39)		
Goodin and Aminoff (28)	61% (36)		
Patterson et al. (62)	13% (15)	0% (8)	

[a]Percentages of patients with abnormally prolonged P3 latencies in each of the three categories: demented and nondemented patients with neurological illnesses and psychiatric patients with either depression or schizophrenia. Numbers in parentheses represent the total number of patients studied in each category.

CLINICAL UTILITY OF THE ERP

The clinical syndrome of dementia describes a deterioration of intellect simultaneously involving several different areas of cognitive function, such as memory, orientation, judgment, and abstraction. Senile dementia of the Alzheimer's type (SDAT) is, at present, the most common (albeit untreatable) cause of dementia, particularly in the elderly, among whom this diagnosis accounts for considerably more than 50% of demented patients in most series (24,49,107). However, other causes of dementia, if recognized early enough, can be successfully treated. As a result, it is necessary to exclude other treatable causes of dementia in all patients. This is particularly important for patients with an apparent deterioration in intellect resulting from a "pseudodementia" caused by depression or other psychiatric illness. These patients cannot be distinguished from those with SDAT by commonly used radiological and laboratory tests, and yet they have an eminently treatable condition. The recording of ERPs has been used most widely in this clinical circumstance.

Several groups have reported that the P$\overline{3}$ component is prolonged in latency and reduced in amplitude in demented patients compared to age-matched controls (Fig. 30.4; Table 30.3) (6,28,38,52,62,65,74,76,94,97,99,104). Squires and co-workers (97) found that 74% of their demented patients had a P$\overline{3}$ latency that was more than 2 standard errors above the normal age–latency regression line (Fig. 30.5). The P$\overline{3}$ amplitude was also reduced significantly in the patients with dementia (38). By contrast, only 3.5% of their nondemented patients with other neurological and psychiatric conditions had a similar prolongation of their P$\overline{3}$ latency (Fig. 30.5). These findings, again, were similar in all diagnostic categories, including depressive illness (Table 30.4). The finding of 74% sensitivity and 96.5% specificity suggests that recording the

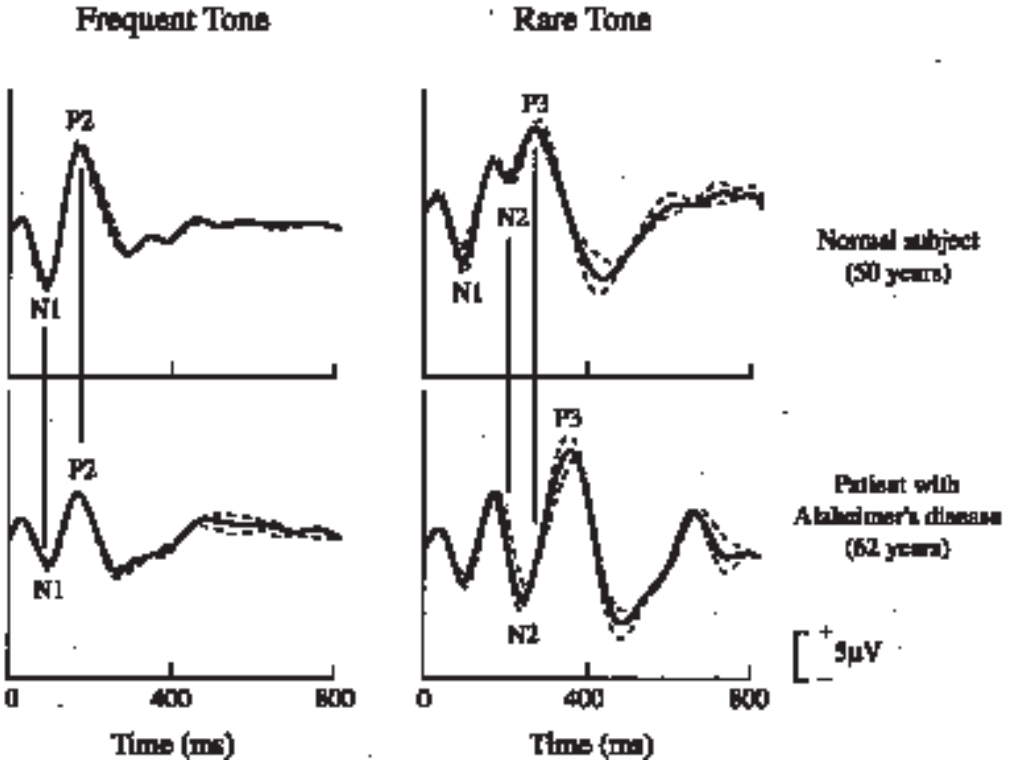

FIG. 30.4. Long-latency ERPs recorded from the vertex in a demented and a nondemented subject of similar age. **Top:** Responses from the nondemented subject. **Bottom:** Responses from the demented subject. Responses to the frequent tone are on the left and those to the rare tone are on the right. The N$\overline{1}$ and P$\overline{2}$ components are similar in the two subjects, whereas the later event-related components (N$\overline{2}$ and P$\overline{3}$) are delayed in the demented subject relative to the nondemented subject. (Modified from Goodin DS, Aminoff MJ. Electrophysiological differences between subtypes of dementia. *Brain* 1986;109:1103–1113.)

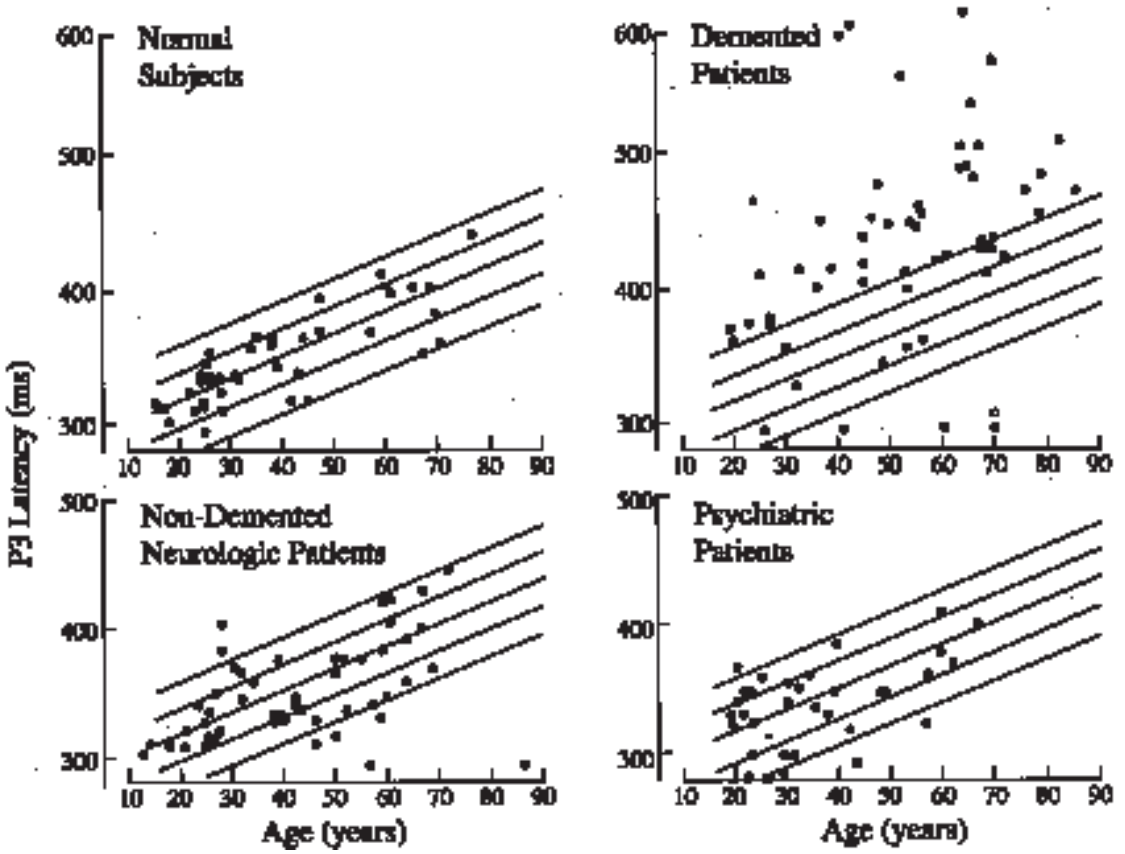

FIG. 30.5. The relationship between P$\overline{3}$ latency and age in three patient groups and in normal subjects. *Open circles* represent persons without an identifiable P$\overline{3}$ response. The normal age–latency regression line (in addition to the 1 and 2 standard error lines) is superimposed on each plot. (Modified from Squires KC, Chippendale TJ, Wrege KS, et al. Electrophysiological assessment of mental function in aging and dementia. In: Poon LW, ed. *Aging in the 1980s*. Washington, DC: American Psychological Association, 1980:125–134.)

P$\overline{3}$ could be quite helpful in the evaluation of demented patients. For example, if the diagnoses of dementia and pseudodementia were thought (on clinical impression) to be equally likely, the finding of a prolonged P$\overline{3}$ latency would effectively establish the diagnosis of dementia beyond reasonable doubt (25). A normal P$\overline{3}$ latency in this circumstance, by contrast, would suggest (but not establish) the diagnosis of pseudodementia.

Most published studies have confirmed these general findings, although the sensitivity of the P$\overline{3}$ latency has varied among reports (see Table 30.3). In addition, although the specificity of the test also has varied among reports, no study has shown a significant prolongation in the P$\overline{3}$ latency of depressed patients or patients with other psychiatric conditions. Thus the sensitivity and specificity of the test, both in the more favorable reports as well as in the average experience, make it useful in the proper clinical setting (25) and give it an important role in the evaluation of selected patients with cognitive impairment.

ERPs also have been studied (33) in patients infected with human immunodeficiency virus (HIV), some of whom were asymptomatic from their infection and others of whom were demented and met other diagnostic criteria for the acquired immunodeficiency syndrome (AIDS). As in other subcortical dementias (see below), patients with the AIDS-dementia complex have a prolongation of the early components of the ERP, particularly of the N$\overline{1}$ component, in addition to the prolongation of later N$\overline{2}$ and P$\overline{3}$ components that occurs in other dementing disorders (see Table 30.4). Almost a

Table 30.4. *P3 latency in neurological and psychiatric illnesses*

	Number	P3 Latency (SE)[a]
Diagnoses of Demented Patients		
Alzheimer's type	13	2.79
Uncertain cause	12	3.17
Toxic-metabolic	11	4.09
Vascular disease	8	4.98
Hydrocephalus	7	2.84
Brain tumor	4	4.20
Multiple sclerosis	2	8.19
Herpes simplex encephalitis	1	0.29
Total	*58*	*3.61*
Diagnoses of Psychiatric Patients		
Depression	12	–0.22
Paranoid schizophrenia	11	–0.30
Manic-depression	6	0.16
Acute schizophrenia	4	–0.23
Total	*33*	*–0.18*
Diagnoses of Nondemented Patients		
Miscellaneous	17	0.20
Brain tumor	8	–0.52
Vascular disease	7	–0.41
Multiple sclerosis	6	–0.42
Parkinsonism	5	0.50
Hydrocephalus	5	0.87
Trauma	3	0.41
Total	*51*	*–0.30*

[a]Indicates the average number of standard errors away from the normal age–latency regression line in each group of patients.

