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A discussion of the incidence of epilepsy is followed by a discussion of etiology including the following causes: genetic and birth factors, infectious diseases, toxic factors, trauma or physical agents, heredofamilial and degenerative disorders, circulatory disturbances, metabolic and nutritional disturbances, and neoplasms. Epileptic seizures are classified by symptoms, duration, precipitating factors, postictal phenomena, behavioral disorders associated with epilepsy, and related paroxysmal disorders; patterns of attack are described. Diagnosis and pathology are considered along with treatment by anticonvulsant drugs (available drugs are listed), dietary and surgical treatment, indications and results of surgery, and prognosis. References follow each chapter. (JM)

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EPILEPSY

A Review of Basic
and Clinical Research

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service

NINDB MONOGRAPH No. 1

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EPILEPSY

a review of basic and clinical research

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Neurological Diseases and Blindness by
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PREFACE

General recognition of the magnitude of the problems associated with the epilepsies stimulated this comprehensive study into the history, basic pathophysiology, and the programs of treatment focused on epilepsy. It is hoped that the information in this review will provide guidelines for areas needing special attention.

This review has been prepared under the sponsorship of the National Institute of Neurological Diseases and Blindness, which has been active in conducting and supporting epilepsy research since the establishment of the Institute in 1950. Appreciation is expressed to its Director, Dr. Richard L. Masland, for his stimulation and encouragement in the development of this report.

P. R.

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INTRODUCTION

Epilepsy has been defined as a group of conditions characterized by recurring convulsions. From the time that records have been made on the illnesses of man, epilepsy has formed a prominent part. The early history of "The Falling Sickness," as recorded by Temkin (1945), Lennox (1960) and others, is an interesting story, but contributed little to an understanding of the true nature of the disorder. The theories of its origin were a mixture of magic and religious fantasy, and according to Thomas Willis (1684), the early approaches to treatment frequently did more harm than good.

In the Hippocratic (1849) collection of medical papers, written about 400 B.C., a physician hinted at the truth when he wrote of epilepsy, "Its origin is hereditary like that of other diseases." (Hippocrates, Adams translation 1849, vol. 2, p. 843 from Lennox.) He recognized that the seat of the trouble was in the brain and expressed the opinion that the precipitating factors of the attack were cold, sun, and winds which changed the consistency of the brain. These cosmic phenomena he considered divine and since they influenced all diseases, all diseases were divine. At the same time they were human because of their physiological substratum. Epilepsy, therefore, should not be treated by magic, he suggested, but rather by diet and drugs.

The first ray of hope for the patient came in 1857 when Sir Charles Locock reported the successful use of bromides in the treatment of hystero-epilepsy. It was not until 1912 when Alfred Hauptmann published "Die Behandlung bei Epilepsie mit Luminal," that seizures were first treated with any degree of success and safety. In 1937, Merritt and Putnam, while testing the ability of drugs to prevent electrically induced convulsions in cats, discovered diphenylhydantoin. The drug was effective without serious side effects, and the following year these investigators reported its successful use in humans. Phenobarbital and diphenylhydantoin continue to be the core of treatment for most patients having epilepsy. Nevertheless, many more drugs have been developed, and some are remarkably effective. Outstanding among them are trimethadione and ethylmethyl succinamide used in the treatment of petit mal, and primidone and mesantoin, used in the more generalized convulsive disorders.

About the same time these advances in drug therapy were occurring, and following the leadership of Hans Berger (1933), the electroencephalogram was being developed, and a new era of understanding and hope opened for the person with epilepsy.

The words of St. Mark of the young man who, since childhood had "a dumb spirit," which "taketh him, it clatheth him down, and he foameth and grindeth his teeth and pineth away" and "cast him both into the fires and into the waters to destroy him," describe very well the seizure and many of the problems of the victim.

Although the convulsive seizure represents the popular conception of epilepsy, it is only a part of the problem. The epilepsies compose a group of disorders in which the common factor is a paroxysmal, excessive, neuronal discharge within the brain.

