Differential diagnosis and treatment of intractable seizures[1]

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Not all intractable seizures are due to epilepsy, and episodes of uncertain origin call for assessment by appropriate diagnostic methods. Once the disorder is found to be epileptic in nature, seizures can be controlled in many patients. Techniques of diagnosis and treatment are reviewed.

Index terms: Anticonvulsants • Brain mapping • Epilepsy • Seizures

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In recent years, there have been significant advances in the methodologies available for the diagnosis and treatment of seizure disorders. Although the techniques involved are of interest for their theoretical implications, we wish to concentrate on their application to clinical care of patients with intractable seizures.

Diagnosis

If seizures are rare and well controlled with ordinary doses of medication, many of these considerations may not seem relevant. On the other hand, if a patient has had frequent and recurrent seizures, no evidence of an underlying structural lesion, good evidence for adequate anticonvulsant blood levels, and normal routine electroencephalograms (EEGs), the diagnosis should be reassessed before continuing therapy. One consideration should always be syncope (for example, orthostatic hypotension, hyperventilation syndrome, or a vasovagal reaction).[1–5] The EEG

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can help in differentiating syncope from a seizure disorder[6]; for example, one channel can be devoted to recording the electrocardiogram, facilitating evaluation of possible cardiac arrhythmia, which can be especially important if an episode occurs during the EEG.

Once syncope has been considered, the EEG is also the primary tool for evaluation of patients with intractable epileptic or psychogenic seizures. However, it is important that only definite seizure discharges are taken as evidence of epilepsy; nonepileptiform transients such as psychomotor variant,[7] "six-per-second spike-and-wave,"[7] small sharp spikes or benign epileptiform transients of sleep,[7–9] 14- and 6-per-second positive spikes,[7] wicket spikes,[7,10] slow-wave transients of the elderly,[11] temporal-parietal rhythmic discharge of adults,[7,12] hyperventilation responses,[11] and hypnogogic or hypnopompic hypersynchrony[7,11,13,14] are all common in persons with no history of seizures and cannot be considered to support a diagnosis of epilepsy (*Figs. 1–3*). The EEG will often reveal no epileptiform abnormalities on a single record, particularly in patients with infrequent seizures. Since normal variants do not clarify the etiology of intractable seizures, additional monitoring may be needed to arrive at a specific diagnosis.

Sleep: In 1947, Gibbs and Gibbs[15] reported that of 174 patients with grand mal seizures, 19% had seizure discharges while awake and 63% had them while asleep. Subsequent studies showed that sleep was necessary to define an epileptiform abnormality in 226 of 667 cases,[16] 23 of 36 patients,[17] 30 of 89 cases,[18] and 23 of 73 patients.[19] However, Bagchi and Jones[20] found that only 10% of their 150 patients had a normal awake EEG followed by an abnormal sleep record, while Gloor et al[21,22] found that sleep records were necessary in only 5%–6% of patients with temporal lobe epilepsy and therefore did not have to be obtained routinely. This latter

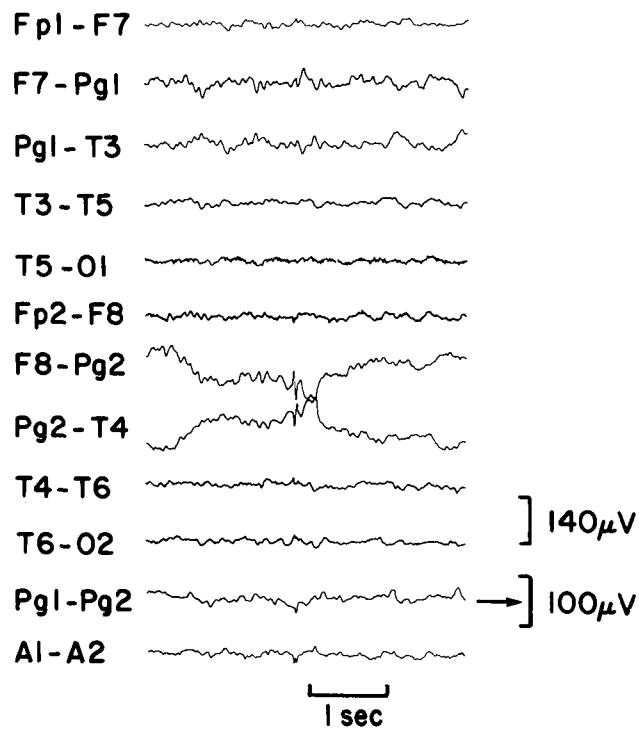


Fig. 2. Benign epileptiform transients of sleep or small sharp spikes in the right temporal region. The transients are of higher amplitude in the scalp-to-nasopharyngeal derivations (F8–Pg2, Pg2–T4) because of the greater interelectrode distances; however, the phase reversals at F8 and T4 indicate that the discharges originate at the scalp. The patient had a history of depression and confusion.

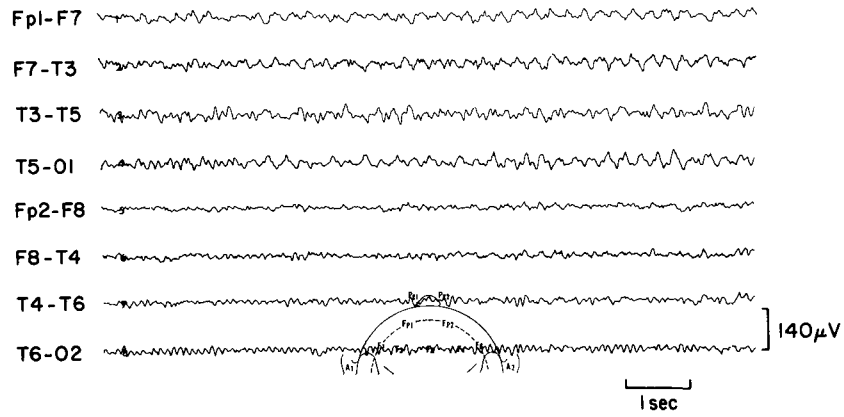


Fig. 1. Rhythmic left temporal psychomotor variant pattern in an adolescent. In addition, the patient had a history of generalized tonic–clonic and absence seizures since the age of 8 years, with 3-Hz spike-and-slow-wave complexes on the EEG.

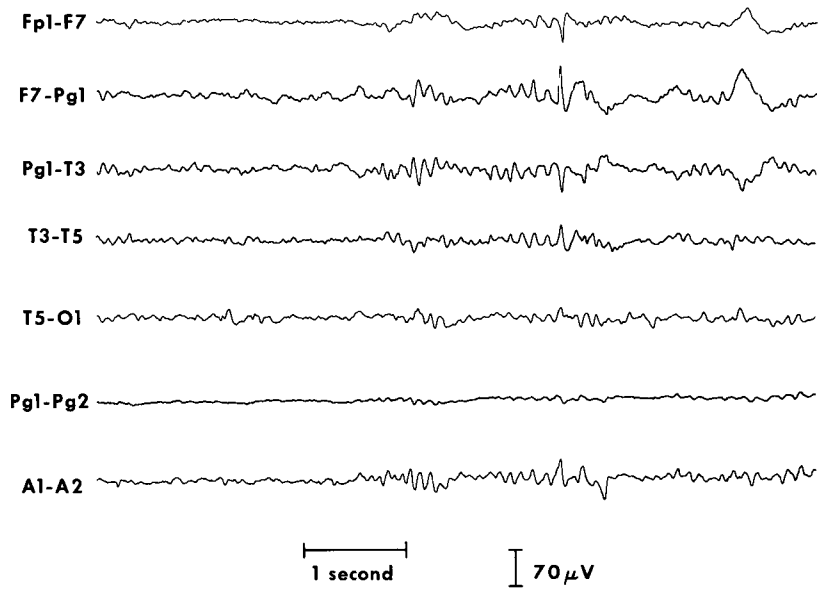


Fig. 3. Wicket spikes in a 71-year-old woman who had experienced fainting spells six months earlier and had not been placed on anticonvulsants. Note run of sharp transients in the left temporal region, one of which is of higher amplitude than the others.

study involved patients referred for epilepsy surgery, who might be expected to have more frequent seizures and thus more frequent epileptiform discharges on the EEG, whether awake or asleep. Nonetheless, the authors agreed that "in patients in whom the waking record remains negative or doubtful . . . especially patients suffering from a high incidence of nocturnal attacks . . . a sleep record is certainly indicated." We have reviewed the records of 30 children with complex partial seizures and focal seizure discharges[23] and found that 8 records showed definite seizure discharges only during sleep while the abnormality was increased in 14 others. Whatever the percentage of patients whose seizure discharges are activated by sleep, its use during the EEG involves little risk to the patient and can be of significant diagnostic benefit.

