Advances in the Medical and Surgical Management of Intractable Partial Complex Seizures* **

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Introduction. Seizures can be due to a variety of acute, subacute, or chronic diseases with different etiologies. Clinically, they may manifest as focal or generalized phenomena (Table 1). Whereas the majority of the patients suffering from partial seizures are easily controlled with medications, in a small number of patients treatment may fail. The failure may be due to incorrect diagnosis or incorrect therapy. The efficacy of medical treatment for seizure disorder depends upon six factors: 1) dosage; 2) the size of the patient; 3) drug interaction; 4) drug specificity for the disease; 5) the nature of the disease for which the drug is used; 6) the mode and frequency of medication.

Dosage of Anticonvulsant. The dosage of anticonvulsant is very important (Table 2). In our experience, the most common cause of failure in treatment of seizure disorders is undermedication. It is also well known that the anticonvulsants in large enough doses can act as convulsants. This is especially true for diphenylhydantoin, benzodiazepines, and lidocaine. An important factor in dosage of drug is patient reliability. Measurement of blood levels of anticonvulsant can be helpful in this respect (Table 3).

Size of the Patient. The size of the patient should be considered in dosage. Measurement according to body surface is safer and more accurate (Table 2). As the child grows, there may be a need to gradually increase the dose of anticonvulsants if seizure control is poor or if the serum level of the anticonvulsant starts to decline.

Drug Interaction. The relationship of multiple drug therapy to its toxic effects on the brain is quite complicated, and many forms of therapeutic failure or toxicity can result.

Combination of Similar Drugs. Failure or toxicity may be the result of a combination of pharmacologically similar drugs. Such a combination may enhance the side effects of drowsiness and ataxia. The patient may suffer from these side effects without attaining therapeutic levels of individual anticonvulsants in the blood. For example, a combination of drugs such as phenobarbital and primidone may result in severe ataxia and drowsiness while measurement of serum levels of phenobarbital and primidone in such patients may show subtherapeutic levels.

The combination of the following pharmacologically similar drugs should be avoided: 1) phenobarbital and primidone, mephobarbital (Mebaral®), and metharbital (Gemonil®); 2) ethosuximide and methsuximide; 3) diphenylhydantoin (DPH) and mephenytoin; 4) trimethadione and paramethadione; 5) benzodiazepines (e.g., combination of diazepam, clonazepam (Clonapin®), chlordiazepoxide); 6) phenobarbital and ethanol; 7) phenobarbital and benzodiazepines.

Combination of Inducers of Drug Metabolism. This combination may result in less effective

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TABLE 1
A Simple Classification of Seizure Disorders*

1. Focal (partial)
   a. cortical
   b. subcortical
   c. both cortical and subcortical
2. Generalized
   a. low threshold (e.g. drug withdrawal, toxic-metabolic, benign febrile seizures)
   b. secondary to focal

* Any of the above may be clinical or subclinical (EEG manifestation).

therapeutic doses of each drug in the blood, and less effective control of seizures, despite toxic side effects.

Whereas the failure may be due to genetic, pharmacological or physiological factors which alter absorption metabolism or excretion of the drug, or the failure may be due to compliance behavior of the patient or to lack of drug specificity for the disease, the clinician may add other anticonvulsants which are inducers of drug metabolism and may result in toxicity without control of seizures. The combination may fail to control the seizures, but may result in side effects of drowsiness (1) and/or hyperactivity, also.

For example, diphenylhydantoin (DPH) at 5 mg/kg/day would result in a stable blood level of the drug (2); however, an occasional patient on the same dosage may represent marked blood accumulation of the drug and toxicity (3), while others on the same dosage may reveal very low drug levels and poor

TABLE 2
Dosage, Therapeutic Drug Levels, Indications, and Side Effects of Routinely Used Anticonvulsants

	Indications	Average Daily Dose (ED 50)	TD 50 (Toxicity) (mg/kg)	Safety Range (TD/ED)	Serum Level‡ Therapeutic Range	Skin Rash Leukopenia	Hyper-activity
DPH (Dilantin®)	F, G, S	5 mg/kg (0.3 g/sqM)	20	4	10–20 μg/ml	±	±
Phenobarbital (Luminal®)	F, G, P, C, S	1.5 mg/kg (0.1 g/sqM)	4.5	3	10–50 μg/ml	±	+++
Primidone (Mysoline®)	L, G	10 mg/kg (0.6 g/sqM)	140	14	4–12 μg/ml	±	+
Ethosuximide (Zarontin®)	P	20 mg/kg (1.2 g/sqM)	150	10	40–100 μg/ml	+	+
Methsuximide (Celontin®)	P, C	10 mg/kg (0.6 g/sqM)	15	1.5	2–7.5 μg/ml	++	+
Trimethadione (Tridione®)	P	20 mg/kg (1.2 g/sqM)	25	1.2	100–1000 μg/ml	+++	+
Diazepam (Valium®)	S, P	2–10 mg IV repeated dose	30	10	150–550 ng/ml	–	++
Clonazepam*	S, P, C	0.3 mg/kg	6	20	20–70 ng/ml	–	+++
Acetazolamide (Diamox®)	P, PMS	500–750 mg/day	200	18	10–75 μg/ml	–	–
Carbamazepine* (Tegretol®)	L, G	400 mg (children)/day 1200 mg (adults)/day	23	1.5	4–6 μg/ml	±	+
ACTH	Infantile spasms	40–80 u				–	–

