The Neuroscientist

http://nro.sagepub.com

Mesial Temporal Lobe Epilepsy: What Have We Learned?

Jerome Engel, Jr

Neuroscientist 2001; 7; 340

The online version of this article can be found at:
http://nro.sagepub.com/cgi/content/abstract/7/4/340

Published by:

http://www.sagepublications.com

Additional services and information for *The Neuroscientist* can be found at:

Email Alerts: http://nro.sagepub.com/cgi/alerts

Subscriptions: http://nro.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007

© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

Mesial Temporal Lobe Epilepsy: What Have We Learned?

JEROME ENGEL, JR.
UCLA School of Medicine
Los Angeles, California

Mesial temporal lobe epilepsy is the most common form of human epilepsy, and its pathophysiological substrate is usually hippocampal sclerosis, the most common epileptogenic lesion encountered in patients with epilepsy. The disabling seizures associated with mesial temporal lobe epilepsy are typically resistant to antiepileptic drugs but can be abolished in most patients by surgical treatment. Anteromesial temporal resection, therefore, is the most common surgical procedure performed to treat epilepsy, and stereotactically implanted intracerebral electrodes are required in some patients to localize the epileptogenic region. This clinical setting provides a large number of patients for invasive in vivo research with microelectrode and microdialysis techniques and in vitro research following surgical resection on a single epileptic disorder. Consequently, much has now been learned about the fundamental neuronal mechanisms underlying the epileptogenic properties of the human hippocampus in mesial temporal lobe epilepsy. Parallel reiterative studies in patients and animal models of this disorder indicate that enhanced inhibition, in addition to enhanced excitation, underlies the appearance of hypersynchronous neuronal discharges responsible for generating spontaneous seizures. Recent studies have elucidated what may be unique electrophysiological markers of epileptogenicity, which could have valuable diagnostic utility. Although basic research on mesial temporal lobe epilepsy may ultimately suggest novel approaches to treatment and prevention, attention must also be given to maximizing the application of available effective treatments. In particular, the safety and efficacy of surgical therapy has greatly improved in recent years, yet this alternative treatment remains seriously underutilized worldwide. An appropriate increase in referral of patients with this surgically remediable syndrome to epilepsy centers will not only relieve a great many patients of their disabling seizures and reduce the burden of epilepsy but will also provide increased opportunities for invasive research that could ultimately result in even more effective therapies or cures. NEUROSCIENTIST 7(4):340–352, 2001

KEY WORDS *Temporal lobe epilepsy, Basic mechanisms, Surgical treatment*

Epileptic disorders due to localized structural brain lesions are referred to as symptomatic (secondary) localization-related epilepsies (Commission on Classification 1989). The syndrome of mesial temporal lobe epilepsy is the most common, and best-defined, form of symptomatic localization-related epilepsy and is characterized by epileptogenic abnormalities in mesial temporal limbic structures (Engel, Williamson, and others 1997). The associated pathological substrate is usually hippocampal sclerosis (Mathern and others 1997), but other discrete structural lesions can also be found alone or in association with hippocampal sclerosis (dual pathology). A recent study at a large epilepsy center in Paris indicated that half of their patients had a diagnosis of temporal lobe epilepsy and that half of these had evidence of hippocampal sclerosis on magnetic resonance imaging (MRI) (Semah and others 1998). Because MRI is not 100% accurate in identifying hippocampal sclerosis, it is likely that this population included an even greater percentage of patients with this pathological substrate, confirming that mesial temporal lobe epilepsy with hippocampal sclerosis is likely to be the most common form of human epilepsy (Engel 1998a).

In the same study, the authors found that a diagnosis of hippocampal sclerosis was associated with the worst prognosis in their patient population. Whereas 50% to 80% of patients with epilepsy can expect to become seizure free with adequate medical treatment (Hauser and Hesdorffer 1990), only 11% of patients in this series with a diagnosis of hippocampal sclerosis, and only 3% with dual pathology, had been seizure free for the previous year. Consequently, mesial temporal lobe epilepsy also appears to be one of the most medically refractory forms of human epilepsy. On the other hand, mesial temporal lobe epilepsy has, for many years, been the epileptic syndrome most commonly, and most effectively,

Original research reported by the author was supported in part by Grants NS-02808, NS-15654, NS-33310, and GM-24839, from the National Institutes of Health, and Contract DE-AC03-76-SF00012 from the Department of Energy.

Address correspondence to: Jerome Engel, Jr., MD, PhD, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095-1769 (e-mail: engel@ucla.edu).

Copyright © 2001 Sage Publications
ISSN 1073-8584
Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

treated by surgical resection (Engel and Shewmon 1993). Mesial temporal lobe epilepsy, therefore, is the prototype of what are now called surgically remediable syndromes (Engel 1996b). These are disorders with a known pathophysiology and natural history, in which medical intractability can be predicted when first-line pharmacotherapy fails, where 70% to 90% of patients with these disorders can expect to become free of disabling seizures with appropriate surgical treatment. Some evidence suggests that surgical treatment is also able to prevent, or reverse, interictal psychiatric and social disturbances that commonly develop in patients with mesial temporal lobe epilepsy, but only if effective intervention occurs early in the course of the disorder (McLachlan and others 1997; Sperling and others 1996).

Recognition of mesial temporal lobe epilepsy as a surgically remediable syndrome, and the development of noninvasive tests to identify the epileptogenic mesial temporal tissue, has had an important impact on clinical diagnostic and therapeutic approaches to epilepsy. Equally important, however, is that epilepsy surgery programs provide neuroscientists with an opportunity to carry out basic research into the fundamental neuronal mechanisms of epilepsy during the course of invasive presurgical evaluations, and following a resective procedure (Spencer and others 1984), which yields specimens of epileptogenic tissue (Engel 1998b; Schwartzkroin 1993). In the epilepsy surgery setting, structural and functional neuroimaging, in vivo electrophysiological monitoring that permits microelectrode (Fried and others 1999) and microdialysis (During and others 1995; Wilson and others 1996) investigations, and in vitro electrophysiological, biochemical, molecular biological, and microanatomical studies of resected specimens have revealed more about the pathophysiology, at the systems, cellular, and subcellular levels, of mesial temporal lobe epilepsy than of any other human epileptic condition.

Although much of the knowledge gained from basic research on mesial temporal lobe epilepsy can be extrapolated to other forms of epilepsy, an important conclusion from this work is that there are many different fundamental neuronal disturbances underlying different types of epilepsy and that in some ways mesial temporal limbic epilepsy represents a unique pathophysiological process. Furthermore, we now also know that more than one seizure type can occur in the same patient, representing different basic epileptogenic mechanisms, and that individual seizures are composed of a series of events, each reflecting a different pathophysiological process and anatomical substrate (Engel, Dichter, and others 1997). The fact that potential antiepileptic compounds are routinely screened with animal models of generalized tonic-clonic seizures and petit mal absences before entering clinical trials (Meldrum 1997) may explain why mesial temporal lobe epilepsy is so often intractable to currently available antiepileptic drugs. It is reasonable to assume that many pharmaceutical agents that would have been effective treatments for the seizures of mesial temporal lobe epilepsy were discarded over the years because they did not possess anticonvulsive or antiabsence properties. The ability to utilize patients with mesial temporal lobe epilepsy in the epilepsy surgery setting to understand the neurobiological disturbances responsible for epileptogenesis and seizure generation in this condition, therefore, should ultimately result in the development of more specific and more effective therapeutic interventions.

Clinical Features

Mesial temporal lobe epilepsy with hippocampal sclerosis has a characteristic clinical presentation (Table 1) (Engel, Williamson, and others 1997). Patients often have a history of complicated febrile seizures or other initial precipitating injuries, such as head trauma or intracerebral infections, within the first 4 or 5 years of life (Mathern and others 1995), suggesting that brain insults during a critical period of development play a role in initiating epileptogenic hippocampal damage. There is also an increased incidence of family history of epilepsy, perhaps indicative of a genetic predisposition to the characteristic cell loss and neuronal reorganization presumed to be responsible for seizure generation in this condition. Spontaneous afebrile seizures usually begin in childhood with either a complex partial or generalized tonic-clonic ictal event. Typically, these seizures initially respond to antiepileptic drugs, and patients may be seizure free for several years. In the intractable form, however, when seizures recur, usually in adolescence or early adulthood, it then becomes difficult or impossible to bring them under control again with medication. This and the fact that interictal behavioral disturbances, particularly depression, often occur when recurrent disabling seizures persist imply that the underlying neuropathological process is to some extent progressive (Engel 1996a; Engel and Shewmon 1991).

