



Prediction of the initial antiepileptic drug for pediatric seizure patients : a multivariate analysis of historical, clinical and EEG data
by Jeffrey Ivan Hunt

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in
Biological Sciences
Montana State University
© Copyright by Jeffrey Ivan Hunt (1983)

Abstract:

This study was performed to seek better parameters for predicting optimal anticonvulsant therapy for pediatric seizure patients. Qualifications for admission were: 1) a diagnosis of a seizure disorder; 2) at least one EEG; 3) anticonvulsant therapy with one of the following: phenobarbital, phenytoin, carbamazepine, or valproic acid; and 4) adequate follow-up to assess drug efficacy.

Pertinent data was extracted from each of the patient's records and was evaluated using multivariate analysis. Discriminant analysis was performed using 16 variables that were significant on ANOVA and contingency tables ($P < .05$). Sixty-five percent of the original study patients were correctly classified by the discriminant functions ($N=155$). Forty-seven percent were controlled on the initial drug selected by their physician. Twenty-five percent would be expected to be correctly classified by chance.

In this population a 2-3 year gap existed from the time of onset of seizures to the time the seizure controlling drug was instituted. Use of the derived formula may be able to eliminate this period of less than optimal control. A prospective study is planned to evaluate the efficacy of routinely using a formula to choose an anticonvulsant drug.

PREDICTION OF THE INITIAL ANTIEPILEPTIC DRUG FOR PEDIATRIC
SEIZURE PATIENTS: A MULTIVARIATE ANALYSIS OF
HISTORICAL, CLINICAL AND EEG DATA

by
Jeffrey Ivan Hunt

A thesis submitted in partial fulfillment
of the requirements for the degree

of
Master of Science
in
Biological Sciences

MONTANA STATE UNIVERSITY
Bozeman, Montana

March, 1983

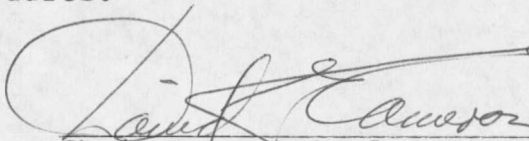
APPROVAL

of a thesis submitted by

Jeffrey Ivan Hunt

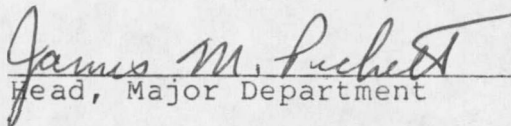
This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

3 March 1983
Date


Chairperson, Graduate Committee

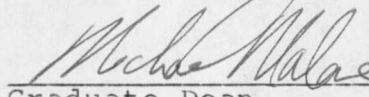
Approved for the Major Department

3/3/83
Date


Head, Major Department

Approved for the College of Graduate Studies

3-3-83
Date


Graduate Dean

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a master's degree at Montana State University, I agree that the Library shall make it available to borrowers under rules of the Library. Brief quotations from this thesis are allowable without special permission; provided that accurate acknowledgment of source is made.

Permission for extensive quotation from or reproduction of this thesis may be granted by my major professor, or in his absence, by the Director of Libraries when, in the opinion of either, the proposed use of the material is for scholarly purposes. Any copying or use of the material in this thesis for financial gain shall not be allowed without my written permission.

Signature

Jeffrey J. Hunt

Date

2/28/83

ACKNOWLEDGMENTS

I gratefully acknowledge the guidance and assistance of Dr. J. V. Murphy and Dr. R. J. Hoffman, Milwaukee, Wisconsin, throughout this project. Thanks also to the following people who constructively reviewed the protocol and/or this manuscript: Dr. D. G. Cameron, Dr. P. D. Pallister, Dr. J. M. Opitz, Dr. C. M. Paden, Dr. J. A. McMillan and Dr. E. R. Vyse. This study was funded in part by a grant from the Milwaukee Chapter of the March of Dimes.

A special thanks to my parents for all their help and support and to Cheryl Flynn for her timely encouragement.

TABLE OF CONTENTS

	Page
1. INTRODUCTION	1
2. GENERAL COMMENTS ON EPILEPSY	4
3. CLASSIFICATION OF THE EPILEPSIES	6
Generalized Seizures.	7
Absence Seizures.	10
Partial (Focal) Seizures.	13
Precipitants of Seizures.	16
Etiology.	18
4. ANTIEPILEPTIC MEDICATION	19
Mechanism of Action of Antiepileptic Medicine	19
Individual Drugs Used by Patients in this Study	21
Phenytoin.	21
Phenobarbital.	23
Carbamazepine.	24
Valproic Acid.	25
5. POLYTHERAPY VS. MONOTHERAPY.	27
6. DISCRIMINANT ANALYSIS AND FACTOR ANALYSIS.	35
Study Goals	39
7. PATIENTS AND METHODS	40
Patients.	40
Assessments of Historical, Clinical and EEG Data	40
Seizure Control	41
Statistical Evaluation.	41
8. RESULTS.	47
9. DISCUSSION	83
Summary	100

TABLE OF CONTENTS (Continued)

	Page
REFERENCES CITED	101
APPENDICES	108
Appendix I.	109
Historical and Clinical Data	110
Appendix II	114
EEG Data	115

LIST OF TABLES

	Page
1. STUDY POPULATION CHARACTERISTICS	48
2. PAST DRUG HISTORY OF PATIENTS CURRENTLY ON MONOTHERAPY	49
3. RESPONSE TO TREATMENT.	51
4. CHI-SQUARE TEST FOR RELATIONSHIP BETWEEN VARIABLE AND DRUG TYPE: FREQUENCIES	52
5. CHI-SQUARE TEST FOR RELATIONSHIP BETWEEN VARIABLES AND DRUG TYPE.	56
6. ANALYSIS OF VARIABLE	57
Age at Onset of Seizure	57
7. ANALYSIS OF VARIABLE	57
Age at Administration of Current Drug	57
8. RESULTS OF STEPWISE DISCRIMINANT ANALYSIS.	58
9. VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS OF ENTIRE POPULATION.	59
10. DISCRIMINANT FUNCTION COEFFICIENTS: ENTIRE POPULATION.	60
11. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS OF ENTIRE POPULATION.	61
12. VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS OF MALES	62
13. DISCRIMINANT FUNCTION COEFFICIENTS: MALES	63
14. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS OF MALES ONLY	64
15. VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS OF FEMALES.	65
16. DISCRIMINANT FUNCTION COEFFICIENTS: FEMALES	66

LIST OF TABLES (Continued)

	Page
17. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS OF FEMALES ONLY.	67
18. VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS WHEN PATIENTS ON CARBAMAZEPINE AND PHENYTOIN WERE COMBINED INTO A SINGLE GROUP . . .	68
19. DISCRIMINANT FUNCTION COEFFICIENTS: PHENYTOIN AND CARBAMAZEPINE AS ONE GROUP. . . .	69
20. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS WHEN PATIENTS ON CARBAMAZEPINE AND PHENYTOIN WERE COMBINED	70
21. VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS WHEN PATIENTS ON CARBAMAZEPINE, PHENYTOIN AND PHENOBARBITAL WERE COMBINED INTO A SINGLE GROUP	71
22. DISCRIMINANT FUNCTION COEFFICIENTS: PHENYTOIN, CARBAMAZEPINE AND PHENOBARBITAL AS ONE GROUP.	72
23. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS WHEN PATIENTS ON CARBAMAZEPINE, PHENYTOIN AND PHENOBARBITAL WERE COMBINED . . .	72
24. VARIABLES IN ORDER OF VALUE IN THE DISCRIMINANT ANALYSIS OF PATIENTS TREATED WITH ONLY ONE DRUG DURING ENTIRETY OF TREATMENT	74
25. DISCRIMINANT FUNCTION COEFFICIENTS: PATIENTS WHO HAVE BEEN TREATED WITH ONLY ONE DRUG DURING ENTIRETY OF TREATMENT	75
26. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS OF PATIENTS TREATED WITH ONLY ONE DRUG DURING ENTIRETY OF TREATMENT	76
27. VARIABLES IN ORDER OF VALUE IN THE DISCRIMINANT ANALYSIS OF PATIENTS WITH A HISTORY OF DRUG THERAPY OTHER THAN CURRENT DRUG.	77

LIST OF TABLES (Continued)

	Page
28. DISCRIMINANT FUNCTION COEFFICIENTS: PATIENTS TREATED WITH OTHER DRUGS IN PAST . . .	78
29. CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS OF PATIENTS TREATED WITH OTHER DRUGS IN THE PAST	79
30. FACTOR ANALYSIS WITH NINE FACTORS PRODUCED. . .	81
31. FACTOR ANALYSIS WITH SEVEN FACTORS PRODUCED . .	82
32. EXAMPLE OF DISCRIMINANT ANALYSIS CLASSIFICATION: PROFILE OF PATIENT #10	95
33. EXAMPLE OF DISCRIMINANT ANALYSIS CLASSIFICATION: PROFILE OF PATIENT #110. . . .	96

ABSTRACT

This study was performed to seek better parameters for predicting optimal anticonvulsant therapy for pediatric seizure patients. Qualifications for admission were: 1) a diagnosis of a seizure disorder; 2) at least one EEG; 3) anticonvulsant therapy with one of the following: phenobarbital, phenytoin, carbamazepine, or valproic acid; and 4) adequate follow-up to assess drug efficacy. Pertinent data was extracted from each of the patient's records and was evaluated using multivariate analysis. Discriminant analysis was performed using 16 variables that were significant on ANOVA and contingency tables ($P < .05$). Sixty-five percent of the original study patients were correctly classified by the discriminant functions ($N=155$). Forty-seven percent were controlled on the initial drug selected by their physician. Twenty-five percent would be expected to be correctly classified by chance.

In this population a 2-3 year gap existed from the time of onset of seizures to the time the seizure controlling drug was instituted. Use of the derived formula may be able to eliminate this period of less than optimal control. A prospective study is planned to evaluate the efficacy of routinely using a formula to choose an anticonvulsant drug.

CHAPTER 1

INTRODUCTION

The reason for performing this study is to seek better parameters for predicting optimal anticonvulsant therapy for seizure patients and to use them in a predictive formula.

The nature of therapeutic drug administration for chronic seizure patients is largely empiric. Clinicians frequently try several anticonvulsants before adequate control is achieved. Prediction of such response in any seizure patient is difficult. Systems of classifications of seizures, that ideally serve as a guide to treatment, exist, but no form of classification is universally accepted despite attempts to make them so (Livingston et al., 1979).

Clinician experience is of great importance in treatment and prognosis yet such experience produces inconsistent results. Patients with similar seizures are not always controlled with the same medication. Clearly the current state of drug therapy could be improved if the factors that contribute to individual differences in response were known.

The failure to predict an adequate response to anticonvulsant therapy may lead to a trial and error approach; the consequences often being an arithmetic

accumulation of medication. This polypharmaceutical approach, in turn, leads to a less than optimal response from the patient due mainly to the difficulty the clinician has in differentiating between the observed effects of the medications (Livingston et al., 1979). Problems that do arise, e.g., toxicity, other adverse effects, or inadequate control, usually results in the raising, lowering, or withdrawing many or all of the drugs, when, in fact, the observed effect likely was the result of a single drug (Livingston et al., 1979).

A polypharmaceutical approach may also be less efficacious. Shorvon et al. (1980) have demonstrated, in a population of seizure patents reduced to monotherapy, a marked reduction in seizure frequency, with some patients becoming completely seizure free. Single drug therapy is best, but it is known that the clinician often has little choice but to try various combinations of drugs in an attempt to provide adequate control. It is when combinations of drugs are tried that precision is lost (Livingston et al., 1979).

Perhaps a more efficient utilization of a patient's historical, clinical and electroencephalographic data would better enable a clinician to treat seizures. This study is a statistical evaluation of routinely collected data; it attempts to reveal heretofore undiscovered factors that favorably or unfavorably influence the therapeutic outcome

of patients with seizure disorders treated with a single drug. In addition, a formula using the predictive factors to choose a drug for a particular patient is evaluated.

CHAPTER 2

GENERAL COMMENTS ON EPILEPSY

Seizures are a common medical problem. Approximately 9% of the population will have at least one seizure during their lifetime, 3% will have more than one and slightly more than 2% will have only febrile seizures (Brown, 1982). Seizures may occur as the first sign of an acute disease and may be single, multiple, or continuous and may occur only in the acute phase or persist for the rest of the patient's life. They may be due to actual pathology of the brain, or be part of generalized systemic disorders such as poisoning, septicemia or metabolic disease (Brown, 1982). Seizures may have a genetic component predisposing otherwise normally intelligent people to have seizures. They can be associated with mental retardation, dementia, cerebral palsy, learning disorders and organic brain problems (Laidlaw and Richens, 1982). Seizures can increase the risk of permanent brain damage if allowed to persist unabated (Rodin, 1968).

Seizures were described by John Hughlings Jackson as "an occasional, an excessive and disorderly discharge of nerve tissue" (Marsden and Reynolds, 1982). The symptoms of a seizure are the result of the excessive and disordered cerebral activity. The term epilepsy is difficult to define. The seizure itself, the disease causing the

seizure, the precipitating cause of the seizure, and the consequences of it all contribute to the overall picture of epilepsy. It is generally agreed that a cardinal feature of epilepsy is a tendency for recurrent seizures. A single seizure is not, therefore, epilepsy.

Epilepsy comprises a series of phenomena, each of which poses a different question. The epileptic has a predisposition to recurrent seizures determined by a variety of causes some identifiable but most unknown. Given a predisposition to seizures the individual attack is triggered by a precipitating cause which can be identified in some cases but is not apparent in many. Biochemical and electrical events occur in the brain during the attack to cause the symptoms and signs of the seizure.

To the clinician it is the differences between the various types of seizures that is important (Marsden and Reynolds, 1982). The clinician is committed to dividing seizures into subgroups in order to prescribe the best medication to the individual patient. A cornerstone of the clinician's management of the epilepsies is their classification (Marsden and Reynolds, 1982).

CHAPTER 3

CLASSIFICATION OF THE EPILEPSIES

The terminology and classification of seizures has evolved over many years creating a variety of interchangeable and confused descriptive terms. The problem has been and is to create a single code to cover three basically incompatible systems of classification, namely, that according to clinical symptoms and signs of the seizure; that relating to the anatomical and electrophysiological evidence as to the source of the seizure; and that defining the cause of the seizure (Marsden and Reynolds, 1982).

The International League Against Epilepsy under Henry Gastaut (1969) formulated a comprehensive classification of seizures to include clinical seizure type, EEG seizure type, EEG interictal expression, anatomic substrate, cause, age, presence or absence of interictal neuropsychiatric changes, the response to therapy and pathophysiology. This was a mammoth classification that was not widely accepted (Marsden and Reynolds, 1982). The problem concerned satisfying the needs of clinicians who require information about prognosis with or without treatment and the needs of research who require detailed information about seizure type that can be readily understood by another lab (Whitty, 1965).

A simplified scheme which highlights some fundamental concepts based on clinical features of seizures and differences in their pathophysiology divides patients into two groups: those with generalized seizures and those with focal seizures. Seizures which start with electrical discharge in both cerebral hemispheres simultaneously are generalized seizures (Gastaut, 1969). Those which start with a focal discharge in one part of the cerebral hemisphere are called focal or partial seizures (Gastaut, 1969). If the affected part of the brain is eloquent the patient experiences an aura, a consciously remembered experience that may be a motor, sensory, visceral or psychic event. The aura points to the part of the brain where the seizure begins (Marsden and Reynolds, 1982). If the site of origin of a seizure is silent the patient may notice nothing until the electrical discharge spreads to an eloquent area or becomes generalized to involve both hemispheres. These are called partial seizures with secondary generalization (Gastaut, 1969).