Data from Goodin DS, Squires KC, Starr A. Long latency event-related components of the auditory evoked potential in dementia. *Brain* 1978;101:635–648.

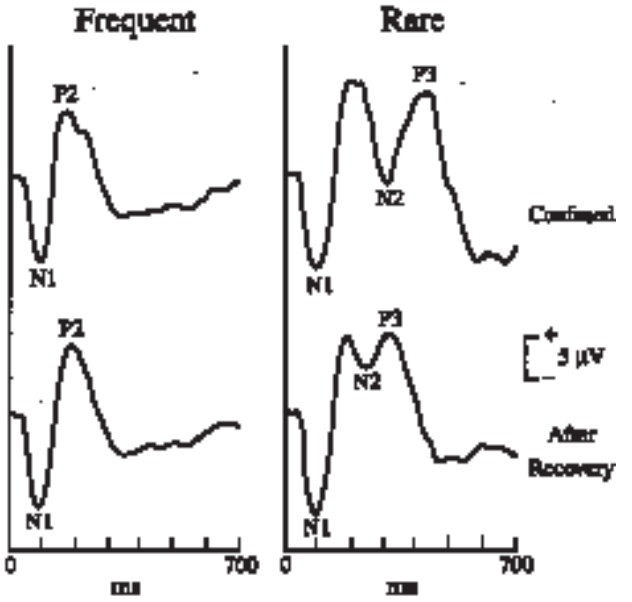

FIG. 30.6. Long-latency ERPs recorded in a man of age 60 who was initially comatose from hyponatremia. Responses to the frequent tone are shown on the left and responses to the rare tone are shown on the right. **Top:** Waveforms recorded while the patient was awake but mentally slow from his metabolic encephalopathy. **Bottom:** Waveforms recorded after he had recovered fully. The stimulus-related N1 and P2 components were unchanged between recordings. The latencies of the N2 and P3 components of the ERP, by contrast, were considerably shorter after the patient had returned to normal mental functioning. (Modified from Goodin DS, Starr A, Chippendale T, et al. Sequential changes in the P3 component of the auditory evoked potential in confusional states and dementing illnesses. *Neurology* 1983;33:1215–1218.)

third of asymptomatic HIV patients in this study had ERP changes similar to those that occurred in patients with dementia. These results suggest that ERPs may be used to identify a subgroup of asymptomatic patients who have a particularly high risk of developing future cognitive difficulties, perhaps thereby identifying patients who require more aggressive treatment.

Because ERPs are known to fluctuate with clinical state (40), they can be used to study the same individual over time in order to provide an objective measure of the changes that occur in cognitive function (Fig. 30.6). This clinical role for ERPs may increase as the therapeutic options for dementia become more prevalent.

The use of the ERP in diseases other than dementia has not been clearly defined. Several authors have reported P3 amplitude to be reduced in schizophrenia (4,5,53,61,65,86,87,90), and some have reported a latency prolongation as well (4,55,65). Similarly, the ERP has been studied in both acute alcohol intoxication and chronic alcohol abuse. In general, the P3 amplitude is reduced in both settings (19,45,64,77–79,88), although, again, latency differences occasionally are reported (64). In addition, some studies have reported that subjects with a family history of alcoholism (and therefore at increased risk of becoming alcoholics) had large-amplitude decrements in

recorded ERPs, unlike subjects without such a history (19,45). As discussed previously, however, such a large normal variation in amplitude exists that the actual clinical utility of these findings in individual patients is uncertain, even though such results may have considerable theoretical importance to our understanding of schizophrenia and of alcoholism.

OTHER USES OF THE ERP

The recording of ERPs also may provide insight into other clinical or theoretical controversies. For example, there has been debate about whether a distinction can be made between the dementia syndrome produced by neocortical diseases such as Alzheimer's disease and that produced by subcortical diseases such as Huntington's or Parkinson's disease (1,11,56). By recording ERPs in patients with these different illnesses, however, Goodin and Aminoff were able to demonstrate differences in the ERP not only between the cortical and subcortical dementias but also within the subcortical group (28,29). Other groups also have investigated the electrophysiological changes that occur in Parkinson's, Huntington's, and Alzheimer's diseases (see ref. 26 for a review), and the reported changes generally have paralleled each other. In this circumstance, ERPs are able to provide direct evidence that, in fact, different subtypes of dementia exist.

Suggestions also have been made in the literature that SDAT represents an acceleration of the normal aging process (e.g., ref. 105). By recording of the ERP, however, it can be demonstrated (e.g., ref. 38) that patients with SDAT have markedly prolonged (i.e., age-inappropriate) $P\overline{3}$ latencies but normal (i.e., age-appropriate) $P\overline{2}$ latencies (see Fig. 30.5). The finding of such a selective effect of dementia on the ERP indicates that the aging process has not simply been accelerated in these patients.

ERPs also have been used to study the central organization utilized by the brain to detect and identify different stimuli, discriminate among them, and select appropriate motor responses to each. As mentioned earlier, many authors have attempted to link different ERP components to the so-called stages of information processing (e.g., stimulus detection, stimulus classification, and response selection) that are presumed to take place during the performance of a discrimination task such as the oddball task used to elicit the $P\overline{3}$ response (15,27,30,32,34,35,43,57–59,81,83,85). Many of these authors assume (either explicitly or implicitly) that the various stages of information processing proceed in a serial manner, with the completion of one stage being a necessary prerequisite for the beginning of the next. However, whether such processing occurs serially or in parallel is controversial.

Several experimental observations bear on this issue. First, not only is the timing of the ERP dependent on the difficulty of the discrimination task (see Fig. 30.2), but the coupling of the motor response to the ERP also varies with task difficulty (Fig. 30.7) and with the response strategy adopted by the subject (30,32,34,35,59). In fact, with particularly easy tasks (18), the entire ERP

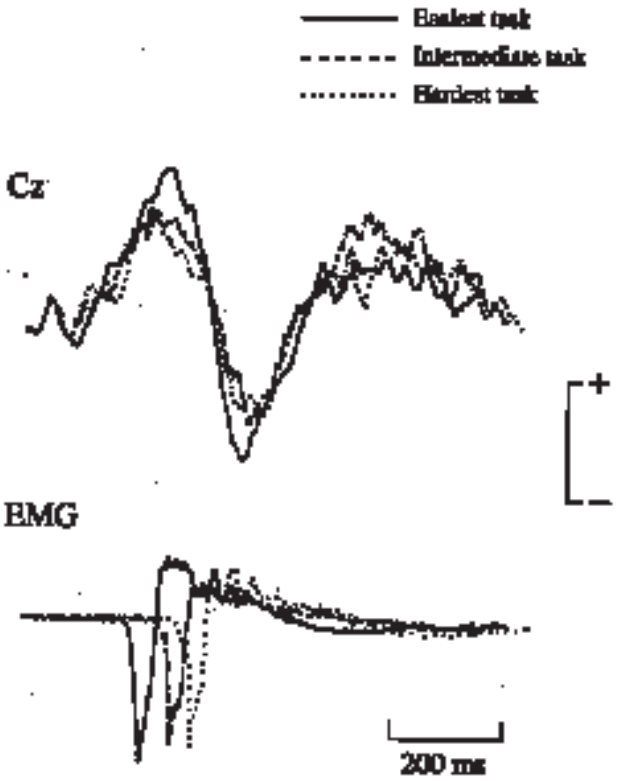

FIG. 30.7. Long-latency response-synchronized ERPs recorded from the vertex when subjects were engaged in tasks of varying difficulty (easiest task: *solid line*; intermediate task: *dashed line*; hardest task: *dotted line*). **Top:** The cerebral responses, which have been aligned with each other. **Bottom:** CMAPs recorded from the responding muscle as described in Figure 30.1. As can be seen, there is a progressive delay between the ERP and the onset of the CMAP as the tasks become harder. (Modified from Goodin DS, Aminoff MJ, Mantle MM. Sensory, discrimination and its relationship to cerebral processing of infrequent stimuli. *Can J Neurol Sci* 1987;14:642–648.)

may actually follow the motor response (see Fig. 30.1). Conversely, when a subject correctly anticipates a future event, the correct motor response may be initiated prior to the onset of the stimulus (35,59). The importance of these observations is that no ERP component can be linked consistently to any specific cerebral process related to the making of such a sensory discrimination (30,32,34,35,59). Moreover, based on comparisons between response-synchronized and stimulus-synchronized averages, the N1 and P2 components of the ERP seem to be on a separate (i.e., parallel) branch of the stimulus processing sequence from the P 165-N2-P3 complex, and errors seem to arise when a response is inappropriately generated from the wrong branch (30). Thus ERPs seem to reflect neural activity in substantially parallel networks and, thereby, provide physiological evidence of parallel processing. Indeed, as a result of considerations such as these, the discrimination and response systems appear to be so intertwined that even the notion of discrete stages of information processing seems somewhat implausible.

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Chapter 31

Intraoperative Monitoring

Ronald G. Emerson and David C. Adams

Monitoring Spinal Cord Function
Somatosensory Evoked Potential Monitoring
Motor Evoked Potential Monitoring
Cranial Nerve and Spinal Root Monitoring
Compound Muscle Action Potentials
Neurotonic Discharges
Acoustic Nerve and Brainstem Auditory Evoked Potential Monitoring
Functional Localization
Detection of Cerebral Ischemia
Electroencephalographic Monitoring
Somatosensory Evoked Potential Monitoring
Monitoring Depth of Anesthesia
References

Neurophysiological techniques have traditionally been used to detect relatively static structural or functional disturbances of the nervous system: for example, demyelinative and mass lesions, encephalopathies, and epileptic disorders. Even when employed in connection with evolving disease processes, electroencephalograms (EEGs) and evoked potentials (Eps) were classically recorded at infrequent intervals, providing only "snapshot" measurements. However, in contrast to other, imaging-based technologies, electrophysiological measures are uniquely well suited to providing almost real-time measures of nervous system function. For this reason, continuous neurophysiological monitoring is now routinely employed intraoperatively during surgical procedures, which entail risk of nervous system injury. For example, intraoperative monitoring is now considered a standard of care during carotid endarterectomy, correction of scoliosis, and resection of acoustic nerve tumors.

Monitoring can reduce the risk of intraoperative neurological damage in two ways: First, monitoring enables detection of neurological injury at a time when it can be reversed or minimized. During scoliosis surgery, for example, deteriorating long tract function can be detected by somatosensory evoked potential (SEP) and motor evoked potential (MEP) monitoring early enough to avert permanent spinal cord damage. Second, neurophysiological techniques can distinguish vital neural structures that may otherwise be difficult to distinguish from surrounding tissue. For example, the rolandic fissure is commonly identified through SEP monitoring during surgery involving cortical resection.

The evolution of intraoperative neurophysiological monitoring strategies has resulted from the collaborative efforts of neurophysiologists, anesthesiologists, and surgeons. Neurophysiologists have modified existing techniques and developed new methods and interpretative strategies for use in the operating room. Anesthesiologists have developed anesthetic techniques

that facilitate neurophysiological monitoring. Surgeons have learned how to best incorporate and appropriately respond to neurophysiological information in a real-time surgical context.