Sleep deprivation: Sleep deprivation for 24 hours has also been used as a method of activating seizure discharges in patients with normal routine records, and previous reports indicated this technique to be successful in 47 of 114 patients in Pratt's series[24] and 31 out of 42 studied by Scollo-Lavizzari et al.[25] Sleep deprivation increases the diagnostic yield even when the patient does not sleep during the recording; again this involves minimal risk and can be of significant diagnostic help.

Repeated and prolonged recordings: One problem in evaluating the effectiveness of techniques involving a second recording is sampling, i.e., a second record may be abnormal simply because additional recordings have been obtained, with sleep, sleep deprivation, or other techniques being incidental. Pratt et al[24] had 33 patients with normal initial EEGs return for a second routine awake record and found that 6 of these were now abnormal, emphasizing the value of obtaining additional information regardless of the state of consciousness of the patient before or during the recording. Therefore, besides additional recordings, we often obtain a longer trace (anywhere from several hours to several days, depending on the frequency of the seizures) in an attempt to document rare epileptiform activity.

Special electrodes: Gloor et al[21,26] stated that they routinely use nasopharyngeal leads in the evaluation of complex partial seizures, and that accurate localization of the seizure focus was possible only with these leads in 71 out of 177 patients who later underwent a temporal lobectomy; some patients also required sphenoidal leads. Pampiglione and Kerridge[27] found that sphenoidal leads demonstrated seizure discharges in 72 patients with normal or nonspecific scalp recordings. In our laboratory, we always try to use nasopharyngeal electrodes in the diagnosis of intractable seizures. While we have found that it

is very unusual to see epileptiform discharges only at the nasopharyngeal electrode, not infrequently the abnormality is much better defined there or at the sphenoidal lead, helping to clarify the epileptiform nature of discharges which are defined more poorly at the scalp electrodes. In addition, electrodes placed between or below the standard 10–20 placements can be of value. The best known of these electrodes is that described by Silverman,[28] which generally overlies the anterior temporal region in an area relatively distant from the standard placement sites.

Drug withdrawal: Anticonvulsants sometimes "mask" seizure discharges during EEG recordings.[29] Although there is a possibility that drug withdrawal might activate areas which were not previously epileptogenic, Spencer et al[30] found that the results after abrupt withdrawal were consistent with those prior to withdrawal in 25 patients. We often withdraw drugs more gradually, over a period of weeks, but our findings regarding the localizing value of the EEG have been identical. Withdrawal of anticonvulsants is often essential in diagnosing intractable seizures of obscure origin.

Chemical activation: Merlis et al[31] reported that pentylenetetrazol activated seizure discharges in 7 out of 16 patients with psychomotor seizures and nondiagnostic awake recordings. However, only 3 patients had focal discharges, which is important since this drug is well known to produce generalized discharges in persons with no history of seizures.[31] Nevertheless, it may be of help diagnostically in selected cases if it produces focal epileptiform discharges or produces a seizure of focal onset which is typical for that patient. Gloor et al[21] employed pentylenetetrazol in 11 of 163 awake recordings to localize the seizures, suggesting that chemical activation may be of value in patients who are being considered for surgery of focal epilepsy and did not have seizures when other methods of activation were employed. However, other authors have reported discrepancies between the location of chemically induced and spontaneous seizures.[32]

Environmental activation: A variety of environmental factors have been reported to produce seizures in susceptible patients, including a flickering light, touch, visual patterns, musical passages,[33] and video arcade games.[34,35] Under these circumstances, one should test the patient with the specific activating agent during the EEG and reproduce the conditions which normally produce a seizure episode as closely as possible.

Video–EEG monitoring: Simultaneous recordings of clinical seizures and epileptiform EEG changes have been used successfully in a number of centers[36–44] to determine which symptoms occur during seizure episodes. In patients with intractable seizures of uncertain origin, this technique can be crucial in demonstrating that epileptiform EEG changes accompany clinical seizure episodes, since one can define the exact time at which a clinical seizure begins and then precisely correlate it with the EEG. It can also be beneficial in demonstrating the etiology of seizure episodes in some patients.[45,46]

Activation by suggestion: If psychogenic causes are suspected, a typical seizure can frequently be induced by suggestion. The combination of a continued normal EEG with a typical unresponsive episode in this setting is highly indicative of a psychogenic seizure disorder[29,47–49] (*Fig. 4*). However, it is important to emphasize that an epileptic seizure can occur during the induction procedure, either due to the stress of the procedure or by chance,[45,46] so that careful analysis of the record is essential.

Because of the considerations outlined above, we routinely ask that patients thought to have seizure disorders sleep no longer than three hours the night before the EEG. We use nasopharyngeal leads and attempt to induce sleep on the first recording, thereby increasing the yield of definite diagnostic findings at the outset with no increase in examination time. When the EEG is normal in a patient with intractable seizures, the patient may be asked to return for a more prolonged recording (2 to 3 hr, 24 hr, or even several days), also under sleep deprivation and using nasopharyngeal leads. Where appropriate, he or she may be asked to taper medication prior to returning.

When drug withdrawal is employed, we usually taper medication over a period of weeks, lowering the drug with the longest half-life first, and try to have the patient remain on the drug with the shortest half-life. For example, if a patient was on both phenobarbital and phenytoin at the time of referral, we would first taper and then discontinue phenobarbital and continue the patient on phenytoin, discontinuing it just prior to EEG. We have encountered no marked increases in seizure frequency during the tapering-off period in patients with previously normal records and one or fewer seizures per week, although we caution patients about this possibility. Our goal

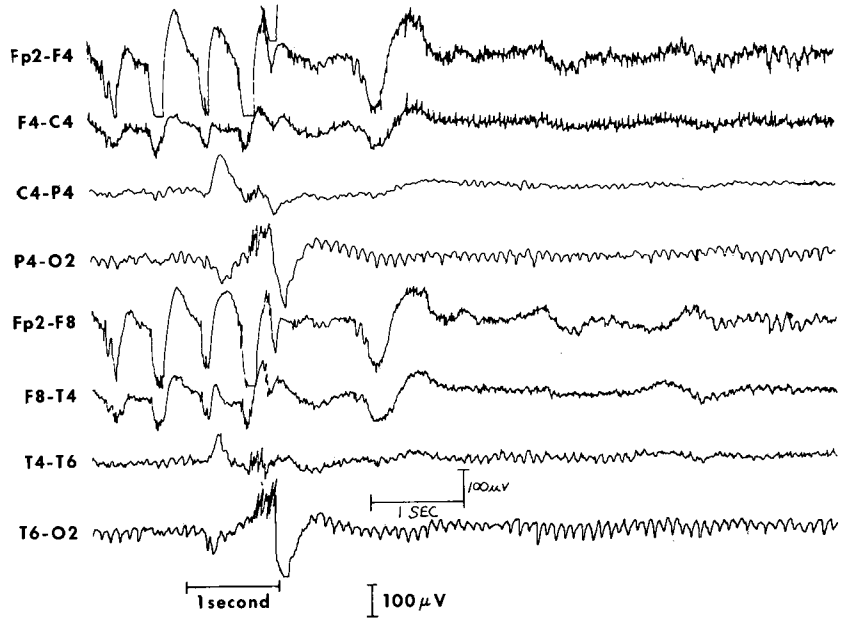


Fig. 4. EEG taken during a psychogenic seizure in a patient who had just evidenced convulsions and was now unresponsive. The combination of lack of response and preserved alpha activity is diagnostic of psychogenic seizures.

is to record definite epileptiform discharges, but not necessarily a seizure. If a patient has had a normal EEG but is experiencing several seizures a week, we might conduct an EEG over a 24-hour period in an effort to record epileptiform discharges or make prolonged recordings over several days in an effort to record an actual episode; moreover, we might taper medication minimally or not at all, since our goals could be achieved without modifying medication. If no epileptiform discharges or seizures occur, we then taper the anticonvulsants. Our objective is to alter the activity of the seizure focus enough to document the etiology of the seizures, but not enough to cause undue clinical deterioration. When a psychogenic seizure disorder is suspected, we attempt to induce an episode during EEG by means of suggestion.[29,43,45,49,50–52] Of 50 patients with seizure episodes documented as psychogenic on the basis of absence of epileptiform changes during a typical seizure episode, which included loss of responsiveness,[45] only 5 had evidence of epilepsy. In another study,[53] epileptiform discharges were noted in 6 out of 51 similar patients. These data indicate that patients with documented psychogenic seizures have a higher incidence of epilepsy than the general population, but the great majority of our patients with psychogenic seizures did not have evidence of epilepsy. No matter what the frequency of epilepsy may be in patients with psychogenic seizures, however, the individual approach remains the same. Diagnosis of concurrent psychogenic and epileptogenic seizures requires EEG evidence of each.