It is accompanied by a sudden disturbance of function of the body or mind. The disturbance, whether it is loss of consciousness, disturbance of the mind, excess or loss of muscle tone or movement, disorders of sensation or special senses or disturbances of the autonomic functions of the body is subservient to the part of the brain involved.

The basic disorder of the epileptic neurone lies in the instability of the cell membrane. It results in an excessive or prolonged neuronal discharge due to excessive depolarization and, possibly, lapses in repolarizing and hyperpolarizing mechanisms. Membrane stability and polarization are intimately related to ionic balances across the membrane and to mechanisms of oxidative metabolism. In addition to intrinsic mechanisms, extrinsic factors contribute to the epileptogenic neurone or neurones; namely, excessive bombardment of cells by impulses arriving over fiber pathways from a distance, and alterations in the chemical environment of cells due to systemic metabolic changes or disorders.

A study of the epilepsies involves the basic neurophysiological events taking place within the neurone or groups of neurones and their dendrites, as well as the extra neuronal abnormal factors contributing to the activities and life of the cell which lead to the epileptic discharge. It also involves the study of incidences, causes, methods of diagnosis, pathology, treatment, prognosis, and generally, the natural history of the disorders.

Epilepsy constitutes a serious social and public health problem. It has been reported that 1 person in 200 suffers from epilepsy. Actually, accurate figures for the number of people who have had a convulsion or epileptic seizure at some time during their lives is unknown. There is no accurate figure, either, of the number of people with brain damage and epileptic seizures who are unable to advance through a normal course of education, be gainfully employed, and adjust normally in society. It is clear that the incidence of epilepsy is increasing. One reason is that formerly many patients with epilepsy would have died of birth injuries or other abnormalities acquired early in life. The effective use of antibiotics and general medical care now are saving many children with meningitis, brain abscesses, encephalitis, severe head injuries, and brain tumors, thus contributing to the increase of disabling disorders.

Any illness or disorder which is capable of affecting the structure or function of the brain may cause seizures. This is why they are better referred to as "the epilepsies." Etiological factors may include congenital anomalies, disorders during intrauterine life, brain injury acquired around the time of birth, infections, trauma, vascular disturbances, metabolic and nutritional disturbances, tumors, degenerative diseases or other genetic disorders.

There are many different types of seizures. However, as yet, no classification has been universally accepted. The attack may be a tonic-clonic type of seizure with loss of consciousness and a postictal confusion state much like that described by St. Mark. This is generally referred to as a grand mal attack. On the other hand, the attack may be a transitory pause, "absence," or loss of consciousness, lasting only a few seconds. This is called a petit mal seizure. The attack may originate in any one part of the brain, and begin with a motor or sensory aura. It may manifest itself with automatisms, delusions, or hallucinations. One could say that there is a different type of attack for every region of the brain involved. In addition to the actual seizure itself, there are behavioral disorders associated with epilepsy which frequently are more disabling than the attacks themselves.

A careful history and physical examination still constitute a most important aspect in the diagnosis and evaluation of epilepsy; however, modern techniques of X-ray and electroencephalography, biochemistry, psychology and others, have done much to elucidate our understanding of the epilepsies.

Anticonvulsant drugs provide the basis of treatment; however, they leave much to be desired and better medications are urgently needed. Some patients with a focal type of epilepsy can be helped with surgical therapy. In addition to medical and surgical therapy, however, all patients require kind and thoughtful consideration to help them take their places in society.

Research studies are being conducted on the phylogenesis and ontogenesis of seizures, the genetics of epilepsy, and the chemistry and physiological background of the epileptic seizure. Studies of experimental epilepsy have done much to improve our understanding of the actual epileptic discharge. Also, new techniques are being developed continuously to advance our knowledge of these disorders. A broad survey indicates that there are many areas in the basic sciences in which further research is urgently needed, particularly in the study of the mode of action of anticonvulsants on the nervous system. There is a particular need to develop new anticonvulsants and to provide the means of testing these compounds safely and carefully.