Intraoperative neurophysiological monitoring continues to evolve with a seemingly continuous stream of literature describing innovative and imaginative approaches to various clinical circumstances. This chapter illustrates how standard diagnostic laboratory techniques have been extended to the intraoperative setting. It serves as an introduction to intraoperative monitoring as it is currently employed rather than as an instruction manual or exhaustive reference.

MONITORING SPINAL CORD FUNCTION

Intraoperative EP monitoring of long tract function is commonly employed during procedures such as spine surgery, neuroradiological procedures, brainstem surgery, and aortic surgery, in which motor and sensory tracts are placed at risk (13,26,32,69,84,89,114,128). There are early reports of the failure of EP monitoring to detect neurological injury (58,34,75). However, at least some of these failures are traceable to human errors, such as monitoring an inappropriate EP, not monitoring for a long enough period, and not recognizing artifact, rather than to inherent limitations of EP monitoring.

In the past, the "wake-up" test (124) was used to verify spinal cord integrity during surgery. However, EP monitoring offers important advantages over the wake-up test. A review of 1,168 scoliosis operations at The Royal Orthopedic Hospital concluded that EP monitoring was more sensitive than the wake-up test (32). In contrast to EP monitoring, the wake-up test provides only a single snapshot of spinal cord integrity and exposes the patient to additional risks, including dislodgment of instrumentation, laminar fractures, venous air embolism, and accidental extubation (9).

Although SEPs are direct measures of posterior column function and MEPs depend on the integrity of descending motor pathways, each modality alone serves as a good measure of spinal cord integrity. Graded changes in both MEPs and SEPs accompany spinal cord injury produced by ischemia, compression, and blunt trauma (8,20,21,24,28,31,59,60,64,65,68,90,105,112). Intraoperative spinal cord compression generally results in degradation of both MEP and SEP signals (82). Concurrent MEP and SEP recording provides an added level of security, inasmuch as, if technical difficulties compromise one monitoring modality, the other is likely to continue functioning. In this manner, SEPs and MEPs are complementary, and optimal monitoring of long tract function ideally entails concurrent recording of both.

However, because SEPs and MEPs are mediated by distinct anatomical pathways, surgical injury to either the motor or sensory system can occur independently (10,11,25,120,131). Their relatively tenuous vascular supply, provided by the anterior spinal artery with large watershed regions along its length, makes the motor tracts particularly vulnerable to ischemia resulting from hypotension, potentially producing loss of motor function without altered SEPs (119,122,131). Monitoring both MEPs and SEPs allows detection of the occasional insult that selectively affects either motor or sensory long tracts separately.

Somatosensory Evoked Potential Monitoring

Although it is similar to techniques employed in the diagnostic laboratory, certain features of intraoperative SEP recording are unique. For example, although many anesthetic agents can attenuate cortical SEP components, making them difficult to record, the use of neuromuscular blocking agents facilitates the recording of subcortical components.

The montages used for recording SEPs in the diagnostic laboratory and in the operating room are determined by the relatively restricted distribution of the primary cortical components and the widespread topography of the subcortical SEP components. Because the primary cortical response for median nerve SEPs, the N$\overline{20}$ response, is confined to the centroparietal scalp opposite the stimulated arm, a bipolar "scalp-to-scalp" recording, between symmetrical centroparietal electrodes, detects it in isolation. However, because the subcortical P$\overline{14}$ and N$\overline{18}$ median nerve responses are widely and symmetrically distributed, a referential "scalp-to-noncephalic" recording, by a scalp electrode ipsilateral to the stimulated median nerve, detects mainly subcortical far-field potentials (see Chapter 29, Figs. 29.5 and 29.29). The posterior tibial nerve SEP has a more complex topography. Although the primary cortical P$\overline{38}$ response is present at the vertex but lateralized to the scalp *ipsilateral* to the stimulated leg, there is considerable individual variation in the "normal" P$\overline{38}$ scalp topography. Thus, it is suggested that two channels, such as Cz-Fpz and C3/4 $_{\text{ipsilateral}}$-Fpz, be used to reliably record P$\overline{38}$ in all patients. A referential Fpz-to-noncephalic derivation detects the subcortical P$\overline{31}$ and P$\overline{34}$ components in isolation (5).

In general, the cortical N$\overline{20}$ and P$\overline{38}$ responses are easily recorded in awake or lightly sedated patients in the diagnostic laboratory. However, changes in the cortical SEP amplitude and latency are often observed while patients are under general anesthesia. This effect typically is most pronounced in infants and young children (42), in lower extremity SEP recordings, and when halogenated

inhalational agents, such as isoflurane and halothane, are used (12,38,94,110). Similar but less prominent effects are also seen with most other anesthetic agents, including narcotics, benzodiazepines, and barbiturates (54,72,94). For these reasons, cortical SEPs are sometimes difficult to record intraoperatively and are insufficiently stable to use for monitoring. Subcortical far-field signals ($\overline{P14}$, $\overline{P31}$), in contrast, are much less affected by anesthetic agents and are often preferred as indicators of spinal cord function (110) (Fig. 31.1).

In the diagnostic laboratory, subcortical far-field potentials can be very difficult to record. Noncephalic referential recordings are often contaminated by movement and muscle related artifacts, particularly in awake patients. In the operating room, the recording of far-field potentials is facilitated by the use of neuromuscular blocking agents, which significantly reduce muscle-related noise (Fig. 31.2).

On occasion, particularly in patients with preexisting neurological deficits, only cortical SEP signals may be recordable, despite the use of neuromuscular blocking agents. In these cases, it is important to limit the use of anesthetic agents that attenuate cortical components. Small variations in the doses of anesthetic drugs, particularly halogenated inhalational agents, can produce changes in SEP amplitude that mimic surgical injury. Etomidate, an intravenous anesthetic agent that increases the amplitude of cortical SEP components, has occasionally been used to augment the cortical response (Fig. 31.3; however, there is a possibility that etomidate could mask intraoperative SEP changes (72).

Surgical spinal cord injury typically results in loss of EP amplitude and degradation in the morphological appearance of the signal. Prolonged latencies tend to be less prominent and consistent findings (32,86). Thus, strategies for intraoperative SEP interpretation differ from those used in standard testing, which rely primarily on response latencies (5). Furthermore, intraoperative SEPs are compared primarily with the patient's baseline values, rather than with those of normative controls. Two general approaches have been developed for intraoperative interpretation of SEP recordings. One is to adopt predefined, somewhat arbitrary limits (typically a 50% decrement

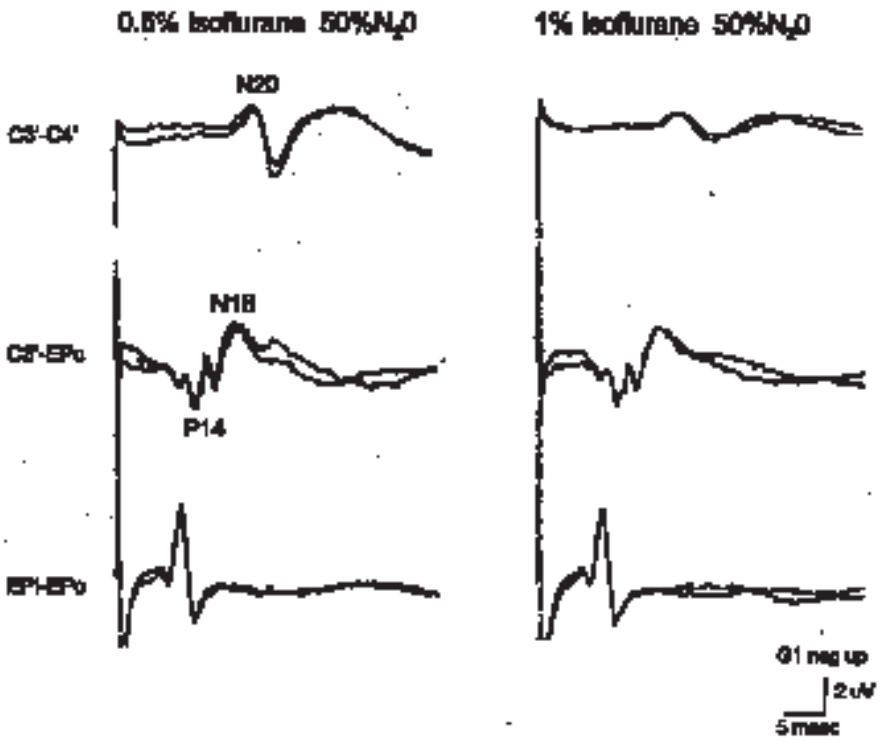


FIG. 31.1. Median SSEP recorded in a patient receiving isoflurane and nitrous oxide. Increasing the concentration of isoflurane from 0.5% to 1% causes attenuation of the $\overline{N20}$ cortical response but does not alter the subcortical $\overline{N18}$ potential. In this and subsequent figures, EPi and EPc refer to electrode locations over Erb's points, ipsilateral and contralateral to the stimulated nerve. C3' and C4' designate electrode locations halfway between C3 and P3 and halfway between C4 and P4, respectively.

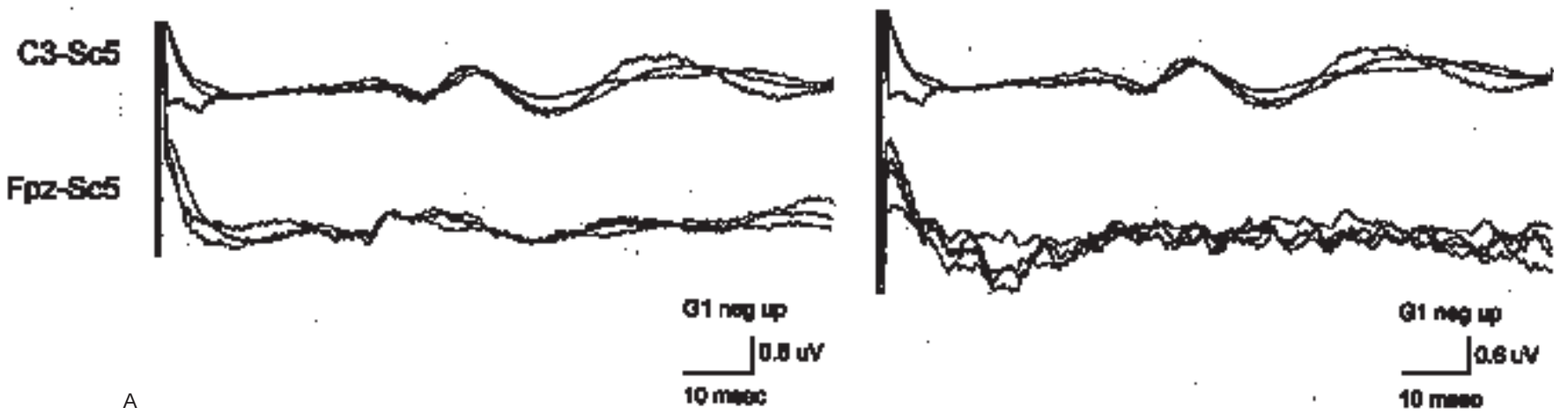


FIG. 31.2. Posterior tibial SSEP recorded during nitrous oxide/fentanyl anesthesia with **(A)** and without **(B)** neuromuscular blockade. In panel *A,* a vecuronium infusion eliminates muscle-related artifact and improves the quality of the subcortical recording (Fpz-SC5). SC5 denotes an recording site over the fifth cervical vertebra.