Medical therapy

General concepts: If intractable symptoms are shown to be due to epilepsy, it is necessary to determine why they are intractable. Reynolds et al[54] indicate that control of seizures correlates highly with plasma anticonvulsant levels. Patients with untreated grand mal seizures had an average of approximately one attack per month. When phenytoin levels were less than 10 μg/mL, the seizure rate fell to one every 10 months, while with levels greater than 10 μg/mL it fell to one every 100 months, implying that the first consideration should be not the dosage but rather the drug level in the blood. Furthermore, many patients with intractable seizures fare as well or better on monotherapy, taking a single drug but at the highest tolerated dose, when compared to polytherapy, taking multiple drugs.[55–61] In part, this appears to be so because these patients can tolerate a higher dose of medication if they are using a single drug, without the development of side effects, whereas if they are taking several drugs, drowsiness, ataxia, or other problems are more likely to develop. Anticonvulsant drug lev-

els are guides which help in evaluating the success of therapy, but they are by no means the final word as to optimal therapy in a given patient. If a patient is seizure-free and has a phenytoin level of 8 μg/mL, one should not automatically increase the dose to obtain an anticonvulsant level in the "therapeutic range." By the same token, it appears that some patients may need to have a phenytoin level of more than 20 μg/mL to achieve complete seizure control without adverse reactions. Terms such as "therapeutic range" are misleading, since they falsely suggest that all levels within that range are equally therapeutic, whereas a higher drug level may be more effective than a lower one in an individual case. The commonly quoted ranges reflect general clinical experience rather than precise experimental studies, and for this reason, some authors have instead emphasized effective blood levels or the levels at which toxic reactions begin.[62,63]

Thus in a patient whose seizures continue at lower doses, regardless of the drug levels obtained, the goal of therapy should be to increase the dosage of a single drug to the highest level tolerable without side effects. Drug levels can help in assessing patient compliance, rate of drug metabolism, and patterns of absorption and excretion and assist in establishing the level at which control was achieved for the purpose of comparison if new seizures develop or toxicity occurs.[62–64]

Reasons for variation in effective or toxic drug levels between patients have been extensively reviewed.[62–65] Although compliance, absorption, and excretion are of concern in many cases, it is particularly important to be aware of the effect of altered protein binding,[66–68] particularly in uremic patients who characteristically have a much higher unbound plasma fraction of drugs such as phenytoin[69] or valproic acid.[70] In such cases, the free drug level in the plasma is important because it is this fraction of the total anticonvulsant load which is readily available for penetration of the brain.[62,65] A low total drug level may result in a high free drug level in these patients. Conversely, in patients with a low free drug fraction, high-dose monotherapy is effective for improving seizure control because standard doses and plasma levels result in relatively low amounts of medication in the central nervous system.[61] Thus if one patient has a total phenytoin level of 40 μg/mL (5% free), a second patient 20 μg/mL (10% free), and a third patient 4 μg/mL, (50% free), all three would have an identical free level (2 μg/mL) and thus an identical amount of drug able to interact with receptors within the brain. Once technical problems are resolved,[64,71,72] free levels may be obtained routinely with total anticonvulsant drug levels (or even replace them) in assessing seizure control and assessing toxicity because of their greater precision in determining the anticonvulsant load to the brain. At the same time, it is important to be aware of the necessity of adequate laboratory support. Pippenger et al[73] demonstrated a wide variation between laboratories with regard to the accuracy of anticonvulsant drug level determinations. In order to improve matters, the Epilepsy Foundation of America and then the American Association for Clinical Chemistry developed a quality assurance program. Although technical proficiency has improved,[74] it is still essential that the laboratory participates in this program or has other methods of quality assurance.

Choice of anticonvulsants: Although authors differ in their choice of antiepileptic drugs,[75–81] most prefer phenobarbital, primidone, phenytoin, carbamazepine, or sodium valproate for generalized tonic–clonic seizures and ethosuximide or sodium valproate for absence seizures. For seizures of focal onset, most employ primidone, phenytoin, and carbamazepine as first-line drugs. If generalized tonic–clonic or partial seizures remain intractable despite high-dose monotherapy using each of these drugs, one can add methsuximide,[82] clorazepate,[83,84] or occasionally sodium valproate as a second drug.[85–87] Our procedure is to determine which first-line drug is most effective and then add either another first-line drug or (if high-dose monotherapy proves ineffective) one of the second-line drugs. We decrease the first drug enough to avoid side effects such as lethargy and ataxia, which become more prominent when two drugs are used, and increase the second drug to the maximum tolerable dose.[60,61] If that drug is not helpful, we try another. Finally, Sterman et al[88,89] have reported that biofeedback is occasionally helpful in patients with intractable complex partial seizures. Although further confirmation is necessary, these reports emphasize that psychological methods may have a place in the management of selected epileptic patients.

Surgical therapy

Patients with medically intractable seizures may be candidates for surgical therapy, provided that there is a reasonable chance that surgery

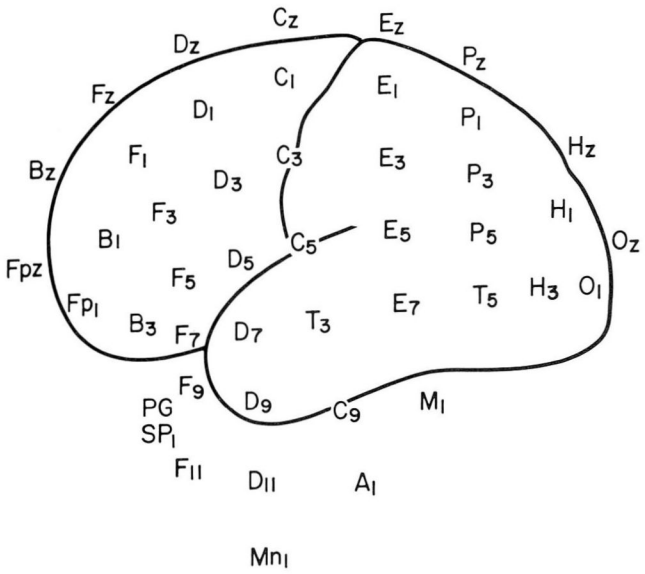


Fig. 5. Schematic map of the terminology used for scalp electrodes [modified from Chatrian[92]]. Extra leads are placed between the standard International 10–20 System electrodes.

could improve seizure control and that the risk of morbidity or secondary functional deficits is acceptably low. Sectioning of the corpus callosum is discussed elsewhere;[90] we wish to consider our own approach toward cortical resection for intractable seizures of focal origin.

Because of the potential morbidity with any intracranial procedure, it is important to first gain as much information as possible using noninvasive means, which can document the topographic distribution of interictal epileptiform discharges and the origin of ictal events. It should be kept in mind that the skull and scalp attenuate the amplitude of the discharge and can slightly alter the distribution of the focus as determined by surface electrodes; however, this potential disadvantage is outweighed by the capability of assessing the extent and distribution of the seizure focus, the likelihood of multiple seizure foci, and the potential relationship of the focus to nonresectable "functional" cortical areas (e.g. primary motor strip, speech area, etc.) by noninvasive means. In order to increase the precision of surface localization, our laboratory uses the standard electrode array (International 10–20 System) plus additional electrodes midway between the 10–20 positions over the area(s) of specific interest.[91–93] In addition, rows of electrodes are placed below the 10–20 positions[91] and nasopharyngeal and/or sphenoidal leads employed in patients with temporal lobe foci to record epileptiform activity from the basal and mesial regions of the temporal lobe (*Figs. 5–9*). Based on cadaver studies, Jasper[94] has noted the location of scalp electrodes in relation to the underlying brain. In