The habitual seizures usually begin with an aura, most commonly a sensation of epigastric rising, although a variety of autonomic and emotional signs and symptoms can occur (Williamson and Engel 1997). Initial elementary motor and sensory signs and symptoms are not a feature of the ictal events, with the exception of olfactory and gustatory auras. Auras invariably occur in isolation, as well as immediately preceding complex partial seizures. This may be a unique feature of hippocampal seizures apparently reflecting seizure-suppressing mechanisms in the hippocampus that are capable of preventing spread of ictal discharge (Lieb and others 1986). The complex partial seizure typically begins with motor arrest and staring, followed by oroalimentary automatisms (e.g., lip-smacking, chewing) and other purposeless movements. Automatisms of the upper limb can be unilateral due to dystonic posturing of the hand and arm contralateral to the site of seizure onset. There can be varying degrees of responsiveness to the environment during the seizure, but postictally there is amnesia for the ictal event, and a

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

Table 1. The syndrome of mesial temporal lobe epilepsy

History
Higher incidence of complicated febrile convulsions or other cerebral insults in the first 5 years of life than in other types of epilepsy.
Family history of epilepsy common.
Onset of habitual seizures usually in latter half of first decade of life.
Auras commonly occur in isolation.
Infrequent secondarily generalized seizures.
Seizures often remit for several years until adolescence or early adulthood.
Seizures often become medically intractable.
Interictal behavioral disturbances can develop, most commonly depression.
Clinical features of seizures
An aura is usually present. The most common is epigastric, often with other autonomic or psychic symptoms, including emotion (e.g., fear). Olfactory or gustatory sensations can occur. Auras usually last several seconds.
Complex partial seizures often begin with arrest and stare; oroalimentary automatisms and complex automatisms are common. Posturing of one arm may occur contralateral to the ictal discharge. The seizure usually lasts 1 to 2 minutes.
The postictal phase usually includes disorientation, recent-memory deficit, amnesia for the event, and dysphasia if seizures begin in the language-dominant hemisphere. This phase lasts several minutes.
Neurologic and laboratory features
Neurologic examination usually normal except for memory deficit.
Unilateral or bilateral independent anterior temporal EEG spikes with maximal amplitude in basal electrodes.
Extracranial ictal EEG activity only with symptoms of complex partial seizure; usually initial or delayed focal rhythmic onset pattern of five to eight per second, maximal amplitude in one basal temporal derivation.
Usually hippocampal atrophy on T_1 and mesial temporal increased signal on T_2-weighted magnetic resonance imaging.
Usually temporal-lobe hypometabolism on interictal positron-emission tomography with fluorodeoxyglucose, often involving ipsilateral portion of the thalamus and basal ganglia.
Usually temporal-lobe hypoperfusion or interictal single photon emission computed tomography and characteristic pattern of hypoperfusion and hypoperfusion on ictal single photon emission computed tomography.
Usually memory dysfunction specific to the involved temporal lobe on neuropsychological testing and amnesia with contralateral intracarotid injection of amobarbital.
Usually decreased n-acetyl aspartate on magnetic resonance spectroscopy.

Adapted from Engel (1993).

period of confusion. Reactive automatisms may also occur during the postictal period.

The laboratory diagnostic hallmark of mesial temporal lobe epilepsy is interictal anterior temporal spike-wave discharges on the EEG, which phase-reverse in basal derivations when recordings are performed with sphenoidal or true temporal electrodes. These may be recorded independently from both mesial temporal areas, even though spontaneous seizures usually are generated from only one side. The typical EEG ictal onset pattern consists of a 5 to 8 Hz rhythmic discharge beginning in one mesial temporal area, either initially or within 30 seconds of a more generalized electrographic change (Risinger and others 1989). Depth electrode recordings, however, reveal that these EEG changes are preceded by long periods of ictal discharges in the mesial temporal structures, often associated with the aura, whereas ictal changes on the EEG are usually not observed until after there is sufficient propagation to produce impairment of consciousness and other observable clinical features of the complex partial seizure. Depth electrode-recorded ictal onsets from the hippocampus are more likely to consist of hypersynchronous discharges than of the buildup of low-voltage fast activity or recruiting rhythm, more commonly seen from the neocortex (Spencer and others 1992; AL Velasco and others 2000) (Fig. 1). Seizures with both types of ictal onset can be seen in individual patients, however. The hypersynchronous discharges are usually restricted to the hippocampus and adjacent structures and either have no clinical correlate or correspond to auras (Fig. 2). Transition to a low-voltage fast ictal pattern appears to be necessary for the propagation that results in motor signs and impairment of consciousness.

Because EEG-recorded interictal and ictal epileptiform abnormalities can be falsely localizing, confirmation of structural or functional disturbances in the electrophysiologically identified epileptogenic mesial temporal area is important when surgical treatment is considered. Confirmation was initially provided by demonstration of material-specific memory and learning disturbances on neuropsychological testing and inability to support memory with contralateral intracarotid amobarbital injection. Today, computerized neuroimaging plays a much more important role (Spencer 1994). Positron emission tomography with fluorodeoxyglucose (FDG-PET) was the first modern neuroimaging tool to offer help in identifying hippocampal sclerosis and other mesial temporal lesions, which appeared as interictal temporal hypometabolism (Engel and others 1982a, 1982b). Hippocampal atrophy on T1-weighted images and mesial temporal signal enhancement on T2-weighted images of structural MRI scans now readily indicate the presence of hippocampal sclerosis in most patients with this condition (Cascino and others 1991; Kuzniecky and Jackson 1995), although FDG-PET appears to remain a more sensitive test for hippocampal

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

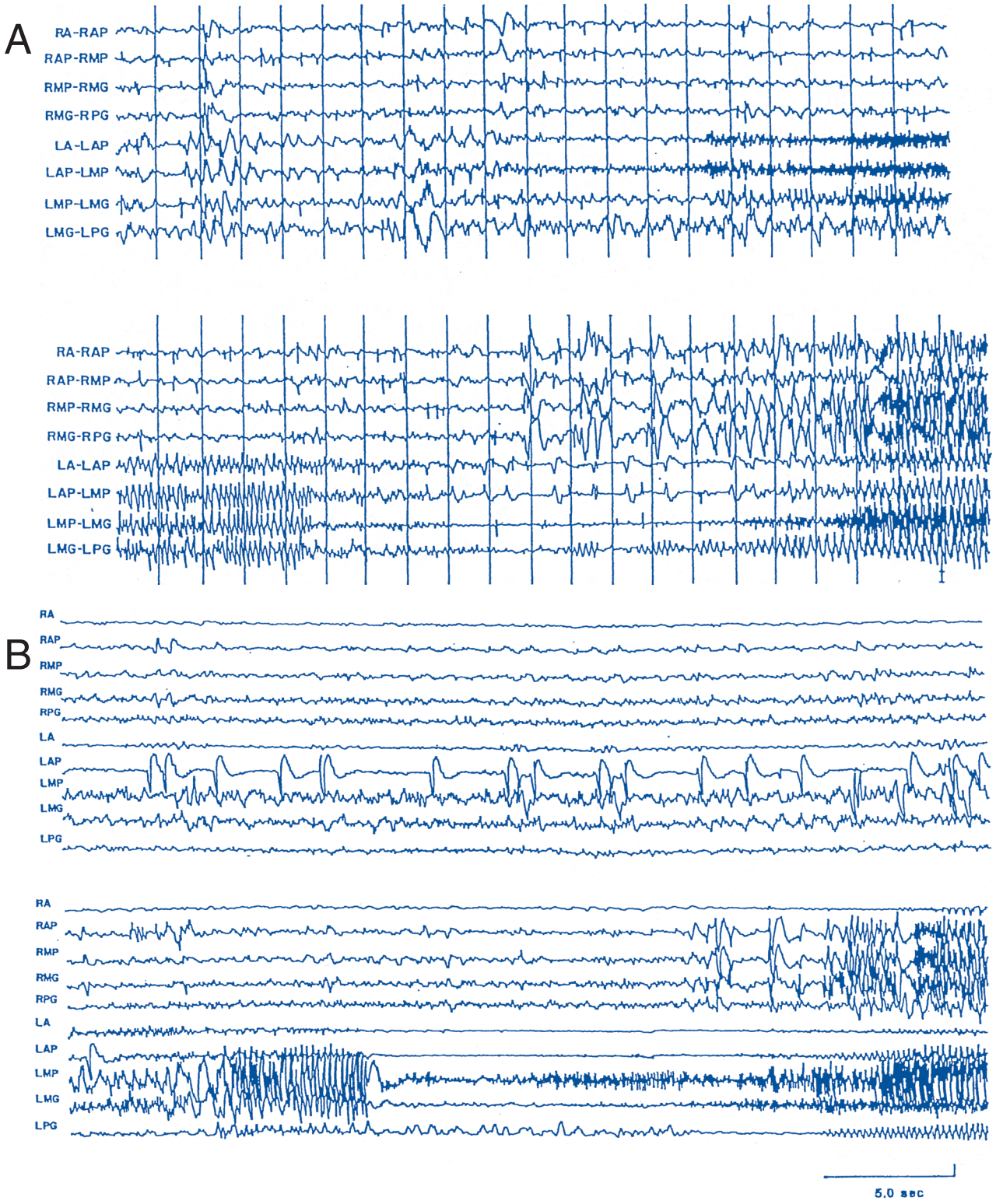

Fig. 1. Examples of depth-recorded mesial temporal ictal onsets. *A*, Low voltage fast seizure onset. Seizure begins with regional decrease in amplitude and increase in frequency of left mesial temporal sites and spreads to the contralateral mesial temporal lobe after 20 sec. Chain montage, with most distal electrode tip of each electrode referred to an adjacent electrode tip. Time calibration between vertical lines = 1.0 sec, amplitude = 200 μV. *B*, Hypersynchronous seizure onset with focal slow spiking, which remained on the left side for 130 sec before spreading to the contralateral mesial temporal lobe. Spread to the other side occurred after development of a high-frequency low-amplitude discharge. An interval of 46 sec was removed between the upper and lower traces. R = right; L = left; A = amygdala; AP = anterior hippocampus; MP = middle hippocampus; MG = middle hippocampus; PG = posterior hippocampus. Calibrations: time 5.0 sec; amplitude 400 μV. From AL Velasco and others (2000), with permission.