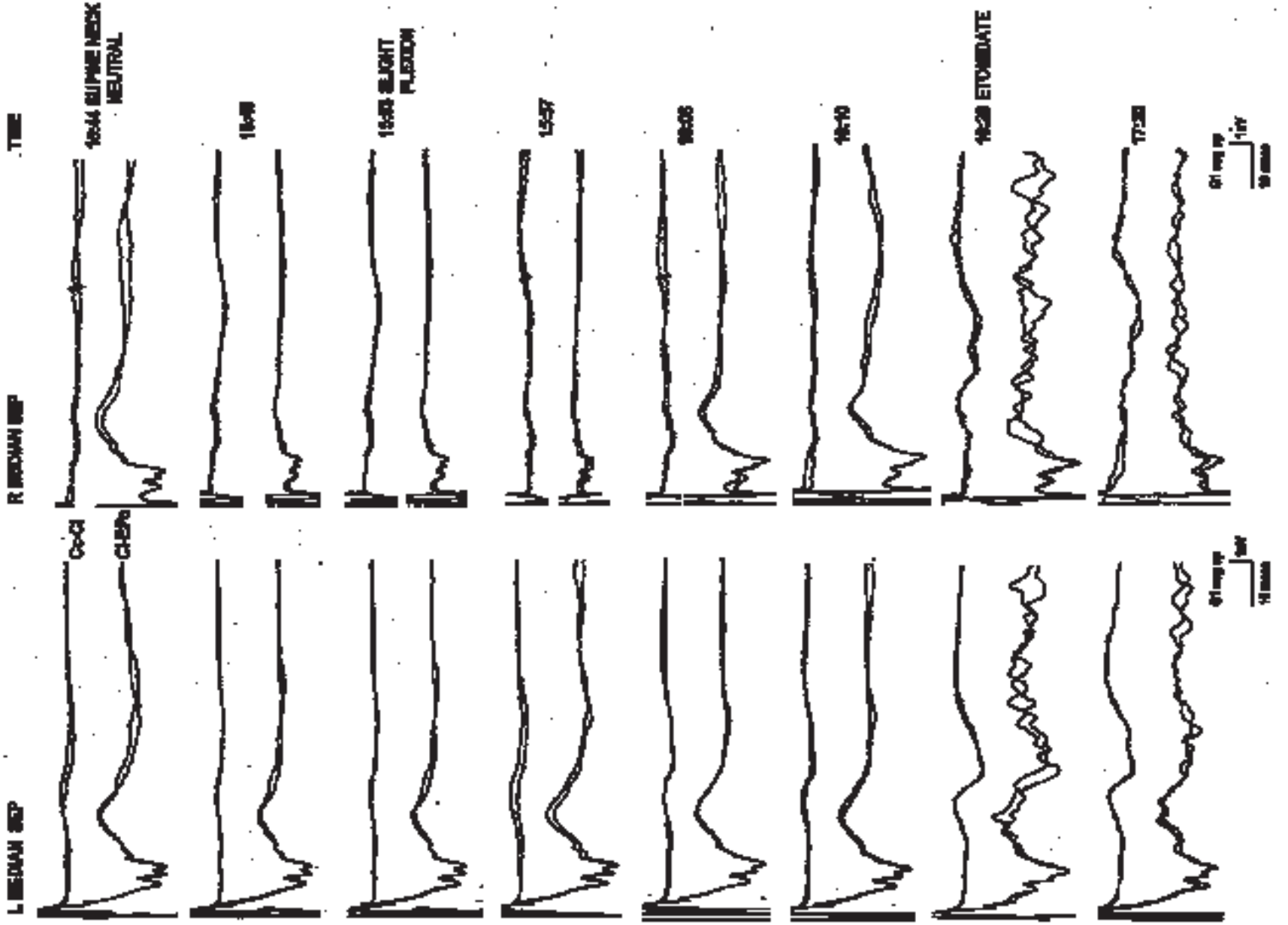
in amplitude or a 10% increase in latenc y), beyond which there is considered to be substantial risk of neurolo gical insult, and to infor m the surgeon when those limits are sur passed. An alternative approach is to infor m the surgeon of changes, even if small, in SEP amplitude, latency, and morphology, that exceed the baseline variability in the patient's recordings. Because this approach enab les the sur geon to better identify the cause of these changes and to use that information to decide whether to take a wait-and-see approach or to act immediately (78), the authors favor its use.

The implications of SEP deterioration depend on the type of sur gery being performed. For example, in the absence of corrective intervention, loss of SEP amplitude during correction of spinal deformities is ominous and carries a high risk of serious neurological injury (32). On the other hand, loss of SEP amplitude during intramedullary surgery is predictive of neurological deficits in the immediate postoperative period but is less predictive of the ultimate outcome (52,126). It may be that, in these cases, surgical manipulation of the spinal cord produces transient conduction b lock without producing per manent axonal injury (126). Furthermore, although the stability of SEPs during intramedullary surgery provides reassurance that neurological injury has not occurred, sudden loss of SEPs does not necessarily indicate permanent injury (52).

Motor Evoked Potential Monitoring

It has long been recognized that the motor cortex can be activated by electrical stimulation (93), b ut the application of motor system stimulation to intraoperative monitoring is a relati vely recent de velopment. Currently, intraoperative MEP monitoring is routine at some centers (44,82,115), although the techniques emplo yed are not y et uniform. Either electrical or magnetic transcranial stimulation or electrical spinal cord stimulation can be used to elicit the MEP response. The "motor" response may be a compound nerve action potential recorded over the spinal cord (13,36) or o ver peripheral nerve (88), or it may be a compound muscle action potential (CMAP) recorded over an appropriate distal muscle (2).

Transcranial stimulation allo ws relatively selective activation of spinal motor pathways because inter vening synapses pre vent retrograde firing of sensory tracts. Direct spinal stimulation, in contrast, acti vates sensory as well as motor pathways. Furthermore, transcranial techniques per mit stimulating electrodes to remain outside of the surgical field. Transcranial stimulation may either fire pyramidal neurons directly or activate cortical interneurons, which then fire pyramidal cells. Direct p yramidal stimulation produces the earlier ,



more stable components of the MEP known as D waves, whereas indirect pyramidal activation results in the longer latency, less stable I waves (4,107). Whereas transcranial electrical stimulation results in both D and I waves, magnetic stimulation generally elicits only I waves (73).

Magnetically elicited transcranial motor evoked potentials (tcm-MEPs) are of limited use for intraoperative monitoring because they are significantly attenuated by most commonly used anesthetics (33,48,50) and vary widely with minor alterations in coil position (Fig. 31.4) (1). Although advances in magnetic coil design and stimulus parameters, such as the use of paired or trains of stimuli, may improve the reliability of tcm-MEPs (123), tcm-MEPs are currently not sufficiently reliable for intraoperative use. Transcranial magnetic stimulation, in contrast, is easily accomplished in awake subjects and it may have a role in the preoperative assessment of patients with spinal cord lesions.

Transcranial electrical motor evoked potentials (tce-MEPs) are also substantially attenuated by the commonly used inhalational anesthetics (39,49,130), generally necessitating the use of intravenous anesthetic techniques (91). Although special high-voltage stimulators have been developed for transcranial stimulation (13,46,129), a method allowing standard SEP stimulators to be used for transcranial stimulation under general anesthesia has been introduced. Rather than a single high-voltage pulse, a series of lower voltage pulses are rapidly delivered (47,91). There is a marked increase in amplitude and a reduction in latency of the tce-MEP at interstimulus intervals of 1 to 3 milliseconds, which presumably reflect temporal summation at cortical or spinal levels (91) (Fig. 31.5).

An alternative MEP technique, suitable for cases in which the region at risk is at or below the upper thoracic cord, entails electrical stimulation of the spinal cord with CMAPs monitored over appropriate muscles. For stimulation, needle electrodes are positioned, either transcutaneously or through the surgical exposure, near the ligamentum flavum at two adjacent vertebral levels (Fig. 31.6). Partial neuromuscular blockade produced by an infusion

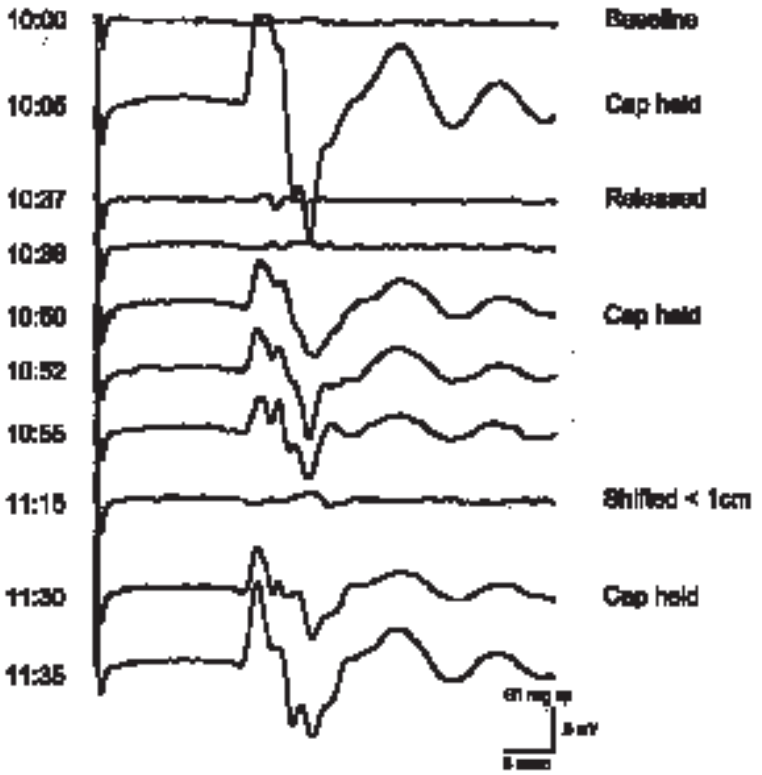


FIG. 31.4. Small movements of the stimulating "skull cap" coil produce large changes in transcranial motor evoked potentials recorded from quadriceps during nitrous oxide/fentanyl anesthesia.

FIG. 31.3. A series of median SSEPs recorded during myringotomy in preparation for cleft palate repair in a 3-year-old child with achondroplasia. Halothane was administered by mask. Baseline recordings showed an intact subcortical response (Ci-Epc) bilaterally. The very low voltage N$\overline{20}$ cortical response (Cc-Ci) is a normal finding in a young child receiving a halogenated anesthetic agent. On the right, N$\overline{18}$ was lost after slight neck flexion and returned when the head was moved to the neutral position. The cleft palate repair was deferred, and during the remainder of the procedure, etomidate was used to facilitate monitoring of the cortical N$\overline{20}$. The patient awoke with no neurological deficits.