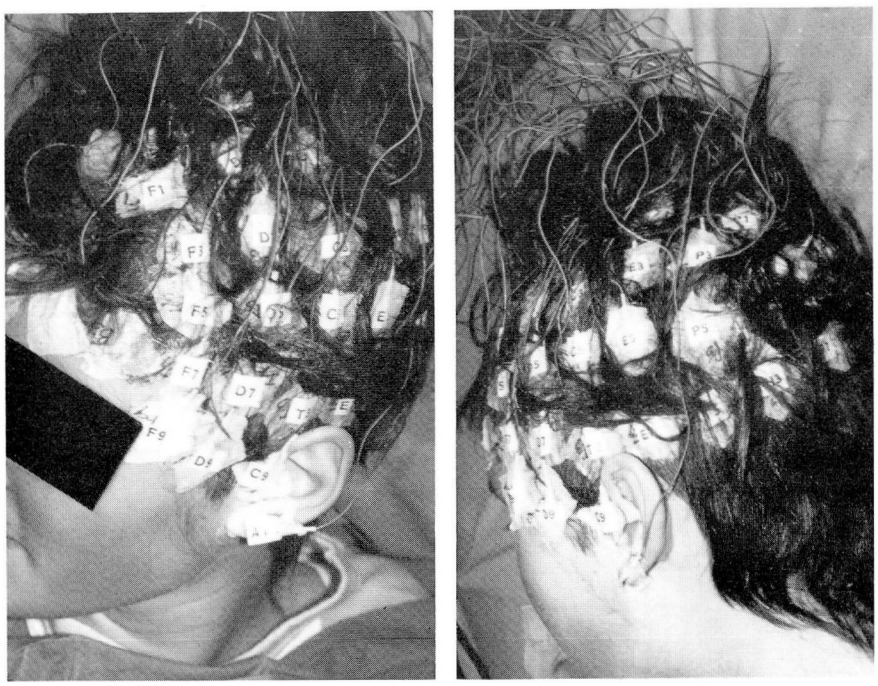


Fig. 6. Placement of electrodes on a patient with intractable seizures who had been admitted for prolonged monitoring.

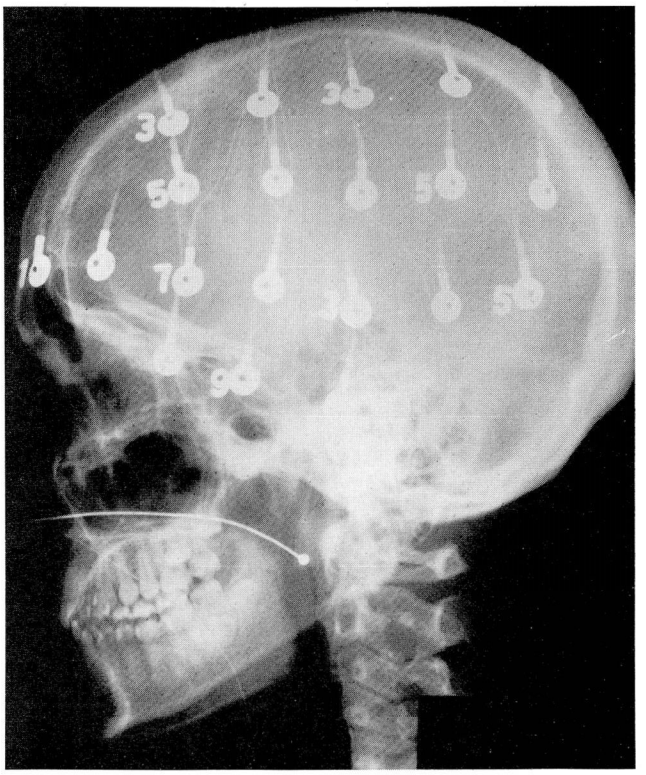
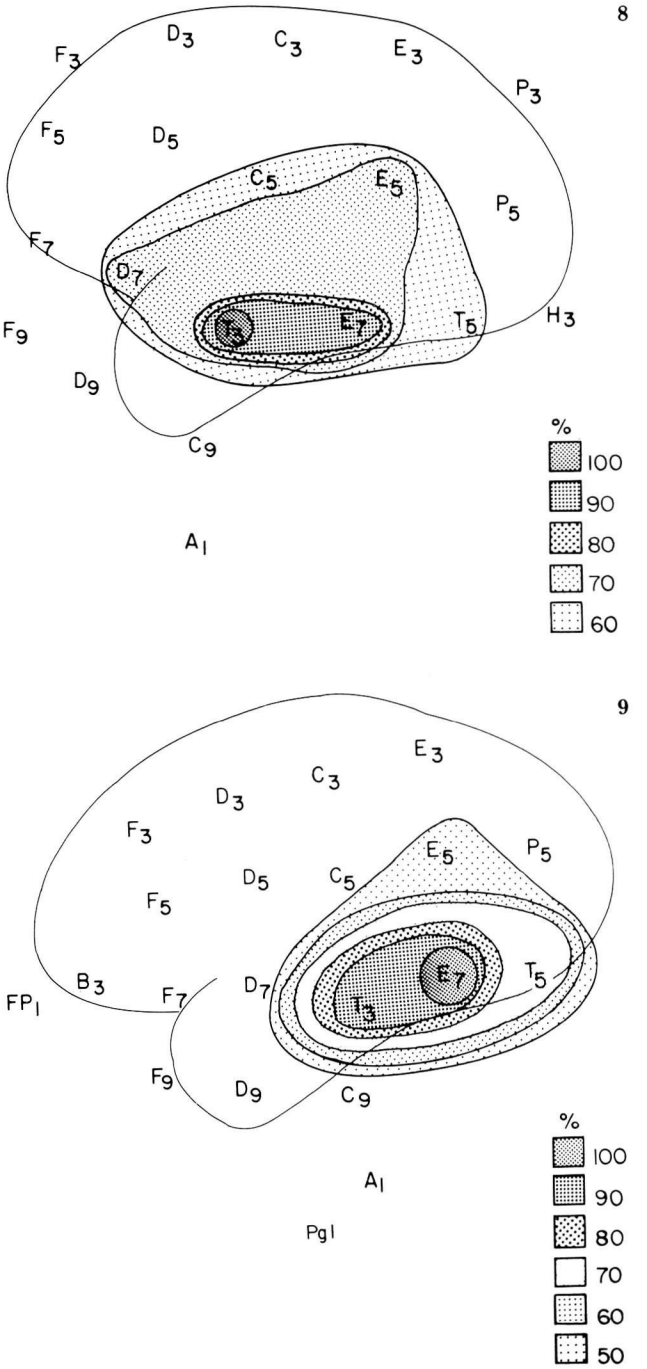


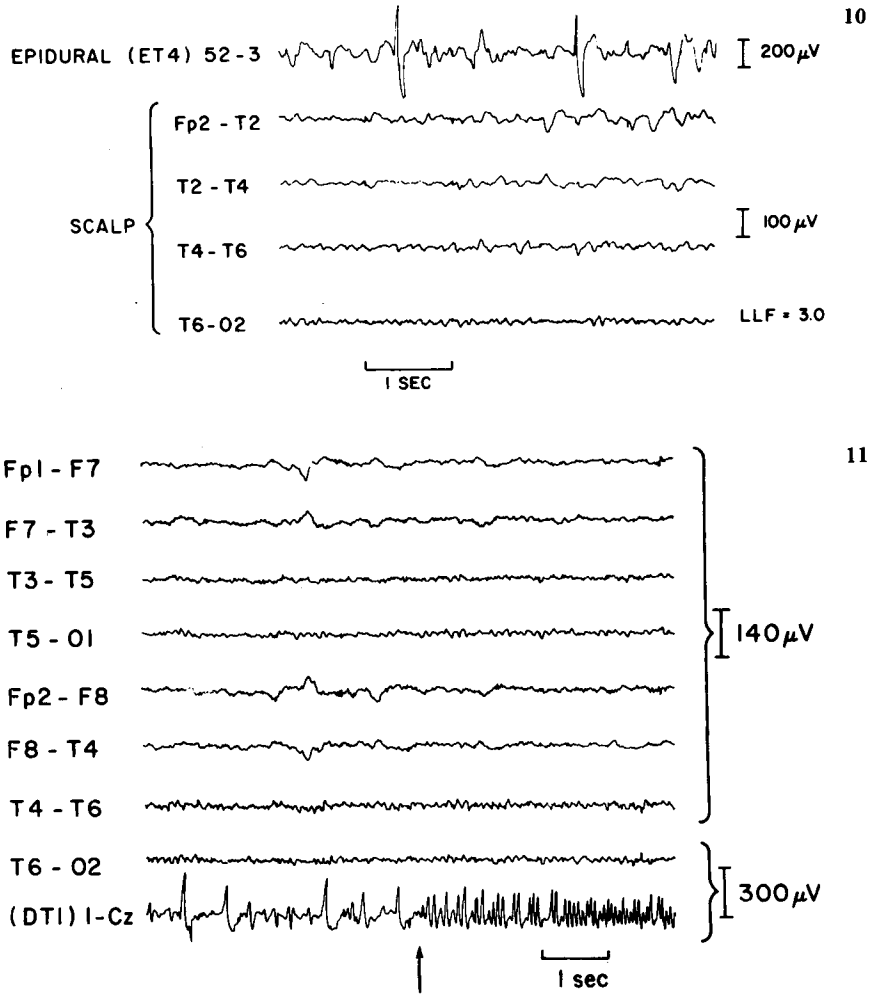
Fig. 7. Skull radiograph of patient with additional electrodes in place. Note that F7 and T3 (denoted by 7 and 3 in photograph) are somewhat distant from the base of the temporal lobe when compared to the added electrodes.