Generalized Seizures

A typical major-motor or tonic-clonic fit is unmistakable and consists of a tonic phase followed by a clonic phase, the whole lasting up to two minutes followed by a further period of five minutes of unarousable stupor. After this, the patient can be awakened but is confused and disoriented and usually prefers to sleep for a few hours.

The patient may awaken with a headache or muscle soreness but will have a clear mind. A cry at the start, cyanosis, frothing at the mouth, emptying the bladder, biting the tongue, are common, but not universal. During the seizure the pupils may dilate, pulse may slow initially, then accelerate, patient sweats profusely, the plantar response is extensor, and the tendon jerks and corneal reflexes are lost. Inevitably, the patient loses consciousness and falls. Grand mal or generalized convulsive seizures do not always conform to this classical picture but they always involve loss of consciousness and convulsion. On some occasions, the seizure may cease after the tonic phase, while sometimes only the clonic phase occurs. Limited fits such as these are common in children and infants (Marsden and Reynolds, 1982).

Grand mal seizures start 1) with bilaterel synchronous EEG discharge and abrupt loss of consciousness without aura, or 2) may follow an aura indicating a focal origin to seizure with secondary spread and generalization, or 3) may follow focal electrical discharge in silent area of cerebral cortex unbeknown to patient but detectable on EEG (Driver and McGillivray, 1982). The nature and location of the neurophysiological events underlying the generalized seizure, be it generalized from onset or focal in origin with secondary generalization, is unknown. Penfield (1954) introduced the concept of a centrencephalic integrating

system to explain the origin of generalized seizures. Abnormal electrical discharge in this centrencephalic system, i.e., the diencephalon and brain stem cause loss of consciousness and a generalized seizure (of either grand mal or absence type). Grand mal seizure of focal origin occur when the abnormal focal cortical discharge spreads to invade this subcortical centrencephalic region (Penfield, 1952).

In patients with primarily generalized seizures, there is no EEG focus, no aura and no focal clinical event either during or after the attack (Driver and McGillivray, 1982). Penfield (1952) claims that such patients have a disorder of the hypothetical centrencephalic system. This is an attractive but unproven hypothesis. Williams (1965) has evidence against a centrencephalic origin for primary epilepsy. He argues that cerebral tumors and other pathological processes, which are strongly epileptogenic in cerebral cortex, rarely cause seizures when located in the thalamus or other subcortical areas.

Relevant to the debate as to the pathophysiological basis of primarily generalized seizures or secondary generalized seizures is that of seizure threshold. Seizure activity can occur in all vertebrate nervous systems and the propensity for seizures increases in parallel with the phylogenetic scale culminating in the highest incidence in man who has the most complex nervous

system (Marsden and Reynolds, 1982). It is apparent that all human beings are capable of having a generalized seizure as exemplified by convulsive therapy for the treatment of endogenous depression (Driver and McGillivray, 1982). Patients vary, however, in their susceptibility to an induced seizure perhaps due to variation in seizure threshold which is presumably set by unknown genetic, neurochemical and other metabolic processes (McKhann and Shooter, 1969). An unusually low seizure threshold may explain why some patients have spontaneous primary generalized seizures. In others, with a higher threshold, the addition of some insult to the brain, such as a tumor or head trauma, may be enough to precipitate seizures. The concept of seizure threshold may explain why patients with identical cerebral pathology do not all have seizures (Hauser, 1982). Furthermore, it implies that genetic factors play a role in partial seizures as well as in primary generalized attacks (Hauser, 1982).

Absence Seizures

The typical brief staring spells of childhood are called petit mal or absence type seizures. Subsequent to the delineation by Gibbs, Davis and Lennox (1936) of the characteristic paroxysm of three per second bilateral synchronous spike and wave discharge accompanying the petit mal attack, clinicians had a greater understanding of the pathogenesis. For 5 to 10 seconds the child loses

consciousness, his eyes stare and he may show minor movements such as blinking or twitching of the face and arms, but he does not fall. Suddenly consciousness is regained but there is total amnesia for the brief period of the attack. The patient looks around for a moment but then resumes his previous occupation. If engaged in conversation before the attack, he will have missed a sentence or two. Such classical petit mal attacks may occur very frequently up to a hundred or more per day (Lennox, 1945).

Not all absence attacks are as simple as this. More complex phenomena, similar to those seen in temporal lobe epilepsy, may occur associated with an otherwise typical 3 Hz. spike and wave EEG paroxysm (Penry and Dreifuss, 1969). The blank spell may last longer and may be accompanied by lip smacking, chewing, or mouthing movements. These are sometimes referred to as complex absence seizures (Gastaut, 1969). It may be impossible on clinical grounds to distinguish such episodes from temporal lobe seizures (Brown, 1982).

An atypical spike-wave discharge of 2 per second can be confused with simple absences (Driver and McGillivray, 1982). This is known as a petit mal variant discharge, also known as Lennox-Gaustaut syndrome, and is associated with a variety of cerebral pathologies and types of seizure and has a very high incidence of progressive mental

deterioration and poor control (Blume, David, and Gomez, 1973).

Simple absences are uncommon and are said to occur in only about 3 per cent of epileptic patients (Livingston, 1965). Absence spells start before the age of 15 in nearly all cases and cease by the age of 20 in 90% of the patients without progression to grand mal seizures (Sato, Dreifuss, and Penry, 1976). This is in contrast to previous studies suggesting a much higher percentage progressing to grand mal seizures (Livingston, 1965).

The EEG abnormality arises from normal background activity, is synchronous, and symmetrical and in most cases is aggravated by hypercapnia induced by hyperventilation (Driver and McGillivray, 1982). Normal children of the same age as those with petit mal often develop a marked slow wave response at about 3 cycles per second in response to hyperventilation (Driver and McGillivray, 1982). The discharge of 3 Hz. spike and wave may also be produced by photic stimulation and sleep (Driver and McGillivray, 1982).

Twin studies have shown a concordance rate for absence seizures as high as 75 per cent for monozygotic twins (Lennox, 1960). The incidence of a positive family history varies with the selection of cases from 16 to 43 per cent (Millichap and Aymat, 1967). The concordance rate for monozygotic twins with 3 Hz. spike and wave paroxysms on

EEG is 84 percent, although often only one of the twins was clinically affected (Hauser, 1982).

Partial (Focal) Seizure

The typical partial motor fit consists of onset of tonic spasm followed soon by repetitive twitching, usually in the angle of the mouth, thumb or great toe, which then spreads in an orderly manner. The fit is due to a discharge in the opposite motor cortex and the spread or march of the seizure reflects the topography of body representation in the motor cortex strip. The convulsive movements may remain confined to their site of onset or may spread to involve one-half of the body and may terminate in a typical grand mal seizure with loss of consciousness. If the left hemisphere is the source, speech may be lost during the attack. Sensory symptoms are common whichever hemisphere is involved. Whether consciousness is lost during such a partial motor seizure depends on the extent of brain involved. It is retained if the seizure remains confined to origin but is usually lost if half the body is affected (Marsden and Reynolds, 1982). Partial motor fits may be followed by a prolonged period of paralysis of the affected limbs (i.e., Todd's Paralysis).

Another form of motor seizure is an adverse attack due to discharge arising in the pre-motor areas of the frontal lobe (Penfield and Welsh, 1951). Typically the head and eyes are forced away from the affected hemisphere,

usually with preservation of consciousness.

Such seizures are sometimes accompanied by an epigastric rising aura and other symptoms that might be confused with epileptic discharge arising in the temporal lobe (Marsden and Reynolds, 1982).

If the patient retains consciousness, loss of speech or frank dysphasia is almost always associated with seizures arising in the dominant hemisphere involving the anterior speech area of Broca or the patient's temporal speech area (Marsden and Reynolds, 1982). Brief stereotyped utterances (speech automatisms) may occur with seizure arising in temporal lobe usually the non-dominant hemisphere.

Sensory fits may be somatic, visual, auditory, olfactory, labyrinthine, or visceral. They usually occur together with other complex phenomena in temporal lobe epilepsy. A seizure arising in the temporal lobe may be associated with an aura of sensation in addition to experiencing profound and disturbing disorders of thought perception and emotion (Marsden and Reynolds, 1982). The characteristic feature of such brief ictal events is that the same sequence of sensation occur each time, that it is repetitively stereotyped, and like most focal epileptic events it lasts for only a brief period (Marsden and Reynolds, 1982).

Periods of automatic, often complex behavior, may

occur during the seizure but usually takes place during the postictal phase (Liddell, 1953). Automatisms may be defined as a state of clouding of consciousness which occur during or immediately after a seizure and during which the individual retains control of posture and muscle tone but performs simple or complex movements and actions without being aware of what is happening (Fenton, 1972). Simple automatisms include lip smacking, chewing, swallowing and fumbling with hands. Complex automatisms consist of seemingly purposeful actions such as undressing, wandering, or running. Such behavior is well coordinated but inappropriate. They are of brief duration and last less than 5 minutes in more than 80% of cases (Knox, 1968). Amnesia for the period of automatism is usually complete. Most automatisms are associated with epilepsy arising in the temporal lobe and it is estimated that about 75% of those patients with complex partial seizures will have periods of automatism (Feidel and Penfield, 1954).

Adult epilepsy of proven temporal lobe origin is almost invariably associated with antero-mesial temporal spike focus on EEG which may be unilateral or independently bilateral, one with or without extratemporal secondary spikes (Driver and McGillivray, 1982). In children with similar temporal lobe symptomatology bursts of bilateral spike and wave complexes similar to those seen in petit mal may be frequent and demonstration of a clear

antero-mesial temporal spike focus can be difficult (Driver and McGillivray, 1982; Brown, 1982). The spike and wave found in the child with temporal lobe epilepsy may represent an inborn tendency to epileptic seizures which following a febrile illness may express as a series of generalized convulsions. The susceptible areas of the brain, especially the hippocampus may be damaged during these attacks producing an epileptogenic temporal lobe lesion (Falconer, 1971; Lennox-Buchthal, 1973).

Patients suffering from complex partial seizures comprised 25% of the total population of epileptic patients seen over an eighteen year period (Currie, 1971). Fifty percent did not have their first attack until after 25 years of age.

Precipitants of Seizures

Reflex epilepsy describes seizures, most commonly grand mal or partial, which are precipitated by a fixed and clearly recognized sensory stimulus (Marsden and Reynolds, 1982). Seizures provoked by repetitive flashing light is the commonest form of reflex epilepsy (Driver and McGillivray, 1982). Electroencephalographic diagnosis utilizes photostimulation as a means of exposing abnormalities in the EEGs of susceptible patients.

One of the outstanding problems in understanding epilepsy is identification of factors which trigger a seizure. The majority of seizures occur without apparent

cause and what triggers them is a mystery. However, there are several known precipitants of seizures. Fever may trigger a seizure in childhood. These are usually benign, although fever may also trigger attacks in patients who have spontaneous seizures. The differentiation of benign febrile seizures early in life from true epilepsy triggered by fever is important for prognosis and management (Brown, 1982).

Many patients have grand mal seizures only at night or during daytime sleep or drowsiness (Gibberd and Bateson, 1974). Sleep enhances epileptic discharges in the EEG and may produce abnormality when daytime recordings while awake are quite normal. Sleep induced by barbituates is thus used as a provocative test in EEG evaluation of epilepsy particularly in suspected complex partial seizures when the resting EEG is normal (Driver and McGillivray, 1982).

The incidence of premenstrual exacerbation of seizures has been reported in up to 63% of women with epilepsy (Ansell and Clark, 1956). It has been reported that estrogens may decrease the seizure threshold (Backstrom, 1976).

A variety of stress factors are known to provoke fits in susceptible individuals (Friis and Lund, 1974). Physical or mental exertion can precipitate fits. Emotional stress precipitates fits in 21% of patients with complex partial seizures (Currie, 1971).

Many drugs are known to provoke fits in susceptible individuals. These include phenothiazines, tricyclic anti-depressants, monoamine oxidase inhibitors, and isoniazid (Marsden and Reynolds, 1982). Fits on withdrawal of drugs are well known (Goodman and Gillman, 1980). Alcohol and barbiturate withdrawal seizures are common. The commonest cause of recurrence of seizures is poor compliance with drug therapy with ensuing withdrawal seizures (Richens, 1982).

Etiology

The known causes of seizures vary with the age at which they start. During infancy, birth injury, congenital defects, metabolic aberrations, and infection are common causes of seizures (Brown, 1982). Between the ages of three and eight months, infantile spasms are present while from six months to five years febrile fits occur. Primary epilepsy usually starts after the age of three and is then the commonest form of epilepsy (Hauser, 1982). Throughout adult life structural brain damage dominates particularly brain tumors in early and middle adult life and vascular disease in later years (Brown, 1982). Head trauma causes seizures throughout life.

CHAPTER 4

ANTIEPILEPTIC MEDICATION

Mechanism of Action of Antiepileptic Medication

There are two general ways in which drugs might abolish or attenuate seizures: 1) effects on pathologically altered neurons of seizure foci to prevent or reduce their excessive discharge, and 2) effects that would reduce the spread of excitation from seizure foci and prevent detonation and disruption of function of normal aggregation of neurons (Rall and Schleifer, 1980).

Most, if not all, antiepileptic agents that are presently available act at least in part by the second mechanism since all modify the ability of the brain to respond to various seizure evoking stimuli (Rall and Schleifer, 1980). A variety of neurophysiological effects of such drugs have been noted including reduction of Na^+ and Ca^{2+} fluxes, potentiation of presynaptic and postsynaptic inhibition, reduction of post-tetanic potentiation, and reduction of evoked response in various monosynaptic or polysynaptic pathways (Rall and Schleifer, 1980). However, mechanisms of action of antiepileptic agents are only poorly understood and all of the above effects generally embarrass normal functions of the brain leading to undesired side effects.

Most of the drugs introduced before 1965 are closely

related in structure to phenobarbital. These include the hydantoins, the deoxybarbiturates, the oxazolidinediones and the succinamides. The agents introduced after 1965 include benzodiazepines, an iminostilbene, and a branched chained carboxylic acid.

The laboratory screening tests for potential antiepileptic drugs have relied heavily on the capacity to modify the effects of maximal electroshock (inhibition of tonic hindlimb extension in mice) and to elevate the dose of the convulsant drug, pentylenetetrazol, required to precipitate tonic-clonic convulsions. The former test usually predicts activity against generalized tonic-clonic and cortical focal convulsions and the latter against absence seizures. There are, however, exceptions to this observation (Rall and Schleifer, 1980).

The ideal antiepileptic drug would suppress all seizures without causing any unwanted effects. Unfortunately, the drugs used currently not only fail to control seizures in some patients but they frequently cause side effects that range in severity from minimal impairment of the CNS to death from aplastic anemia (Rall and Schleifer, 1980). The physician who treats epileptic patients is thus faced with the task of selecting the appropriate drug which best controls seizures in an individual patient with an acceptable level of untoward effects.