ED—Effective dose
C—Complex (myoclonic akinetic, focal and gen., "petit mal variant")
F—Focal seizure
G—Generalized
L—Limbic (Temporal lobe, etc.)
P—Petit mal
PMS—Premenstrual seizures
S—Status epilepticus
g/sqM—gram per square body meter
TD—toxic dose
±—Rare
+—Infrequent
++—Occasional
+++—Not uncommon
*—Use as anticonvulsant experimental
‡—Gross guidelines

TABLE 3
Measurement of Blood Levels of Anticonvulsants

1. Patient reliability
2. Undermedication and overmedication (typical and atypical toxicity; acute and chronic toxicity)
3. Drug interaction
4. Seizure aggravation by anticonvulsants
5. Neurologic deterioration due to drugs vs other causes
6. Use of anticonvulsants in hepatic or nephritic patients

seizure control (4). Notwithstanding this variability in individual patients, the clinician may become frustrated with the patient's lack of response to treatment. Without further inquiry as to the cause of this lack of response, the clinician may add subtherapeutic doses of other drug inducers. The combination is apt to fail.

The combination of the following inducers of drug metabolism should be avoided: 1) phenobarbital and antipyrine; 2) phenobarbital and butazones; 3) phenobarbital and diphenylhydantoin (DPH); 4) phenobarbital and gyrseofulvin; 5) chlordiazepoxide and Coumadin®.

Drug interaction is variable from case to case; however, high anticonvulsant levels are achieved of each drug, if the metabolic inducers are not given simultaneously (5). If in some cases a combination of drugs seems to be more effective, it is most likely that subtherapeutic doses of each agent have been used to begin with. This is especially true in combining phenobarbital and DPH.

The combination of phenobarbital and DPH is in vogue. While in occasional patients such a combination may be more rewarding than the individual use of phenobarbital or DPH, in our study of 182 patients suffering from focal as well as generalized seizures (Table 4), patients responded better to phenobarbital or DPH alone than to the combination of the two drugs. When the patients were randomly divided into three groups, the group receiving DPH and phenobarbital in combination had more tendency to suffer from side effects of drowsiness and ataxia, and therapeutic levels of the anticonvulsants could not be achieved in most cases without the complications of undesired side effects. The patients who received single anticonvulsants had a higher level of serum anticonvulsants with fewer side effects of drowsiness, poor appetite, and hyperactivity. The patients in the combination group had more rapid control of seizure disorder from the start, but did not fare as well in the long-term follow-up. This was blamed on the fact that the patients on combination therapy did not follow the treatment schedule as religiously as the patients in other groups because of the side effects. The patients receiving individual anticonvulsants had a delay of two-to-five days in complete control of their seizures, but had better control of seizure disorder when followed for a period of over two years (Table 4).

Drug toxicity can be enhanced by the use of *hormones* such as salt-retaining hormones or by the use of *psychotherapeutic drugs* such as phenothiazines. It is a well-known fact that phenothiazines can exacerbate seizures in some patients; this is especially true in patients suffering from limbic system originated seizures. This does not, however, contraindicate the use of phenothiazines in the epileptic patients. The use of some phenothiazine drugs may be absolutely necessary to control the emotional problems which

TABLE 4
Treatment of Focal and Generalized Seizures in 182 Randomly Distributed Patients
Age Range 6–37 Years with a Two-Year Follow-up

	No. of Patients	Mean Blood DPH (μg/ml)	Mean Blood Phenobarbital (μg/ml)	Therapeutic Failures in Two Years
DPH 5.0 mg/kg/day	61	11	—	13 (21.3%)
Phenobarbital 1.5 mg/kg/day	51	—	12.3	16 (27.1%)
Combination	62	6.2	7.1	24 (38.6%)

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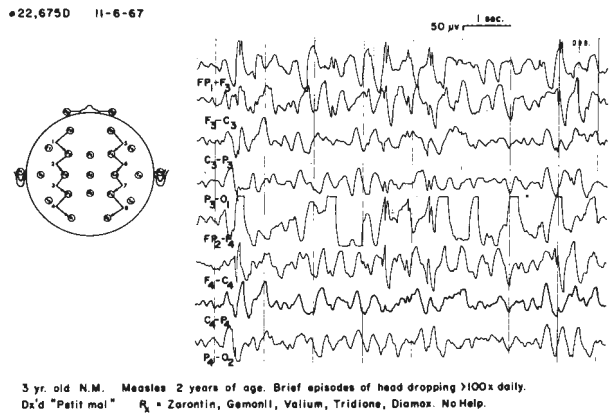


Fig. 1*A*—Frequent, partial, complex seizures in a three-year-old boy diagnosed as "petit mal" without success.