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

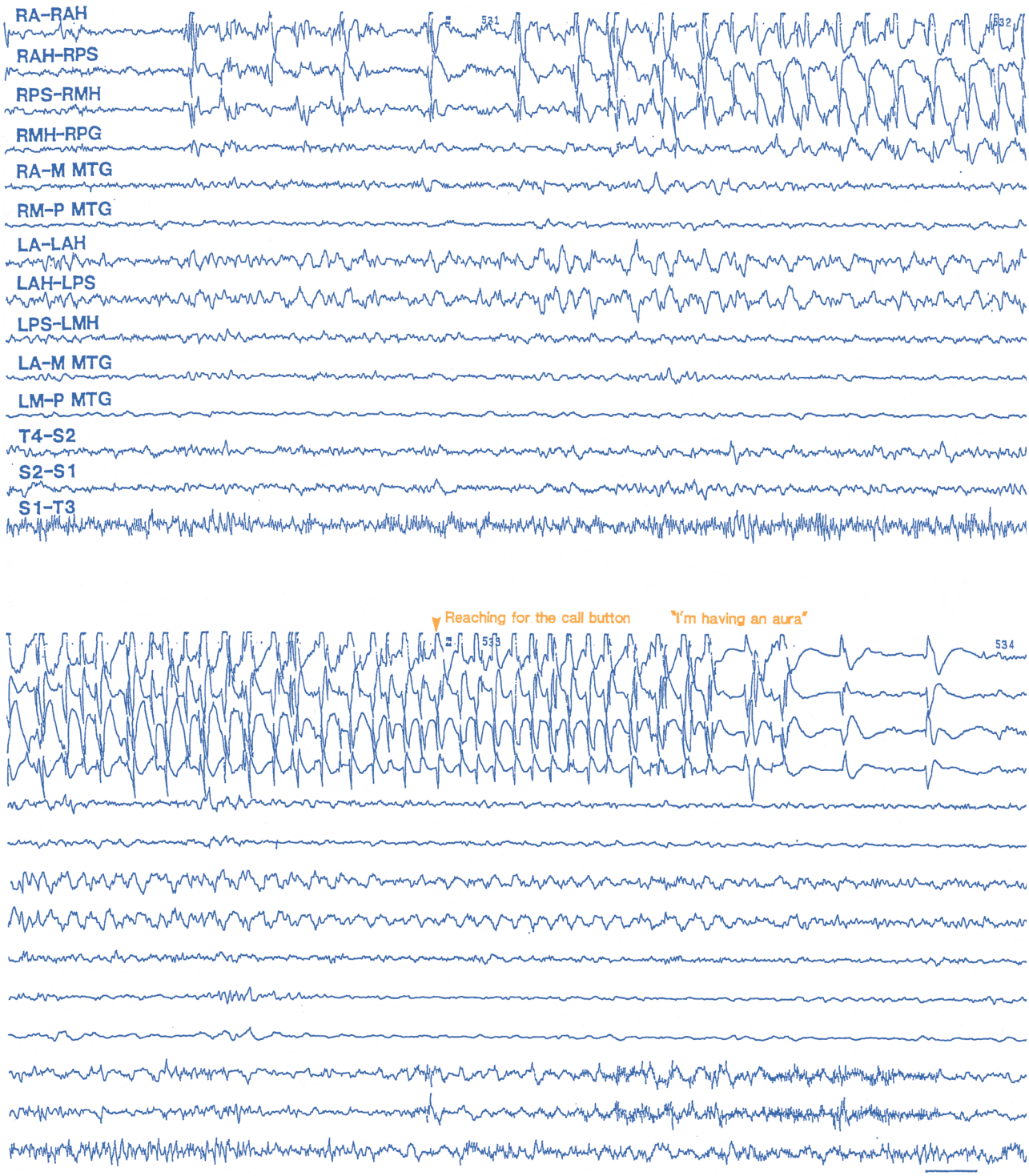

Fig. 2. Forty continuous seconds of an EEG recorded from depth, sphenoidal, and scalp electrodes during a simple partial seizure of the right temporal lobe. Ictal onset consists of an increase in interictal spike discharges, maximal at the right anterior hippocampal electrode (left portion of the upper panel). After 8 to 9 sec, these spikes become regular, eventually developing into a 3-Hz spike-and-wave pattern involving all derivations from the right mesial temporal lobe. Note that no low-voltage fast activity is seen, either initially or at any part of the ictal episode. The patient reached for the call button at the arrow, at which point regular slow activity is also seen in the left anterior hippocampus and in the right sphenoidal electrode. The patient then indicated an aura consisting of a sensation of fear in her stomach. Depth electrode locations indicated as in Figure 1. Superficial contacts from anterior (A), mid (M), and posterior (P) depth electrodes recorded from cortex of middle temporal gyrus (MTG). Calibration 1 sec. From Engel (1989), with permission.

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

sclerosis (Subramanian and others 2001; Knowlton and others 1997). A typical pattern of temporal hyper- and hypoperfusion with ictal single photon emission computed tomography (Newton and others 1995) and a reduction of N-acetyl aspartate with magnetic resonance spectroscopy (Kuzniecky and Jackson 1995) also aid in identifying nonepileptic disturbances associated with the epileptogenic mesial temporal lobe. Diagnosis of hippocampal sclerosis and other mesial temporal structural lesions can now be so reliably identified with these neuroimaging techniques that they often constitute the primary diagnostic approach for mesial temporal lobe epilepsy, with EEG being relegated to a confirmatory role. EEG remains necessary, however, to demonstrate that any imaging-identified structural or functional disturbance is epileptogenic.

Historical Perspectives

A hardening of the hippocampus in some patients with epilepsy and odd behavior was first noted in 1829 (Bouchet and Cazauvieilh 1825), and the classical microanatomical features of hippocampal sclerosis were described by the end of the nineteenth century (Bratz 1899; Sommer 1880). It was about this time when Hughlings Jackson (1898) concluded that epilepsy consisted of more than generalized tonic-clonic convulsions and that seizures characterized by a "dreamy state" were associated with a gross lesion in the mesial temporal area. With the advent of EEG, it eventually became clear that psychomotor seizures originated in the mesial temporal lobe (Jasper 1941), but hippocampal sclerosis was thought to be a result, rather than a cause, of chronic epilepsy. The EEG also made it possible to localize temporal lobe epileptogenic abnormalities for surgical resection (Bailey and Gibbs 1951), which in turn provided opportunities to elucidate the role of hippocampal sclerosis. Although many patients with this disorder had a history of complicated febrile convulsions, supporting a conclusion that hippocampal sclerosis is the result of epileptic seizures, it also became apparent that patients usually became seizure free following removal of this lesion, suggesting that it might also be the cause of epilepsy (Falconer 1971).

Hypotheses regarding the epileptogenicity of hippocampal sclerosis were pursued in epilepsy surgery programs, and in-vivo research became possible not only intraoperatively but also chronically with the common use of stereotactically implanted depth electrodes to better localize the epileptogenic region (Talairach and others 1974). Paul Crandall was the first to carry out long-term depth electrode recordings of spontaneous seizures (Crandall and others 1963), in association with EEG telemetry monitoring (Dymond and others 1971), and to combine this with a standardized presurgical electrophysiological protocol and detailed investigations of mesial temporal structures that were removed en bloc. As a result of a virtual worldwide explosion in recent years in the number of programs offering surgical treatment for epilepsy, and widespread adaptation of this research strategy, mesial temporal lobe epilepsy has, for many years, been the most studied form of human epilepsy.