It is generally held that complete control of seizures can be achieved in up to 50% of patients and possibly another 25% can be improved significantly (Meinardi, 1977). The degree of success is largely dependent on the type of seizure and the extent of neurological abnormality. As is discussed below, absence seizures respond well to one group of drugs and generalized tonic-clonic and cortical focal convulsions are usually adequately controlled by another group. Temporal lobe seizure tends to be refractory to therapy and responds only to some of the agents in the second group (Coatsworth and Penry, 1972; Rall and Schleifer, 1980).

Measurement of drug concentration in plasma greatly facilitates antiepileptic drug management. There are limitations, however, for some drugs clinical effects correlate well with their concentrations in plasma but for others the correlation is extremely poor (Symposium, 1978).

Individual Drugs Used by Patients in this Study

Phenytoin

Phenytoin is a primary drug for all types of epilepsy except absence seizures (Rall and Schleifer, 1980). A 5-phenyl or other aromatic substituent appears essential for activity against classical generalized tonic-clonic seizures and for abolition of the maximal electroshock pattern in laboratory animals (Rall and Schleifer, 1980).

Phenytoin has a demonstrated ability to limit the development of maximal seizure activity and to reduce the spread of the seizure process from an active focus (Rall and Schleifer, 1980). An excitatory effect on the cerebellum, activating inhibitory pathways that extend to the cerebral cortex, has been suggested to contribute to the anticonvulsant effect of phenytoin (Halpern and Julien, 1972). A stabilizing effect of phenytoin on all neural membranes has been reported which contributes to the reduction in posttetanic potentiation of synaptic transmission (Esplin, 1957; Woodbury, 1969). Phenytoin decreases the resting fluxes of sodium and calcium ions that flow during depolarization and the activation of the outward potassium current is decreased, leading to a lengthened refractory period and a decrease in repetitive firing (Ayala and Johnston, 1977).

Toxic effects primarily are dose and duration of therapy related. Cerebellar and vestibular dysfunction, behavior changes, increased seizure frequency, gingival hyperplasia, osteomalacia, megaloblastic anemia, and hirsutism are among the more commonly reported untoward effects of phenytoin (Rall and Schleifer, 1980).

Phenytoin interacts with other antiepileptic drugs (Rall and Schleifer, 1980). Phenytoin concentration is decreased when given with carbamazepine and increased or decreased when given with phenobarbital (Rall and

Schleifer, 1980). The concentration of carbamazepine and phenobarbital are conversely affected.

Phenobarbital

Phenobarbital was one of the first effective organic antiepileptic agents and is still one of the more effective and widely used drug for this purpose (Rall and Schleifer, 1980).

The structure-activity relationship of the barbiturate indicates that maximal anticonvulsant activity is obtained when one substituent at position 5 is a phenyl group (Rall and Schleifer, 1980). The capacity of phenobarbital to exert maximal anticonvulsant action at doses below those required for hypnosis determines its clinical utility as an antiepileptic (Rall and Schleifer, 1980).

Phenobarbital limits the spread of seizure activity and also elevates seizure threshold (Rall and Schleifer, 1980). The ability of phenobarbital to reduce the spread of seizures may depend on the potentiation of inhibitory pathways that are recruited during discharge of epileptogenic foci (Rall and Schleifer, 1980).

Phenobarbital may cause sedation in adults, irritability and hyperactivity in children, and confusion in elderly adults (Rall and Schleifer, 1980). Other adverse effects include ataxia, rash, and megaloblastic anemia (Rall and Schleifer, 1980).

Interactions between phenobarbital and other drugs

usually involve induction of the microsomal enzyme system by phenobarbital (Rall and Schleifer, 1980). Concentration of phenobarbital in plasma may be elevated by as much as 40% during concurrent administration of valproic acid (Rall and Schleifer, 1980).

Carbamazepine

Carbamazepine was approved in the United States for use as an antiepileptic drug in 1974. It is related chemically to the tricyclic antidepressants. It is a derivative of iminostilbene with a carbonyl group at the 5 position. This moiety is essential for potent anti-epileptic activity (Rall and Schleifer, 1980).

The anticonvulsant effects of carbamazepine in animals resemble those of phenytoin (Rall and Schleifer, 1980). At therapeutic concentrations carbamazepine can inhibit maximal electroshock seizure, abolish focal brain discharge induced by locally applied penicillin, and suppress seizure activity caused by similarly applied alumina cream (Rall and Schleifer, 1980). It is more effective than phenytoin in raising the threshold for minimal electroshock seizures and in blocking seizures in response to pentylenetetrazol (Rall and Schleifer, 1980).

The more frequent untoward effects of carbamazepine include diplopia, blurred vision, drowsiness, dizziness, nausea, vomiting, and ataxia (Rall and Schleifer, 1980).

Valproic Acid.

Valproic acid is the latest antiepileptic drug to be approved for use in the United States. Valproic acid is a simple branched chain carboxylic acid. The branched chain carboxylic acid is necessary for activity (Rall and Schleifer, 1980).

Valproic acid has antiepileptic activity against a variety of types of seizures while causing only minimal sedation and other CNS side effects. It prevents pentylenetetrazol induced seizures in mice but with less potency than phenobarbital (Rall and Schleifer, 1980). It also eliminates hindlimb extension in mice subjected to maximal electroshock but only at relatively high doses (Rall and Schleifer, 1980).

The mechanism of action of valproate is unknown, although several investigators have proposed a possible interaction with the metabolism of GABA in the brain (Pinder, 1977; Bruni and Wilder, 1979). GABA is considered an inhibitory neurotransmitter in the brain. It has been suggested that selective increase in GABA in synaptic regions may be promoted by inhibition of GABA transaminase or succinic semialdehyde dehydrogenase, inhibition of reuptake by glial cells and nerve endings, or some combination of these actions (Pinder, 1977; Bruni and Wilder, 1979).

The incidence of toxicity associated with the use of

valproic acid is remarkably low compared to the other antiepileptic drugs (Rall and Schleifer, 1980). The most common side effects are anorexia, nausea, and vomiting. CNS effects occur infrequently.

The interaction with other drugs have been noted above.

CHAPTER 5

POLYTHERAPY VS. MONOTHERAPY

Epilepsy begins before the age of twenty in approximately three quarters of patients (Häuser, 1982). With the possible exception of classical petit mal seizures, which tend to show natural remission with age, most seizure disorders are chronic and have poor long term prognosis (Rodin, 1968). In addition, the prognosis tends to be worse the longer the history of epilepsy prior to effective treatment (Rodin, 1968). It is apparent, however, that there is a great range of severity and many patients do have severe and frequent seizures which are not adequately controllable with available modern treatment. Because the basic causes of seizures are poorly understood, there is very little rational therapy (Reynold and Shorvon, 1981). The drugs which have been found empirically to be useful merely suppress seizure activity during the period of their administration. Even in patients whose seizures have been well controlled for two or more years the relapse rate on withdrawal of therapy has been 20-40% (Holowach, 1972).

Epilepsy is a chronic long term problem for which it is necessary to take medication for many years. There is a natural tendency, as the seizures persist, to add more and newer drugs as they become available (Reynolds and Shorvon,

1981). This has contributed to the problem of polytherapy which exists to a great degree in Western countries.

Surveys of institutionalized and non-institutionalized patients with seizures show that the mean number of anticonvulsant drugs per patient is between 2 and 3.6 (Guelen, 1975; Wilkinson, 1981).

The problem of polytherapy is further compounded by lack of agreement as to the most suitable choice of drugs for different seizure disorders. There may be general agreement as to which classes of drugs work for a particular seizure disorder but there is little agreement as to which of these drugs should be used first, which second, and so on. The main reason for the varying opinion is that there is very little scientific evidence on which to make a rational choice (Reynolds and Shorvon, 1981).

In his survey of published papers on the therapeutic efficacy of antiepileptic drugs, Coatsworth (1971) classified studies into two types: clinical trials, i.e., prospective studies in which some sort of formal design was evident, and case reports, i.e., studies in retrospect. The latter were in the majority. In only 2 of 110 clinical trials reviewed was observer bias removed by use of double blind studies. The studies also lacked an adequate description of the type of epilepsy being studied. Because of these weaknesses in design and reporting, few firm conclusions could be drawn.

Shorvon (1980) reviewed 155 trials of phenytoin and carbamazepine. There were improvements in design but deficiencies were still remarkable with little or no attempt at appropriate statistical evaluation.

The major antiepileptic drugs are rarely evaluated as monotherapy or in previously untreated patients. Likewise, neither have the major drugs been compared to one another adequately (Reynolds and Shorvon, 1981). The little evidence that is available suggests that there is little to choose between them for antiepileptic efficacy (Coatsworth and Penry, 1972; Shorvon and Reynolds, 1980).

White (1966) compared phenytoin with phenobarbital and found no difference between these drugs in a carefully controlled trial in 20 patients with partial seizures. Booker (1972) retrospectively studied 107 patients with tonic-clonic and complex partial seizures finding no difference between phenytoin and phenobarbital. Comparison of carbamazepine with conventional drugs in major epilepsy have shown it to be at equal efficacy. Bird (1966) compared carbamazepine's effect with that of phenytoin, phenobarbital, or primidone given singly or in combination to 46 mentally subnormal patients. No difference in fit frequency was found between those patients whose treatment changed to carbamazepine and those who remained on their conventional therapy. Cereghino (1974) studied 45 patients with mainly partial and secondarily generalized convulsive

seizures. Regular medication was replaced by one of three treatments on a double blind basis; phenytoin, phenobarbital or carbamazepine. Each patient received each test drug for 21 days in randomized sequence. The effects of the three drugs were clinically and statistically undistinguishable although individually some patients were controlled better on one of the drugs over the other two. Troupin (1974) found no difference between carbamazepine and phenytoin when used as sole treatment in patients with complex partial and tonic-clonic seizures. Dose (1970) in an open comparative study found carbamazepine equal in effectiveness to phenytoin and primidone. In a double blind comparison of carbamazepine and phenytoin, Troupin (1977) found the drugs to be of equal efficacy though carbamazepine had fewer side effects.

In general, valproic acid is less effective in partial seizures than in primary generalized tonic-clonic or absence seizures (Simon and Penry, 1975; Pinder, 1977). No controlled studies have been performed in which valproic acid has been compared with other drugs in major epilepsy.

Valproic acid is particularly effective in absences accompanied by 3 per second spike and wave on the EEG. Most studies have shown that about two-thirds of patients with simple or complex absences show a 75-100% reduction in seizures with valproic acid (Simon and Penry, 1975; Pinder, 1977). In a controlled comparative trial of valproic acid

and ethosuximide, Suzuke (1972) showed that valproic acid was indistinguishable from the then drug of choice ethosuximide. However, ethosuximide has the disadvantage of not being active against co-existing tonic-clonic fits (Richen, 1982).

In view of the above discussion, it is not surprising that in practice the choice of drugs has been based mainly on opinion, habit, cost and relevance of potential side effects (Reynolds and Shorvon, 1981).

Traditionally, a seizure patient has been treated by trial and error. Probably the most common approach has been to begin with one drug and gradually increase its dose until the seizures were controlled or until acute toxic symptoms developed in which case the dose was slightly reduced. Blood level monitoring has made this process more efficient by following known therapeutic guidelines for concentration of the drug in plasma. Often, however, a patient may not conform to these arbitrary boundaries and may require more or less drug to achieve an optimal level. If seizures continued, which often happened perhaps due to poor compliance, the next step was to add another drug and build it up in the same way (Reynolds and Shorvon, 1981). In this way, many patients ended up on multiple drugs.

Chronic toxicity, drug interactions, inability to evaluate a single drug's effect, and exacerbation of seizures are all problems associated with polytherapy

Reynolds, 1975; Richens, 1976; Perucca, 1979; Reynolds and Shorvon, 1980).

In view of the widespread practice of polytherapy, and in spite of the above problems, one might expect there to be good evidence to justify it. There is very little such evidence. Shorvon and Reynolds (1977) retrospectively reviewed 44 adults, with chronic epilepsy, on two anti-convulsants to assess the impact of the second drug on seizure control. Seizure control improved by 50% or more in six months after the addition of the second drug in only 36%. When the blood levels of the two drugs are measured, improved control was related to optimum levels of at least one of the drugs.

Prospective studies of the potential for monotherapy in previously untreated adolescent or adult epileptic patients with grand mal and/or partial seizures have been undertaken (Reynolds et al., 1976; Shorvon et al., 1978; Gailbraith et al., 1979). Their policy was to start with a small dose of one drug, phenytoin or carbamazepine, and, if seizures recurred, to increase the dose by small increments either until seizures were controlled or until the upper end of the optimum range had been reached. In 54 patients treated with phenytoin for a mean duration of 41 months and 42 with carbamazepine for a mean of 26 months, 72% and 76%, respectively, were completely controlled. The failure rate for optimum monotherapy was no higher than 17%. Callaghan

(1978) reported complete control in 10 out of 11 patients followed prospectively for a mean of 14 months from the start of treatment with carbamazepine assisted by blood level monitoring.

Studies undertaken to demonstrate the potential for reducing polytherapy in 40 chronic outpatients with grand mal or partial seizures were successful in 72% who were followed prospectively for a year before and after reduction (Shorvon and Reynolds, 1978). Withdrawal problems and pressure to take action in the face of continued seizures caused the failure of 28%. Seizure control actually improved in 55% of those successfully reduced.

The availability of blood level monitoring which reveals the reason for recurrences of seizures prevents unnecessary escalation toward polytherapy (Reynolds and Shorvon, 1981). This is a major reason monotherapy is successful. Another possible reason is the application of effective monotherapy early in the natural history of the disorder. Rodin (1968) confirmed that the longer the history of epilepsy the worse in general was the prognosis.

It is apparent that monotherapy, whether in previously treated or untreated patients, is the most beneficial for epileptic patients. Choosing the drug to use first in a patient is difficult because: 1) there are several to

choose from; 2) each is similarly effective; 3) the patient may not fit well into the tripartite classification scheme. The clinician at this point chooses the drug he/she knows best even though it ultimately may not be the best for the control of the patient's seizures. Blood level monitoring only helps after the initial drug has been chosen.

A systematic approach is needed to select the appropriate anticonvulsant drug for each patient. Given the immense amount of discrete data collected at the initial visit, including history, physical examination, laboratory data, and EEG findings, a more sophisticated individualized technique needs to be employed to utilize the data efficiently and constructively. The problem that needs to be addressed concerns deciding which facts about an individual's seizure are important to know and how much weight do they each carry in relation to the others in determining which medication is best for him/her. Multivariate analysis of retrospectively collected data is the first step in this process.

CHAPTER 6

DISCRIMINANT ANALYSIS AND FACTOR ANALYSIS

Discriminant analysis was used in an attempt to distinguish statistically the four anticonvulsant drug groups. To do this, discrete clinical, historical and electroencephalographic data were collected because it is known that certain of these measure characteristics on which the groups are expected to differ (Gastaut, 1969). The mathematical objective of discriminant analysis is to weigh and linearly combine the discriminating variables in some fashion so that the groups are forced to be as statistically distinct as possible (Klecka, 1975). For example, for the four drug groups studied, EEG characteristics would probably help discriminate between them. Patients with a focal abnormality would likely be classified into phenytoin or carbamazepine groups instead of valproic acid. Of course, no single variable will perfectly differentiate between the four drug groups. By taking several variables and mathematically combining them it is hoped that the four groups will be distinct with minimal overlap. Some measurements are clearly going to be more sensitive for one of the drugs. For example, 3 Hz. spike and wave, staring blankly, and precipitation of seizures by hyperventilation will point more toward valproic acid. These same variables will be strongly

negative for carbamazepine, phenytoin and phenobarbital. The variable 3 Hz. spike and wave will have greater weight in predicting valproic acid than will a positive family history of seizures.