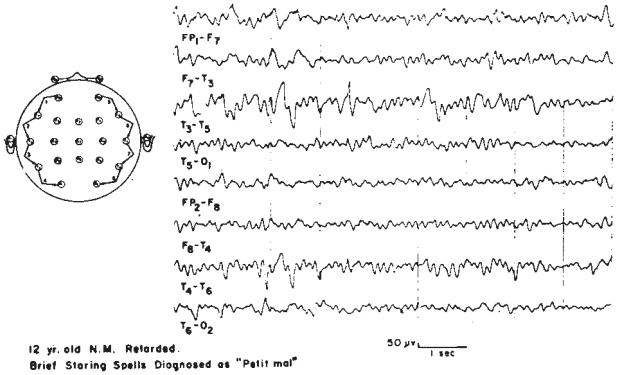


Fig. 2—Temporal lobe seizures in a 12-year-old boy misdiagnosed as "petit mal."

may be more incapacitating than the seizures themselves. Among the phenothiazines, however, the epileptogenic effect is variable. For example, chlorpromazine (Thorazine®) is a much stronger epileptogenic agent than thioridazine (Mellaril®); the use of the latter drug is more strongly preferred of the two.

Drug Specificity for the Disease. Whereas in therapeutic doses, anticonvulsants have in common the characteristic of raising the threshold of the seizure discharge, clinical experience has revealed that some of the anticonvulsants are more useful for specific forms of seizures. The review study by Coatsworth (6) has demonstrated that ethosuximide is more effective in the treatment of petit mal. Trimethadione is less effective in petit mal and is not effective in treatment of generalized convulsive seizures. Primidone is more helpful in the treatment of limbic (psychomotor) seizures and is not effective in petit mal seizures. If these guidelines are used, the medical treatment will be more successful (Table 2).

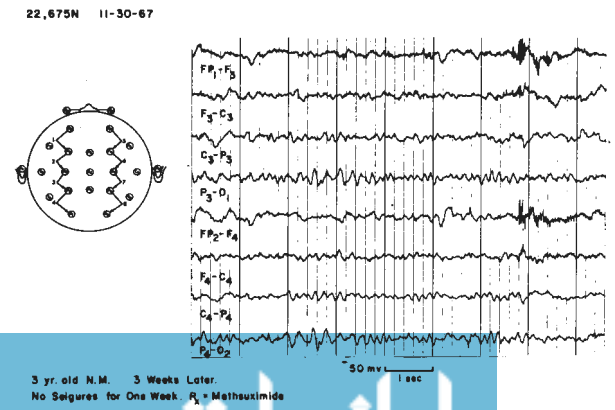


Fig. 1*B*—Methsuximide, 300 mg per day, stopped the seizures.

It should be kept in mind that an anticonvulsant may be very effective experimentally for a specific form of seizure, but it may have a narrow safety range measured by toxic dose compared to effective dose (7) (Table 2). The toxic side effects will limit the usefulness of such an anticonvulsant. This is true for trimethadione and phenacemide. Phenacemide, an anticonvulsant tried for treatment of temporal lobe seizures, is so toxic that its use is unwarranted (6).

The Nature of the Disease for Which the Drug is Used. Therapeutic failure may be the result of *incorrect diagnosis* such as the treatment of hysterical seizures with anticonvulsants. Other examples may include treatment of psychosensory seizures originating from the temporal lobe, misdiagnosed as petit mal, with medications for petit mal seizure or treatment of complex infantile seizures as "petit mal" seizures (Figs. 1, 2).

Electroencephalography (EEG) can be a priceless tool in confirming the diagnosis. One cannot always rely on clinical expertise and judgment in diagnosis of seizure disorder; EEG must be used as a guideline for accurate diagnosis and treatment.

Accurate diagnosis of etiologic factors in seizure disorder is most important in the treatment of *neonatal seizures.* More than half of these neonatal seizures may be caused by correctable factors such as calcium, magnesium, glucose, or pyridoxine metabolism disturbance (8). If instead of correcting these metabolic disturbances, anticonvulsants in large doses are used, the infant can easily be born toxic.

The problem of the "breakthrough effect" can play a significant role in drug toxicity. This problem refers to the phenomenon of the loss of control of seizures despite adequate therapeutic blood levels of

anticonvulsants after a few months or years of successful treatment. Some anticonvulsants are more apt to develop this problem. These include acetazolamide (Diamox®), nitrazepam (Mogadon®), and, to a lesser extent, diazepam (Valium®) and clonazepam (Clonopin®).

In our experience, the breakthrough effect may also be related to the etiologic factors. In rare cases of slow-growing gliomas with temporal or frontal lobe seizures, the breakthrough effect may herald the presence of the tumor *years before the tumor can be visualized by contrast studies.*

The Mode and Frequency of Medication. The route and the frequency of administration of anticonvulsants plays a role in efficacy and toxicity. The frequency of administration should be approximately equal to the half-life of the drug (which is quite different from one drug to another).