addition, we obtain skull radiographs with the electrodes in place so that we can determine their precise relationship to the anterior and middle fossae in each patient. Ictal and interictal discharges of definite epileptiform significance are then analyzed as to frequency and distribution by recording referentially between the closely spaced scalp electrodes and one distant from the epileptiform focus (or foci). The amplitude of the discharge at each electrode is measured, the point of maximum amplitude determined, and those at the other electrodes expressed as a percentage of the maximum. An isopotential map can then be drawn, indicating the distribution of measured activity. In general, epileptiform discharges are accurately localized at the scalp in the case of convexity foci, compared to the findings with implanted electrodes. However, in the case of mesial or basal foci, there are alterations in surface distribution.[93] For example, mesial and anterior temporal epileptiform discharges tend to be recorded over the inferior frontal or even fronto-polar region as well as over the tip of the temporal lobe. Nasopharyngeal and sphenoidal



Figs. 8 and 9. Two topographic maps of interictal epileptiform discharges (same patient as in *Fig. 6*) The extra electrodes help to define the presence of a posterior temporal focus.

leads are helpful in patients with mesial temporal foci, but not foci localized to the tip. Seizures of focal origin may not be reflected at the surface (*Figs. 10 and 11*), presumably because a relatively large area of the cortical surface must be generating a spike before it can be recorded with scalp



Figs. 10 and 11. Comparison of implanted and scalp electrodes in the recording of interictal (*Fig. 9*) and ictal (*Fig. 10*) activity in 2 patients with complex partial seizures. An epidural strip of electrodes was used for channel 1 in *Figure 9* and depth electrodes for channel 9 in *Figure 10*. No clear epileptiform activity can be observed at the surface.

electrodes.[95–97] For this reason, epileptiform activity may not be detectable at the scalp at the onset of seizures if the activity is restricted to a relatively small area of the cortex. In this context, Lieb et al[98] have noted that the scalp EEG may not record epileptiform activity during auras, or during episodes not accompanied by altered behavior. It is precisely these (simple partial) seizure episodes which may be limited to restricted areas. Thus at the time a seizure is reflected at the scalp surface, it may have projected from the initial focus to a large number of other areas on both sides of the head. Video–EEG monitoring can be helpful in this regard, since it can determine whether the clinical episode occurs before, during, or after the onset of the EEG seizure pattern and whether the topographic distribution of interictal epileptiform discharges is similar to that seen at seizure onset.[32,99,100] Functional tests, such as psychological evaluation, dichotic auditory stimulation, decrease of fast activity on pentothal activation, memory testing after intracarotid amobarbital injections (Wada test), and investigation for areas of hypometabolism on positron computed tomography (PCT) have been advocated as additional methods for determining the location of the ictal focus.[101,102] Engel et al[102] concluded that the latter three tests provided information which complemented that obtained with stereotactically implanted depth electrodes

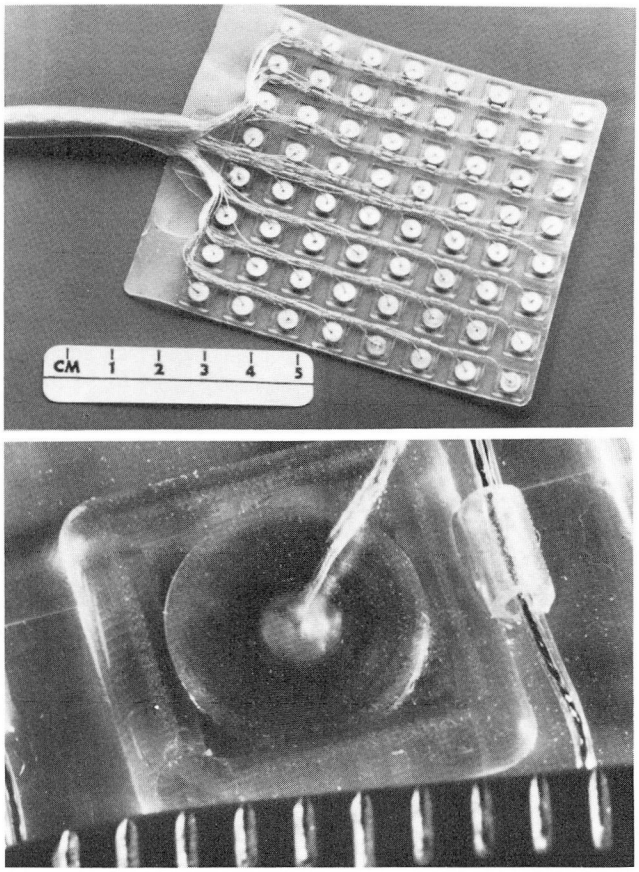


Fig. 12. Subdural 8 × 8 electrode array with centers separated by 1 cm; 1 × 4 electrode strips are also routinely employed and the size of the larger electrode array is modified according to the needs of the patient.

(SEEG). Electrical and chemical techniques for inducing interictal or ictal epileptiform activity do not appear to be consistently accurate.[32]

Because of the limitations of surface EEGs and other noninvasive techniques, a number of centers use SEEGs to further lateralize seizure onset, either routinely or in cases where noninvasive studies do not provide definite data.[102–104] Most such probes have multiple contacts stretching from the convexity to the depth of the brain, suggesting that they would be of value in assessing a variety of structures. However, these electrodes have particularly been used to assess activity in mesial cortical structures. One possible difficulty is that each contact along the probe assesses activity from a relatively restricted region. Also, even with precise stereotaxic placement, slight anatomical variations between hemispheres may result in the contacts on each side not being in precisely homotopic regions. In practice, seizures appear to originate in a wide enough region that such slight variations are not clinically relevant. However, in other circumstances, they may be more significant. For example, in case 107 of Engel et al,[102] surface ictal epileptiform activity was recorded only on the side opposite the temporal lobe eventually selected for removal on the basis of PCT and other functional data.[102] Although depth recorded ictal onset and PCT data were concordant, the authors noted that the former "consisted of very low voltage fast activity reflected in only a few electrodes and could easily have been missed if another montage had been used." Apparently, then, minor differences in activity may dramatically affect the recorded physiological information. Presumably not only different recording montages, but also slight differences in placement or underlying regional anatomy could be important.

Although time of onset is critical in lateralizing the seizure focus, interictal epileptiform activity is also recorded by depth electrodes. However, Wieser et al[32] found that interictal lateralization information agreed with that obtained from spontaneous ictal events in only two thirds of seizures, and the data from depth recordings of Engel et al[102] indicated that the side of seizure onset agreed with interictal spike frequency in only 2 out of 7 patients and with interictal spike autonomy in only 4. These conclusions would seem to suggest that interictal spikes recorded from depth electrodes are unreliable as indicators of the seizure focus; however, it is possible that morphological data (i.e., "what is a spike") might demonstrate that certain types of interictal discharges are more reliable in this regard.

Since Wieser et al[32] found that the epileptogenic zone included the lateral temporal cortex in 58% of cases, the limited coverage of SEEGs could affect surgery in a large number of cases and might explain some of the discrepancies reported from studies with depth electrodes. In addition, although it is important to know which temporal lobe to remove, it is also necessary to determine how much of the lobe to remove to achieve optimal seizure control in view of the evidence for multiple potentially epileptogenic areas within the lobe of interest as opposed to a single small focus.