Rodin (1968) used discriminant analysis to provide clinicians with a formula on the basis of which one could give a reasonably accurate prediction of the prognosis for a particular patient with seizures. Two subgroups were formed from 181 inpatients, each of which had the required completed information on eight characters. Eighty-one patients formed subgroup I and did not have any seizures in the hospital while on anticonvulsant medication. The other group, consisting of 100 patients, had at least one seizure in spite of adequate drug treatment. This discriminant analysis function program classified correctly 76% of the patients who did not have seizures in the hospital, and 81% of those who continued to have attacks. The total correct classification was 78%. By chance, one would expect 50% correct classification.

Discriminant analysis is widely used in biology and medicine. It has, for example, been used for taxonomic purposes. Grover (1963) converted nine measurements of the skulls of two samples of wild asses into discriminant functions. The discrimination, despite small numbers, clearly distinguished the two groups.

A form of discriminant analysis was used by Goldman

(1982) to determine whether data available to physicians in the emergency room can accurately identify which patients with acute chest pain are having myocardial infarction. Using nine clinical factors, a decision protocol based on discriminant functions was constructed. In prospective testing on 468 patients the protocol performed as well as the physicians' judgment. An integration of the protocol with those physicians' judgment resulted in a classification system that had significantly improved specificity and preserved sensitivity.

Factor analysis was performed to confirm associations thought to exist between clinical, EEG and historical variables that were produced by discriminant analysis. The first step in factor analysis involves calculation of appropriate measures of association for a set of relevant variables. A correlation matrix is created in this case by calculating the correlations between each of the discrete variables in a process known as R-factor analysis (Kim, 1975). The second step in factor analysis is to transform the given set of variables into a new set of composite variables that are unrelated. One is determining what is the best combination of variables that would account for more variance in the data as a whole than any other linear combination of variables. The second component is defined as the second best linear combination of variables under the condition that the second component is orthogonal to

the first. Subsequent components are defined similarly until all the variance in the factor analysis is exhausted. The final step in factor analysis is rotation of the axis defining the variables to make more clear their patterning into distinct groups (Kim, 1975).

Rodin (1968) used factor analysis to demonstrate syndromes that may exist within a group of childhood epilepsies which might have a bearing on prognosis. Eight factors were obtained with four being of relevance in regard to follow-up findings. Factor I dealt with characteristics of school achievement, II with EEG patterns during first months of life, III with characteristics leading to institutionalization as a result of illness, and IV with seizure state at time of follow-up. The conclusions suggested were 1) that EEG is likely to improve if seizure disorder did not start in infancy; 2) a child with one seizure type, no history of status epilepticus, and whose seizures are brief is not likely to deteriorate to a level requiring institutionalization; and 3) children who have no evidence of mental retardation and a normal neurological examination are likely to show improvement in their seizures.

Study Goals

Multivariate analysis of variables collected from patients with seizures to discover parameters for use in a predictive formula for seizure patients has not been reported. Discriminant analysis was employed in this study to determine if the data available to the initial physician can be more efficiently used to predict the optimum controlling drug for a seizure patient. Factor analysis was employed to delineate clearly those parameters which are predictive.

CHAPTER 7

PATIENTS AND METHODS

Patients

This study included all patients attending Milwaukee Children's Hospital, Department of Neurology Seizure Clinic, that met the following criteria: 1) the diagnosis of a seizure disorder made on the basis of the judgment of Dr. J. V. Murphy, Dr. H. M. Swick, or Dr. P. Ellison (all pediatric neurologists); 2) at least one EEG was available; 3) anticonvulsant monotherapy was being used with one of the following: phenobarbital, phenytoin, carbamazepine, or valproic acid; and 4) patient follow-up was long enough for the clinician to assess drug efficacy.

Assessment of Historical, Clinical and EEG Data

Historical data were coded for use in the Statistical Package for the Social Sciences (SPSS). This list of variables is presented in full in Appendix I. The data included information on sex, age at onset of seizures, age of administration of current drug, description of ictal event, precipitating factor (if any), duration of seizures, percent reduction in seizures after treatment, family history of seizures or a known genetic syndrome, complications during pregnancy and delivery, developmental delay, and any neurological illness, trauma or operation.

Clinical data also were coded for use in the SPSS.

Physical parameters included height, weight and head circumference. Appendix I lists the neurological functions which were assessed on physical examination. Intelligence was recorded as normal or mildly, moderately, severely or profoundly retarded.

The EEGs were coded for use in SPSS. The interictal, and, if present, the ictal characteristics of the EEG were recorded. Characteristics included (see Appendix II) were background rhythm, location of abnormalities, description of abnormalities, and activation techniques.

Seizure Control

The percent reduction in seizure frequency was determined after achieving therapeutic blood levels using blood level monitoring and clinical assessment of toxicity from too high a dose. The period of time necessary to determine the drug's efficacy varied depending on the frequency of seizures before using the current drug. With an effective drug, a patient with daily seizures had a change within days of reaching therapeutic levels, while for a patient with weekly or monthly seizures, a proportionately longer period of observation was required before efficacy could be assessed accurately.

Statistical Evaluation

Statistical evaluation of the data included analysis of variance, chi-square analysis, discriminant analysis and factor analysis. The significant ($F < .05$ or $P < .05$)

variables from the first two procedures were used in the latter two.

One-way analysis of variance was performed on continuous data; age at onset of seizures, age at administration of current drug, height, weight and head circumference. The SPSS subprogram ONEWAY was used to compute F-ratios and probabilities to determine if differences existed between drug types.

The SPSS subprogram CROSSTABS was used to compute the chi-square statistic to determine whether or not the collected variables were related to drug type, i.e., phenobarbital, carbamazepine, phenytoin or valproic acid. In this study, all variables relating to drug type with $P < .05$ were studied further with discriminant analysis and factor analysis. Those variables which were not significant may have had an impact on the response to drug type selected, but in the multivariate analysis they would be masked by those that were found to be more strongly associated.

The SPSS subprogram DISCRIMINANT utilized the collection of significant variables from chi-square analysis in a stepwise selection of variables of increasing discriminating power. The full set of independent variables contains excess information about the group differences or variable which may not be very useful in discriminating among the groups so some of the variables

will not be included in the final discrimination. This is also related to the strength of association the variables have with drug type selected. By sequentially selecting the next best discriminator at each step a reduced set of variables will be found which is almost as good as the full set (Klecka, 1975).

As variables are selected for inclusion, some variables previously selected may lose their discriminating power. This occurs because the information that they contain about group differences is now available in some combination of the other included variables (Klecka, 1975). At the beginning of each step, each of the previously selected variables is tested to determine if it still makes a sufficient contribution to discrimination (Klecka, 1975). If any are eligible for removal, the least useful is eliminated. A variable which has been removed at one step may reenter at a later step if it satisfies the selection criterion at that time (Klecka, 1975). A variable is considered for selection only if its partial multivariate F ratio is larger than a specified value. The partial multivariate F ratio measures the discrimination introduced by the variable after taking into account the discrimination achieved by the other selected variables (Klecka, 1975). This partial F test is performed before the variable is evaluated on the stepwise entry criterion. If the partial F is too small, the variable is not

considered for inclusion (Klecka, 1975).

The use of a stepwise procedure results in an optimal set of variables being selected which will provide the best discrimination (Klecka, 1975).

In discriminant analysis, each drug group will be treated as a point and each derived discriminant function will define the location of that point relative to the others (Klecka, 1975). The subprogram DISCRIMINANT prints out for each discriminant function their standardized coefficient. The coefficients are multiplied by the selected standardized discriminating variables and the products of each are added together to produce a discriminant score. There is a separate score for each case on each function.

The discriminant scores are used to derive classification functions for each group. This is a way in which the derived discriminant functions are tested. By classifying the cases used to derive the functions in the first place and comparing predicted group membership with actual group membership one can empirically measure the success in discrimination by observing the proportion of correct classifications (Klecka, 1975).

The derived classification coefficients are multiplied by the values for the variable. These products are summed together with a constant to produce a classification score. There is a separate score calculated for each group. The

subprogram DISCRIMINANT converts these scores into probabilities of group membership. A case is assigned to the group for which it has the greater probability of membership.

Factor analysis was carried out by SPSS subprogram FACTOR (Kim, 1975). The significant variables from chi-square analysis and drug type were included in a correlation matrix. Factors were extracted in order of their contribution to the variance of the data. The number of factors was not limited in the first run so that all possibilities were produced regardless of the contribution the latter factors extracted made to the variance. The second run was limited to seven factors to "squeeze" the data in an attempt to clarify ambiguous patterns. Option VARIMAX was used to rotate the factors in both runs. This method simplifies the columns of the factor matrix so that only the most important variables load on each factor.

The variable or variables which load heaviest (i.e. correlation coefficient greater than .25) on a particular factor can be used arbitrarily to name that factor. For example, a factor with variables valproic acid, 3 Hz. spike and wave on EEG and seizures exacerbated by hyperventilation could in this study be called a "valproic acid" factor. Similarly, for the other factors produced, the combinations of variables may suggest patterns which can be named using the names of the other drugs studied.

Conceivably, factors may be produced which have no correlation with drug type. These are named based on that trend existing in the variable combination for that factor.

CHAPTER 8

RESULTS

The characteristics of the population studied are shown in table 1. There is a significant difference ($P < .05$) in the number of males and females on phenytoin and carbamazepine. An average of 2.6 years elapsed in these patients from the time of onset of seizures to the present monotherapy.

The past treatment of the population is shown in table 2. Fifty-three percent of the patients were treated with one or more drugs other than the present monotherapy in the past. Sixty-two percent of the 93 patients treated with phenobarbital, 48% of the 67 patients treated with phenytoin, 23% of the 74 patients treated with carbamazepine, and 20% of the 54 patients treated with valproic acid were taken off the drug because of lack of efficiency, occurrence of side effects, or both. In this study all 173 patients who were currently treated with only one drug were included for further analysis.

TABLE 1
STUDY POPULATION CHARACTERISTICS

DRUG	N	SEX		AGE AT ONSET (Years)	AGE AT ADMINISTRATION (Years)	DIFFERENCE (Years)
		M	F			
Phenobarbital	39	19	20	3.8	5.9	2.1
Phenytoin	35	26	9	6.4	8.6	2.2
Carbamazepine	56	21	35	6.0	9.0	3.0
Valproic Acid	43	25	18	3.7	6.9	3.2
TOTAL	173	91	82	$\bar{x}=5.0$	$\bar{X}=7.6$	$\bar{X}=2.6$ D

TABLE 2

PAST DRUG HISTORY OF PATIENTS CURRENTLY ON MONOTHERAPY

CURRENT DRUG	NUMBER MAINTAINED	PAST TREATMENT					TOTAL
		VPA ¹	CBZ ²	PH ³	PB ⁴	TWO OR MORE ⁵	
Phenobarbital (PB)	31	0	0	5	0	4	39
Phenytoin (PH)	15	0	2	0	13	5	35
Carbamazepine (CBZ)	18	4	0	5	17	12	56
Valproic Acid (VPA)	18	0	2	1	10	12	43
Total	82	4	4	11	40	33	173

1. Number of patients treated only with Valproic Acid in the past.
2. Number of patients treated only with carbamazepine in the past.
3. Number of patients treated only with phenytoin in the past.
4. Number of patients treated only with phenobarbital in the past.
5. Number of patients treated with two or more of the above drugs or other anticonvulsants concurrently or consecutively in the past.

The responses to treatment with monotherapy are listed in table 3. Eighty-nine percent of the patients achieved a 90-100% reduction in seizure frequency following treatment. Eleven percent achieved less than this reduction but it was considered the best control the patient had yet achieved. The length of time necessary to assess an individuals reduction in seizures was based on the frequency of seizure prior to treatment. Twenty-eight percent of the 173 patients had daily seizures, 12% had weekly seizures, 13% had monthly seizures, and 47% had yearly seizures.

The relationship between variables and drug type was determined using CROSSTABS on SPSS which produced contingency tables, chi-square statistics, and p-values. The significant variables ($P < .05$) are listed in table 4 with the actual frequencies.

TABLE 3
RESPONSE TO TREATMENT

SEIZURE REDUCTION	DRUG TYPE				TOTAL
	PB	PH	CBZ	VPA	
0-30%	0	0	2	0	2
30-60%	2	4	4	7	18
60-90%	1	5	9	5	20
90-100%	36	26	41	31	134
Total	39	35	56	43	173

TABLE 4

CHI-SQUARE TEST FOR RELATIONSHIP BETWEEN VARIABLES AND DRUG TYPE: FREQUENCIES

CHARACTERS	PB	PH	CBZ	VPA	TOTAL	
Bizarre ictal psychic behavior	4	0	13	0	17	
None recorded	35	35	43	43	156	
Polyspikes on EEG	1	1	0	8	10	
None recorded	38	34	56	35	163	
Sex: Male	19	26	21	25	91	
Female	20	9	35	18	82	
Diagnosis of hyperactivity	0	6	1	4	11	
None recorded	39	29	55	39	162	
Generalized EEG abnormality	13	14	17	27	71	52
Not generalized or normal	26	21	39	16	102	
EEG abnormality exacerbated by hyperventilation	20	15	29	22	86	
Not exacerbated	13	18	17	9	57	
Technique not used	6	2	10	12	30	
Recurrent headache	5	9	13	1	28	
None recorded	34	26	43	42	145	
Onset of ictal movement: generalized	24	22	20	31	97	
focal	15	11	34	11	71	
neither	0	2	2	1	5	

TABLE 4 (Continued)

CHARACTERS	PB	PH	CBZ	VPA	TOTAL
2-4 Hz. spike and wave on EEG	8	5	6	16	35
None recorded	31	30	50	27	138
Seizures precipitated by fever	22	11	14	18	65
None recorded	17	24	42	25	108
Delivered by forceps	4	0	0	1	5
None recorded	34	31	53	41	159
*(9 patients without this information)					
Speech abnormality	3	1	3	9	16
None recorded	36	34	53	34	157
Alpha 9+ Hz. on EEG	12	11	20	4	47
None recorded	27	24	36	39	126
EEG abnormally exacerbated by photic stimulation	3	4	14	10	31
None recorded	18	18	32	15	83
Techniques not used	18	13	10	18	58
Characteristics of ictal movement					
tonic	2	3	4	3	12
clonic	9	6	12	5	32
tonic-clonic	24	16	14	19	73
no movement	3	8	20	12	43
atonic	1	2	6	4	13

TABLE 4 (Continued)

CHARACTERS	PB	PH	CBZ	VPA	TOTAL
Metabolic errors	1	0	1	5	7
None recorded	38	35	55	38	165
History of CNS infection	5	9	13	1	28
None recorded	34	26	43	42	145
History of trauma precipitated seizures	8	5	3	2	18
None recorded	31	30	53	41	155
Infancy abnormal (seizures, delay, CNS disease)	19	20	35	16	90
Infancy normal	20	15	21	27	83

The p-values for the variables are listed in table 5.