Diphenylhydantoin (DPH). The approximate half-life of DPH in man ranges from 4–50 hours according to various studies. The mean figure is 22 hours. Unfortunately, all patients do not fall in the mean rate of plasma half-life. As a result, single-dose administration of DPH can cause fluctuations of the drug level in the blood in a small number of patients causing confusion in treatment. This method, which apparently can be quite effective in adults (9), can cause some complication in children. In our experience, a single-dose administration of DPH can be irritative to the stomach, causing nausea and vomiting. There is no need, however, of dividing the dosage of DPH to more than two times per day. *This drug should never be given intramuscularly (IM),* but can be administered intravenously or by mouth; IM use causes necrosis of muscle and DPH is not transferred to the blood from the muscle in any significant therapeutic dose. *DPH should not be mixed with other IV fluids* because it is strongly alkaline.

Long-term administration of over 7 mg/kg of DPH causes lethargy, drowsiness, diplopia, confusion, and ataxia; ataxia and nystagmus are crude signs of toxicity. Rarely, hyperactivity, poor school performance, psychosis, hallucinations, and delusions may result. Hirsutism, seen in three-fourths of all patients taking DPH, is annoying but not serious. Gum hypertrophy is also frequently seen and can become so severe as to necessitate excision.

Morbilliform rash may occur in 2% of patients; in these cases, DPH will have to be discontinued. Even though some patients can later be restarted on the drug, this is a risky practice. The rare complications of blood dyscrasia and hepatitis definitely necessitate the permanent discontinuation of all hydantoins.

A common benign side effect of DPH is lymphadenopathy. We have seen this to be misdiagnosed as lymphoma or lymphosarcoma. Lupus erythematosus (LE) is a rare complication which clears up after the discontinuation of DPH. The family history is positive for LE in one-fifth of these patients. Another rare complication of DPH therapy is a mild megaloblastic anemia which can be corrected with 0.1 mg folic acid daily.

Phenobarbital. This anticonvulsant has a half-life of three-to-six days in man. As a result, a single daily dose should be efficient and effective. This single dose is best given at bedtime.

The main side effect of this drug is drowsiness and/or aggravation of preexisting hyperactivity. This side effect can be effectively overcome by the addition of methylphenidate (Ritalin®), 10–30 mg in divided doses in the morning and at noon. A scarlatiniform rash may develop in 2% of patients. This necessitates discontinuation of the drug as does allergic erythematosus rash.

Primidone (Mysoline®). This drug has a plasma half-life of 4–19 hours in man with a mean of eight hours. It should not be given as a single dose, and preferably should be given every four-to-eight hours; tolerance to this drug develops slowly.

Diazepam (Valium®). This drug is effective mainly as an anticonvulsant for the control of status epilepticus. It should be given in IV form in frequent doses. The half-life of this drug is not more than three

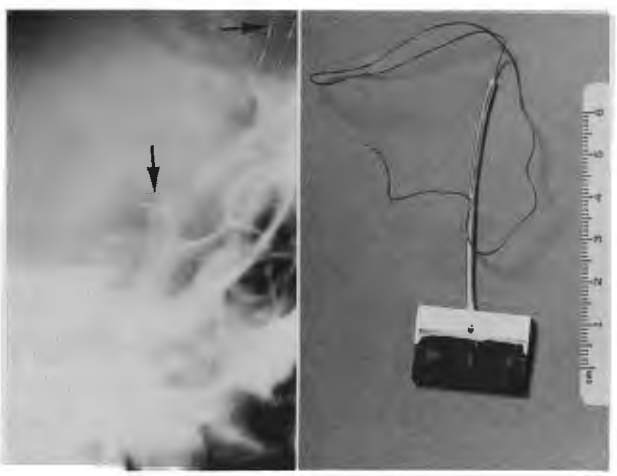


Fig. 3—Manning (16) depth electrode. (*Right*) The depth electrode with six exposure points 5–10 mm apart. (*Left*) The electrodes seen in the middle fossa and anterior fossa of the skull. Arrows show points of exposure.

TABLE 5
Cases of Intractable Seizures Excluded After Adjustment of Standard Rx*

Undermedication	6
Drug interaction	4
Drug toxicity	1
Wrong diagnosis and Rx:	
petit mal vs limbic seizures**	4
petit mal vs complex seizures***	5
hyperventilation syndrome	1
conversion reaction	2
1 hypoglycemia, 1 lead poisoning and 1 congenital heart disease	3
Total	26

* Of the 70 patients referred for intractable seizure, 26 were satisfactorily treated after correction of diagnosis or adjustment of medication.

** One case treated successfully with primidone alone, three cases with carbamazepine.

*** All five responded favorably to methsuximide.

hours. As a result, frequent injections should be given until the seizure is under control. Diazepam should not be given IM or by mouth for the treatment of status epilepticus; neither should it be mixed with other IV medications; it is most incompatible with most other IV fluids. This incompatibility manifests itself in the form of venous blood coagulation and pulmonary embolus, which may have been the major factor in blaming this drug for the rare complications of respiratory arrest and death that are due to benzodiazepines.