Research into Fundamental Neuronal Mechanisms

For many years, invasive research on basic mechanisms of epilepsy was limited to experimental animal models. Studies carried out largely in the neocortical experimental penicillin focus revealed that the interictal EEG spike reflected summated paroxysmal depolarization shifts (PDS) of neuronal membranes that generated abnormal bursts of action potentials, whereas the aftercoming slow wave corresponded to membrane afterhyperpolarization (AH) (Matsumoto and Ajmone-Marsan 1964a). The PDS appears to be due to calcium currents, which depolarize the axon hillock, resulting in generation of rapidly recurring sodium spikes, characterizing the epileptogenic bursting neuron. The mechanisms that terminate this excitatory event and produce the following inhibitory hyperpolarization in part involve calcium-dependent potassium currents and in part enhanced excitation of GABAergic inhibitory interneurons. The interictal spike-wave complex, therefore, represents increased inhibition, as well as increased excitation (Engel, Dichter, and others 1997). In this animal model, transition to ictus is associated with replacement of the presumably protective AH with a prolonged afterdepolarization, which greatly lengthens the spike burst duration (Matsumoto and Ajmone-Marsan 1964b). During this time, additional neurons are recruited into the ictal process with local spread and long-tract propagation that ultimately results in a behavioral seizure. The EEG correlate of this process is a buildup of low-voltage fast activity referred to as a recruiting rhythm. Such disinhibitory ictal onsets are characteristic of generalized tonic-clonic convulsions, and it was presumed from these experiments that the fundamental neuronal mechanisms underlying generalized convulsions and focal seizures differed only in the spatial extent of the initial disinhibitory events.

Although it was a prevalently held belief, for many years, that increased excitation and/or decreased inhibition were common to all forms of epileptic seizure generation, it was recognized that at least one seizure type, the typical absence associated with petit mal epilepsy, is associated with a rhythmic three-per-second EEG spike-and-wave discharge that cannot be reconciled with the disinhibitory type of recruiting rhythm observed with other ictal events. Furthermore, absence seizures respond to a different class of antiepileptic medication and can actually be exacerbated by drugs used to treat generalized tonic-clonic seizures. Studies using an experimental animal model of petit mal epilepsy, produced by intramuscular injection of high doses of penicillin in the cat, revealed that the slow waves of the rhythmic spike-and-wave discharges, like the slow waves of the interictal spike-and-wave, reflect GABA-mediated inhibition (Giaretta and others 1987). Consequently,

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

absence seizures represent abnormal neuronal hypersynchrony; rather than involving disinhibitory mechanisms, these phenomena require enhanced inhibition, along with enhanced excitation. Subsequent investigations have revealed that this hypersynchrony is mediated by rhythmic discharges of GABAergic inhibitory neurons in the reticular nucleus of the thalamus and that these pacemaking events depend on low-threshold calcium channels that rhythmically open during sustained hyperpolarization (Coulter and others 1989). Antiabsence medications appear to work by selectively blocking these channels, whereas drugs that enhance inhibition may exacerbate absence seizures.

An anonymous investigator once stated that the best model of a cat is a cat, and preferably the same cat. Invasive studies of human epilepsy, therefore, should ideally be carried out in patients with epilepsy rather than in experimental animal models. As already noted, invasive in vivo and in vitro basic research on patients with epilepsy is most easily accomplished in the setting of an epilepsy surgery program, and the most readily available human subjects for such investigations have mesial temporal lobe epilepsy. Detailed electrophysiological and morphological studies in this condition have failed to demonstrate evidence for a loss of inhibition, and indeed inhibition is actually enhanced, interictally, in the human epileptic hippocampus (Engel 1996c; Engel and Wilson 1986). The threshold for stimulation-induced afterdischarge is increased in the hippocampus responsible for generating spontaneous seizures (Cherlow and others 1977), and paired-pulse suppression, rather than paired-pulse facilitation, occurs with perforant path stimulation on this side (Wilson and others 1998). On examination of the resected hippocampal specimen, inhibitory terminals are not only present but also increased on surviving principal neurons, and GABAergic interneurons appear to be selectively preserved (Babb 1992). Single-cell recordings reveal a higher degree of neuronal synchrony in the epileptogenic hippocampus compared with the contralateral side, and this synchrony occurs predominantly among cells that demonstrate prolonged poststimulus inhibition (Isokawa-Akesson and others 1989).

Evidence for enhanced excitation also exists in mesial temporal lobe epilepsy. Microanatomical and immunocytochemical investigations of resected hippocampus reveal that hippocampal sclerosis is characterized by selective loss of somatostatin and neuropeptide Y containing inhibitory neurons in the dentate hilus (DeLanerolle and others 1992) and aberrant sprouting of dentate granule cell axons, or mossy fibers, which project back into the region of their proximal dendrites (Sutula and others 1989). Although the recurrent mossy fibers could conceivably produce powerful monosynaptic excitatory feedback circuits, they could also synapse with inhibitory innerneurons in this region, which would enhance inhibition (Nusser and others 1998). The role of mossy fiber sprouting in hippocampal epileptogenesis is controversial in view of the fact that experimental interventions in animals that prevent sprouting do not impair the acquisition of epileptic properties (Longo and Mello 1997). In vitro intracellular recordings from sclerotic hippocampal slices reveal abnormal afterdepolarizations that generate multiple action potentials in dentate granule cells exhibiting pathologic changes in dentate morphology, suggesting that these neurons are hyperexcitable (Isokawa and others 1997). However, in acutely dissociated cell preparations from the sclerotic hippocampus, there is loss of calbindin associated with reduced excitatory calcium currents (Nägerl and others 2000). Whereas a characteristic of the acute experimental epileptogenic lesions in animals is a high percentage of neurons that abnormally burst in synchrony, in vivo microelectrode recordings from epileptogenic hippocampi in patients indicate that bursting neurons, although present, are only rarely encountered, and synchrony among them is difficult to demonstrate (Colder and others 1996a, 1996b).

Although the demonstration of increased interictal inhibition in patients with mesial temporal lobe epilepsy could be interpreted to reflect a homeostatic mechanism that maintains the interictal state, the role of inhibition in promoting synchrony, and its association with other abnormalities that enhance excitation, suggests that these disturbances contribute to abnormal hypersynchrony, which could then be a mechanism for ictal generation (Engel, Dichter, and others 1997). Indeed, as noted previously, depth electrode studies of ictal onsets in patients with mesial temporal lobe epilepsy reveal that the initial pattern in the hippocampus is more likely to be a hypersynchronous one, similar to the spike-wave discharges of petit mal absences, than the focal disinhibitory recruiting rhythm observed in the neocortical penicillin focus (AL Velasco and others 2000). Therefore, at least two mechanisms for initiating focal seizures in mesial temporal lobe epilepsy exist, often in the same patient. One appears to be more common in the hippocampus itself and is characterized by hypersynchronous discharges, presumably involving enhanced inhibition as well as enhanced excitation. The other gives rise to a recruiting rhythm, which is more often associated with onsets outside the hippocampus proper, and most likely reflects a loss of protective inhibition. Current research is now focusing on the possibility that enhanced inhibition, as well as enhanced excitation, particularly in the entorhinal cortex-dentate circuit, is responsible for the onset of hypersynchronous discharges (Bragin and others 2000; Engel and others 2001). These hypersynchronous discharges characteristically do not propagate, perhaps as a result of inhibitory mechanisms involving the dentate hilus, referred to as the dentate gate (Lothman and others 1991), and they either have no behavioral correlate or are associated with auras. Breakdown of the dentate gate may be reflected by transition to a disinhibitory low-voltage fast ictal discharge, which usually precedes propagation out of the mesial temporal structures, producing the clinical manifestations of complex partial seizures.

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

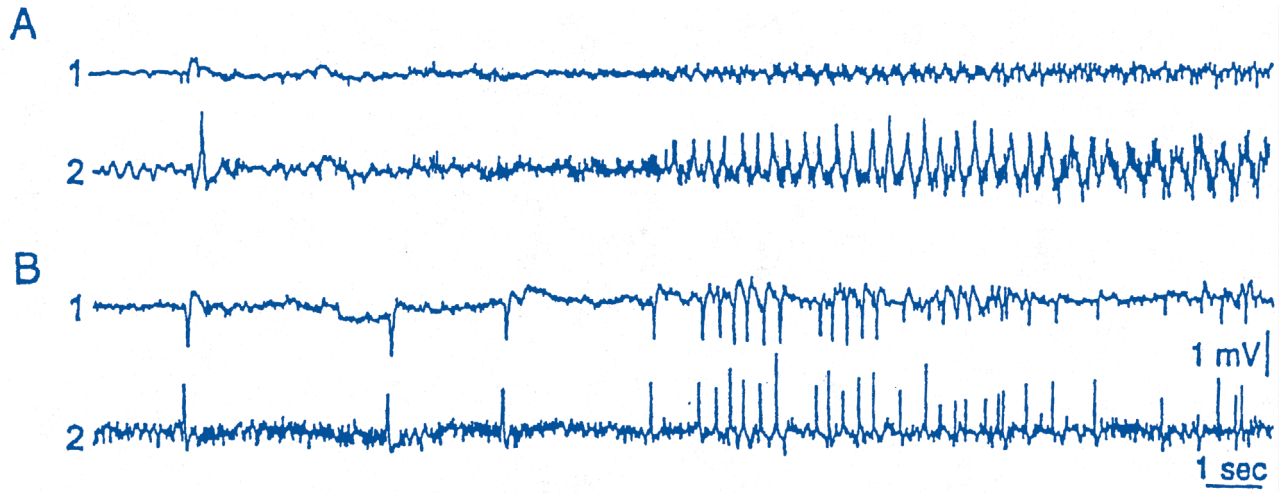

Fig. 3. Examples of two different types of seizure onsets in KA-treated rats with recurrent spontaneous seizures. *A*, low-voltage fast onset. *B*, Hypersynchronous onset. *1* indicates records from hippocampus and *2* indicates records from entorhinal cortex. From Engel and others (2001), with permission.