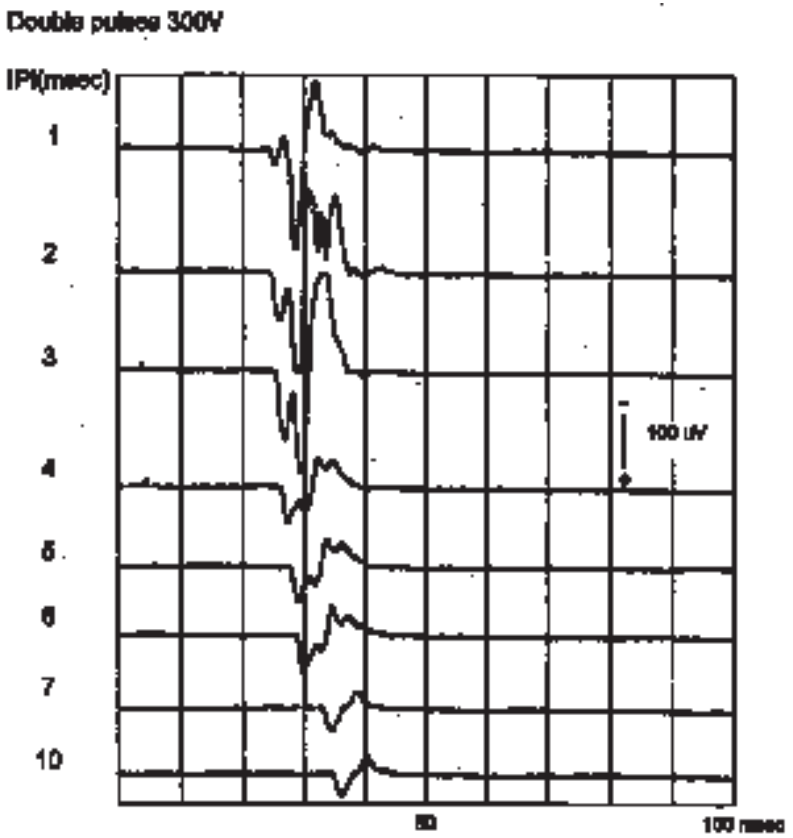


FIG. 31.5. Effect of interpulse interval (IPI) on transcranial electrical motor evoked potentials (MEPs) recorded from abductor digit minimi using paired pulses. Interpeak intervals of less than 2 milliseconds produced the highest amplitude and shortest latency MEPs. (From Jones et al, 1966, with permission).

of non-depolarizing muscle relaxant eliminates movements that would interfere with surgery but allows CMAPs to be easily recorded, even when the patient has been given potent inhalational anesthetic drugs (2). Stimulation is achieved with single pulses, 10 to 40 mA and 0.1 to 0.3 milliseconds in duration, or with brief trains of similar pulses (2,74). Typically, 2 to 20 such stimuli delivered at 0.5 Hz are averaged, producing an updated MEP every few seconds. As with transcranial electrical stimulation, several pulses delivered in rapid succession may produce higher amplitude MEPs and help

FIG. 31.6. For spinal cord stimulation, electrode tips lie close to the ligamentum flavum at two adjacent vertebral levels.

overcome the effects of anesthetic agents (74). Although it is possible to record "neurogenic motor evoked potentials" over mixed nerve or spinal cord, these recordings represent a composite of both orthodromic motor signals and antidromic sensory signals (88). It has been suggested that, under certain circumstances, antidromic sensory volleys produced by direct stimulation for spinal cord monitoring could activate motor neurons in the ventral horn (95,116). In cats anesthetized with ketamine, Mochida et al. (74) demonstrated that dorsal column stimulation could abolish CMAPs to single pulse spinal cord stimulation. However, they observed that paired pulses produced much larger CMAPs that were not affected by dorsal column section, and they concluded that these were mediated by spinal motor pathways. Furthermore, potent inhalational agents known to suppress spinal reflexes (103) would probably diminish any contribution of antidromic sensory volley. An important benefit of recording CMAPs is that they incorporate the ventral gray matter of the spinal cord in the monitored pathway, which is a site of potential operative injury (2,18,60).

Figure 31.7 illustrates a case in which permanent paraplegia was probably prevented by MEP and SEP monitoring during correction of severe

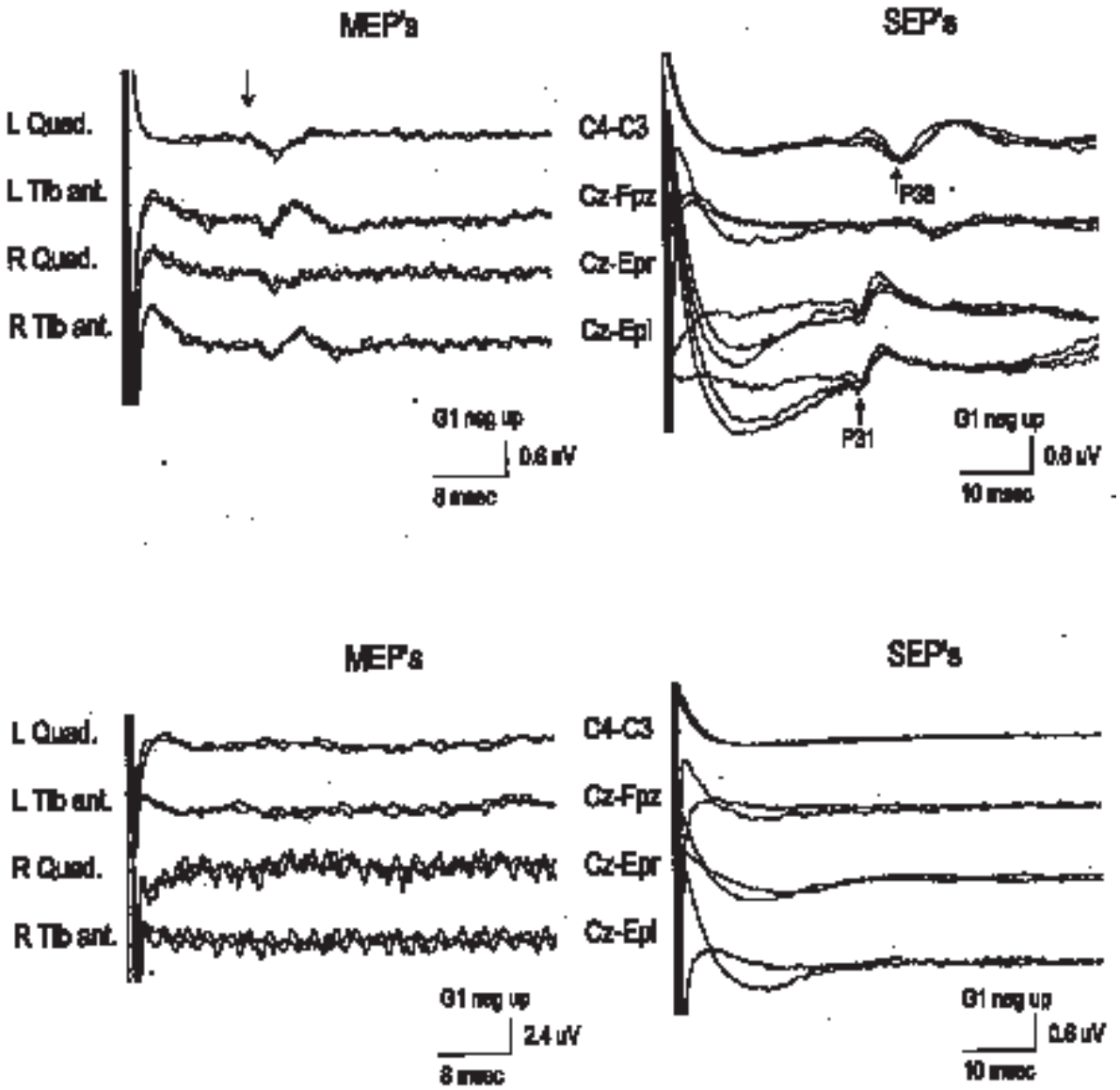


FIG. 31.7. Loss of both motor evoked potentials and SSEPs after distraction in a 14-year-old girl with severe thoracolumbar scoliosis. **A:** Baseline. **B:** After distraction. EPr and EPl denote electrode positions over right and left Erb's points.

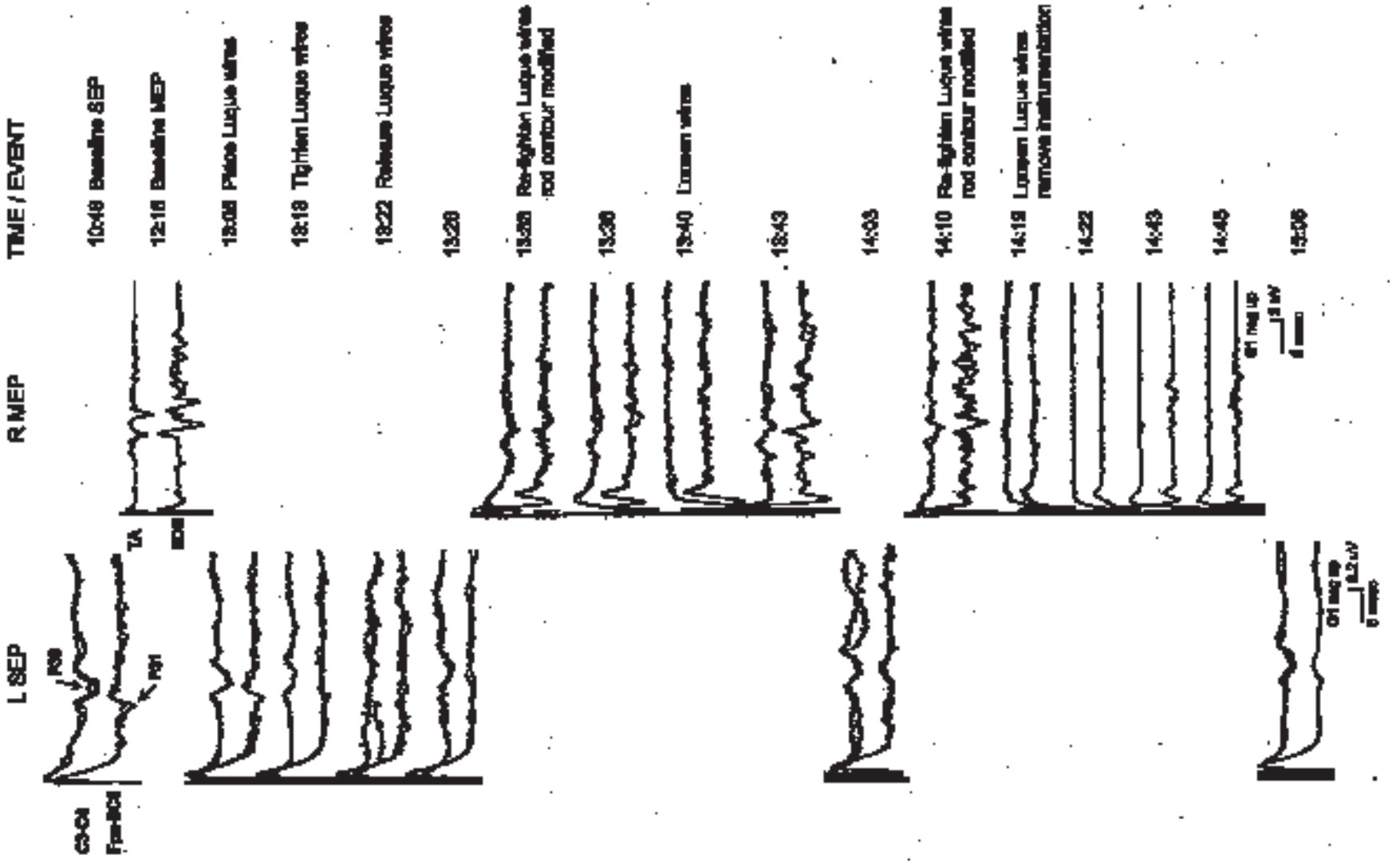


FIG. 31.8. SSEPs and motor evoked potentials monitored in a 17-year-old girl during scoliosis surgery with Luque segmental spinal instrumentation. Each time the wires were tightened, there was reversible loss of monitored potentials. Therefore, the instrumentation was removed, and the patient was treated with a body cast. Although paraplegic immediately postoperatively, the patient recovered to baseline examination levels within 2 weeks and was ambulatory at discharge.

thoracolumbar scoliosis. After multiple osteotomies and spinal distraction, both MEPs and SEPs were lost. Thereafter the distraction was reduced and the spine was stabilized, but the EPs remained absent. Although an emergency computed tomographic myelogram was negative, the patient was paraplegic postoperatively; the injury was attributed to overdistraction. Motor function returned over the ensuing several months, and the patient currently is fully ambulatory.