Clonazepam. This is an effective anticonvulsant in the treatment of petit mal as well as complex minor motor seizures (10, 11). Its half-life is five-to-six hours and it should be given by mouth every six hours. The major side effects are drowsiness (when given in toxic doses) and aggravation of hyperactivity. The hyperactivity can be corrected by treatment with methylphenidate (Ritalin®).

Trimethadione. Because of the high tendency for toxicity in the form of skin rash, blood dyscrasias, as well as hemeralopia, and because the diones are not as effective anticonvulsants as succinimides (6), we

TABLE 6
Results of Treatment with Clonazepam in 44 Cases of Uncontrollable Seizures

Type of Seizures	Number of Cases	EEG	Follow-up EEG*	Results of Rx**
Petit mal (absence)	5	Gen. S & W	Infrequent or no S & W; focal S 2 cases; slow background 3 cases	++++ 3 cases ± 2 cases
Photic sensitive	3	Photoconvulsive	Normal	++++
Petit mal status (absence-continuing)	1	Cont. S & W	Slow background No S & W	++++
Sylvian	1	Mid-temporal S	Less frequent S	++++
Myoclonic	5	S & W plus frontal or temporal S	No change	+++ 3 cases ± 2 cases
Temporal lobe (psychomotor, psychosensory)	7	Temporal S	Slightly less frequent S	++++ 4 cases ±*** 3 cases
Focal cortical	4	Focal S (motor 3, Occip. 1)	No change	++ 3 cases ± 1 case†
Akinetic	10	S & W, poly S 8‡ plus frontal 3 temporal S 2 hemispheric 1	±	+++ 6 cases ++ 2 cases ± 2 cases
Complex (akinetic and myoclonic)	7	Focal or gen. multiple spikes	±	± 6 cases ++ 1 case
Infantile spasm	2	Hypsarrhythmia	No change	− 2 cases

S & W—spike and waves

* Low voltage fast activity was invariably present

** 4+ excellent control, −3+ over 75%, 2+ over 50%, + over 25% decrease of seizures, − no change

*** ± temporary effect

‡ Simultaneous EEG anomalies were common

† Expired (meningitis)

TABLE 7
Results of Surgical (Ablation) Therapy in Eight Intractable Seizure Patients with a Two-to-Eight Year Follow-up

Seizure	X-Ray Fingings	Age at Onset of Seizures	Age at Surgery	Procedure	Pathology	Seizure Control* After 2–7 Years
Psychomotor	Neg	8 yrs	14 yrs	temporal lobectomy	glioma III	++**
Psychomotor	Neg	9 yrs	15 yrs	temporal lobectomy	oligodendro-glioma	+++
Akinetic	Neg	11 yrs	17 yrs	temporal lobectomy	no lesion	+++
Akinetic	Neg	9 yrs	21 yrs	temporal lobectomy	gliosis	++++
Akinetic & adversive	Neg	2 yrs	6 yrs	frontal lobe section	AV malformation	++++
Akinetic & grand mal	Neg	12 yrs	22 yrs	frontal lobe section	gliotic cyst	++++
Complex (akinetic, focal, gen.)	Hemiatrophy	Birth	11 yrs	Hemi-spherectomy	atrophy	++++
Grand mal	R. occip. cyst	1 yr	19 yrs	Removal of cyst	gliosis	±†

* 4+ excellent control, −3+ over 75%, 2+ over 50%, +over 25% decrease of seizures, − No change
** 4 years postop, post Ro-Rx, and post chemo-Rx
† Died of *E. coli* meningitis 13 months postop

have abandoned the use of this drug altogether. The usual dose in children with petit mal is 300–900 mg/-day in two-to-three doses.

Succinimides. At present, ethosuximide (Zarontin®) is the drug of choice for petit mal seizures (6). It can aggravate generalized convulsive episodes in akinetic and temporal lobe seizure patients (12). Because of its long half-life, once- or twice-daily doses should be sufficient. It is metabolized as quickly in children as in adults.

Methsuximide (Celontin®). In our experience, this has been a very useful drug in the treatment of difficult to control (akinetic, myoclonic, etc.) seizures. One daily dose seems to be sufficient. It has more tendency for toxic side effects than does ethosuximide (Table 2). Phenylsuccimide, a biproduct of this drug, has a long half-life and can cause deep coma (13).

Carbamazepine (Tegretol®). Because of fluctuation in blood levels, this drug should be administered three-to-four times daily. Blood levels of over 7 μg/ml may result in ataxia, nausea, diplopia, dysarthria, and drowsiness, all dose-related (Table 2).