There are still many questions relating to the natural histories of the disorders which await answers. Many problems at a clinical level remain to be solved by single or collaborative studies. Finally, there is a need to find ways of making the best in medical therapy available to all patients.

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General Review of Epilepsy

EPIDEMIOLOGY

The accurate incidence of epilepsy is not known. The difficulties involved in diagnosis (e.g., whether the patient with one or two seizures may be considered an epileptic, whether the seizures resulting from a known brain disease, such as phenylketonuria or brain tumors, constitute epilepsy), as well as the reluctance on the part of doctors and patients to report the disorder, complicate the problem of determining the true incidence.

Kurland (1959, 1960) conducted a study over a ten year period to determine the incidence and prevalence of convulsive disorders in a small urban community (Rochester, Minn.). Although he believed that a large majority, if not all, of the local residents with diagnosed convulsive disorders were included in the survey, the computed rates must be considered as minimal values. Recurrent convulsive disorders were classified as grand mal, petit mal, focal, including temporal lobe and psychomotor; and miscellaneous seizures. Febrile convulsions were considered separately. For the recurrent disorders the average annual incidence rate, age-adjusted to the U.S. population, is about 31 per 100,000 per year. The incidence rates are higher among males than among females for all types of seizures combined, and for most individual categories. The incidence rate for primary grand mal seizures is highest in infancy and early childhood and decreases rapidly after adolescence; the same is noted for petit mal cases. For the secondary grand mal and focal seizure groups, the highest incidence rates appear at the extremes of the age scale. Abnormalities relating to birth and development in infancy presumably were responsible for the high rate in childhood, whereas toxicity (alcoholic), vascular disease, and brain tumors were important precipitating factors in the older age group. The prevalence rates for all types of epilepsy, age adjusted to the U.S. population, is 3.7 per 1,000 population. This is comparable to that found in the study on Guam

(Lessell, Torres and Kurland, 1962) where the rate was 3 per 1,000. All such studies are open to criticism from one approach or another. In the Rochester study, Kurland is probably correct when he suggests that the rates are minimal since patients who had only one "known" convulsive attack were not included. Furthermore, despite the unusual nature of the community, the possibility of patients being "undeclared" or being treated elsewhere also must be considered.

There were 101 children who had convulsions during febrile episodes. This means only 10 a year. For a city with a 30,000 population this seems to be an incredibly small number. Lessell, Torres and Kurland's (1962) studies, on Guam, of febrile convulsions would tend to substantiate this criticism. The incidence was 5 per 1,000. Lennox suggests (1960) that something like 2 percent of children in the community have one or more febrile convulsions in their first 5 years, or perhaps 2.5 percent at any age. The evidence for this figure is not very sound.

Taknaka and Aramitsu (1962) studied 626 patients with epilepsy at the Hiroshima University Hospital and concluded that the incidence of epilepsy in infancy and childhood was increasing. It was interesting that 15.5 percent had past histories of febrile convulsions.

Ueki and Sato found the incidence of epilepsy in Niigata City to be 17.3 per 100,000 population. They estimated that if the ages were limited from birth to 14, the incidence would be 32 per 100,000 population. The highest incidence was from 10 to 14 years. Grand mal seizures were most common in all age groups. Psychomotor seizures rapidly increased between ages 10 and 14. These investigators reported that seizures could be controlled in 54 percent of all cases.

For a review of the statistical background of epilepsy, reference should be made to Lennox, chapter 15 (1960).

As part of a genetic study, Metrakos and Metrakos (1960) found that the prevalence of children with a history of at least one convulsion, irrespective of cause, was 11.50 ± 1.01 percent among 1,000 serial admissions to the Montreal Children's Hospital. If children who were admitted to the hospital because of their convulsions were omitted from the study, the prevalence would be reduced to 8.76 ± 9.91 percent. The prevalence would be reduced still further, to 6.55 ± 0.80 percent, if children who had convulsions as an associated symptom of their diseases were also omitted.