The authors reported their experience of 116 spine or spinal cord surgical cases monitored with SEPs and MEPs elicited by electrical spinal cord stimulation (82). In eight cases in which MEPs and SEPs deteriorated, and in an additional case in which only MEPs changed, there were corresponding postoperative motor deficits. In four cases, intraoperative MEP deterioration prompted changes in surgical management. In two patients undergoing correction of scoliosis, there was repeated reversible loss of MEPs and SEPs during spinal instrumentation. In both cases, instrumentation was removed, and patients were placed in body casts (Fig. 31.8). In another patient with severe kyphoscoliosis and spinal stenosis, MEP and SEP signals were lost during anterior decompression, prompting early termination of the surgery and delaying a planned second operation. In the fourth case, a vessel supplying a spinal cord arteriovenous malformation was spared after temporary occlusion was found to produce reversible loss of MEPs. One of these four patients died of a concurrent illness; the other three had good neurological recoveries. Because intraoperative SEP and MEP monitoring does not add any substantial risk to the patient, the only cost is monetary (22). The costs associated with a single avoidable case of neurological injury could well dwarf the expense of monitoring several hundred cases.

CRANIAL NERVE AND SPINAL ROOT MONITORING

Intraoperative neurophysiological monitoring both facilitates identification of cranial nerves and spinal roots and allows continuous assessment of their functional integrity. The facial nerve is monitored during resection of acoustic neuromas and other cerebellopontine angle surgeries, during which it may be injured or accidentally severed. These risks are increased with large tumors, which may either engulf the facial nerve or distort its appearance. Reduced rates of morbidity after acoustic neuroma surgery performed with facial nerve monitoring have been confirmed by several studies (40,57,83). At the Mayo Clinic, 91 monitored acoustic neuroma operations were compared with unmonitored controls matched for patient age, tumor size, and year of surgery; results demonstrated a threefold reduction in the rate of facial paralysis in the monitored cases (40).

In a similar manner, cranial nerves III, IV, and VI may be monitored during cavernous sinus surgery (111), and the lower cranial nerves may be monitored during skull base surgery (76). During surgery that places the spinal roots at risk (such as spinal cord untethering, placement of pedicle screws for instrumentation, and certain types of tumor resection), spinal root monitoring may be indicated (30,44,45,55).

Compound Muscle Action Potentials

Monitoring of CMAPs over appropriate muscles can be used to identify cranial nerves or spinal roots when scarring or anatomical distortion makes visual identification difficult. In contrast to the clinical laboratory setting in which constant-current stimulators are preferred, constant-voltage stimulators are often more suitable for intraoperative use. In stimulating within the operative site, constant voltage stimulators are better able to compensate for variable shunting of current through ambient fluid and to deliver a constant depolarizing current to a nerve (77,127).

Either surface or intramuscular electrodes may be used to record CMAPs. A monopolar probe is directed by the surgeon. Initially, nerve roots are located through the use of relatively high stimulation intensities. Then the intensity is decreased to selectively stimulate only the target root in order to confirm its identity and establish its stimulation threshold. In general, stimulation thresholds are 0.03 to 0.1 mA for cranial nerves and slightly higher for nerve roots. Higher stimulation intensities (about three times threshold) are used to confirm that an intended area of resection does not contain nerve, and lower stimulation intensity (near threshold) is used to confirm identity of the nerve. Elevation of the stimulus threshold may reflect nerve injury and an increased likelihood of postoperative deficit (51). Stimulation near a nerve may fail to produce a CMAP if the nerve has been injured, causing conduction block, or has been transected proximal to the site of stimulation.

The close relationship of the many muscles of the face can lead to ambiguity in recordings. Electrodes in muscles innervated by cranial nerve VII may also record signals generated the masseter and temporalis muscles, innervated by cranial nerve V. However, latencies of these responses differ and can be used to distinguish them. For example, after intracranial stimu-

lation, cranial nerve VII has an onset latency of about 6 milliseconds, whereas cranial nerve Vm has a latency of only 3 milliseconds. Similarly, activation of lateral rectus muscle from cranial nerve VI stimulation is observed in the orbicularis oculi channel but can be properly identified by its latency (127) (Fig. 31.9).

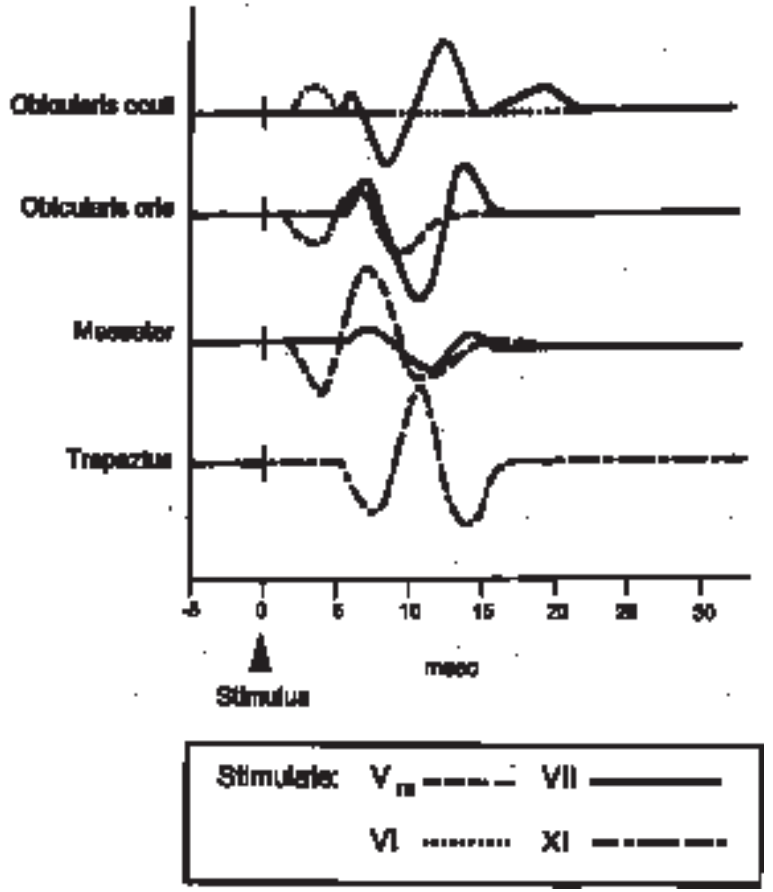


FIG. 31.9. The proximity of various cranial muscles results in "cross-talk" between recording sites. Characteristic latency differences help distinguish among responses to stimulation of cranial nerves Vm, VII, VI, and XI. (Reproduced from Yingling CD, Gardi JN. Intraoperative monitoring of facial and cochlear nerves during acoustic neuroma surgery. *Otolaryngol Clin North Am* 1992;25:413–448.)

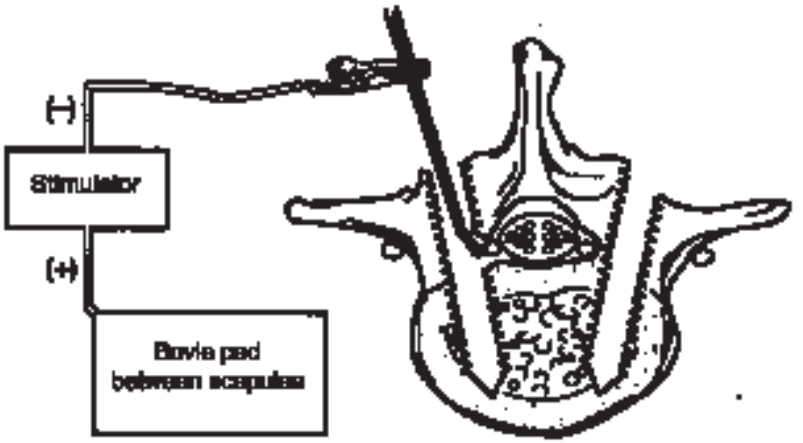


FIG. 31.10. Method for testing of lumbar pedicle screw hole integrity before screw placement. (From Calancie B, Madsen P, Lebwohl N. Stimulus-evoked EMG monitoring during transpedicular lumbosacral instrumentation. *Spine* 1994;19:2780–2786.)

CMAP thresholds are employed to test the placement of metal screws used for transpedicular spinal fixation. Postoperative radiculopathy may result from inadvertent penetration of the pedicle cortex with a screw. Either the wall of the intended screw hole or the screw itself is stimulated (Fig. 31.10), and the threshold for stimulation is measured by recording over the corresponding muscles (Fig. 31.11). Intact bone surrounding the screw provides insulation between it and the adjacent root. If the bone is perforated, a low-impedance path is created, lowering the stimulation threshold. Thresholds below 6 to 11 mA are suggestive of pedicle wall breakthrough (14,17,66).

Neurotonic Discharges

Mechanical nerve stimulation can produce neurotonic electromyographic discharges. In contrast to CMAPs, which can be recorded with surface electrodes, these discharges are best recorded with intramuscular electrodes (23). Although partial neuromuscular blockade allows monitoring of CMAPs, its use precludes reliable recording of neurotonic discharges (51). Instead, higher concentrations of inhaled anesthetics are

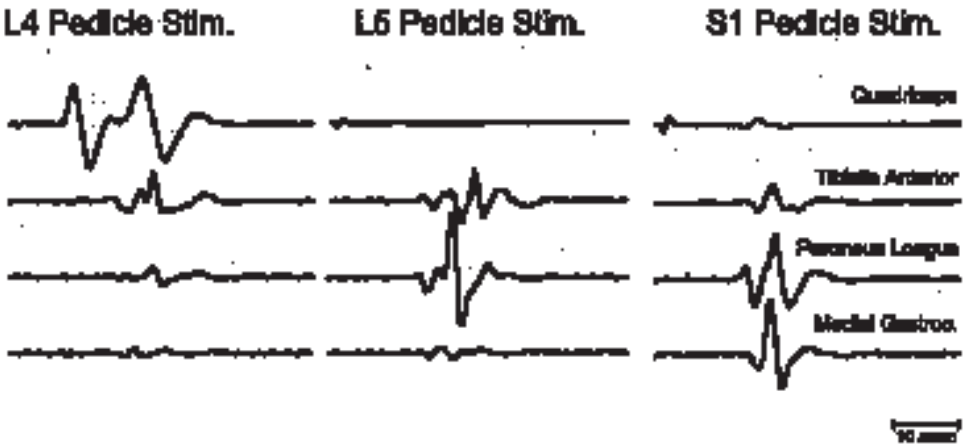


FIG. 31.11. Compound muscle action potentials from lower extremity muscles after stimulation of L4, L5, and S1 pedicle screws at 1 to 2 mA above threshold. (Reproduced from Calancie B, Madsen P, Lebwohl N. Stimulus-evoked EMG monitoring during transpedicular lumbosacral instrumentation. *Spine* 1994;19:2780–2786.)