One way analysis of variance was performed on the variables age at onset of seizures, and age of administration of current drug therapy. The mean age, the range, the F ratio and F probability are listed in tables 6-7.

Discriminant analysis was carried out with an N of 155. Eighteen cases had missing data and were eliminated from further analysis.

The number of steps taken in the discriminant analysis to produce the greatest percentage of correct classification with the fewest variables are listed in table 8.

The variables which were of greatest usefulness in the discrimination between the drug groups are listed in table 9 with the value of Wilk's Lambda. Discriminant analysis minimizes the value of Wilk's Lambda with each step. Those variables contributing most to the discrimination reduce Wilk's Lambda proportionately more.

TABLE 5

CHI-SQUARE TEST FOR RELATIONSHIP BETWEEN
VARIABLES AND DRUG TYPE

Character	P-value
Bizarre ictal psychic behavior	.01
Presence of polyspikes on EEG	.01
Sex	.01
Diagnosis of hyperactivity	.01
EEG abnormality generalized	.01
EEG abnormality exacerbated by hyperventilation	.01
Recurrent headache	.01
Generalized or focal onset of ictal movement	.01
Presence of 2-4 Hz. spike and wave on EEG	.01
Seizures precipitated by fever	.02
Forceps delivery	.02
Presence of speech abnormality	.03
Presence of Alpha 9+ Hz. on EEG	.03
EEG abnormality exacerbated by photic stimulation	.03
Characteristic of ictal movement: tonic, clonic, tonic-clonic, atonic, no movement	.04
Presence of metabolic errors	.04
History of CNS infection	.04
History of trauma precipitated seizures	.05
Abnormal infancy	.05

TABLE 6

ANALYSIS OF VARIANCE

Age at onset of seizures:

<u>Drug group</u>	<u>Count</u>	<u>Mean (years)</u>	<u>Range</u>
Phenobarbital	39	3.8	0.3 - 17.0
Phenytoin	35	6.5	1.0 - 16.0
Carbamazepine	56	6.0	0.1 - 17.0
Valproic Acid	43	3.7	0.2 - 12.0

F ratio = 5.5

F probability = 0.001

TABLE 7

ANALYSIS OF VARIANCE

Age at administration of current drug:

<u>Drug Group</u>	<u>Count</u>	<u>Mean (years)</u>	<u>Range (years)</u>
Phenobarbital	39	5.9	0.5 - 19.0
Phenytoin	35	8.6	2.0 - 20.0
Carbamazepine	56	9.0	1.0 - 23.0
Valproic acid	73	6.9	0.5 - 18.0

F ratio = 4.1

F probability = .008

TABLE 8

RESULTS OF STEPWISE DISCRIMINANT ANALYSIS

STEP	PERCENT CORRECTLY CLASSIFIED
4	49.0
6	53.0
8	52.5
10	58.0
12	59.0
14	60.6
16	65.2
18	65.2

The discriminant analysis derived 3 discriminant functions from the 16 variables listed in table 9. Function 1 accounted for 41.4% of the total variance, function 2, 32.0% and function 3, 26.6%.

The discriminant function coefficients for the variables are listed in table 10 so that the coefficients contributing most to a function are clustered together. The larger the coefficient the greater weight it has in the discrimination. Negative values impact with the magnitude listed but in the opposite direction. Function 1 could arbitrarily be called a valproic acid function, factor 2 a carbamazepine/phenytoin function, and factor 3 a phenobarbital function.

TABLE 9

VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS
OF ENTIRE POPULATION

Step	Variable	Wilk's Lambda
1	Presence of polyspikes on EEG	.87
2	Bizarre ictal psychic behavior	.77
3	Seizures environmentally induced	.71
4	EEG abnormality exacerbated by photic stimulation	.65
5	Sex	.60
6	Presence of 2-4 Hz. spike and wave	.56
7	Forceps delivery	.53
8	Presence of metabolic errors	.49
9	EEG abnormality exacerbated by H.V.	.46
10	Characteristics of ictal movements	.44
11	Presence of Alpha 9+ Hz.	.41
12	Recurrent headache	.39
13	Age at administration	.37
14	EEG abnormality generalized	.37
15	Generalized or focal onset of ictal movement	.36
16	Age at onset	.33

TABLE 10

DISCRIMINANT FUNCTION COEFFICIENTS

ENTIRE POPULATION

Character	Function		
	<u>1</u>	<u>2</u>	<u>3</u>
Presence of polyspikes on EEG:	.61	.03	.06
Metabolic errors	-.51	-.09	-.12
Characteristics of ictal movement	-.42	.00	.16
Recurrent headache	-.37	-.32	-.15
Generalized EEG abnormality	.30	-.15	-.02
2-4 Hz. spike and wave	.25	-.1	.14
Sex	-.03	-.73	-.15
EEG abnormality exacerbated by hyperventilation	-.34	.57	.04
Age at onset of seizure	-.07	.54	-.15
Bizarre ictal psychic behavior	.05	.52	-.15
Alpha 9+ Hz. on EEG	-.33	.39	.39
Generalized or focal onset of ictal movement	.14	-.33	.20
Seizures precipitated by fever	.06	.05	.06
Age at onset of administration of current drug	-.08	-.26	.54
Forceps delivery	-.06	.29	.48
EEG exacerbated by photic stimulation	.36	-.30	.46

The subprogram DISCRIMINANT derived classification equations for each of the four drug groups studied and classified the original cases. Each case was assigned based on the highest probability of membership calculated. The results of this classification are listed in table 11. Misclassification was highest between carbamazepine and phenytoin.

TABLE 11

CLASSIFICATION RESULTS FROM DISCRIMINANT
ANALYSIS OF ENTIRE POPULATION

Actual	N	Predicted Group Membership			
		PB	PH	CBZ	VPA
PB (%)	37	24 (64.9)	3 (8.1)	8 (21.6)	2 (5.4)
PH (%)	28	4 (14.3)	19 (67.9)	3 (10.7)	2 (7.11)
CBZ (%)	51	4 (7.8)	11 21.6)	35 (68.6)	1 (2.0)
VPA (%)	39	7 (17.9)	6 (15.4)	3 (7.7)	23 (59.0)

Percent of grouped cases correctly classified: 65.2%

The sex of the patient was shown to be important in choosing a drug. It is known, however, that female patients who are seen in this seizure clinic are not routinely started on phenytoin because of the intolerable cosmetic side effects. This is a variable stressing clinician habit rather than emphasizing a biological difference in response to seizure medication between males and females. To assess the contribution of the other variables without sex as a contributing factor discriminant analysis was performed on males and females separately.

The number of variables contributing to the discrimination and their value for males only are listed in table 12. The value of the discriminant function coefficients are listed in table 13. Function 1 accounts

TABLE 12

VARIABLES IN ORDER OF VALUE IN DISCRIMINANT
ANALYSIS OF MALES

Step	Variables	Wilk's Lambda
1	Bizarre ictal psychic behavior	.78
2	CNS infection	.62
3	Polyspikes on EEG	.53
4	Recurrent headache	.47
5	Seizure precipitated by fever	.42
6	Forceps delivery	.37
7	Alpha 9+ Hz. on EEG	.34
8	2-4 Hz. spike and wave on EEG	.31
9	Metabolic errors	.28
10	Age at administration of current drug	.26
11	Age at onset of seizures	.25
12	Abnormal infancy	.24
13	Generalized or focal onset of ictal movement	.22
14	Speech abnormality	.21

TABLE 13

DISCRIMINANT FUNCTION COEFFICIENTS

MALES

Variable	Function		
	<u>1</u>	<u>2</u>	<u>3</u>
Recurrent headache	-.60	-.20	-.06
CNS infection	.57	-.33	-.39
Seizures precipitated by fever	.55	.09	.17
Forceps delivery	.47	-.16	.21
Alpha 9+ Hz.	.46	-.32	.02
Metabolic error	.20	.61	-.08
Polyspikes on EEG	-.07	.45	.09
Abnormal infancy	.05	-.39	-.22
2-4 Hz. spike and wave	.16	.38	.06
Generalized or focal onset of ictal movement	.14	.33	-.17
Bizarre ictal psychic behavior	.26	.03	.84
Age at administration of current drug	.33	.27	-.81
Age at onset of seizures	-.03	-.53	.54
Speech abnormality	.14	.28	.29

for 43% of the variance, function 2 40.3% and function 3 16.6%. Function 2 could be arbitrarily named a valproic acid function since the variables making it up impact the most upon that drug group.

Function 1 and 3 are a combination of variables which do not suggest a clear pattern favoring one drug over another. The classification of the original male cases is presented in table 14. Carbamazepine is most frequently misclassified into the phenytoin category.

TABLE 14

CLASSIFICATION RESULTS FROM DISCRIMINANT
ANALYSIS OF MALES ONLY

Actual	N	Predicted Group Membership			
		PB	PH	CBZ	VPA
PB (%)	17	13 (70.5)	1 (5.9)	1 (5.9)	2 (11.8)
PH (%)	21	0 (0.0)	18 (85.7)	2 (9.5)	1 (4.8)
CBZ (%)	19	0 (0.0)	7 (36.8)	11 (57.9)	1 (5.3)
VPA (%)	22	3 (13.6)	3 (13.6)	0 (0.0)	16 (72.7)

Percent of grouped cases correctly classified: 73.4%

The variable contributing most to the discrimination of the drug types for females are listed in table 15. The importance of each variable for male and female is different. The discriminant function coefficients are listed in table 16. Function 1 accounted for 39.4% of the variance, function 2, 31.6%, and function 3, 29%. No clear patterns are suggested by the clustering of the variables. The classification equation derived from these functions classified the female cases only. The results are listed in table 17. The total percent of grouped cases correctly classified for males and females separately was higher than when the cases were classified as a single population.

TABLE 15

VARIABLES IN ORDER OF VALUE IN DISCRIMINANT
ANALYSIS OF FEMALES

Step	Variable	Wilk's Lambda
1	Presence of polyspikes on EEG	.85
2	Diagnosis of hyperactivity	.75
3	Seizures environmentally induced	.65
4	EEG abnormality exacerbated by photic stimulation	.57
5	Generalized or focal onset of ictal movement	.49
6	EEG abnormality exacerbated by hyperventilation	.44
7	CNS trauma	.40
8	Generalized EEG abnormality	.36
9	Age at administration of current drug	.33
10	Bizarre ictal psychic behavior	.30
11	Age at onset of seizures	.29
12	Characteristics of ictal movements	.27

TABLE 16

DISCRIMINANT FUNCTION COEFFICIENTS

FEMALES

Variable	Function		
	<u>1</u>	<u>2</u>	<u>3</u>
EEG abnormality exacerbated by hyperventilation	.94	.17	-.08
Generalized EEG abnormality	-.52	-.06	-.15
EEG abnormality exacerbated by photic stimulation	-.51	-.47	-.26
Polyspikes on EEG	-.46	.18	-.15
Characteristics of ictal movement	.37	-.21	-.04
Age at administration of current drug	.20	.91	.04
Seizure precipitated by fever	.01	.72	.13
Generalized or focal onset of ictal movements	-.12	.35	.17
Diagnosis of hyperactivity	.02	.02	.88
Age at onset of seizures	-.00	-.35	-.63
CNS trauma	.21	.21	.47

TABLE 17

CLASSIFICATION RESULTS FROM DISCRIMINANT
ANALYSIS OF FEMALES ONLY

Actual	N	Predicted Group Membership			
		PB	PH	CBZ	VPA
PB (%)	20	11 (55.0)	3 (15.0)	5 (25.0)	1 (5.0)
PH (%)	8	2 (25.0)	5 (62.5)	1 (12.5)	0 (0.0)
CBZ (%)	34	4 (11.8)	0 (0.0)	27 (79.4)	3 (8.8)
VPA (%)	17	2 (11.8)	1 (5.9)	2 (11.8)	12 (70.6)

Percent of grouped cases correctly classified: 69.6%

To assess the impact of considering the phenytoin and carbamazepine groups as separate when they may be indistinguishable, the two groups were combined into one for discriminant analysis. The variables which were most important are in table 18. The discriminant function coefficients are listed in table 19. Two functions were derived, function 1 accounting for 63.2% of the variance and function 2 accounting for 36.9%. The results of classification of original cases when phenytoin and carbamazepine groups were one combined group are listed in table 20. The percent of grouped cases correctly classified is about 10 percentage points higher than when carbamazepine and phenytoin groups were separate.

TABLE 18

VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS
WHEN PATIENTS ON CARBAMAZEPINE AND PHENYTOIN
WERE COMBINED INTO A SINGLE GROUP

Step	Variable	Wilk's Lambda
1	Polyspikes on EEG	.87
2	Seizure precipitated by fever	.79
3	Recurrent headache	.74
4	Characteristics of ictal movements	.70
5	Forceps delivery	.66
6	Alpha +9 Hz. on EEG	.63
7	Age at administration of current drug	.60
8	Metabolic errors	.56
9	2-4 Hz. spike and wave on EEG	.53
10	Generalized or focal onset of ictal movement	.51
11	Generalized EEG abnormality	.50
12	Speech abnormality	.49
13	CNS infection	.47
14	EEG abnormality exacerbated by photic stimulation	.46

TABLE 19

DISCRIMINANT FUNCTION COEFFICIENTS
PHENYTOIN AND CARBAMAZEPINE AS ONE GROUP

Variable	Function	
	1	2
Polyspikes on EEG	.57	.03
Metabolic errors	.46	-.04
Alpha 9+ Hz. on EEG	-.42	.36
Characteristics of ictal movement	-.37	.14
Generalized EEG abnormality	.34	-.01
Speech abnormality	.31	.07
Diagnosis of hyperactivity	-.26	-.23
Generalized or focal onset of ictal movement	.24	.17
Seizure precipitated by fever	.05	.59
Age at administration of current drug	-.11	.43
Forceps delivery	-.09	.42
EEG abnormality exacerbated by photic stimulation	.15	-.33
CNS infection	-.22	.26
2-4 Hz. spike and wave on EEG	.17	.19

TABLE 20

CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS
WHEN PATIENTS ON CARBAMAZEPINE AND
PHENYTOIN WERE COMBINED

Actual	N	Predicted Group Membership		
		PB	PH plus CBZ	VPA
PB (%)	37	25 (67.5)	9 (24.3)	3 (8.1)
PH plus CBZ (%)	80	10 (12.5)	63 (78.8)	7 (8.8)
VPA (%)	42	7 (16.7)	7 (16.7)	28 (66.7)

Percent of grouped cases correctly classified: 72.9%.

Misclassification of phenobarbital cases into the separate or combined carbamazepine and phenytoin groups prompted me to combine all three into a single group to assess the impact on the discriminant analysis results. The list of important variables in this analysis are in table 21. Only one discriminant function was derived accounting for all of the variance. The discriminant coefficients are listed in table 22. The classification results are listed in table 23. The percent of grouped cases correctly classified is greater than any of the other analyses although with only two groups to discriminate the chance of misclassification is less.