It is clear that any condition that affects the brain, either physically or chemically predisposes the patient to seizures of one kind or another. The likelihood of the patient's developing seizures is dependent upon the nature and severity of the insult, the age of the patient, genetic background, and changes in the metabolic state. In no one case can an accurate prediction be made. The following table suggests the relative frequency of seizures in some disorders.

TABLE I—Relative Frequency of Epilepsy in Specific Disorders

	Percent
Porencephaly -----	44
Naef, R. W., Arch. Neurol. and Psychiat. 80: 133, 1958	
Closed brain trauma-----	5.6
Dereux, J. and Dereux, J. F., Rev. Oto-Neuro-Ophth. 30: 48, 1958	
Hypertensive encephalopathy-----	20
Hudson, A. J. and Hyland, H. H., Ann. Int. Med. 49: 1049, 1958	
Carotid insufficiency-----	20
Keirns, M. M. and Whiteleather, J. E., Amer. J. Roentg. 81: 929, 1959	
Spontaneous intracerebral hematoma-----	55
Silverman, D., Groff, R. A., Sagen, W., Neurology 9: 75, 1959	
Systemic lupus erythematosus-----	18.2
Copeland, G. D., von Kapeller, D., Stern, T. N., Amer. J. Med. Sc. 236: 318, 1958	
Cerebral cysticercosis-----	22
Lombardo, L., Mateos, J. H., Neurology 11: 825 1961	
Cerebral cysticercosis-----	37
Stepien, L. J., J. Neurosurg. 19: 505, 1962	
Multiple sclerosis-----	4.5
Drake, W. E., Macrae, D., Neurology, 11: 810 1961	
Bacterial meningitis-----	4
Kresky, B., et al., Arch. Pediat. 79: 63, 1962	
Cerebral astrocytomas-----	48
Gonzales, D. and Elvidge, A. R., J. Neurosurg. 19: 470, 1962	

Menigiomata (Supratentorial)-----	54
DeVet, A. C. and Ponsen, H. Neurochirurgie 8: 363, 1962	
Phenylketonuria -----	36
Partington, M. W., Pediatrics 27: 465, 1961	
Phenylketonuria-----	26
Paine, R., Pediatrics 20: 290, 1957	
Supratentorial tumor in children-----	25
Backus, R. E., Millichap, J. G., Pediatrics 29: 978, 1962	
Infratentorial tumor in children-----	12
Backus, R. E., Millichap, J. G., Pediatrics 29: 978, 1962	

Although only approximate figures on the incidence are known, there is no question that the epilepsies constitute a grave problem. It may cause complete disability and inability to work. It may be related to cerebral palsy, mental retardation or behavior disorders which prevent the patient from getting or keeping a job. The economic loss to the country is great. The associated social stigma, fear and superstition cause great unhappiness for the patient and concern for the family.

Further study of its incidence is not likely to reveal its causes or method of prevention; however, it will clearly bring to the attention of the public at large and legislators in particular, the seriousness of the problem of epilepsy. It will enable them to realize the great cost of caring for the disabled patient having epilepsy, with or without allied conditions, as well as the need for further research into the causes, methods of prevention and treatment.

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ETIOLOGY

The causes of epilepsy are multiple. The seizure itself, is a symptom of an underlying disorder of the brain which may be structural, chemical, physiological or a combination of all three. The basic physico-chemical phenomena that take place may be common to all seizures, but the cause varies from patient to patient. It is preferable to refer to them as "the epilepsies." Today, after a careful history and examination, a cause can usually be found. A strong family history may indicate that it is truly a genetic disorder. There may be a history of a difficult birth, postnatal head trauma, a nutritional or toxic disorder, tumor and so on. Frequently, one has to consider the possibility of many causes that lower the threshold and induce seizures.