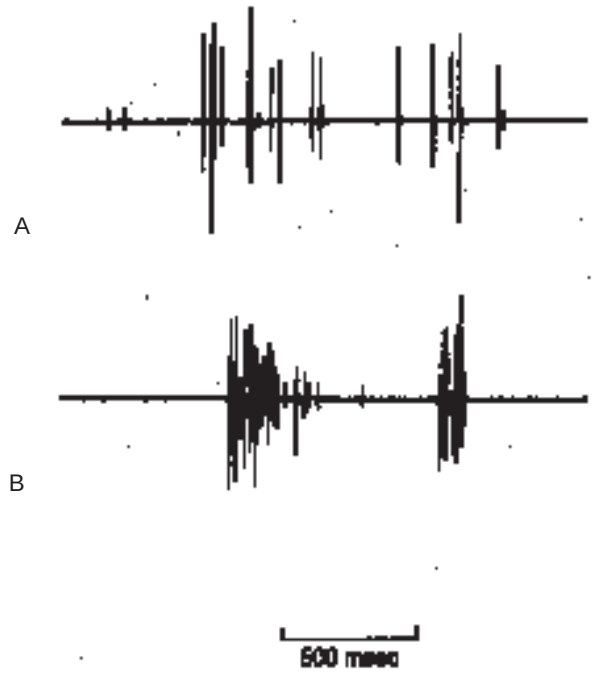


FIG. 31.12. Brief burst electromyographic response recorded with blunt dissection **(A)** and after a rapid squirt with Ringer's lactate solution **(B)** during acoustic neuroma surgery. (From Prass RL, Luders H. Acoustic (loudspeaker) facial electromyographic monitoring: part 1. Evoked electromyographic activity during acoustic neuroma resection. *Neurosurgery* 1986;19:392–400.)

typically used to achieve relaxation when neurotonic discharges are recorded.

Mechanical stimulation—for example, from dissecting instruments and irrigation—produces brief (<1-second) bursts of motor unit potentials that occur with the mechanical stimulus and fatigue on repeat stimulation (Fig. 31.12). Easily elicited, relatively synchronous bursts indicate functional integrity of the nerve distal to the stimulated site. Loss of this response may signal nerve injury (97). However, because injured nerves may not be sensitive to mechanical stimulation, and because severing a nerve may produce only a minimal electromyographic response (51), mechanically elicited discharges should be supplemented with periodic electrical stimulation.

Prolonged asynchronous "train" discharges lasting up to several seconds or minutes signal nerve damage. These may result from ischemia, heating, or prolonged mechanical deformation, and their onset may be delayed seconds to minutes after the insult (Fig. 31.13). On the basis of their sounds when monitored on a loudspeaker, two types of tonic discharges, 50- to -100-Hz "bomber" discharges or 1- to 50-Hz "popcorn" discharges have been described (97). Both have been associated with postoperative neurological deficits (23,98). The frequent association of train discharges with lateral-to-medial facial nerve traction during acoustic neuroma surgery led Prass and Luders (98) to identify that manipulation as a likely source of nerve injury and to modify their dissection strategy to minimize it.

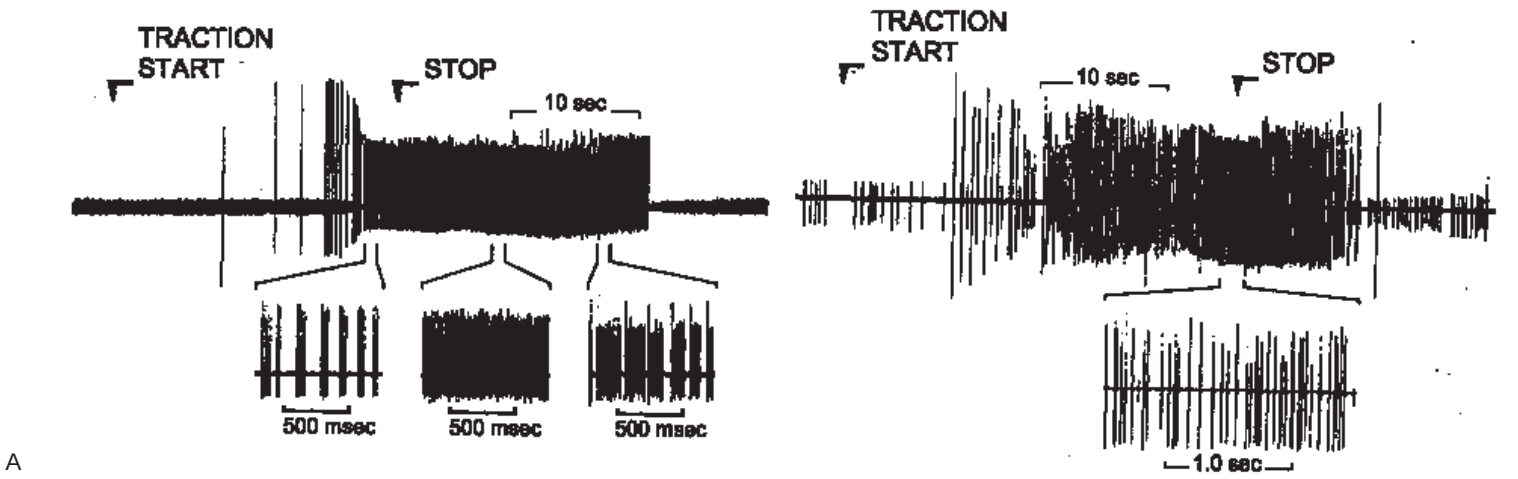


FIG. 31.13. Prolonged "bomber" **(A)** and "popcorn" **(B)** train discharges produced by lateral to medial facial nerve traction. (From Prass RL, Luders H. Acoustic (loudspeaker) facial electromyographic monitoring: part 1. Evoked electromyographic activity during acoustic neuroma resection. *Neurosurgery* 1986;19:392–400.)

ACOUSTIC NERVE AND BRAINSTEM AUDITORY EVOKED POTENTIAL MONITORING

Brainstem auditory evoked potentials (BAEPs) reflect the functional integrity of the cochlea, auditory nerve, and brainstem auditory pathways. Accordingly, BAEPs are monitored during cerebellopontine angle surgery to help preserve auditory nerve function. They may be recorded intraoperatively to assess brainstem function. Clinically relevant components of the BAEP are wave I, generated by the acoustic nerve; wave III, generated in the lower pons and wave V, generated in the lower midbrain.

Intraoperatively, BAEPs are recorded in a manner similar to that employed in the clinical laboratory, except that bulky headphones are replaced either with small earphones that can be inserted or with molded earplugs. In the operating room, a faster stimulation rate, typically 30 Hz rather than 10 Hz, is often used. Although this results in a small reduction in signal amplitude, it allows more rapid signal acquisition. BAEPs are largely unaffected by general anesthetic drugs, although potent inhalational agents may produce small increases in wave V latency (27,61,67). Similarly, decreases in core temperature, as well as local cooling at the surgical site, increase wave V latency approximately 0.2 millisecond per degree Celsius (127).

The utility of monitoring BAEPs to preserve hearing was demonstrated by a study in which the outcomes of 70 microvascular decompressions for trigeminal neuralgia or hemifacial spasm monitored with BAEP were compared to those of 152 historical control procedures performed without monitoring (99). The incidence of profound hearing loss was 0% in the monitored group, in comparison with 6.6% in the unmonitored group (99). Similarly, the efficacy of BAEP monitoring to reduce the risk of hearing loss during acoustic neuroma surgery is well documented (41,53,81,113, 125). In another study, 90 consecutive monitored acoustic neuroma resections were compared with 90 unmonitored historical controls; hearing was preserved in 79% of the monitored patients but in only 42% of the unmonitored patients for tumors smaller than 1.1 cm in diameter (98). BAEP monitoring in patients with tumors larger than 2 cm is unlikely to be of significant benefit because preservation of hearing is unlikely in such patients (41).

In general, a 50% or greater loss of wave V amplitude or a 0.5-millisecond or greater increase in wave V latency is recognized as a potentially

important alteration in the BAEP waveform (15,41,99). Surgical maneuvers most likely to cause deterioration of BAEPs include electrocautery near the auditory nerve, pulling of the tumor -nerve bundle, drilling of the inter nal auditory canal, and direct manipulation of the auditor y nerve (19,71). Because BAEP monitoring is capable of providing feedback to the surgeon at approximately 1- to 2-minute intervals, it is suggested that the most dangerous maneuvers be performed in incremental steps, in order to use BAEP feedback to guide the resection. Simply pausing may allow the deteriorated BAEP signals to recover (71,96).

Modified recording techniques, such as recording directl y from the cochlear nerve (19,106) or from near the brainstem (70,79), have been introduced to provide more rapid feedback to the surgeon. These techniques offer improved signal-to-noise ratios, potentially allowing changes to be detected within seconds rather than minutes.

Although it provides direct surveillance of only the portion of brainstem between the lower pons and the lower midbrain, BAEP monitoring is sensitive to manipulations of the brainstem and may be used to assess its integrity (6). In patients with lar ge cerebellopontine angle tumors, it has been observed that the w ave V latencies measured after stimulation of the ear opposite the lesions are more closely related to brainstem manipulation than either the wave V amplitude or other hemodynamic parameters (6).

FUNCTIONAL LOCALIZATION

Intraoperative visual identif ication of the central sulcus ma y be difficult; however, it is easily identified functionally through the use of median nerve SEPs recorded from a cortical electrode array. Because activation of area 3b in the posterior bank of the central f issure produces the initial component of N$\overline{20}$, a horizontal dipole—positive precentrally and negative postcentrally—is recorded from a ro w electrodes traversing the central sulcus (Fig. 31.14). (62,63). Demonstration of this phase re versal is critical for accurate localization of the rolandic fissure, and if the surgical exposure does not permit placement of sufficient cortical electrodes, comparison of cor tical SEPs with those recorded simultaneousl y from scalp electrodes may be helpful (62).

The precentral cor tex can also be identif ied through the use of direct electrical stimulation with 50-Hz trains and obser ving target muscles for movement. However, electrical cor tical stimulation ma y be dif ficult in young children, whose motor cortices are difficult to stimulate electrically (37,62,87).