TABLE 21

VARIABLES IN ORDER OF VALUE IN DISCRIMINANT ANALYSIS
WHEN PATIENTS ON CARBAMAZEPINE, PHENYTOIN AND
PHENOBARBITAL WERE COMBINED INTO A SINGLE GROUP

Step	Variable	Wilk's Lambda
1	2-4 Hz. spike and wave	.87
2	Polyspikes on EEG	.82
3	Metabolic errors	.76
4	Alpha +9 Hz.	.73
5	Characteristics of ictal movement	.70
6	Generalized EEG abnormality	.68
7	Generalized or focal onset of ictal movement	.67
8	Speech abnormality	.65
9	Recurrent headache	.64
10	CNS infection	.63
11	EEG abnormality exacerbated by photic stimulation	.62

TABLE 22

DISCRIMINANT FUNCTION COEFFICIENTS
PHENYTOIN, CARBAMAZEPINE AND PHENOBARBITAL AS ONE GROUP

Variable	Function <u>1</u>
Polyspikes on EEG	.57
Metabolic errors	.43
Characteristics of ictal movement	-.34
Generalized EEG abnormality	.32
Alpha 9+ Hz. on EEG	-.31
Speech abnormality	.29
Recurrent headache	-.24
Generalized or focal onset of ictal movement	.23
EEG abnormality exacerbated by photic stimulation	.19
2-4 Hz. spike and wave on EEG	.19

TABLE 23

CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS
WHEN PATIENTS ON CARBAMAZEPINE, PHENYTOIN AND
PHENOBARBITAL WERE COMBINED

Actual	N	Predicted Group Membership	
		PB, CBZ and PH	VPA
PB, CBZ and PH (%)	127	115 (90.6)	12 (9.4)
VPA (%)	43	13 (30.2)	30 (69.8)

Percent of grouped cases correctly classified: 85.29%

Discriminant analysis was performed separately on those patients who had been treated with only one drug for the entirety of their treatment and on those patients who had been treated with one or more other drugs in the past.

The important variables in the discriminant analysis of patients having been treated with only one drug are listed in table 24. The discriminant function coefficients for each variable are listed in table 25. Function 1 accounted for 39.4% of the variance, function 2 for 32.4%, and function 3 28.3%. The results of the classification using the discriminant functions are listed in table 26.

The variables contributing most to the discrimination of drug types for patients with histories of drug therapy other than that presently prescribed are listed in table 27. The discriminant function coefficients for these patients are listed in table 28. Function 1 accounted for 40.1%, function 2 for 36.9% and function 3 for 23.0% of the variance. The classification results of this analysis are listed in table 29.

TABLE 24

VARIABLES IN ORDER OF VALUE IN THE DISCRIMINANT
ANALYSIS OF PATIENTS TREATED WITH ONLY ONE
DRUG DURING ENTIRETY OF TREATMENT

Step	Variable	Wilk's Lambda
1	Age at administration of current drug	.82
2	Polyspikes on EEG	.67
3	Seizure precipitated by fever	.54
4	Generalized EEG abnormality	.45
5	EEG abnormality exacerbated by hyperventilation	.39
6	Bizarre ictal psychic behavior	.35
7	Sex	.32
8	Alpha 9+ Hz. on EEG	.29
9	EEG abnormality exacerbated by photic stimulation	.26
10	Metabolic error	.22
11	CNS trauma	.21
12	Age at onset of seizures	.19
13	Generalized or focal onset of ictal movement	.18
14	CNS infection	.17

TABLE 25

DISCRIMINANT FUNCTION COEFFICIENTS
 PATIENTS WHO HAVE BEEN TREATED WITH ONLY ONE DRUG
 FOR ENTIRETY OF TREATMENT

Variables	Function		
	<u>1</u>	<u>2</u>	<u>3</u>
Generalized EEG abnormality	-.73	-.09	-.00
Age at onset of seizure	.71	-.13	-.38
Polyspikes on EEG	-.67	.32	.47
Characteristics of ictal movement	.31	-.26	.01
CNS infection	.31	.16	.13
EEG abnormality exacerbated by photic stimulation	-.03	1.02	-.14
Alpha 9+ Hz. on EEG	.07	-.74	.26
Seizure precipitated by fever	.09	-.60	.17
Metabolic error	-.17	.57	.48
Bizarre ictal psychic behavior	.37	.52	.12
Age at administration of current drug	-.13	-.03	1.67
EEG abnormality exacerbated by hyperventilation	.44	-.04	.93
CNS trauma	-.15	-.13	.63
Sex	-.22	.42	-.43

TABLE 26

CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS
OF PATIENTS TREATED WITH ONLY ONE DRUG
DURING ENTIRETY OF TREATMENT

Actual	N	Predicted Group Membership			
		PB	PH	CBZ	VPA
PB (%)	30	24 (80.0)	1 (3.3)	4 (13.3)	1 (3.3)
PH (%)	14	1 (7.1)	10 (71.4)	0 (0.0)	3 (5.6)
CBZ (%)	18	2 (11.1)	3 (16.7)	12 (66.7)	1 (5.6)
VPA	18	1 (5.6)	3 (16.7)	1 (5.6)	13 (72.2)

Percent of grouped cases correctly classified: 73.75%

TABLE 27

VARIABLES IN ORDER OF VALUE IN THE DISCRIMINANT
ANALYSIS OF PATIENTS WITH A HISTORY OF DRUG
THERAPY OTHER THAN CURRENT DRUG

Step	Variable	Wilk's Lambda
1	Generalized or focal onset of ictal movement	.79
2	Alpha 9+ Hz. on EEG	.60
3	Sex	.49
4	Speech abnormality	.41
5	Metabolic errors	.37
6	2-4 spike and wave on EEG	.32
7	Seizures precipitated by fever	.30
8	Age at administration of current drug	.27
9	Characteristics of ictal movement	.26
10	Forceps delivery	.24
11	Recurrent headache	.23

TABLE 28

DISCRIMINANT FUNCTION COEFFICIENTS
PATIENTS TREATED WITH OTHER DRUGS IN PAST

Variable	Function		
	<u>1</u>	<u>2</u>	<u>3</u>
Sex	.79	-.03	.32
Generalized or focal onset of ictal movement	.63	.26	.36
Age at administration of current drug	-.45	-.41	.13
Alpha 9+ Hz. on EEG	-.45	-.41	.13
Metabolic errors	-.16	.79	.05
Speech abnormality	.15	.70	.24
Characteristics of ictal movement	.10	-.42	-.19
2-4 Hz. spike and wave	.12	.39	.23
Forceps delivery	-.13	-.55	.66
Seizures precipitated by fever	.08	.04	.56
Recurrent headache	.26	-.14	-.40

TABLE 29

CLASSIFICATION RESULTS FROM DISCRIMINANT ANALYSIS
OF PATIENTS TREATED WITH OTHER DRUGS IN THE PAST

Actual	N	Predicted Group Membership			
		PB	PH	CBZ	VPA
PB (%)	8	5 (62.5)	1 (12.5)	1 (12.5)	1 (12.5)
PH (%)	16	0 (4.0)	12 (75.0)	1 (6.3)	3 (18.8)
CBZ (%)	36	4 (11.1)	5 (13.9)	27 (75.0)	0 (0.0)
VPA (%)	24	1 (4.2)	5 (20.8)	2 (8.3)	16 (66.7)

Percent of grouped cases currently classified: 71.4%

The desire to determine which, if any, variables correlated highly with any one particular drug type prompted the use of factor analysis. The results of factor analysis without limitation as to the number of factors produced are listed in table 30. Nine factors were produced and are listed with the variables that make them up. The factor name was chosen arbitrarily from this list. Phenytoin, valproic acid, carbamazepine, and phenobarbital each are correlated with specific variables. There are no correlating variables with phenobarbital in factor 5. The first two factors are not associated with any drug type.

Limiting the number of factors to seven did not greatly change the patterns of correlation. Factors 1 and 3 did not correlate with any drug type. Valproic acid was

correlated in factors 5 and 6 with EEG data.

Carbamazepine, phenobarbital and phenytoin remained difficult to isolate with any particular variables. Factor 7 had only metabolic errors correlating highly with it. These results are listed in table 31.

TABLE 30

FACTOR ANALYSIS WITH NINE FACTORS PRODUCED

Number	Name	Variables	Correlation Coefficients
1	Age	Age at administration of current drug	.79
		Age at onset of seizures	.95
		Alpha 9+ Hz.	-.54
		EEG abnormality exacerbated by hyperventilation	-.39
2	Activation	EEG abnormality exacerbated by photic stimulation	.58
		EEG abnormality exacerbated by hyperventilation	.88
3	Valproic Acid I	Polyspikes on EEG	.52
		Speech abnormality	.33
		Valproic Acid	.73
4	Phenytoin I	Sex	.40
		Diagnosis of hyperactivity	.36
		Phenytoin	.80
		Carbamazepine	-.48
5	Phenobarbital	None	--
		Phenobarbital	.86
6	Valproic Acid II	Generalized EEG abnormality	.53
		2-4 Hz. spike and wave	.76
		Valproic acid	.39
7	Carbamazepine	Focal onset of movement	.47
		Bizarre ictal psychic behavior	.37
		Carbamazepine	.42
8	Phenobarbital II	CNS trauma	.61
		Seizures precipitated by fever	.54
		Phenobarbital	.28
9	Unknown	Metabolic errors	-.42
		CNS infection	.34
		Phenytoin	.31
		Valproic acid	-.64

TABLE 31

FACTOR ANALYSIS WITH SEVEN FACTORS PRODUCED

Number	Name	Variables	Correlation Coefficients
1	Age/Activation	Age at administration of current drug	.88
		Age at onset of seizures	.83
		Alpha 9+ Hz. on EEG	-.56
		EEG abnormality exacerbated	
		- by hyperventilation	-.44
		- by photic stimulation	-.31
2	Phenytoin/Carbamazepine	Diagnosis of hyperactivity	.35
		Sex	.31
		Carbamazepine	-.47
		Phenytoin	.92
3	Activation	EEG abnormality exacerbated	
		- by photic stimulation	.88
		- by hyperventilation	.56
4	Phenobarbital	Seizures precipitated by fever	.47
		CNS trauma	.39
		Phenobarbital	.77
		Carbamazepine	-.49
5	Valproic Acid I	Polyspikes on EEG	.51
		EEG abnormality exacerbated by hyperventilation	.31
		Speech abnormality	.34
		Abnormal infancy	-.31
		Valproic acid	.64
6	Valproic Acid II	2-4 Spike and Wave	.68
		Generalized EEG abnormality	.47
		Valproic acid	.43
		Carbamazepine	-.44
7	Unknown	Metabolic errors	.45

CHAPTER 9

DISCUSSION

The aim of this study was the isolation of predictive parameters from routinely collected data about a patient with a seizure disorder which would enable clinicians to choose more often the seizure controlling drug on the initial visit. To this end, multivariate analysis of data from patients who achieved optimal or near optimal control with a single drug was employed to determine if there were any unique patterns existing in these patients that would be predictive for a particular drug type in a newly diagnosed seizure patient with similar patterns. Several patterns did emerge. However, in each instance it would be difficult to prescribe an anticonvulsant drug based strictly on these emergent criteria.

Discussion of the variables which were found to be related to drug type is necessary, especially with regard to why they were significant and what value they have in a future drug selection process. The majority of the variables found to be important were historical. Some concerned the description of the ictal event while others were causal. The variables will be considered by category, i.e., historical, clinical or EEG.

The presence of bizarre ictal psychic behavior contributed highly to the separation of the drug groups.

It is a unique behavior that occurs mostly in patients with temporal lobe seizures. Temporal lobe seizures are most often treated with carbamazepine. The presence of the phenomenon in new patients will predict strongly for carbamazepine.

Seizures which are precipitated by fever are usually benign although 2% do go on to have recurrent afebrile seizures (Lennox-Buchthal, 1982). Patients exhibiting this phenomenon in this study were judged to have recurrent epilepsy and were treated apparently successfully most often with phenobarbital. It is a strong predictor for phenobarbital when observed in newly diagnosed seizure patients.

Delivery of patients by forceps at birth was a discriminator mostly for phenytoin. Its value as a predictor assumes association with birth trauma secondary to the use of forceps. However, the majority of patients delivered with forceps do not develop seizures. Furthermore, birth histories are often quite spare and often have no information about the type of delivery. It was the most frequently missed piece of data in this study. For future use, the variables should be replaced with birth trauma resulting from forceps or other instruments.

Metabolic errors in patients with epilepsy in this study were rare. Most of those recorded to have a metabolic error were being treated with valproic acid.

There were two patients who had diet-controlled PKU. Although seizures are associated with this disease, it is impossible to determine if they result from the sequelae of the disease or if they arose coincidentally. Two of the patients had a mucopolysaccharidoses, one with Hunter and one with Hurler syndrome. Both syndromes are associated with seizures (Gastaut, 1969). In the Hunter case, valproic acid was the first drug prescribed while for the Hurler case, valproic acid was the drug remaining after several others had been weaned. Three of the patients were mentally retarded secondary to suspected, but unidentified, metabolic errors. All of the patients experienced generalized seizures. There is no apparent reason why valproic acid should be any better for the patient with a systemic metabolic error than any of the other major anti-convulsants. It remains to be explained whether this variable will be a valuable predictor of valproic acid.

The features of ictal movements, i.e., tonic clonic, tonic-clonic, atonic or no movement distinguished generalized convulsive from generalized non-convulsive seizures. Valproic acid was prescribed more often for generalized non-convulsive seizures while phenobarbital, carbamazepine and phenytoin were prescribed for generalized convulsive seizures. In this respect, the variable is a valuable predictor of drug type. All classifications presently used by clinicians to prescribe drugs incorporate

this variable.

The description of the onset of the ictal movement clinically distinguished between focal and generalized seizures. Carbamazepine was the favorite drug to use for patients with a focal onset. Empirically, there is no difference between the efficacy of carbamazepine and phenytoin for partial seizures (Bird et al., 1966; Ceraghino, 1977). In this study clinicians prescribing behavior may have contributed to the significance of this variable.

The presence of recurrent headache may indicate an underlying systemic or focal process. The variable correlated highest with phenytoin on factor analysis although phenobarbital and carbamazepine were also correlated with it to some degree. Its use as a predictor of drug type is in itself quite poor because there are many individuals with recurrent headache who do not have seizures. However, when associated with other known pathologies, such as migraine, tumor, CVA or trauma, it becomes more important.

The diagnosis of hyperactivity is most often made in boys (Barkley, 1981). Phenytoin was prescribed significantly more often to boys than to girls for reasons to be discussed. Furthermore, hyperactivity is a contraindication to the use of phenobarbital (Livingston, 1979). These two factors may account for the higher

correlation between hyperactivity and phenytoin on factor analysis. Not surprisingly, the diagnosis of hyperactivity impacted negatively on phenytoin in the discriminant analysis of the female population. It may be possible, in any event, that phenytoin is a better drug for patients with hyperactivity and seizures. This remains to be proven.

Patients with histories of CNS infection or CNS trauma were more often prescribed phenytoin, phenobarbital and carbamazepine. Residual CNS pathology is implied with both variables. As predictors of drug type they seem to be valuable in separating the valproic acid group from the other three.

A history of an abnormal infancy is a weak predictor of drug type. The abnormalities recorded included seizures, developmental delay and systemic disease. It is not specific enough to be of great value in separating one drug group from another.

Age of onset of seizures was important in the discrimination of drug type. Patients taking phenobarbital tended to be younger (3.8 years). This may reflect the high percentage of patients presenting between 2 and 3 years of age with fever induced seizures who were taking phenobarbital. Patients taking valproic acid were also young (3.7 years). This may reflect the earlier onset of absence type seizures which are best treated with valproic

acid (Pinder et al., 1977). Patients taking phenytoin and carbamazepine presented later (6.0 and 6.4 years). The primary generalized and partial seizures treated by these drugs present later (Brown, 1982).