The following etiological classification is meant as a guide. It has been useful as a reminder that there are many causes of epilepsy. More important, it serves as an index, especially for storing and retrieving case records of patients with epilepsy due to specific causes. It has also proven useful as a part of the "information retrieval key word dictionary" at the National Institute of Neurological Diseases and Blindness, for storage of literature related to the etiology, pathology and treatment of these specific disorders as related to epilepsy.

Epilepsy due to:

Genetic and Birth Factors

- Genetic influence (idiopathic, cryptogenic, essential)
- Congenital abnormalities (including chromosome abnormalities)
- Antenatal factors (infections, drugs, anoxia, etc.)
- Perinatal factors
 - Birth trauma
 - Asphyxia neonatorum
 - Perinatal infections

- Perinatal jaundice
- Prematurity

Infectious Disorders

- Meningitis
 - Purulent
 - Tuberculous
 - Virus
 - Parasitic and fungus
- Epidural or subdural abscess
- Brain abscess and granuloma
 - Metastatic
 - Direct spread
- Encephalitis
 - Virus
 - Other (including parasites)
- Fever (febrile convulsions)

Toxic Factors

- Inorganic substance (e.g. carbon monoxide)
- Metallic substance (e.g. lead, mercury)
- Organic substance
 - Alcohol
 - Other
- Drugs
- Allergic disorder
 - Ingestion of foreign protein
 - Vaccination or injection of foreign protein
- Pregnancy
- Other (uremia or other toxic medical conditions)

Trauma or Physical Agents

- Acute craniocerebral injuries
- Subdural or epidural hematoma and effusion
- Post-traumatic meningo-cerebral cicatrix
- Anoxia or hyperoxia (including drowning)

Circulatory Disturbances

- Subarachnoid hemorrhage
- Sinus thrombosis

Encephalomalacia due to

- Thrombosis
- Embolus
- Hemorrhage

Hypertensive encephalopathy

- Arteriosclerosis and arterial occlusive disease, intracranial and extracranial
- Vasospasm (e.g. migraine)
- Syncope
- Changes in blood (anemia, hemorrhagic diathesis)

Metabolic and Nutritional Disturbances

Electrolyte and water imbalance

- Sodium
- Calcium
- Hydration or dehydration
- Other

Carbohydrate metabolism

- Hypoglycemia
- Diabetes
- Glycogen storage disease

Protein metabolism

- Phenylketonuria
- Porphyria
- Other

Fat metabolism

- Lipoid storage diseases
- Other

Vitamin deficiency

- Pyridoxine deficiency
- Other

Endocrine disorders

- Menstruation
- Other

Neoplasms

- Primary intracranial
- Metastatic
- Lymphoma and leukemia
- Blood vessel tumors and vascular malformations (e.g. arteriovenous malformation, Sturge-Weber syndrome)

Heredofamilial and Degenerative Diseases

- Multiple sclerosis
- Leucoencephalopathy
- Tuberose sclerosis
- Cerebellar degeneration with convulsions
- Other

Psychogenic Causes

Cause Unknown

Genetic and Birth Factors

The Role of Genetics in the Epilepsies

Early in the century epilepsy was divided into two types, idiopathic and symptomatic. The term "idiopathic" inferred that the cause was not known, the brain was structurally intact, and heredity was an important contributing factor. Other terms meaning the same thing, such as "cryptogenic," "essential," and "genetic" were used. "Symptomatic" inferred a type of epilepsy where the cause was known. The attitude today, in the light of the most recent genetic studies, is that a genetic or hereditary factor is present in all of the epilepsies. The greater this factor the more likely are seizures to occur in a specific cerebral disorder.