Patients with mesial temporal lobe epilepsy who are candidates for surgical treatment are already in an advanced stage of the disorder, which limits the scope of research that can be carried out in an epilepsy surgery setting. For instance, the development of the epileptogenic process, the progressive nature of epilepsy, and the pursuit of questions that would require unethical or highly expensive procedures are not possible. Consequently, parallel reiterative research involving appropriate animal models remains an essential part of any research strategy aimed at understanding basic mechanisms of this clinical disorder. One animal model of mesial temporal lobe epilepsy with hippocampal sclerosis is produced by intrahippocampal injection of kainic acid, which causes unilateral neuronal loss and reorganization similar to that encountered with hippocampal sclerosis, as well as spontaneous seizures that originate in limbic structures (Mathern and others 1993; Bragin and others 1999b, 1999c). Interestingly, as in the human, there are two discrete electrographic ictal onsets that can be recorded from these kainite rats, one consisting of hypersynchronous discharges, which is unassociated with observable behavioral change, and the other that consists of low-voltage fast activity that propagates and produces a typical limbic clinical seizure (Bragin and others 1999c) (Fig. 3). Studies in these animals support the concept that interictal and ictal hypersynchronous epileptiform discharges reflect enhanced excitation and inhibition within the entorhinal cortex-dentate circuit, but a unique interictal epileptiform EEG event was recently observed in the course of wide-band microelectrode recording (Bragin 1999a, 1999b). Very rapid (250–500 Hz) oscillations, termed *fast ripples*, appear on interictal spikes emanating from areas that generate spontaneous seizures, but not on interictal spikes arising from areas that are not capable of generating spontaneous seizures (Fig. 4). Brief runs of slower (30–80 Hz) gamma oscillations also occur interictally as nonspecific epileptiform abnormalities but are associated with fast ripples to create a fast-ripple tail-gamma complex only in areas where spontaneous seizures begin. The fact that fast ripples and tail gamma reflect epileptogenicity, and not merely structural damage associated with the epileptogenic hippocampus, is evidenced by the fact that spikes that make up hypersynchronous ictal onsets are initially associated with fast ripples and eventually fast-ripple tail-gamma complexes in the rat (Fig. 5), whereas low voltage fast ictal onsets in this animal begin with a single spike associated with fast ripples (Bragin and others 1999c) (Fig. 6).

Identical fast ripples and tail-gamma oscillations are seen with wide-band microelectrode recordings from the human mesial temporal lobe, and again occur only on the side that gives rise to habitual ictal onsets (Bragin and others 1999b) (Fig. 4). Whereas normal fast (80–200 Hz) oscillations, or ripples, which are believed to reflect inhibitory activity (Ylinen and others 1995), are unaltered in the epileptic hippocampus (Bragin and others 1999a), fast ripples have a different distribution and relationship to unit activity. These events may reflect field potentials of clusters of synchronously bursting neurons (Bragin and others 2000), which are difficult to detect by single cell recording. Fast ripples, therefore, could be a much more robust way of localizing regions of brain tissue containing the synchronous bursting neurons that characterize epileptogenic tissue.

Future Prospects

The primary objective of investigations into fundamental neuronal mechanisms of mesial temporal lobe epilepsy, using human material where possible and animal

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

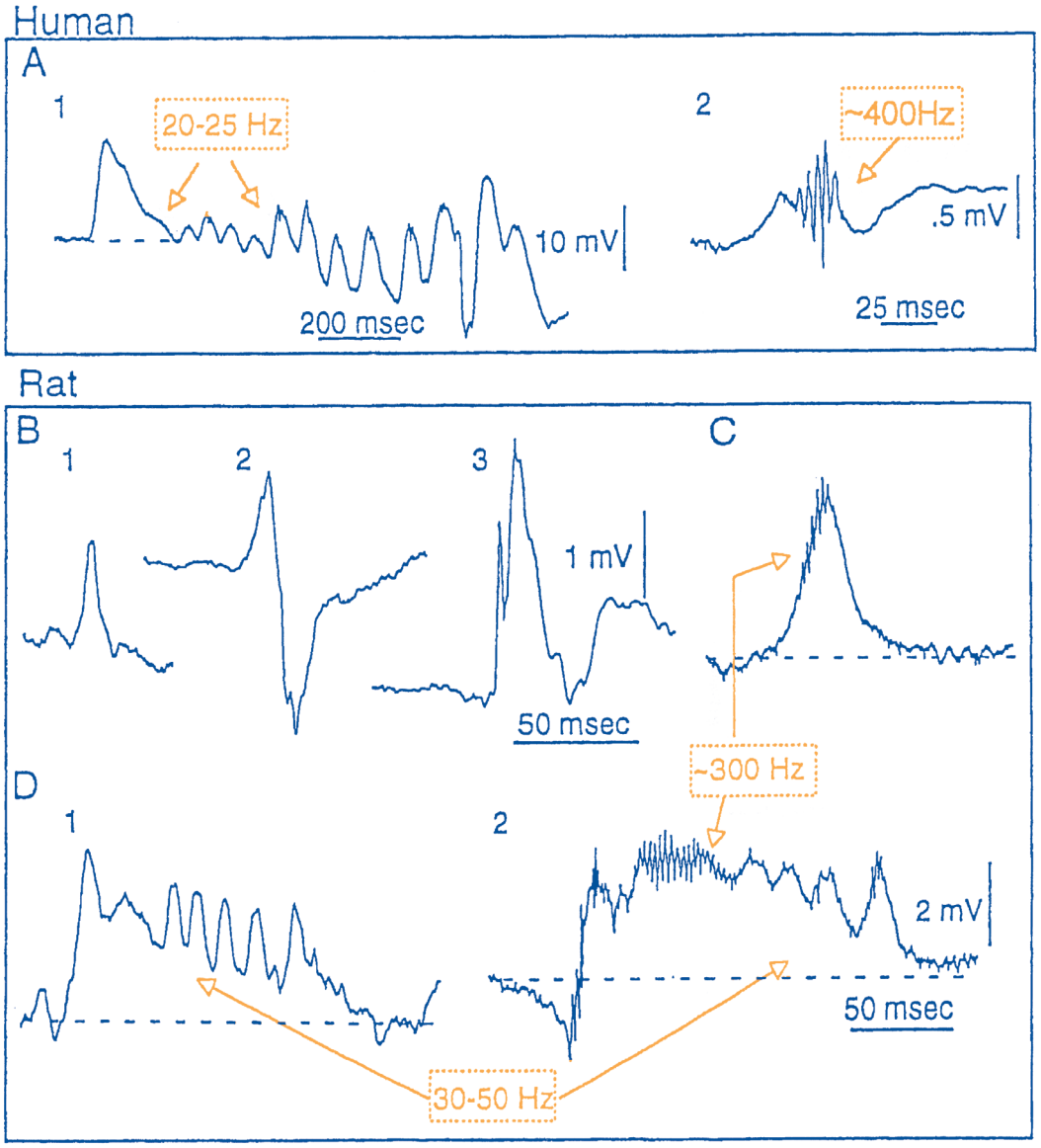

Fig. 4. Examples of interictal events in a patient with mesial temporal lobe epilepsy (*A*) and KA-treated rat (*B–D*). *A1*, Tail gamma oscillation. *A2*, Fast ripple. *B1–3*, Interictal spikes. *C*, Fast ripple. *D1*, Tail gamma. *D2*, Fast-ripple tail-gamma complex. The numbers within dashed boxes show the frequency of oscillations indicated by arrows. Modified from Bragin and others (1999b and 1999c), with permission.

models when necessary, is to devise more rational methods of treatment and prevention. Elucidation of the differences between the pathophysiological basis of epileptogenesis and seizure generation in mesial temporal lobe epilepsy, and those of neocortical and other forms of epilepsy, will help us understand why currently available antiepileptic drugs are often ineffective in this limbic disorder and suggest alternate interventions directed at defects unique to hippocampal epileptogenesis. Perhaps gene chip technology will someday identify which patients are likely to be susceptible to the characteristic cell loss and neuronal reorganization responsible for hippocampal sclerosis, and drugs, or other treatments, can be devised to prevent this process following potentially epileptogenic cerebral insults. Recognizing the importance of enhanced inhibition in the initiation of hypersynchronous ictal onsets should result in emphasis on means of causing desynchronization, rather than decreasing excitation or increasing inhibition, as a strategy to prevent limbic seizure generation. These could be pharmacological or physical, for instance, using implanted or superficial electrodes to predict seizures (Le Van Quyen and others 2001) or identify ictal onset as a trigger for direct brain, or distant, stimulation. There is evidence from one study in patients that electrical stimulation of the hippocampus reduces spontaneous