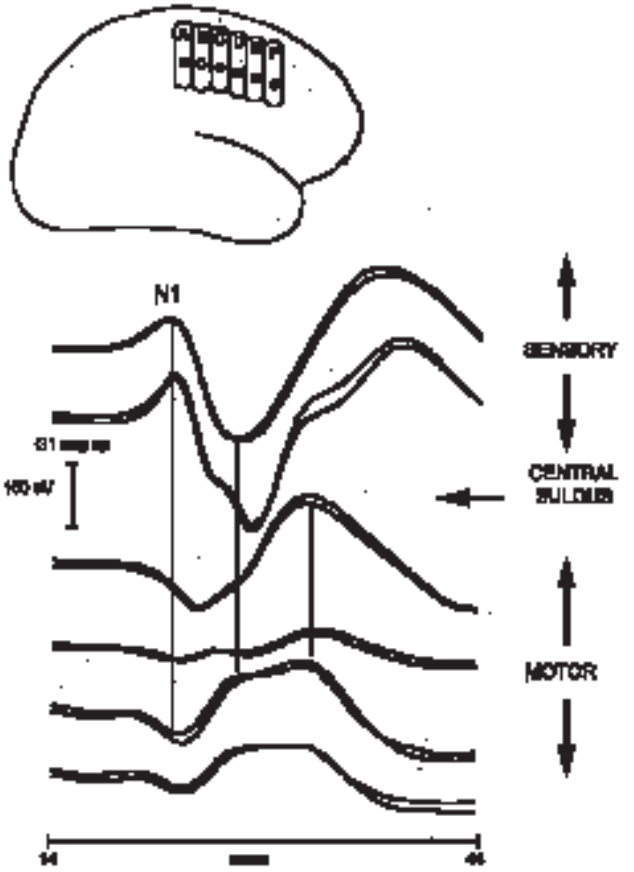


FIG. 31.14. The primary cortical response to median nerve stimulation (labeled N1) demonstrates a characteristic phase reversal when recorded from electrodes on their side of the central sulcus. (From Lueders H, Lesser RP, Hahn J, et al. Cortical somatosensory evoked potentials in response to hand stimulation. *J Neurosurg* 1983;58:885–894.)

DETECTION OF CEREBRAL ISCHEMIA

The rationale for using EEG and EP recording techniques to monitor patients at risk for cerebral ischemia is based on the obser vation that neuronal activity is measurab ly altered before cellular inte grity is lost (7). Under normal conditions, global cerebral b lood flow is approximately 50

mL per 100 g of brain tissue per minute, and oxygen consumption is in the range of 3 to 3.5 mL per 100 g of brain tissue per minute (117). Although influenced by anesthetic drugs and brain temperature, ischemic EEG changes generally occur at a cerebral blood flow of 20 mL per 100 g of brain tissue per minute, and isoelectric EEG changes occur at a cerebral blood flow below 12 mL per 100 g of brain tissue per minute. In the absence of cerebral protective agents, further decline in cerebral blood flow may result in loss of cellular integrity and in permanent neuronal injury (117).

Electroencephalographic Monitoring

Ischemic EEG changes typically consist of a progressive loss of fast frequency activity and an increase in slow frequency activity, followed by loss of amplitude, ultimately leading to electrical silence. In patients undergoing carotid endarterectomy, intraoperative EEG changes are correlated both with changes in regional cerebral blood flow, as measured by intracarotid xenon 133 injection (117), and with postoperative neurological deficits (16,102,117). Nonetheless, the ultimate clinical utility of EEG during carotid surgery has been debated (100). Although selective arterial shunting on the basis of EEG evidence of cerebral ischemia during carotid cross-clamping, rather than universal placement of a temporary shunt, is an inherently attractive notion, there is no conclusive evidence that selective shunting improves outcome after carotid surgery. This may, at least in part, be explained by the relatively low overall incidence of stroke after carotid surgery, along with the observation that cerebral embolism, rather than global ischemia, is the most common cause of cerebral injury after carotid endarterectomy.

In order to facilitate EEG monitoring, techniques have been developed to simplify and condense EEG data. Most commonly, the fast Fourier transform is used to convert EEG to the frequency domain, and methods of display such as the compressed spectral array (CSA) are used to depict the amplitude or power of the EEG in various frequency ranges. Although CSA can function as a useful graphic summary of the EEG background, the CSA or other forms of spectral analysis alone cannot enable the clinician to reliably distinguish between real EEG changes and artifacts from sources such as skeletal muscle activity, cardiac electrical activity, and external electrical devices (85) (Fig. 31.15). For this reason, the American Clinical Neurophysiology Society has indicated that the clinical application of quantitative EEG techniques such as CSA should be "considered to be limited and adjunctive" (5).

Successful intraoperative use of EEG to warn of cerebral ischemia requires that ischemic related alterations in the EEG be distinguished from potentially similar changes resulting from other causes, including effects of anesthetic drugs, surgical stimulation, and changes in temperature and carbon dioxide tension, in addition to artifacts. Failure to recognize this leads to overinterpretation. It is likely that data reduction techniques such as CSA, intended to make the EEG "easier" to read, may in fact make this distinction more difficult. For example, although increases in delta power on EEG power spectra were interpreted as "ischemic" patterns and used as the basis the initiation of "therapeutic interventions" during cardiopulmonary bypass (29), similar increase in delta power were commonly observed in a control population of patients undergoing abdominal surgery (3).

Somatosensory Evoked Potential Monitoring

Intraoperative SEP recording has also been used to detect ischemia during cerebrovascular procedures such as carotid endarterectomy (43), clipping of cerebral aneurysms (43,80,108,118), and various neuroradiological procedures (128). Because the generators of the primary cortical $\overline{N20}$ component of the median nerve SEP lie within the territory of the middle cerebral artery, these have been used to monitor cortical function during carotid enterectomy. The SEP that is being monitored must correspond with the cortical territory at risk. For example, whereas median nerve SEPs are appropriate for surgery involving the internal carotid and middle cerebral arteries, they are not appropriate for surgery involving aneurysms of the anterior circulation. In one series, reversible changes occurred of N20 occurred in approximately 10% and irreversible changes in 0.7% of 994 patients undergoing carotid enterectomy (43). The incidence of SEP abnormalities during carotid cross-clamping correlated with the degree of contralateral carotid stenosis, and all patients with irreversible changes had corresponding postoperative deficits (43).

Although SEP and EEG monitoring have been shown to have similar sensitivities and specificities during carotid enterectomy (56), EEG monitoring appears to have the advantages of being somewhat less complicated, providing continuous real-time feedback, and surveying the function of more widespread cortical regions.

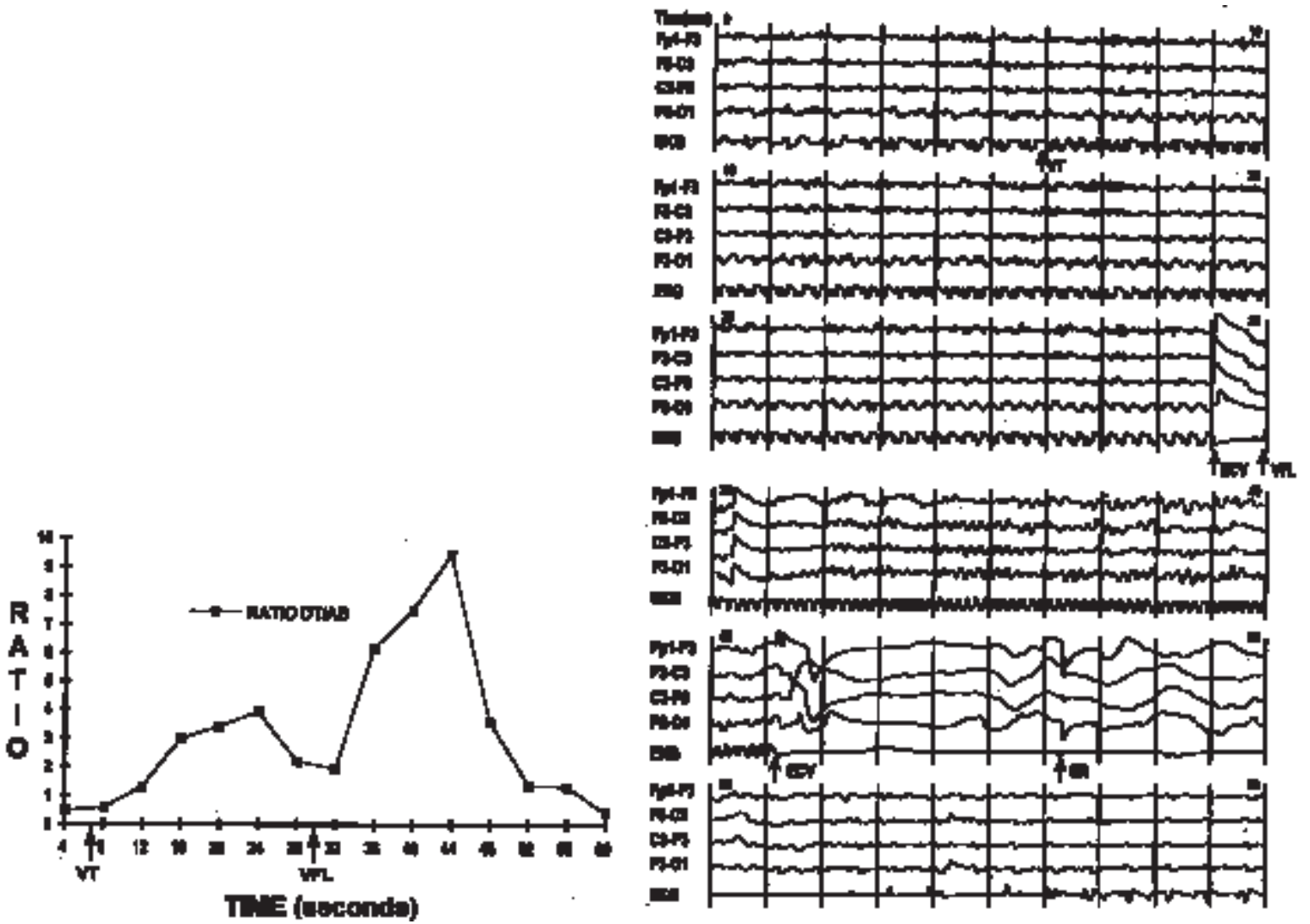


FIG. 31.15. Apparent increase in the delta/theta–to–alpha/beta power ratio during ventricular tachycardia and ventricular flutter **(A).** Careful inspection of the raw electroencephalogram **(B)** reveals that the graph in panel *A* depicts changes in power spectrum of the electrocardiographic artifact. (From Adams DC, Heyer EJ, Emerson RG, et al. The reliability of quantitative electroencephalography as an indicator of cerebral ischemia. *Anesth Analg* 1995;81:80–83.)

MONITORING DEPTH OF ANESTHESIA

The EEG effects of virtually every inhaled and intravenous anesthetic agent have been described (124). Certain measures based on EEG frequency analysis, such as the spectral edge frequency, have been correlated with hemodynamic responses to noxious stimuli during specific anesthetic regimens (104). However, attempts to correlate various EEG parameters over a broad range of anesthetic techniques with clinical measurements of anesthetic depth, such as movement to incision, have not produced uniform results (121). More complex measures, such as the "EEG bispectrum," which incorporates phase relationships of the various frequency components of the EEG along with other EEG descriptors, have been proposed as better measures of anesthetic depth (35,101,109,121).

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