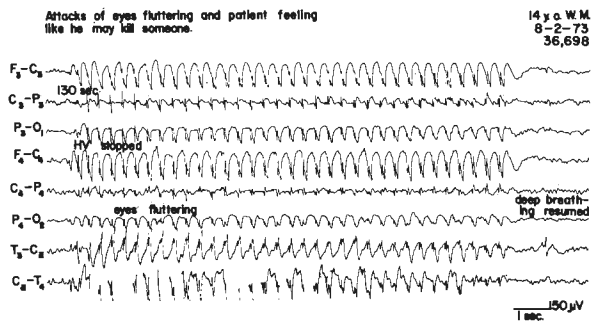


Fig. 4—EEG of 14-year-old boy suffering from psychosensory seizures with concomitant fluttering of eyes. Note 3/sec S&W followed by a left temporal spike transient. Poor response to ethosuximide treatment.

TABLE 8
Outcome of 70 Cases of Difficult Seizure Control with Two-to-Eight-Year Follow-up

Management	Patients	Successful Rx
Drug adjustment, misdiagnosis	26	23
Clonazepam	44*	27
Surgery	[8]*	6
Total	70	56
Failures—14 cases (20%)**		

* The surgical cases were from the clonazepam failure group.
** The failure rate was descreased from 100% to 20%.

TABLE 9
Results of Medical and Surgical Treatment in 32 Patients Suffering from Akinetic Seizures*

	Patients	Intractable
Lennox syndrome (age at onset birth–5 yrs, average IQ 78)	7	5
Complex Akinetic (age of onset 1–12 yrs, average IQ 82) and Myoclonic	18	6
Late Onset Akinetic (age of onset 5–13 yrs, average IQ 89)	7	—
Total	32	11

* Note the relationship of patients' age to the prognostic response to therapy—the later the age of onset of the disease, the better the prognosis.

Rare serious, allergic-type complications of blood dyscrasia, hepatitis, and skin rash may necessitate discontinuation of this drug (14); however, this drug can be quite safe and effective in the treatment of seizure disorders in children (15).

Adrenocorticotrophin (ACTH). This is the drug of choice in infantile spasm. Although it can cause cushingoid features, this side effect is worth coping with. Every-other-day dose decreases this side effect.

Management of Intractable Seizures. The following is our experience with the management of intractable seizures.

Material and Method. Seventy intractable partial seizures were studied and followed for two-to-eight years. Patients who demonstrated the evidence of brain tumor or arteriovenous (AV) malformation on contrast studies were excluded from this study. The 70 patients were evaluated for medical or surgical treatment. Age range was 2–34 years with an average of 14 years. The majority of patients were in childhood and teen-age groups. Thirty-eight were female, 32 were male.

The depth electrode studies were done on the patients who had failed to respond to medical treatment, and regardless of the type of generalized EEG discharges, showed focal spikes in their ictal, interictal, or postictal EEG recordings. Manning (16) depth electrode was used. This is a fine depth electrode, thinner than other types, which can be inserted with little risk of trauma (Fig. 3); its six exposure points, 5–10 mm apart, facilitate recording several points in depth.

The depth studies were performed immediately after contrast studies, psychological tests, as well as an intra-arterial amobarbital test for diagnosis of cerebral dominance. The ventricular air remaining from the air encephalogram was an important guide in locating the position of the depth electrodes. The depth electrode studies consisted of the study of the suspicious focal discharge as well as symmetrical depth electrodes positioned in temporal lobes, frontal lobes, and thalamic nuclei. The temporal lobe electrodes were inserted from the posterior temporal region, advancing towards the amygdaloid nucleus with the tip of the electrodes resting adjacent to this nucleus (Fig. 3). This method would provide a recording from surface to depth, from posterior to anterior aspects of the temporal lobes, and would facilitate localization of the abnormal discharges. An average of ten days-to-two weeks of recordings were done and an attempt was made to record an ictus on depth electrode recording of all patients with the help of all-night EEG recordings or EEG telemetry recordings.

Results. Twenty of the patients were helped by adjustment of standard medical treatment (Table 5). Six patients were found to have been misdiagnosed. This group consisted of one patient with lead poisoning, one with hypoglycemia, and one patient with congenital heart disease.

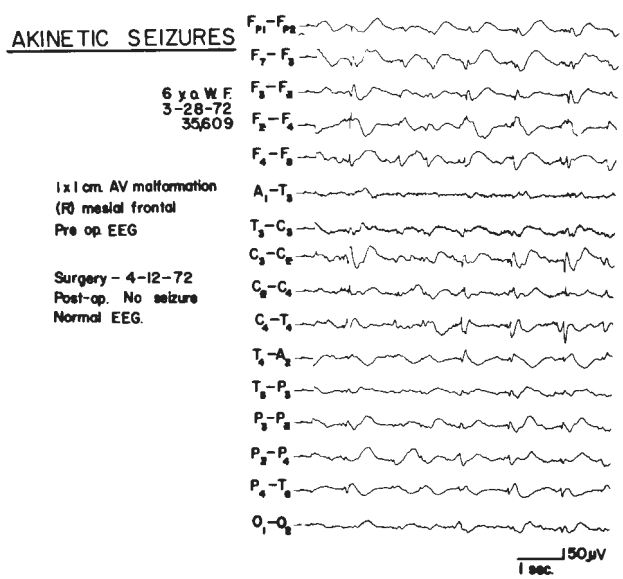


Fig. 5—Six-year-old girl suffering from intractable seizures. Surface EEG recording shows slow S&W. EEG returned to normal after removal of a right mesial frontal AV formation.