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

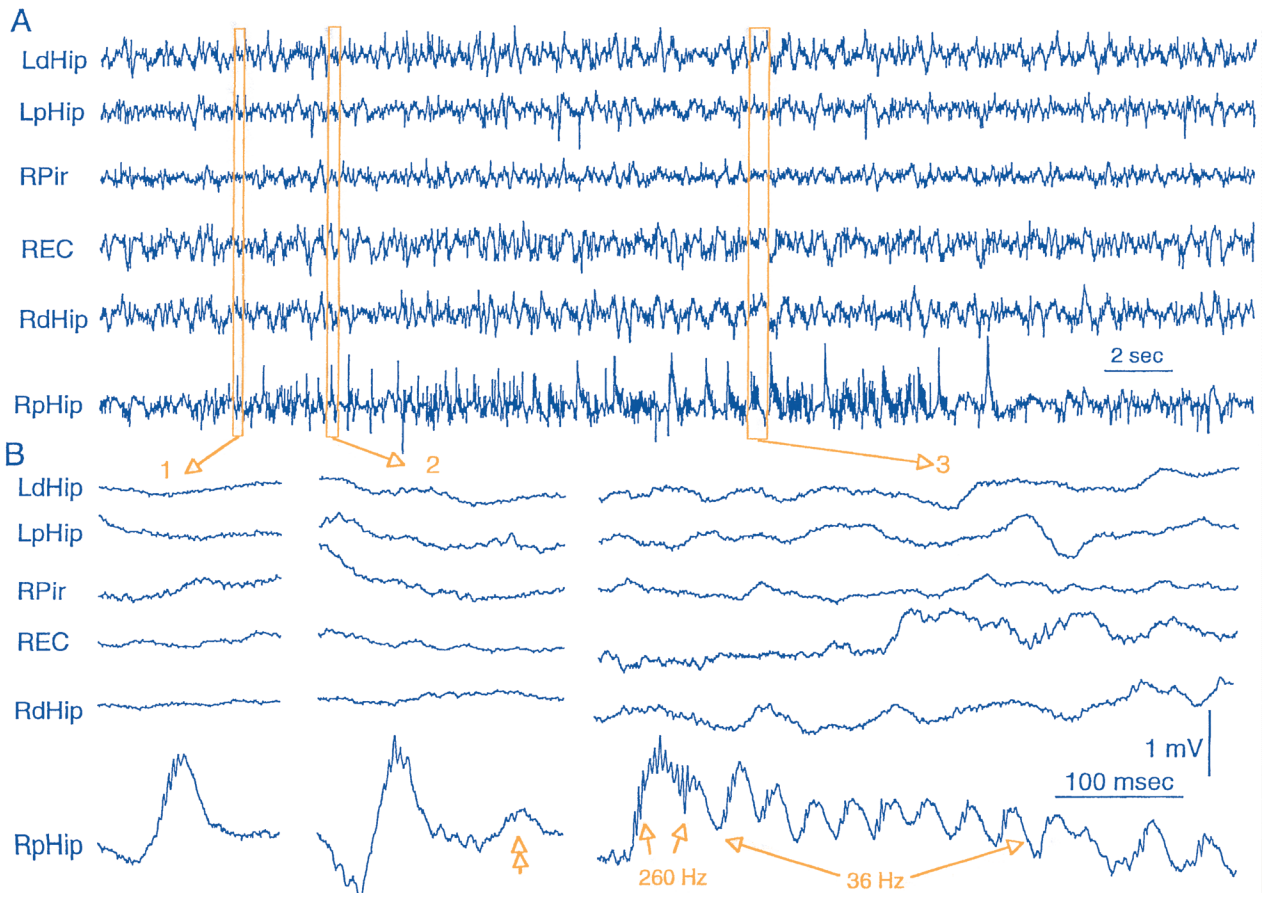

Fig. 5. *A*, Example of a hypersynchronous ictal discharge originating in the lesioned hippocampus of a KA rat. *B*, Expanded parts of the seizure are indicated by dashed boxes. *1*, Fast ripples superimposed on positive waves at the beginning of the seizure. *2*, An additional wave appears during development of the seizure (double arrowhead). *3*, Fast-ripple tail-gamma complex. All are recorded only from right posterior hippocampus. R = right; L = left; d = dorsal; p = posterior; Hip = hippocampus; Pir = piriform cortex; EC = entorhinal cortex. Modified from Bragin and others (1999c), with permission.

seizure occurrence (M Velasco and others 2000), and that hippocampal kindling increases the seizure generation threshold in the kainate rat (Bragin and others 2001).

Elucidating pathophysiological mechanisms, and anatomical substrates, of epileptogenesis in mesial temporal lobe epilepsy will also aid diagnosis. If fast ripples do prove to be a marker of epileptogenicity, then this phenomenon could have significant clinical value for delineating the epileptogenic region for surgical removal. Such a marker, whether it be fast ripples or not, could also be extremely useful for screening the therapeutic effectiveness of specific antiepileptic agents in individual patients without necessitating the current tedious and time-consuming trial-and-error approach, which requires waiting to see whether another seizure will occur. Use of fast ripples for these clinical purposes would be facilitated by diagnostic techniques that permit their identification noninvasively. It is conceivable that magnetoencephalography (Ebersole and others 1995) may ultimately be capable of recording, and localizing, such fast-frequency activity. It is also highly likely that the metabolic correlates of interictal spikes with fast ripples, which presumably reflect a unique neuronal mechanism, will be different from the metabolic correlates of interictal spikes that do not contain fast ripples. If this is the case, then functional imaging techniques, such as functional MRI approaches that subtract acquisition during interictal spikes from acquisition when no interictal spikes occur (Krakow and others 1999), will be able to distinguish between spikes generated in the epileptogenic region and spikes that are propagated or arise from tissue that cannot give rise to spontaneous seizures.

In addition to basic and clinical research aimed at identifying novel pharmacotherapeutic approaches and alternative therapy for mesial temporal lobe epilepsy, future investigations also must consider improving the application of effective therapies that already exist. In particular, surgical treatment for epilepsy is greatly underutilized in the industrialized world and, until recently, considered to be an unattainable luxury in developing countries with limited resources for health care. The treatment gap for surgical therapy of epilepsy, currently the only treatment capable of curing this

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

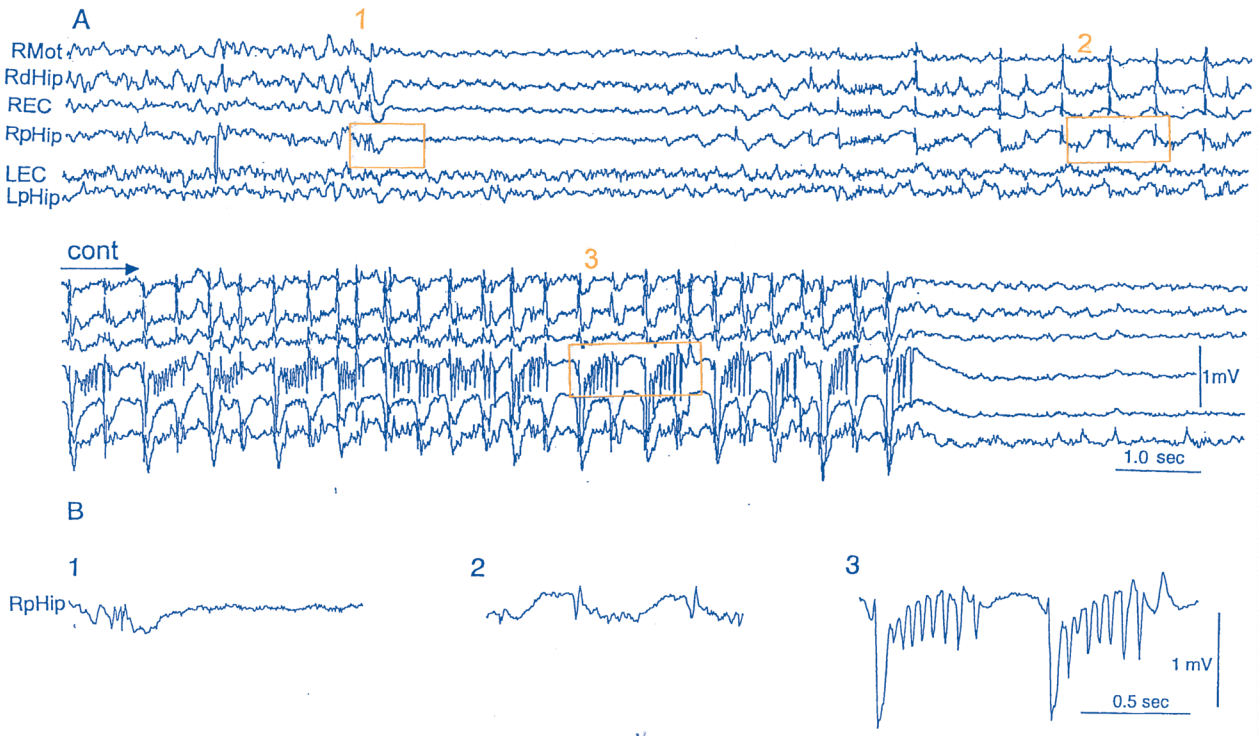

Fig. 6. *A*, Example of a low-voltage fast-ictal onset with initial 5-Hz waves in a KA rat that gradually increase in amplitude, transforming into spike-and-wave and spike-burst patterns. This last pattern is more obvious in RpHip; however, it is also visible in REC, RdHip, and LpHip. *B*, Expanded examples of the seizure onset (*1*) and spike-wave (*2*) and spike-burst (*3*) patterns in the RpHip are indicated by dashed boxes. Note that the seizure onset is a single spike with fast ripples. Abbreviations as in Figure 5. Mot = motor cortex. Modified from Bragin and others (1999c), with permission.