Interestingly, on factor analysis age of onset of seizures did not correlate highly with any drug type, yet was an important contributor to the variance along with age at administration of the current drug. Since there is no assumption about the underlying structure of the data forcing an association with drug type, it is likely that the very highly correlated age variables dominated. They are doublets, i.e., variables with different names but describing the same entity. For future analysis or selection processes, these variables should be combined into a single variable describing the age at onset of seizures.

Sex was an important variable in the discriminant and factor analysis. This is a reflection of clinician prescribing behavior. In most instances phenytoin was not prescribed to young girls because the adverse cosmetic side effects were less tolerable to them. Carbamazepine was prescribed instead.

The list of variables found to be important when discriminant analysis was done by separate sex were essentially similar. Bizarre ictal psychic behavior was more important for males while the diagnosis of

hyperactivity was more important for females. In both instances males were more often affected. Hyperactivity as it relates to sex was discussed above. Most authors have found higher incidence rates for temporal lobe epilepsy in males (Hauser, 1982). The EEG variables were of similar value with regard to the separation of drug types between the sexes.

The presence of a speech abnormality was an indication of CNS pathology, developmental delay or both. Its value as a predictor is similar to that of forceps delivery and recurrent headache. There are many people with speech problems who haven't developed seizures. Again, this variable must be one of several predictors if it is to be of value for predictions on drug type.

The EEG variables that demonstrated value in a differentiating between drugs may be rearranged to eliminate redundancy. The presence of polyspikes on EEG was always associated with valproic acid use. Polyspikes are an ambiguous entity that may be unilateral or bilaterally synchronous. They may be temporal, frontal or generalized. They are an indication of epileptogenic activity but are not associated with a specific clinical seizure type. In this study they were always generalized. They may be related to those patients with 2-4 Hz. spike and wave on EEG and those with a generalized EEG abnormality. They did not, however, correlate within the

same factor on factor analysis indicating a degree of difference between them. The entities, i.e., 2-4 Hz. spike and wave on EEG and generalized EEG abnormality, are definitely doublets since most 2-4 Hz. spike and wave patterns are generalized. They were closely correlated within the same factors on factor analysis and were of similar discriminating value on discriminant analysis. Nevertheless, when these phenomenon present on the EEG, they strongly predict for valproic acid.

Another pair of EEG doublets are the activation parameters hyperventilation and photic stimulation. For reasons not clear, they are very closely correlated and, in fact, dominate the variance of an entire factor on factor analysis without being associated with any drug type. Both techniques are used primarily to elicit an absence type seizure (Marsden and Reynolds, 1982). They can sometimes cause other susceptible individuals to exhibit abnormal EEG phenomena (Driver and McGillivray, 1982). The confusion arises in the interpretation of abnormal EEG findings in the absence of clear cut seizure activity. Not all patients who were recorded as having a positive exacerbation of the EEG abnormalities had definite seizures. Those that did were probably on valproic acid. Those that showed abnormal slowing or an unusually slow recovery from hyperventilation may have been on another drug type since they may not have classical absence seizures. Similarly,

for photic-stimulation those patients demonstrating a slow recovery from a normal driving response were recorded as positive. The variables are not clear predictors although they did demonstrate a correlation between susceptible patients whose EEG was easily disturbed by the activating techniques perhaps indicating a decreased seizure threshold in these patients. In the future the response to the activation should be definite seizure activity versus mild to moderate changes in the background activity.

The presence of alpha rhythm with frequency greater than 9 Hz. up to 11 Hz. represents the upper limits of normal. This pattern is not known to be associated with definite pathology or any particular seizure type. It was included in the study for descriptive purposes. It was inversely correlated with the maturation of the patient in years but was not correlated with drug type. Perhaps the younger the patient the slower the alpha frequency recorded. It is known that the younger the brain the greater the predominance of slower wave forms (Brown, 1982). As a predictive variable it separates the phenytoin and carbamazepine groups from the phenobarbital and valproic acid groups just as the age variables tend to do.

The second aim of this study was to assess the accuracy of the derived classification formulas. The formulas were based upon the unique contribution each significant variable made to the differentiation of the

drug types.

For the population as a whole the percent correctly classified was 62.5%. This was better than the 47% who were placed on the seizure controlling drug by the initially prescribing physician. One would expect 25% to be correctly placed by chance. In many cases, however, the initially prescribing physician was in the private sector and referred the patient to the seizure clinic. It is difficult, then, to compare adequately the classification results obtained in the study to the actual number of patients remaining on the originally prescribed drug when many different physicians with different levels of experience were involved. Nevertheless, it is important to note the greater than two year span from the time of onset of seizures to the age at administration of current drug. According to Rodin (1968), this amount of time with less than optimal control of seizures can worsen a patient's prognosis. Perhaps this gap would have been smaller had all the patients been seen by the specialty staff at the time or had the primary physicians been equipped with a readily available formula to help them select a drug.

The percent correctly classified was increased up to 85% when the drug groups were combined so as to isolate valproic acid from the other three drugs studied. This high percentage confirms the many reports that phenytoin, carbamazepine and phenobarbital are similarly efficacious.

It also demonstrates that misclassification occurs even when the simplest choice between two drug types is to be made. It exemplifies the problem acknowledged in most comparative studies (Bird et al., 1960; Cereghino, 1974; Shorvon et al., 1980) that overall for any individual patient with seizures there are several drugs which will work equally well. However, there are those patients who do exist (e.g. 91 patients in this study treated with other drugs in the past) who will achieve optimal control with only one of these several drugs.

This study attempted to simplify the drug selection process by providing an easy to use formula. Factor analysis did not, however, provide clear patterns of variables for use in a simple table form. The derived formula resulting from discriminant analysis are necessary for optimal selection success. Unfortunately, these results are not convincing enough to be potentially useful to clinicians. A prospective study is being undertaken to confirm the retrospectively derived classification formulas.

The question arises, however, as to which of the several classification formulas derived should be used in the study. The percent correctly classified for the previously treated patients and for the previously untreated patients was a higher value than that achieved for the population as a whole. However, the greater N used

in the entire population implies greater validity of the formula (Klecka, 1975). The decision as to which to incorporate will be based on further statistical evaluation of the differences between previously treated and untreated patients. As it stands, those previously treated seem to be described more by variables implying CNS pathology while the newly diagnosed patients were described more by EEG data which indicate a more primary seizure problem. If they are different, then the classification formula from previously untreated patients will be employed for new patients coming into the seizure clinic.

The study will be set up to compare clinician judgment and the classification formula results. New patients will be randomly assigned to the clinician judgment group and to the classification group. For the clinician judgment group a drug will be chosen based on his/her expertise. For the classification group a drug will be prescribed based on probability of membership in a certain drug group. Two examples, one a success, the other a failure, of patient classification results from this study are shown in tables 32 and 33.

TABLE 32

EXAMPLE OF DISCRIMINANT ANALYSIS CLASSIFICATION

PROFILE OF PATIENT #10

<u>CHARACTER</u>	<u>RESPONSE</u>
Presence of polyspikes	Yes
Bizarre ictal psychic behavior	Yes
Seizures precipitated by fever	Yes
EEG exacerbated by photic stimulation	No
Sex	Male
Presence of 2-4 Hz. spike and wave on EEG	No
Forceps delivery	No
Metabolic errors	No
EEG exacerbated by hyperventilation	Yes
Ictal movements	Clonic
Presence of Alpha 9 plus Hz.	No
Recurrent headache	No
Age of administration	5 years
EEG abnormality generalized	Yes
Generalized or focal onset of movement	Generalized
Age of onset	10 months
Highest Probability Group	Valproic Acid 0.9996
Second Highest Group	Phenytoin 0.0002
Actual Group	Valproic Acid

TABLE 33

EXAMPLE OF DISCRIMINANT ANALYSIS CLASSIFICATION

PROFILE OF PATIENT #110

<u>CHARACTER</u>	<u>RESPONSE</u>
Presence of polyspikes	No
Bizarre ictal psychic behavior	No
Environmentally determined course	No
EEG exacerbated by photic stimulation	Yes
Sex	Male
Presence of 2-4 Hz. spike and wave on EEG	No
Metabolic errors	No
Forceps delivery	No
EEG exacerbated by hyperventilation	Yes
Ictal movements	Clonic
Presence of Alpha 9 plus Hz.	No
Recurrent headache	No
Age of administration	4 years
EEG abnormality generalized	No
Generalized or focal onset of movement	Focal
Age of onset	4 years

Highest Probability Group	Phenytoin 0.4970
Second Highest Group	Carbamazepine 0.4129
Actual Group	Carbamazepine

The probabilities for the highest and second highest group will be recorded for later evaluation, i.e., what is the minimum probability which will accurately choose the seizure controlling drug. If subsequent to an adequate follow-up a patient's seizures are not controlled by optimal levels of the initial drug, a change will be made to a drug of the clinician's choice. Both will be recorded for evaluation.

The likely outcome is that the discriminant analysis formula and clinician judgment are equally accurate. This is probable because the formula was based on a clinician responding to the various electrophysiological, clinical and historical markers for different seizure types and his experience with the drugs that seem to control these seizures. Clinicians consciously or unconsciously go through the multivariate analysis within their mind before prescribing a drug. The patterns elicited from those previously treated patients who were controlled with a single drug should have provided new information about difference between patients with similar seizure types. Unfortunately, no clear patterns emerged.

In this study it was assumed that the drug the patient was on was the best drug for him or her. This was entirely based on the assumption that the control achieved over the duration of the follow-up was optimal and that it would remain optimal. Unfortunately, this assumption may not be

valid in all cases because especially in children seizure types tend to change over the years so that a child may exhibit symptoms and signs of two or three different seizure types (Brown, 1982). In addition, patients with seizures are known to break through the medication requiring increased dosage or a change in drug (Livingston, 1979). There is a subpopulation of epileptics who spontaneously remit, and there is a subpopulation who are chronically refractory to therapy. While it is easy to identify the latter group, the former group of patients must also be considered whenever success of drug therapy is achieved (Rodin, 1968).

Why is this study important if clinician judgment is said to be equally accurate when compared to classification formulas? The study is potentially significant because many physicians prescribing anticonvulsants in primary practice are not extremely familiar with seizures, the classifications of seizures or the antiseizure medications (Reynolds and Shorvon, 1981). This has contributed to polytherapy (Reynolds and Shorvon, 1981) and to the greater than two year span during which most of the patients in this study were under less than optimal seizure control. It would be valuable, then, to have a simple list of criteria to follow when choosing an anticonvulsant. Unfortunately, as mentioned above, factor analysis did not produce enough meaningful variables so that when present in

an individual seizure patient would point toward a certain drug for that patient. However, the classification formula could become reasonably accurate. If it can be improved upon during the prospective study, it could easily be programmed into any basic computer. This would by-pass the sometimes unwieldy classification systems now in use.

One of the problems with such an idea is that there are many other anticonvulsant drugs on the market. This study assumed, as mentioned above, that patients belonged on that drug. Such a program would limit clinicians to the four drugs studied here. Perhaps an expansion to include other drugs could be explored in the future.

A computer-based program to help select an anticonvulsant medication should be used with caution and should not replace adequate knowledge of the patient's overall condition and of the potential adverse reactions of the drug selected. The literature of the various aspects of chronic use of anticonvulsants is growing (Dam, 1982). Therefore, included into any future program should be the recorded list of chronic side-effects and their consequences so that ultimately clinicians should be able to select the antiepileptic drug with the smallest risk of adverse reactions to the patients or their offspring.

SUMMARY

This study attempted to isolate predictive parameters from routinely collected data to enable clinicians to more often choose the seizure controlling anticonvulsant and to use them in a classification formula. There were no heretofore unknown variables that were discovered which would simplify the choosing of anticonvulsant medication. However, there may be potential in using many of the previously known variables in a mathematical formula which is computer based to predict medication.

REFERENCES CITED

REFERENCES CITED

1. Anderson, V.E. Family studies of epilepsy. In Genetic Basis of the Epilepsies. Anderson, W.E., Hauser, W.A., Penry, J.K., Sing, C.S. (eds). Raven Press, New York, 1982, pp. 103-112.
2. Ansell, B. and Clarke, J. The role of water retention in menstruating epileptics. Lancet 2: 7232, 1956.
3. Backstrom, T. Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. Acta Neurologica Scandinavia 54: 321, 1976.
4. Barkley, R.A. Hyperactive Children: A handbook for diagnosis and treatment. Guilford Press, New York, 1981.
5. Bird, C.K., Griffin, B.B., Mikkesewslan, J.M., and Galbraith, A.W., Tegretol (Carbamazepine): A controlled trial of a new anticonvulsant. British Journal Psychiatry 112: 737-742, 1966.
6. Blume, W.T., David, P.B., and Gomez, M.R. Generalized sharp and slow wave complexes: Association with clinical features and long term follow-up. Brain 96: 289, 1973.
7. Booker, H.E. Phenobarbital, mephobarbital and methital: Relation of plasma levels and clinical control. In Antiepileptic Drugs. Woodbury, D.M., Penry, J.K., Schmidt, M.D. (eds). Raven Press, New York, 1972, p. 403.
8. Brown, J.K. Fits in children. In a Textbook of Epilepsy, Laidlaw, J., Richens, A. (eds). Churchill Livingstone, New York, 1982, pp. 34-66.
9. Bruni, J. and Wilder, B.J. Valproic Acid. Archives of Neurology 36: 393, 1979.
10. Calahan, H., O'Callaghan, M., Duggan, B., and Feely, M. Carbamazepine as a single drug in the treatment of epilepsy. Journal of Neurology, Neurosurgery and Psychiatry 41: 707-912, 1973.
11. Cereghino, J.J., Brock, J.J., Van Meter, J.C., Penry, J.K., Smith, L.D., and White, B.G.: Carbamazepine for epilepsy. Neurology, May, 1974, 401-410.

12. Coatsworth, J.J. and Penry, J.K. Clinical efficacy and use. In *Antiepileptic Drugs*. Woodbury, D.M., Penry, J.K., Schmidt, R.D. (eds). Raven Press, New York, 1972, pp. 87-96.
13. Currie, S., Heathfield, K., Henson, R., and Scott, O. Clinical course and prognosis of temporal lobe epilepsy. A survey of 666 patients. *Brain* 94: 173, 1971.
14. Doose, H., Helmien, H., Katz, E., Kunkel, H., Mathes, H., Oberholfer, G., Penin, H., Rake, F., Scheffer, P., and Voigt, M. Modern methods of assessing antiepileptic drugs. *Pharmakopsychiatrika Neuropsychopharmakologika* 3: 277, 1970.
15. Driver, M.V. and McGillivray, B.B. Electroencephalography In a *Textbook of Epilepsy*, Laidlaw, J., Richens, A. (eds). Churchill Livingstone, New York, 1982, pp. 155-195.
16. Esplin, D.W. Effects of diphenylhydantoin on synaptic transmission in cat spinal cord and stellate ganglion. *Journal Pharmacology and Experimental Therapeutics* 120: 301-323, 1957.
17. Falconer, M.A. Mesial temporal sclerosis (Ammon's horn sclerosis) as a common cause of epilepsy. *Lancet* 2: 767, 1974.
18. Fenton, G.W. Epilepsy and automatisms. *British Journal of Hospital Medicine* 7: 57, 1972.
19. Feindel, W. and Penfield, W. Localization of discharge in temporal lobe automatism. *Archives of Neurology and Psychiatry* 10: 233, 1954.
20. Friis, M.L. and Lund, M. Stress convulsions. *Archives of Neurology* 31: 155, 1974.
21. Gastaut, H. Clinical and electroencephalographical classification of seizures. *Epilepsia* 10 (supplement): 1-28, 1969.
22. Gastaut, H. On genetic transmission of epilepsies. *Epilepsia* 10: 3-6, 1969.
23. Gibberd, F. and Bateson, M.C. Sleep epilepsy: Its pattern and prognosis. *British Medical Journal* 2: 403, 1974.