The remaining 44 patients were tried on a benzodiazepine—clonazepam (Table 6). This drug was most effective in petit mal, petit mal status, and photosensitive seizures. It was less effective in complex seizures and infantile spasm (hypsarrhythmia).

Of the 27 patients who failed to respond to clonazepam therapy, 15 underwent depth electrode studies. Of these 15 patients, eight eventually had surgical treatment. These eight patients were selected after the depth electrode studies revealed that the epileptogenic focus was the source of the patients' clinical seizures and was amenable to surgical treatment (Table 7).

Despite the fact that repeated angiography and air encephalography performed in intervals as far apart as three-to-six years were negative before operation, with the help of depth electrodes, lesions such as tumors and AV malformation were found at the site of epileptogenic focus (Table 7). The end result was a drop of failure rate from 100% before the study to 20% at the completion of this study (Table 8).

Discussion. The clinical and surface EEG diagnoses are not always accurate. The interictal surface EEG findings do not necessarily correlate with the region of the epileptogenic focus, and may not be localizing in even half of the partial, adversive, or controversive seizures (17, 18). Simultaneous depth and surface recordings in patients with petit mal epilepsy reveal inconclusive data regarding the site of origin of both the spike and slow wave discharges (19–21).

Experimentally in the monkey, the electrical and behavioral characteristics of petit mal epilepsy have been demonstrated by the production of bilateral cortical epileptogenic foci (22). It has been shown that the focal cortical paroxysmal discharge has a tendency for subcortical propagation before maturation and a tendency for cortical propagation after maturation (23). A synchronized EEG discharge is not necessarily synonymous with subcortical origin. A cortical focus can give rise to similar seizure manifestations (29). In occasional cases, the suppression of the generalized 3/sec spike and wave (S & W) discharges by medication may help demonstrate the cortical epileptogenic focus (10). The diagnosis of petit mal does not necessarily point to a subcortical origin for the generalized discharges, and occasionally, a limbic system focus may mimic the petit mal attacks (Fig. 4). The limbic system has been demonstrated to extend to subcortical structures as well (30). Even in the cases of "typical petit mal," the generalized S & W on EEG may be accompanied by complex behavior and automatism which may be environmentally influenced (31, 32). They may be accompanied by increased or decreased postural tone of the body (31, 32). The above may explain the complexity of the subject partial seizures and the problem of misdiagnosis or incorrect treatment.

A large number of patients in this study (Tables 6, 7) suffered from akinetic seizures. This form of seizure (33–35) may be accompanied by slow S & W discharges on EEG—the "petit mal variant" (36, 37). The akinetic and atonic seizures seem to form a syndrome variable in etiologies as well as in EEG findings. The "Lennox syndrome" (37), a name which has been used synonymously for these seizures, is characterized by 1) *age of onset,* usually below six years of age; 2) *complex seizure manifestations,* such as akinetic and myoclonic seizures; 3) *retardation;* 4) *resistance to treatment;* and 5) *generalized slow S & W discharges plus other abnormalities* in three-fourths of cases (38, 39). Whereas this syndrome comprises the majority of akinetic seizures in young children who are also retarded, it does not encompass the entire spectrum of akinetic seizures.

When the akinetic seizures occur in the older age patients, or in patients who do not have other aspects of Lennox syndrome (such as retardation), the prognosis seems to be more favorable. This is reflected clearly in our study of 32 akinetic seizure patients (Table 9). The EEG findings, usually that of slow S & W discharges in Lennox syndrome, may demonstrate focal discharges in older age patients (40–44). Our depth electrode studies confirm cortical origin of the epileptogenic focus in some of these patients (Figs. 5, 6; Table 7).

Depth electrode studies may be very helpful in care of seizure patients if the following minimal criteria are met: 1) the use of the *thinnest possible depth electrodes;* 2) a *suggestion of focal discharges* on surface recording; 3) the confirmation of cerebral dominance by intra-arterial *amobarbital test* before any surgical procedure; and 4) the *recording of the ictal event* from the surgically resectable epileptogenic focus.

In our experience (Table 7), repeated negative contrast studies over the years do not rule out the possibility of brain tumor or AV malformation as the cause of seizure disorder (Fig. 5). Crandall (45), in his experience with depth electrode studies in seven intractable partial seizures, noted one patient suffering