For the past several years, we have placed plates of disc electrodes over the convexity to provide wider coverage in patients with intractable seizures[93,105–107] (*Fig. 12*). In addition, strips of electrodes can be placed under the frontal or temporal lobe, directed toward the basal and mesial structures.[93,105] These electrodes are used

to record ictal and interictal epileptiform activity, and the use of multiple contacts over the convexity provides wide coverage of this region. Both groups of electrodes are also used for cortical stimulation[108–114] and for recording evoked potentials[106,115,116] and thus for location of areas crucial in controlling motor, sensory, language-related, or other functions. As they are left in place continuously, these electrodes can be used to record spontaneous ictal events as well as for functional localization outside the surgical setting. The electrodes are stainless steel disks 7 mm in diameter imbedded in Dow–Corning MDX clean-grade elastomer with a center-to-center separation of 1 cm. The entire grid is tailored to fit each patient according to the clinical problem. To increase the flexibility and compliance of the grid in relation to the underlying cortex, our current array is "waffled," with the elastomer between two electrodes being thinner than that at the electrodes. This grid allows the physician to evaluate for the presence of significant epileptogenic areas in the lateral temporal cortex[117–119] as noted by Wieser et al[32] and supported by the finding by Engel et al[120] of lateral temporal hypometabolism during PCT scanning of patients with complex partial seizures.[120] Since memory testing during intracarotid amobarbital administration and psychological evaluation can be used to infer the safety of removing mesial structures presumably related to memory, the next crucial question is: how much of the lateral temporal cortex is epileptogenic and how much can be safely removed without affecting speech and other complex psychological functions? Although experience has suggested that standard anatomical landmarks can be used to determine the limits of the cortical excision in most patients with temporal lobe epileptic foci, there are well-described exceptions which emphasize the importance of considering that the speech-related region of the cortex may be located farther anteriorly or posteriorly than usual in some patients.[121,122] Speech testing can be performed in the operating room, but time is limited; moreover, this is only possible in cooperative or older patients who can remain awake during surgery. Chronic subdural electrode arrays allow detailed testing (including both evoked potentials and cortical stimulation) to be performed outside the operating room over a period of several days, thus increasing the precision with which crucial functional areas can be localized and the confidence with which the remaining cortex can be excised. This technique also allows delineation of crucial functional areas outside the temporal lobe, e.g., near the motor strip[109,112,116] or in the occipital lobe.[111] In such cases, we stimulate the cortex and use evoked potentials to delineate those structures which cannot be removed without producing clinically significant deficits and then remove as much of the epileptogenic focus as possible, leaving functionally crucial areas intact. We have employed this approach in about 50 patients over the past five years, revising our technique as experience was gained. The Montreal experience suggests that follow-up for at least four years is necessary in assessing the results of surgery, and we are only now beginning to accumulate this expertise in a significant number of patients. However, our initial results have been comparable to those reported by other groups.[103,123,124] This technique has been particularly helpful in patients with epileptogenic foci involving regions which otherwise might have seemed too risky to remove.

Conclusion

In some patients, intractable seizures are best treated by using diagnostic techniques which demonstate that they are of syncopal or psychogenic origin, cannot be treated with anticonvulsants, and require other therapeutic approaches. In many other patients the disorder is not cured but rather controlled through modification of medication. If seizures remain uncontrolled, surgery can significantly reduce their frequency in selected patients, but surgery should be thought of as a complement to, rather than as a replacement for medication until complete control is demonstrated for a sufficient length of time. The fact that some patients are not candidates for surgery, or do not improve despite such measures, underscores the need for further drug trials, improved surgical techniques, and the development of alternative approaches.

References

1. Lyle CB Jr, Monroe JT Jr, Flinn DE, Lamb LE. Micturition syncope. Report of 24 cases. N Engl J Med 1961; **265**:982–986.
2. Wayne HH. Syncope. Physiological considerations and an analysis of the clinical characteristics in 510 patients. Am J Med 1961; **30**:418–438.
3. Schoenberg BS, Kuglitsch JF, Karnes WE. Micturition syncope—not a single entity. JAMA 1974; **229**:1631–1633.
4. Fisher CM. Syncope of obscure nature. Can J Neurol Sci 1979; **6**:7–20.

5. Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. N Engl J Med 1983; **309:**197–204.
6. Dinner DS, Lesser RP, Morris HH, Lueders H. Electroclinical study of convulsive syncope: a case report. Central Association of Electroencephalographers, March 26, 1983.
7. Pedley TA. EEG patterns that mimic epileptiform discharges but have no association with seizures. [In] Henry CE, ed. Current Clinical Neurophysiology. Update on EEG and Evoked Potentials. New York, Elsevier, 1980, pp 307–336.
8. White JC, Langston JW, Pedley TA. Benign epileptiform transients of sleep. Clarification of the small sharp spike controversy. Neurology (Minneap) 1977; **27:**1061–1068.
9. Reiher J, Lebel M, Klass DW. Small sharp spikes (SSS): reassessment of electroencephalographic characteristics and clinical significance. Electroencephalogr Clin Neurophysiol 1977; **43:**775.
10. Reiher J, Lebel M. Wicket spikes: clinical correlates of a previously undescribed EEG pattern. Can J Neurol Sci 1977; **4:**39–47.
11. Kellaway P. An orderly approach to visual analysis: the parameters of the normal EEG in adults and children. [In] Klass DW, Daly DD, eds. Current Practice of Clinical Electroencephalography. New York, Raven Press, 1979, pp 69–147.
12. Westmoreland BF, Klass DW. A distinctive rhythmic EEG discharge of adults. Electroencephalogr Clin Neurophysiol 1981; **51:**186–191.
13. Bennett DR, Ziter FA, Liske EA. Electroencephalographic study of sleep deprivation in flying personnel. Neurology (Minneap) 1969; **19:**375–377.
14. Rodin EA, Luby ED, Gottlieb JS. The electroencephalogram during prolonged experimental sleep deprivation. Electroencephalogr Clin Neurophysiol 1962; **14:**544–551.
15. Gibbs EL, Gibbs FA. Diagnostic and localizing value of electroencephalographic studies in sleep. Proc Assoc Res Nerv Ment Dis 1947; **26:**366–376.
16. Silverman D, Morisaki A. Re-evaluation of sleep electroencephalography. Electroencephalogr Clin Neurophysiol 1958; **10:**425–431.
17. White P, Dyken M, Grant P, Jackson L. Electroencephalographic abnormalities during sleep as related to the temporal distribution of seizures. Epilepsia 1962; **3:**167–174.
18. Mattson RH, Pratt KL, Calverley JR: Electroencephalograms of epileptics following sleep deprivation. Arch Neurol 1965; **13:**310–315.
19. Niedermeyer E, Rocca U. The diagnostic significance of sleep electroencephalograms in temporal lobe epilepsy. A comparison of scalp and depth tracings. Europ Neurol 1972; **7:**119–129.
20. Bagchi BK, Jones EV. Variable temporal lobe foci in waking and sleep. Electroencephalogr Clin Neurophysiol 1951; **3:**384.
21. Gloor P, Tsai C, Haddad F, Jasper HH. The lack of necessity for sleep in the EEG or ECG diagnosis of temporal seizures. Electroencephalogr Clin Neurophysiol 1957: **9:**379–380.
22. Gloor P, Tsai C. Haddad F. An assessment of the value of sleep-electroencephalography for the diagnosis of temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1958; **10:**633–648.
23. Dinner DS, Lueders H, Rothner AD, Erenberg EG. Complex partial seizures of childhood onset. A clinical and EEG study. Neurology 1981; **31**(suppl):143.
24. Pratt KL, Mattson RH, Weikers NJ, Williams R. EEG activation of epileptics following sleep deprivation: a prospective study of 114 cases. Electroencephalogr Clin Neurophysiol 1968; **24:**11–15.
25. Scollo-Lavizzari G, Pralle W, Radue EW. Comparative study of efficacy of waking and sleep recordings following sleep deprivation as an activation method in the diagnosis of epilepsy. Eur Neurol 1977; **15:**121–123.
26. Rovit RL, Gloor P, Rasmussen T. Sphenoidal electrodes in the electrographic study of patients with temporal lobe epilepsy. An evaluation. J Neurosurg 1961; **18:**151–158.
27. Pampiglione G, Kerridge J. EEG abnormalities from the temporal lobe studied with sphenoidal electrodes. J Neurol Neurosurg Psychiatr 1956; **19:**117–129.
28. Silverman D. The anterior temporal electrode and the ten-twenty system. Electroencephalogr Clin Neurophysiol 1960; **12:**735–737.
29. Ramani SV, Quesney LF, Olson D, Gumnit RJ. Diagnosis of hysterical seizures in epileptic patients. Am J Psychiatry 1980; **137:**705–709.
30. Spencer SS, Spencer DD, Williamson PD, Mattson RH. Ictal effects of anticonvulsant medication withdrawal in epileptic patients. Epilepsia 1981; **22:**297–307.
31. Merlis JK, Grossman C, Henriksen GF. Comparative effectiveness of sleep and metrazol-activated electroencephalography. Electroencephalogr Clin Neurophysiol 1951; **3:**71–78.
32. Wieser HG, Bancaud J, Talairach J, Bonis A, Szikla G. Comparative value of spontaneous and chemically and electrically induced seizures in establishing the lateralization of temporal lobe seizures. Epilepsia 1979; **20:**47–59.
33. Klass DW, Fischer-Williams M. Sensory stimulation, sleep and sleep deprivation. [In] Naquet R, ed. Activation and Provocation Methods in Clinical Neurophysiology. Handbook of Electroencephalography and Clinical Neurophysiology, Vol 3, Pt D, Amsterdam, Elsevier, 1976, pp 5–73.
34. Rushton DN. "Space invader" epilepsy. Lancet 1981; **1:**501.
35. Glista GG, Frank HG, Tracy FW. Video games and seizures. Arch Neurol 1983; **40:**588.
36. Penry JK, Dreifuss FE. Automatisms associated with the absence of petit mal epilepsy. Arch Neurol 1969; **21:**142–149.
37. Browne TR, Penry JK, Porter RJ, Dreifuss FE. Responsiveness before, during, and after spike-wave paroxysms. Neurology (Minneap) 1974; **24:**659–665.
38. Penry JK, Porter RJ, Dreifuss FE. Simultaneous recording of absence seizures with video tape and electroencephalography. A study of 374 seizures in 48 patients. Brain 1975; **98:**427–440.
39. Escueta AV, Kunze U, Waddell G, Boxley J, Nadel A. Lapse of consciousness and automatisms in temporal lobe epilepsy: a videotape analysis. Neurology (Minneap) 1977; **27:**144–155.
40. Belafsky MA, Carwille S, Miller P, Waddell G, Boxley-Johnson J, Delgado-Escueta AV. Prolonged epileptic twilight states: continuous recordings with nasopharyngeal electrodes and videotape analysis. Neurology (Minneap) 1978; **28:**239–245.
41. Delgado-Escueta AV, Mattson RH, King L, et al. The nature of aggression during epileptic seizures. N Engl J Med 1981; **305:**711–716.
42. Escueta AV, Bacsal FE, Treiman DM. Complex partial seizures on closed-circuit television and EEG: a study of 691 attacks in 79 patients. Ann Neurol 1982; **11:**292–300.
43. Delgado-Escueta AV. Epileptogenic paroxysms: modern approaches and clinical correlations. Neurology (Minneap) 1979;**29:**1014–1022.