24. Gibbs, F.A., Davies, H., and Lennox, W.G. The EEG in epilepsy and in conditions of impaired consciousness. *Archives of Neurology and Psychiatry* 34: 1133, 1935.
25. Goldman, L., Weinberg, M., Olslen, R., Cook, E.F., and Finsberg, H. A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *New England Journal Medicine* 307: 588, 1982.
26. Groves, C.P. Results of a multivariate analysis on the skulls of Asiatic wild asses. *Annals of Natural History* 6: 229-336, 1963.
27. Guelin, P.M., Vanderklein, E., and Wondstra, U. Statistical analysis of pharmacokinetic parameters in epileptic patients chronically treated with antiepileptic drugs. In *Clinical Pharmacology of Antiepileptic Drugs*, Schneider, H., Janz D., Gardner-Thorpe C., Meinhard, H., Sherwin, A.L. (eds). Springer-Verlag, Berlin, 1975, pp. 2-10.
28. Halpern, L.M. and Julien, R.M. Augmentation of cerebellar purkinje cell discharge rate after phenytoin. *Epilepsia* 13: 377-385, 1972.
29. Hauser, W.A. Genetics and the clinical characteristics of seizures. In *Genetic Basis of the Epileptics*, Anderson, V.E., Hauser, W., Penry, J.K., Sing, C.F. (eds). Raven Press, New York, 1982, pp. 3-11.
30. Holowack, J., Thurston, D.L., and O'Leary, T. Prognosis in childhood epilepsy. *New England Journal of Medicine* 268: 169, 1972.
31. Jeavons, P.M., Clark, J.E., and Mahesowric, M.C. Treatment of generalized epilepsies of childhood and adolescence with sodium valproate. *Developmental Medicine of Child Neurology* 19: 9-25, 1977.
32. Klecka, W.R. Discriminant analysis. In *Statistical Package for the Social Sciences*. Nie, H.H., Hull, C.H., Jenkins, J.G., Steinbrenner, K., Bent, B.H. (eds). McGraw Hill, New York, 1975.
33. Kim, J. Factor analysis. In *Statistical Package for the Social Sciences*, Hie, H.H., Hull, C.H., Jenkins, J.G., Steinbrenner, F., Bent, B.H. (eds). McGraw Hill, New York, 1975.

34. Knox, S.J. Epileptic automatisms and violence. *Medical Science and Law* 8: 96, 1968.
35. Lennox, W.G. The petit mal epilepsies. *Journal of the American Medical Association* 127: 1069, 1945.
36. Lennox, W.G. *Epilepsy and Related Disorders*. Little Brown and Co., London, 1960.
37. Lennox-Buchthal, M.A. Febrile convulsions. In *a Textbook of Epilepsy*, Laidlaw, J., Richens, A. (eds). Churchill Livingstone, New York, 1982, pp. 68-88.
38. Liddell, D.W. Observations on epileptic automatisms in a mental hospital population. *Journal of Mental Science* 99: 732, 1953.
39. Livingston, S., Tomas, I., Pauli, L.L., and Rider, R.V. Petit mal epilepsy: Results of a prolonged follow-up study of 112 patients. *Journal of the American Medical Association* 194: 227, 1965.
40. Livingston, S., Prince, J., and Pauli, L.L. Medical treatment of epilepsy. *Pediatric Annals* 8: 4, 1979.
41. Marsden, C.D. and Reynolds, E.H. Neurology in a *Textbook of Epilepsy*, Laidlaw, J., Richens, A. (eds). Churchill Livingstone, New York, 1982, pp. 90-132.
42. McKhann, G.M. and Shooter, E.M. Genetics of seizure susceptibility. In *Basic Mechanisms of the Epilepsies*, Jasper, H., Ward, A., Pope, W. (eds). Little, Brown and Co., Boston, 1969, pp. 689-700.
43. Meinardi, H., Van Heycopten, M., Meijer, J., and Bongers, E. Long term control of seizures. In *Epilepsy: The Eighth International Symposium*, Penry, J.K. (ed). Raven Press, New York, 1977, pp. 17-26.
44. Millichap, J.G. and Aymat, F. Treatment and prognosis of petit mal epilepsy. *Pediatric Neurology* 14: 905, 1967.
45. Penfield, W. and Welch, K. The supplementary motor area of the cerebral cortex. *Archives of Neurology and Psychiatry* 66: 289, 1951.

46. Penfield, W. *Epilepsy and the Functional Anatomy of the Human Brain*. Little, Brown and Co., Boston, 1954.
47. Penry, J.K. and Dreifuss, F.E. Automatisms associated with absence of petit mal epilepsy. *Archives of Neurology* 21: 142, 1969.
48. Perucca, E., Garratt, S., Hebdige, S. and Richens, A. Effect of close increments on serum carbamazepine concentration in epileptic patients. *Clinical Pharmacokinetics*, 1979.
49. Pinder, R.M., Brogden, R.N., Speight, T.M. and Avery, G.S. Sodium valproate: A review of its pharmacological properties and therapeutic efficacy in epilepsy. *Drugs*, 13: 81, 1977.
50. Rall, T.W. and Schleifer, L.S. Drugs effective in the treatment of the epilepsies. In *The Pharmacological Basis of Therapeutics*, Goodman, L.S., Gilman, A. (eds). Sixth Edition, 1980, pp. 448-475.
51. Reynolds, E.H., Chadwick, D., and Galbraith, A.W. One drug (phenytoin) in treatment of epilepsy. *Lancet*, May 1, 1976, pp. 923-926.
52. Reynolds, E.H. and Shorvon, S.D. Monotherapy or polytherapy for epilepsy? *Epilepsia* 22: 1-10, 1981.
53. Richens, A. Serum phenytoin levels in management of epilepsy. *Lancet* 2: 247, 1975.
54. Rodin, E.A. *The Prognosis of Patients with Epilepsy*. Charles C. Thomas, Springfield, Illinois, 1968, pp. 175-342.
55. Sato, S., Dreifuss, F.E., and Penry, J.K. Prognostic factors in absence seizures. *Neurology* 26: 798, 1976.
56. Shorvon, S.D. and Reynolds, E. Unnecessary polypharmacy for epilepsy. *British Medical Journal* 24 June 1977, pp. 1635-1637.
57. Shorvon, S.D., Chadwick, D., Galbraith, A.W., and Reynolds, E.H. One drug for epilepsy. *British Medical Journal* 2: 1023-1025, 1979.

58. Shorvon, S.D. and Reynolds, E.H. Reduction in polypharmacy for epilepsy. *British Medical Journal* 2: 1023-1025, 1979.
59. Shorvon, S.D., Johnson, A.L., and Reynolds, E.H. Statistical and theoretical considerations in the design of anticonvulsant trials. An analysis of 155 trials of phenytoin and carbamazepine. Communication to the 12th International Epilepsy Symposium, Copenhagen, 1980.
60. Simon, D. and Penry, J.K. Sodium di-N-propylacetate in the treatment of epilepsy. A review, *Epilepsia* 16: 549-573, 1975.
61. Simonsen, N., Olsen, L.P., Kuhl, V., Lund, M., and Wendelboe, J. A comparative controlled study between carbamazepine and diphenylhydantoin in psychomotor epilepsy. *Epilepsia* 17: 169-176, 1976.
62. Suzuke, M., Maruyama, H., Ishibashi, Y., Ogawa, S., Seki, T., Hoshino, M., Maekawa, K., Yo, T., and Sato, Y. A double blind comparative trial of sodium dipropylacetate and ethosuximide in epilepsy in children. *Medical Progress* 82: 470, 1972.
63. Symposium. Antiepileptic Drugs: Quantitative Analysis and Interpretation. Pippinger, C.E., Penry, J.K., Kuhl, H. (eds). Raven Press, New York, 1978.
64. Troupin, A.S., Green, T.R., and Halpern, L.M. Carbamazepine as an anticonvulsant. A controlled double-blind comparison with diphenylhydantoin. *Acta Neurologica Scandinavica* (Suppl.) 60, 1975, p. 13.
65. Williams, D. The thalamus and epilepsy. *Brain* 88: 539, 1965.
66. White, P.T., Plott, D., and Nox, J. Relative anticonvulsant potency at primidone: A double-blind comparison. *Archives of Neurology* 14: 31, 1966.
67. Whitty, C.M. A note on the classification of epilepsy. *Lancet* 1: 99, 1965.
68. Woodbury, D.M. and Kemp, J.W. Some possible mechanisms of action of antiepileptic drugs. *Pharmakopsychiatrika Neuropsychopharmakologika* 3: 201-226, 1970.

APPENDICES

APPENDIX I

CLINICAL AND HISTORICAL DATA COLLECTED

CLINICAL AND HISTORICAL DATA COLLECTED

Basic data

a) Drug type

b) Response

- 1. exacerbation of seizures
- 2. 0-30% reduction in seizures
- 3. 30-60% reduction in seizures
- 4. 60-90% reduction in seizures
- 5. 90-100% reduction in seizures

Frequency

c) Age at onset of seizures

d) Age at administration of current drug

e) Sex

Description of ictal event

f) Ictal unconsciousness or unresponsiveness:

Yes or No

g) Aura

- no aura
- olfactory
- auditory
- visual
- motor
- somatosensory
- visceral
- vestibular
- anxiety

---	---
---	---
---	---
---	---
---	---
---	---
---	---
---	---
---	---

h) Onset of ictal movement

- generalized
- focal
- neither

---	---
---	---
---	---

i) Ictal movements

- tonic
- clonic
- tonic-clonic

---	---
---	---
---	---

j) Eye movement

- staring
- rolled back
- to one side
- back and forth
- blinking
- no movement recorded

---	---
---	---
---	---
---	---
---	---
---	---

k) Automatisms

---	---
-----	-----

1) Confused state	Yes or No	
- during ictus	----	----
- after ictus	----	----
- during and after	----	----
- no confusion	----	----
m) Bizarre ictal psychic behavior	----	----
n) Post ictal characteristics		
- clumsiness	----	----
- headache	----	----
- both	----	----
- paresis	----	----
- none above	----	----
o) Autonomic symptoms		
- loss of control bowel/bladder	----	----
p) Precipitants		
- stress	----	----
- menstruation	----	----
- sleep	----	----
- photic stimulation	----	----
- hyperventilation	----	----
- sensory provoked	----	----
- drug withdrawal	----	----
- fluid balance	----	----
- fever	----	----
- exercise	----	----
- trauma	----	----
q) Family history		
- occurrence in siblings	----	----
- occurrence in parents	----	----
- occurrence any relative	----	----
r) Frequency seizures		
- daily	----	----
- weekly	----	----
- monthly	----	----
- yearly	----	----
s) Pregnancy history		
- normal	----	----
- drug exposure	----	----
- trauma	----	----
- illness	----	----
- RH incompatibility	----	----
- hemorrhaging	----	----

t) Delivery history	Yes or No	
- normal	---	---
- oxygen required	---	---
- intubation	---	---
- breech delivery	---	---
- prolonged labor	---	---
- forceps delivery	---	---
- anesthesia	---	---
- premature	---	---
- post-term	---	---
- neonatal seizures	---	---
- kernicterus	---	---
- C-section	---	---
u) Infancy history		
- normal	---	---
- seizures	---	---
- psychomotor delay	---	---
v) Physical parameters		
- height percentile		
- weight percentile		
- OFC percentile		
w) Neurologic parameters		
- impaired vision	---	---
- impaired hearing	---	---
- hypertonia	---	---
- hypotonia	---	---
- spasticity	---	---
- cerebellar function abnormal	---	---
- speech abnormality	---	---
- sensory loss	---	---
x) Intelligence		
- normal	---	---
- mildly retarded	---	---
- moderately retarded	---	---
- severely retarded	---	---
y) Course of condition		
- nocturnal only	---	---
- premenstrual	---	---
- inconsistent	---	---
z) Past illness		
- cerebral palsy	---	---
- metabolic errors	---	---
- CNS infection	---	---
- recurrent headache	---	---
- allergies	---	---
- hyperactivity	---	---

	Yes or No	
- structured abnormality	---	---
- CNS surgery	---	---
- head trauma (unconscious)	---	---
- head trauma (conscious)	---	---
aa) Adverse effects of past drugs .		
- hyperactivity	---	---
- lethargy	---	---
- fever	---	---
- ataxia	---	---
- hepatic toxicity	---	---
- weight gain	---	---
- gingival hyperplasia	---	---
bb) Other anticonvulsants		
- phenobarbital	---	---
- phenytoin	---	---
- carbamazepine	---	---
- valproic acid	---	---
- others	---	---

APPENDIX II

EEG DATA

EEG DATA

Background:

	Yes	No
Alpha 8-9	_____	_____
Alpha +9	_____	_____
Alpha well-developed	_____	_____
Minimal fast	_____	_____
Marked fast	_____	_____

Abnormality

Yes	No
-----	----

Alertness:

1. Awake	_____	_____
2. Asleep	_____	_____

Location:

3. Focal	_____	_____
4. Right	_____	_____
5. Left	_____	_____
6. Hemisphere	_____	_____
7. Frontal	_____	_____
8. Parietal	_____	_____
9. Occipital	_____	_____
10. Anterior Temporal	_____	_____
11. Middle Temporal	_____	_____
12. Posterior Temporal	_____	_____
13. Midline	_____	_____
14. Bilateral	_____	_____
15. Right Dominant	_____	_____
16. Left Dominant	_____	_____
17. Varying Dominance	_____	_____
18. Generalized	_____	_____
19. Asymmetry	_____	_____

Synchrony:

20. Synchronous	_____	_____
21. Asynchronous	_____	_____

Abnormality	
Yes	No

Slowing:

- 24. Slow (0.5 - 3.5 cps)
- 25. Slow (4 - 7.5 cps)
- 26. Rhythmic
- 27. Arrhythmic

_____	_____
_____	_____
_____	_____
_____	_____

Paroxysmal Activity:

- 28. Spikes
- 29. Sharp waves
- 30. Polyspikes
- 31. Polyspike waves (multiple spike and wave)
- 32. Spike-wave forms (2-4 Hz.) (sharp wave)

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Other Patterns of Uncertain Significance:

- 33. 6 Hz. spike and slow waves (phantom spike waves)
- 34. 14 and 6 positive spikes
- 35. Rhythmic Temporal Theta (psychomotor variant)
- 36. Small sharp spikes
- 37. Photomyogenic response

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Activation and Special Recording Techniques:

- 38. Awakening
- 39. Drowsy
- 40. Sleep
- 41. Hyperventilation
- 42. Photic-stimulation

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

MONTANA STATE UNIVERSITY LIBRARIES
stks N378.H913@Theses RL
Prediction of the initial antiepileptic



3 1762 00169237 3

MAIN

N378
H913
cap. 2

X