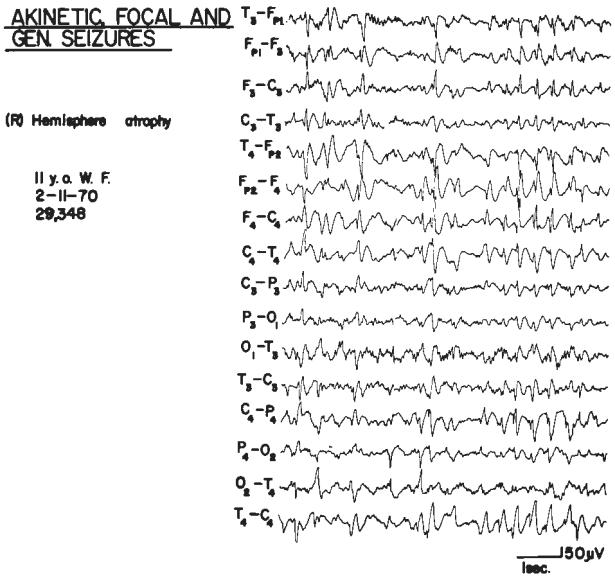


Fig. 6A—Eleven-year-old girl with intractable seizures and left-sided hemiplegia since birth. Surface EEG recording shows bilateral multispikes.

from corpus callosum astrocytoma who suffered from attacks of becoming rigid and falling backward as well as psychomotor seizures. This patient, along with another patient who had a small meningeal angioma, had negative contrast studies. Page et al.

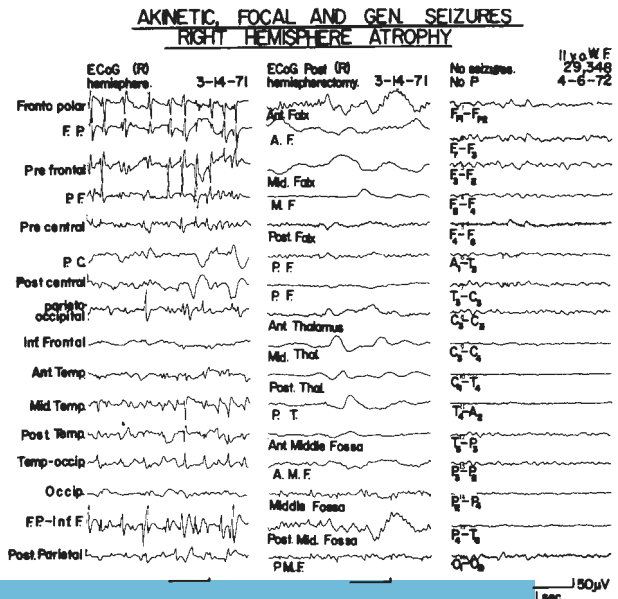
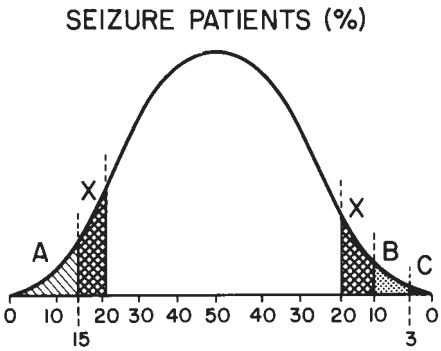


Fig. 6B—Electrocortiography (ECoG) before and after hemispherectomy. Right-postoperative surface EEG shows no more spikes. Patient is seizure free. No more need for anticonvulsant therapy.



A UNDER-MEDICATION ; OR WRONG TREATMENT
B TOXICITY ; OR WRONG DIAGNOSIS
C SURGICAL TREATMENT ; PROGRESSIVE LESIONS
X PARTIAL CONTROL

Fig. 7—Comparison of the results of therapy among seizure patients referred to the seizure control clinic. As noted, undermedication and overmedication comprise the majority of failure cases.

(46), while underlining the importance of brain tumor as the causative factor in rare cases of childhood seizure disorders, emphasized the fact that a change of seizure pattern in EEG or in behavioral school performance should make one suspicious of the possibility of brain tumor as the causative factor.

It is concluded that with adjustment of treatment, accurate diagnostic work-up, trial of new anticonvulsants, and surgical therapy for partial seizures, the failure rate may drop from 100% to 20% (Table 8, Fig. 7).

Prevention of Seizure Disorders. The knowledge about seizure disorders has advanced to the point of considering prevention.

Prenatal Prevention. Maternal toxoplasmosis, syphilis, and cytomegalovirus infections should be diagnosed and aggressively treated. Maternal hygiene and nutrition play a role in the size of the child. The low birth-weight children are at risk for neonatal seizure disorders.

Neonatal and Infantile Prevention. Early diagnosis and effective treatment of neonatal meningitis can prevent the late complications of intractable seizures. Immunization, especially for measles and mumps, should be strongly encouraged. Febrile seizures should be aggressively treated and prevented by antipyretic and anticonvulsant (phenobarbital) therapy to prevent mesial and temporal anoxic damage and subsequent late-onset temporal lobe seizures.

Prevention of Head Injury. Prevention of head injury by the use of seat-belts in the car, and by encouraging the schools to avoid building cement floors under swings in the playground can be helpful.

The Role of Eugenics. The role of eugenics is limited to such diseases as Huntington's chorea, phenylketonuria, and mucopolysaccharidosis; however, intermarriage among families with high risk seizure disorders may be discouraged.

Psychosocial Aspects. This is one area where unfortunately no recent progress has been made. The general public still has a medieval attitude toward epileptics. More education for the public as well as for health officials is needed.

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