44. Desai BT, Porter RJ, Penry JK. Psychogenic seizures. A study of 42 attacks in six patients, with intensive monitoring. Arch Neurol 1982; **39:**202–209.
45. Lesser RP, Lueders H, Dinner DS. Evidence for epilepsy is rare in patients with psychogenic seizures. Neurology 1983; **33:**502–504.
46. Lesser RP, Lueders H, Conomy J, Furlan AJ, Dinner DS. Sensory seizure mimicking a psychogenic seizure. Neurology (Minneap) 1983; **33:**800–802.
47. Massey EW, Riley TL. Pseudoseizures: recognition and treatment. Psychosomatics 1980; **21:**987–991, 996–997.
48. Remick RA, Wada JA. Complex partial and pseudoseizure disorders. Am J Psychiat 1979; **136:**320–323.
49. Riley TL, Berndt T. The role of EEG technologist in delineating pseudoseizures. Am J EEG Technol 1980; **20:**89–96.
50. Liske E, Forster FM. Pseudoseizures: a problem in the diagnosis and management of epileptic patients. Neurology (Minneap) 1964; **14:**41–49.
51. Schwarz BE, Bickford RG, Rasmussen WC. Hypnotic phemonena, including hypnotically activated seizures, studied with the electroencephalogram. J Nerv Ment Dis 1955; **122:**564–574.
52. Ferriss GS. The recognition of nonepileptic seizures. South Med J 1959;**52:**1557–1567.
53. Cohen RJ, Suter C. Hysterical seizures: suggestion as a provocative EEG test. Ann Neurol 1982; **11:**391–395.
54. Reynolds EH, Chadwick D, Galbraith AW. One drug (phenytoin) in the treatment of epilepsy. Lancet 1976; **1:**923–926.
55. Shorvon SD, Reynolds EH. Reduction in polympharmacy for epilepsy. Br Med J 1979; **2:**1023–1025.
56. Shorvon SD, Galbraith AW, Laundy M, Vydelinqum L, Reynolds EH. Monotherapy for epilepsy. [In] Antiepileptic Therapy: Advances in drug monitoring. New York, Raven Press, 1979, pp 213–220.
57. Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? Epilepsia 1981; **22:**1–10.
58. Gannaway DJ, Mawer GE. Transfer from multiple to single antiepileptic drug therapy. Lancet 1981; **1:**217.
59. Thompson PJ, Trimble MR. Changing to one anticonvulsant. Lancet 1981; **1:**447.
60. Schmidt D. Reduction of two-drug therapy in intractable epilepsy. Epilepsia 1983; **24:**368–376.
61. Lesser RP, Pippenger CE, Lueders H, Dinner DS. High dose monotherapy in the treatment of intractable seizures: acute toxic effects and therapeutic efficacy. Neurology 1983; **33**(suppl 2):233.
62. Pippenger CE. Rationale and clinical application of therapeutic drug monitoring. Pediatr Clin North Am 1980; **27:**891–925.
63. Penry JK, Newmark ME. The use of antiepileptic drugs. Ann Intern Med 1979; **90:**207–218.
64. Johannessen SI. Antiepileptic drugs: pharmacokinetic and clinical aspects. Ther Drug Monit 1981; **3:**17–37.
65. Eadie MJ. Plasma level monitoring of anticonvulsants. Clin Pharmacokinet 1976; **1:**52–66.
66. Booker HE, Darcey B. Serum concentrations of free diphenylhydantoin and their relationship to clinical intoxication. Epilepsia 1973; **14:**177–184.
67. Lunde PKM, Rane A, Yaffe SJ, Lund L, Sjogvist F. Plasma protein binding of diphenylhydantoin in man. Interaction with other drugs and the effect of temperature and plasma dilution. Clin Pharmacol Ther 1970; **11:**846–855.
68. Hooper WD, Dubetz DK, Bochner F, et al. Plasma protein binding of carbamazepine. Clin Pharmacol Ther 1975; **17:**433–440.
69. Reidenberg MM, Odar-Cederlöf I, von Bahr C, Borga O, Sjovist F. Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. N Engl J Med 1971; **285:**264–267.
70. Gugler R, Mueller G. Plasma protein binding of valproic acid in healthy subjects and in patients with renal disease. Br J Clin Pharmacol 1978; **5:**441–446.
71. Flachs H, Rasmussen JM. Renal disease may increase apparent phenytoin in serum as measured by enzyme-multiplied immunoassay. Clin Chem 1980; **26:**361.
72. McDonald DM, Kabra PM. Renal disease may increase apparent phenytoin in serum as measured by enzyme-multiplied immunoassay. Clin Chem 1980; **26:**361–362.
73. Pippenger CE, Penry JK, White BG, Daly DD, Buddington R. Interlaboratory variability in determination of plasma antiepileptic drug concentrations. Arch Neurol 1976; **33:**351–355.
74. Pippenger CE, Paris-Kutt H, Penry JK, Daly DD. Proficiency testing in determinations of antiepileptic drugs. J Anal Toxicol 1977; **1:**118–122.
75. Daly DD. Drug therapy in convulsive disorders. Proc Staff Meetings Mayo Clinic 1957; **32:**257–268.
76. Millichap JG. Drug treatment of convulsive disorders. N Engl J Med 1972; **286:**464–469.
77. Troupin AS. The choice of anticonvulsants. Proceedings of the 25th Western Institute on Epilepsy, March 26, 1975.
78. Jeavons PM. Choice of drug therapy in epilepsy. Practitioner 1977; **219:**542–556.
79. Livingston S, Pruce I. General principles for administration of prophylactic antiepileptic drugs. Medical Digest 1978; **24:**11–20.
80. Reynolds EH. Drug treatment of epilepsy. Lancet 1978; **2:**721–725.
81. Drugs for epilepsy. Med Lett Drugs Ther 1979; **21:**25–28.
82. Wilder BJ, Buchanan RA. Methsuximide for refractory complex partial seizures. Neurology (NY) 1981; **31:**741–744.
83. Berchou RC, Rodin EA, Russell ME. Clorazepate therapy for refractory seizures. Neurology (NY) 1981; **31:**1483–1485.
84. Troupin AS, Friel P, Wilensky AJ, Morretti-Ojemann L, Levy RH, Feigl P. Evaluation of clorazepate (Tranxene) as an anticonvulsant—a pilot study. Neurology (Minneap) 1979; **29:**458–466.
85. Simon D, Penry JK. Sodium di-N-propylacetate (DPA) in the treatment of epilepsy. A review. Epilepsia 1975; **16:**549–573.
86. Jeavons PM, Clark JE. Sodium valproate in treatment of epilepsy. Br Med J 1974; **2:**584–586.
87. Browne TR. Drug therapy: valproic acid. N Engl J Med 1980; **302:**661–666.
88. Sterman MB, Macdonald LR, Stone RK. Biofeedback training of the sensorimotor electroenceophalogram rhythm in man: effects on epilepsy. Epilepsia 1974; **15:**395–416.
89. Sterman MB, Macdonald LR. Effects of central cortical EEG feedback training on incidence of poorly controlled seizures. Epilepsia 1978; **19:**207–222.
90. Blume WT. Corpus callosum section for seizure control: rationale and review of experimental and clinical data. Cleve Clin Q 1984; **51:**319–332.
91. Morris HH, Lueders H, Lesser RP, Dinner DS. Value of multiple electrodes in addition to standard 10/20 system electrodes in localizing epileptiform activity. 15th Epilepsy International Symposium, Washington, D. C., September 1983.
92. Chatrian G, Berganini L, Dondey M, Klass DW, Lennox-Buchtal M, Petersén I. A glossary of terms most commonly