disorder, is huge: perhaps 100,000 to 200,000 people with intractable epilepsy in the United States are potential candidates for surgical treatment, whereas only approximately 2,000 a year actually receive surgery (Engel and Shewmon 1993). Twenty-five to fifty percent of these potential surgical candidates most likely have mesial temporal lobe epilepsy (Semah and others 1998; Engel 1998a), and 80% to 90% of these patients can expect to become free of disabling seizures following appropriate surgical treatment (Engel 1996b). Furthermore, most surgical candidates are currently referred to epilepsy surgery centers too late in the course of their disorder to reverse or prevent psychological and social consequences of disabling seizures that occur during critical periods of adolescence and adulthood, when essential interpersonal and vocational skills are acquired. Because such patients remain dependent on family and society, it has been difficult to demonstrate that surgical treatment is cost-effective.

Early surgical intervention for surgically remediable syndromes such as mesial temporal lobe epilepsy can prevent or reverse disabling behavioral consequences of epilepsy and should be the treatment of choice in these surgically remediable conditions (Engel 1996b). Furthermore, early surgical intervention for intractable epilepsies such as mesial temporal lobe epilepsy, where presurgical evaluation can be performed noninvasively, would be cost-effective even in developing countries that do not have facilities for more sophisticated intracranial investigations. Indeed, in the last few years there has been an increasing effort to establish epilepsy surgery programs in the developing world (Wieser and Silfvenius 2000). The continued reticence of patients and physicians to consider surgical treatment in industrialized countries, like the United States, however, is difficult to understand. To a large extent, this may reflect a failure to educate the medical community about the recent advances in epilepsy surgery that have made it such a safe and effective therapeutic alternative. In particular, it is now essential that referring physicians be disabused of the outdated view of epilepsy surgery as a last-resort alternative treatment for medically refractory epilepsy, and rather view it as the treatment of choice for patients with surgically remediable syndromes such as mesial temporal lobe epilepsy. In fact, the recent introduction of seven new antiepileptic drugs has made the concept of medically refractory epilepsy meaningless, because it could literally take a lifetime to try a patient on all possible drugs alone and in combination.

An important step in promoting early surgical treatment for mesial temporal lobe epilepsy would be to perform a multicenter randomized controlled trial of early surgical intervention for this disorder to determine if it is superior to continued medical treatment when disabling seizures persist after only two or three first-line drugs are appropriately administered. An application to

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

carry out such a trial has been submitted to the National Institutes of Health (Engel 1999). It is hoped that the trial will be approved and funded and that definitive results will significantly improve the quality of life of people with mesial temporal lobe epilepsy by making early surgical intervention the treatment of choice.

References

Babb TL. 1992. GABA neurons, synapses and inhibition in human hippocampal epilepsy. In: Speckmann E-J, Gutnick MJ, editors. Epilepsy and inhibition. München: Urban and Schwarzenberg. p 375–97.

Bailey P, Gibbs FA. 1951. The surgical treatment of psychomotor epilepsy. J Am Med Assoc 145:365–70.

Bouchet C, Cazauvieilh JB. 1825. De l'epilepsie consideree dans ses rapports avec l'alienation mentale. Arch Gen Med 9:510–42.

Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsáki G. 1999a. High frequency oscillations in human brain. Hippocampus 9:137–42.

Bragin A, Engel J Jr, Wilson CL, Fried I, Mathern GW. 1999b. Hippocampal and entorhinal cortex high frequency oscillations (100-500 Hz) in kainic acid-treated rats with chronic seizures and human epileptic brain. Epilepsia 40:127–37.

Bragin A, Engel J Jr, Wilson CL, Vizentin E, Mathern GW. 1999c. Electrophysiologic analysis of a chronic seizure model after unilateral hippocampal KA injection. Epilepsia 40:1210–21.

Bragin A, Wilson CL, Engel J Jr. 2000. Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: a hypothesis. Epilepsia 41(Suppl 6):S144–52.

Bragin A, Wilson CL, Engel J Jr. 2001. Consequences of kindling on epileptic excitability in kainate-treated rats. Submitted.

Bratz E. 1899. Ammonshornbefunde der epileptischen. Arch Psychiatr Nervenkr 31:820–36.

Cascino GD, Jack CR Jr, Parisi JE, Sharbrough FW, Hirschorn KA, Meyer FB, and others. 1991. Magnetic resonance imaging-based volume studies in temporal lobe epilepsy: pathological considerations. Ann Neurol 30:31–6.

Cherlow DG, Dymond AM, Crandall PH, Walter RD, Serafetinides EA. 1977. Evoked response and after-discharge thresholds to electrical stimulation in temporal lobe epileptics. Arch Neurol 34:527–31.

Colder BW, Frysinger RC, Wilson CL, Harper RM, Engel J Jr. 1996a. Decreased neuronal burst discharge near site of seizure onset in epileptic human temporal lobes. Epilepsia 37:113–21.

Colder BW, Wilson CL, Frysinger RC, Chao LC, Harper RM, Engel J Jr. 1996b. Neuronal synchrony in relation to burst discharge in epileptic human temporal lobes. J Neurophysiol 75:2496–508.

Commission on Classification and Terminology of the International League Against Epilepsy. 1989. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 30:389–99.

Coulter DA, Huguenard JR, Prince DA. 1989. Specific petit mal anticonvulsants reduce calcium currents in thalamic neurons. Neurosci Lett 98:74–8.

Crandall PH, Walter RD, Rand RW. 1963. Clinical applications of studies on stereotactically implanted electrodes in temporal lobe epilepsy. J Neurosurg 20:827–40.

DeLanerolle NC, Brines ML, Kim JH, Williamson A, Philips MF, Spencer DD. 1992. Neurochemical remodeling of the hippocampus in human temporal lobe epilepsy. In: Engel J Jr, Wasterlain C, Cavalheiro EA, Heinemann U, Avanzini G, editors. Molecular neurobiology of epilepsy (Epilepsy Res Suppl 9). Amsterdam: Elsevier. p 205–20.

During MJ, Ryder KM, Spencer DD. 1995. Hippocampal GABA transporter function in temporal-lobe epilepsy. Nature 376:174–7.

Dymond AM, Sweizig JR, Crandall PH, Hanley J. 1971. Clinical application of an EEG radio telemetry system. Proc Rocky Mountain Bioengineering Symp. p 16–20.

Ebersole JS, Eliashiv SD, Smith JR, Squires KC. 1995. Applications of magnetic source imaging in evaluation of candidates for epilepsy surgery. Neuroimaging Clin N Am 5:1–22.

Engel J Jr. 1989. Seizures and epilepsy. Philadelphia: F.A. Davis.

Engel J Jr. 1993. Update on surgical treatment of the epilepsies. Neurology 43:1612–17.

Engel J Jr. 1996a. Clinical evidence for the progressive nature of epilepsy. Epilepsy Res (Suppl 12):9–20.

Engel J Jr. 1996b. Current concepts: surgery for seizures. N Engl J Med 334:647–52.

Engel J Jr. 1996c. Excitation and inhibition in epilepsy. Can J Neurol Sci 23:167–74.

Engel J Jr. 1998a. Etiology as a risk factor for medically refractory epilepsy: a case for early surgical intervention. Neurology 51:1243–44.

Engel J Jr. 1998b. Research on the human brain in an epilepsy surgery setting. Epilepsy Res 32:1–11.

Engel J Jr. 1999. The timing of surgical intervention for mesial temporal lobe epilepsy: a plan for a randomized clinical trial. Arch Neurol 56:1338–41.

Engel J Jr, Brown WJ, Kuhl DE, Phelps ME, Mazziotta JC, Crandall PH. 1982a. Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. Ann Neurol 12:518–28.

Engel J Jr, Dichter M, Schwartzkroin P. 1997. Basic mechanisms of human epilepsy. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven. p 499–512.

Engel J Jr, Kuhl DE, Phelps ME, Mazziotta JC. 1982b. Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. Ann Neurol 12:510–17.

Engel J Jr, Shewmon DA. 1991. Impact of the kindling phenomenon on clinical epileptology. In: Morrell F, editor. Kindling and synaptic plasticity. Cambridge, MA: Birkhäuser Boston. p 195–210.