used by clinical electroencephalographers. Electroencephalogr Clin Neurophysiol 1974; **37:**538–548.
93. Lueders H, Hahn J, Lesser R, Dinner DS, Rothner D, Erenberg G. Localization of epileptogenic spike foci: comparative study of closely spaced scalp electrodes, nasopharyngeal, sphenoidal, subdural, and depth electrodes. [In] Akimoto H, Kazamatsuri H, Seino M, Ward A, eds. Advances in Epileptology: XII Epilepsy International Symposium, September 1981. New York, Raven Press, 1982, pp 185–189.
94. Jasper HH. The ten-twenty electrode system of the international federation. Electroencephalogr Clin Neurophysiol 1958; **10:**371–375.
95. Brazier MAB. The electrical fields at the surface of the head during sleep. Electroencephalogr Clin Neurophysiol 1949; **1:**195–204.
96. Cooper R, Winter AL, Crow HJ, Walter WG. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. Electroencephalogr Clin Neurophysiol 1965; **18:**217–228.
97. Nuñez PL. Electrical fields of the brain. New York, Oxford University Press, 1981.
98. Lieb JP, Walsh GO, Babb TL, Walter RD, Crandall PH. A comparison of EEG seizure patterns recorded with surface and depth electrodes in patients with temporal lobe epilepsy. Epilepsia 1976; **17:**137–160.
99. Bancaud J, Talairach J, Bonis A, Bordas-Ferrer M. Anomalies E.E.G. intercritiques bitemporales asynchrones dans le épilepsies unilatérales (à propos d'une épilepsie d'origine tumorale). Rev Neurol (Paris) 1969; **121:**369–379. [Fre]
100. Bancaud J, Ribet MF, Chagot D. Origine comparée des paroxysmes de pointes "infra-clinique" et des crises électrocliniques spontanées dans l'épilepsie. Rev Electroencephalogr Neurophysiol Clin 1975; **5;**63–66.
101. Milner B. Psychological aspects of focal epilepsy and its neurosurgical management. Adv Neurol 1975; **8:**299–321.
102. Engel J Jr, Rausch R, Lieb JP, Kuhl DE, Crandall PH. Correlation of criteria used for localizing epileptic foci in patients considered for surgical therapy of epilepsy. Ann Neurol 1981; **9:**215–224.
103. Spencer SS. Depth electroencephalography in selection of refractory epilepsy for surgery. Ann Neurol 1981; **9:**207–214.
104. Delgado-Escueta AV, Nashold B, Freedman M, et al. Videotaping epileptic attacks during stereoelectroencephalography. Neurology (Minneap) 1979; **29:**473–489.
105. Lesser RP, Hahn J, Lueders H, Rothner AD, Erenberg G. The use of chronic subdural electrodes for cortical mapping of speech. Epilepsia 1981; **22:**240.
106. Goldring S. A method for surgical management of focal epilepsy, especially as it relates to children. J Neurosurg 1978; **49:**344–356.
107. Levy WJ, Hahn JH, Lueders H, Lesser R. Chronic cortical electrode array for seizure investigation. Childs Brain 1982; **9:**48–52.
108. Lesser RP, Lueders H, Hahn J, et al. Location of the speech area in candidates for temporal lobectomy: results of extraoperative studies. Neurology 1982; **32:**A91.
109. Lesser RP, Lueders H, Hahn J, Cohen L, Dinner DS. Results of extraoperative stimulation of the frontal speech area. Epilepsia 1983; **24:**259.
110. Lesser RP, Lueders H, Dinner DS, Hahn J. The anatomical relationship of the frontal speech area to the inferior motor strip: results of extraoperative cortical stimulation. Neurology 1983; **33**(suppl 2):63.
111. Morris HH, Lueders H, Lesser RP, Dinner DS, Hahn J. Transient neuropsychological parietal lobe abnormalities produced by electrical stimulation in man. Neurology 1983; **33**(suppl 2):64.
112. Lueders H, Lesser RP, Dinner DS, Hahn J, Salanga V, Morris HH. The second sensory area in man: evoked potential and electrical stimulation studies. Neurology 1983; **33**(suppl 2):185.
113. Lueders H, Lesser RP, Dinner DS, Morris HH, Hahn J. Inhibition of motor activity of electrical stimulation of the human cortex. Epilepsia 1983; **24:**519.
114. Lesser RP, Lueders H, Dinner DS, Hahn J, Cohen L. The location of speech and writing functions in the frontal language area: results of extraoperative cortical stimulation. Brain 1984; 107:275–291.
115. Lueders H, Lesser RP, Dinner DS, Morris HH, Klem G. Ipsilateral somatosensory evoked potentials recorded directly from the human cortex. Central Association of Electroencephalographers, Indianapolis, March 26, 1983.
116. Lueders H, Lesser RP, Hahn J, Dinner DS, Klem G. Cortical somatosensory evoked potentials in response to hand stimulation. J Neurosurg 1983; **58:**885–894.
117. Dinner DS, Lueders H, Lesser RP, Hahn J. Extensive temporal lobectomy of the dominant hemisphere: a case report. Epilepsia 1983; **24:**261.
118. Dudley AW, Estes M, Lueders H, Lesser RP, Hahn JF, Morris HH, Dinner DS. Neuronal heterotopias and focal epilepsy. 15th Epilepsy International Symposium, Washington, D.C., September 1983.
119. Dinner D, Lueders H, Lesser RP, Rothner AD, Erenberg G. Incidence of mesial temporal epileptogenic foci in complex partial seizures. Neurology 1982; **32:**A91.
120. Engel J Jr, Brown WJ, Kuhl DE, Phelps ME, Mazziotta JC, Crandall PH. Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. Ann Neurol 1982; **12:**518–528.
121. Rasmussen T, Milner B. Clinical and surgical studies of the cerebral speech areas in man. [In] Zülch KJ, Creutzfeldt O, Galbraith GC, eds. Otfrid Foerster Symposium on Cerebral Localization. New York, Springer-Verlag, 1975, pp 238–257.
122. Ojemann GA. Individual variability in cortical localization of language. J Neurosurg 1979; **50:**164–169.
123. Davidson S, Falconer MA. Outcome of surgery in 40 children with temporal-lobe epilepsy. Lancet 1975; **1:**1260–1263.
124. Engel J Jr, Driver MV, Falconer MA. Electrophysiological correlates of pathology and surgical results in temporal lobe epilepsy. Brain 1975; **98:**129–156.