Engel J Jr, Shewmon DA. 1993. Overview: who should be considered a surgical candidate? In: Engel J Jr, editor. Surgical treatment of the epilepsies, 2nd ed. New York: Raven. p 23–34.

Engel J Jr, Williamson PD, Wieser H-G. 1997. Mesial temporal lobe epilepsy. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven. p 2417–2426.

Engel J Jr, Wilson CL. 1986. Evidence for enhanced synaptic inhibition in epilepsy. In: Nisticò G, Morselli PL, Lloyd KG, Fariello RG, Engel J Jr, editors. Neurotransmitters, seizures and epilepsy, III. New York: Raven. p 1–13.

Engel J Jr, Wilson C, Bragin A. 2001. Advances in understanding the process of epileptogenesis based on patient material: what can the patient tell us? Submitted.

Falconer MA. 1971. Genetic and related aetiological factors in temporal lobe epilepsy: a review. Epilepsia 12:13–31.

Fried I, Wilson CL, Maidment NT, Engel J Jr, Behnke E, Fields TA, and others. 1999. Cerebral microdialysis combined with single-neuron and electroencephalographic recording in neurosurgical patients. J Neurosurg 91:697–705.

Giaretta D, Avoli M, Gloor P. 1987. Intracellular recordings in pericruciate neurons during spike and wave discharges of feline generalized penicillin epilepsy. Brain Res 405:68–79.

Hauser WA, Hesdorffer DH. 1990. Epilepsy: frequency, causes and consequences. New York: Demos.

Isokawa M, Levesque M, Fried I, Engel J Jr. 1997. Glutamate currents in morphologically identified human dentate granule cells in temporal lobe epilepsy. J Neurophysiol 77:3355–69.

Isokawa-Akesson M, Wilson CL, Babb TL. 1989. Prolonged inhibition in synchronously firing human hippocampal neurons. Epilepsy Res 3:236–47.

Jackson JH. 1898. Case of epilepsy with tasting movements and "dreaming state"—very small patch of softening in the left uncinate gyrus. Brain 21:580–90.

Jasper HH. 1941. Electroencephalography. In: Penfield W, Erickson TC, editors. Epilepsy and cerebral localization. Springfield, IL: Charles C Thomas. p 380–454.

Knowlton RC, Laxer KD, Ende G, Hawkins RA, Wong STC, Matson GB, and others. 1997. Presurgical multimodality in electroencephalographic lateralized temporal lobe epilepsy. Ann Neurol 42:829–37.

Krakow K, Woermann FG, Symms MR, Allen PJ, Lemieux L, Barker GJ, and others. 1999. EEG-triggered functional MRI of interictal

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.

epileptiform activity in patients with partial seizures. Brain 122:1679–88.
Kuzniecky RI, Jackson GD. 1995. Magnetic resonance in epilepsy. New York: Raven.
Le Van Quyen M, Martinerie J, Navarro V, Boon P, D'Havé M, Adam C, and others. 2001. Anticipation of epileptic seizures from standard EEG recordings. Lancet. 357:160–1.
Lieb JP, Engel J Jr, Babb TL. 1986. Interhemispheric propagation time of human hippocampal seizures: I. Relationship to surgical outcome. Epilepsia 27:286–93.
Longo B, Mello LEAM. 1997. Blockade of pilocarpine- or kainate-induced mossy fiber sprouting by cycloheximide does not prevent subsequent epileptogenesis in rats. Neurosci Lett 226:163–6.
Lothman EW, Bertram EH III, Stringer JL. 1991. Functional anatomy of hippocampal seizures. Prog Neurobiol 37:1–82.
Mathern GW, Babb TL, Armstrong DL. 1997. Hippocampal sclerosis. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven. p 133–55.
Mathern GW, Babb TL, Vickrey BG, Melendez M, Pretorius JK. 1995. The clinical-pathogenic mechanisms of hippocampal neuron loss and surgical outcomes in temporal lobe epilepsy. Brain 118:105–18.
Mathern GW, Cifuentes F, Leite JP, Pretorius JK, Babb TL. 1993. Hippocampal EEG excitability and chronic spontaneous seizures are associated with aberrant synaptic reorganization in the rat kainate model. Electroencephalogr Clin Neurophysiol 87:326–39.
Matsumoto H, Ajmone-Marsan C. 1964a. Cortical cellular phenomena in experimental epilepsy: interictal manifestations. Exp Neurol 9:286–304.
Matsumoto H, Ajmone-Marsan C. 1964b. Cortical cellular phenomena in experimental epilepsy: ictal manifestations. Exp Neurol 9:305–26.
McLachlan RS, Rose KJ, Derry PA, Bonnar C, Blume WT, Girvin JP. 1997. Health-related quality of life and seizure control in temporal lobe epilepsy. Ann Neurol 41:482–9.
Meldrum BS. 1997. Current strategies for designing and identifying new antiepileptic drugs. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven. p 1405–16.
Nägerl UV, Mody I, Jeub M, Lie AA, Elger CE, Beck H. 2000. Surviving granule cells of the sclerotic human hippocampus have reduced Ca^{2+} influx because of a loss of calbindin-D_{28k} in temporal lobe epilepsy. J Neurosci 20:1831–36.
Newton MR, Berkovic SF, Austin MC, Rowe CC, McKay WJ, Bladin PF. 1995. SPECT in the localisation of extratemporal and temporal seizure foci. J Neurol Neurosurg Psychiatry 59:26–30.
Nusser Z, Hájos N, Somogyi P, Mody I. 1998. Increased number of synaptic $GABA_A$ receptors underlies potentiation at hippocampal inhibitory synapses. Nature 395:172–7.
Risinger MW, Engel J Jr, Van Ness PC, Henry TR, Crandall PH. 1989. Ictal localization of temporal lobe seizures with scalp/sphenoidal recordings. Neurology 39:1288–93.
Schwartzkroin PA. 1993. Basic research in the setting of an epilepsy surgery center. In: Engel J Jr, editor. Surgical treatment of the epilepsies, 2nd ed. New York: Raven. p 755–73.
Semah F, Picot M-C, Adam C, Broglin D, Arzimanoglou A, Bazin B, and others. 1998. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 51:1256–62.
Sommer W. 1880. Erkrankung des ammonshorns als aetiologisches moment der epilepsie. Arch Psychiatr Nervenkr 10:631–75.
Spencer DD, Spencer SS, Mattson RH, Williamson PD, Novelly RA. 1984. Access to the posterior medial temporal lobe structure in surgical treatment of temporal lobe epilepsy. Neurosurgery 15:667–71.
Spencer S. 1994. The relative contributions of MRI, SPECT, and PET imaging in epilepsy. Epilepsia 35(Suppl 6):S72–89.
Spencer SS, Guimaraes P, Katz A, Kim J, Spencer D. 1992. Morphological patterns of seizures recorded intracranially. Epilepsia 33:537–45.
Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. 1996. Temporal lobectomy for refractory epilepsy. JAMA 276:470–5.
Subramanian I, Engel J Jr, Mullin P, Dewar S, Curran J, Mathern G, and others. 2001. Noninvasive criteria for surgical treatment of mesial temporal lobe epilepsy, a surgically remediable epileptic syndrome. Submitted.
Sutula T, Cascino G, Cavazos J, Parada I, Ramirez L. 1989. Mossy fiber synaptic reorganization in the epileptic human temporal lobe. Ann Neurol 26:321–30.
Talairach J, Bancaud J, Szikla G, Bonis A, Geier S, Vedrenne C. 1974. Approche nouvelle de la neurochirurgie de l'epilepsie. Méthodologie stéréotaxique et résultats thérapeutiques. Neurochirurgie 20(Suppl 1). p 240.
Velasco AL, Wilson CL, Babb TL, Engel J Jr. 2000. Functional and anatomic correlates of two frequently observed temporal lobe seizure-onset patterns. Neural Plast 7:49–63.
Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, and others. 2000. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41:158–69.
Wieser HG, Silfvenius H, editors. 2000. Epilepsy surgery in developing countries. Epilepsia 41 (Suppl 4). p 50.
Williamson PD, Engel J Jr. 1997. Complex partial seizures. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven. p 557–66.
Wilson CL, Khan SU, Engel J Jr, Isokawa M, Babb TL, Behnke EJ. 1998. Paired pulse suppression and facilitation in human epileptogenic hippocampal formation. Epilepsy Res 31:211–30.
Wilson CL, Maidment NT, Shomer MH, Behnke EJ, Ackerson L, Fried I, and others. 1996. Comparison of seizure related amino acid release in human epileptic hippocampus versus a chronic, kainate rat model of hippocampal epilepsy. Epilepsy Res 26:245–54.
Ylinen A, Bragin A, Nádasdy Z, Jando G, Szabo I, Sik A, and others. 1995. Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. J Neurosci 15:30–46.

Downloaded from http://nro.sagepub.com at UNIV CALIFORNIA SAN DIEGO on March 13, 2007
© 2001 SAGE Publications. All rights reserved. Not for commercial use or unauthorized distribution.