It was William Lennox who started the postwar interest in the genetics of epilepsy when in 1951, he published the results of a genetic study on 4,231 epileptics, and 20,000 near relatives. He showed that there was a significantly higher incidence of seizures in families of patients with "essential" epilepsy than in families of patients with "symptomatic" epilepsy. By "essential," he meant that no cause could be demonstrated, and by "symptomatic" he meant those with an antecedent history of brain injury. This was really the first significant work since it was first suggested by Hippocrates centuries before, proving that there was an hereditary factor in epilepsy. A subsequent study by Lennox and Jolly (1954) on 173 twin pairs tended to support the previous findings; however, there were those who continued to criticize their conclusions.

In 1950, Alström reported on a study of the near relatives of 897 patients with epilepsy. He found the prevalence of epilepsy was no higher in these relatives than the prevalence in the same control group used by Lennox. This work was not generally accepted and subsequent work by Metrakos and others have most certainly disproved Alström's conclusions.

In 1940 Lennox, Gibbs and Gibbs first suggested that cortical dysrhythmia underlying the epileptic diathesis was inherited as a Mendelian dominant factor. Harvald (1954) divided his index cases according to their electroencephalograms and studied the relatives of 203 "cryptogenic" and 34 "symptomatic" epileptics. He estimated the morbidity risk for parents, siblings and offspring to be between 4.2 and 5.1 percent for the cryptogenic group, and 1 percent for the symptomatic group. The morbidity risk in the whole group (2.65 to 3.2 percent) was significantly higher than in the general Danish population (0.46 percent). Harvald con-

cluded that epilepsy was not a single genetic entity and that its inheritance was probably polygenic.

Ounsted (1955), working with 1,000 children who had "any sort of fit," concluded that genetic factors were important in all types of seizures. On the other hand, in 1960, Eisner, Pauli, and Livingston interviewed members of families of 669 epileptic patients, including 3,361 close relatives, and of 460 control patients, including 2,858 close relatives. They concluded that hereditary transmission of epilepsy could not be demonstrated nor could it be ruled out. They suggested that familial aggregation of idiopathic major motor epilepsy may be due to familial aggregation of perinatal brain injury, to inheritance, or to a combination of these factors.

The most comprehensive study on the genetic aspects of epilepsy is that being carried out by Metrakos and Metrakos. At the time of their last report they had studied approximately 1,200 families of epileptics and 400 control families, as well as more than 3,000 electroencephalograms on patients, parents and siblings.

They first reported (1960) on their findings in centrencephalic epilepsy, which, by definition, has a characteristic electroencephalogram, a paroxysmal bilaterally synchronous 3 per second wave-and-spike or a slight variant of this. They compared 211 typical and atypical centrencephalic patients, with 112 controls, drawn from hospital patients who had no history of convulsion and whose electroencephalograms were within normal or borderline normal limits.

Their findings clearly demonstrated a familial distribution of convulsions. As the genetic distance between the relative studied and the patient increases, the prevalence of affected individuals decreases (from approximately 13 percent in the parents and siblings to approximately 2 percent in the grandparents and cousins) in the case of the centrencephalic group. On the other hand, it tends to fluctuate within narrower limits, around 2 percent, for each class of relatives in the control group. When all the relatives were considered together, prevalence for the centrencephalic group was 2.2 times greater and significantly higher than for the control group.

In view of the fact that the patients selected for this study were ascertained primarily on the basis of a highly specific type of abnormality in their electroencephalograms, the EEG findings of 195 parents of centrencephalic and 84 parents of control probands were also compared. On the whole, no startling differences were found; for both groups the total number of EEG abnormalities was approximately 14 percent. However, 15 of the 195 parents of the centrencephalic

group had a centrencephalic type of EEG abnormality, whereas only 2 of the 84 control parents had such an abnormality in their EEG's. The difference between the 2 percentages, 7.7 and 2.4 percent, is statistically significant.

The EEG data for 223 siblings of patients with centrencephalic epilepsy and 103 siblings of controls showed a striking difference. In the centrencephalic group there were approximately twice as many siblings with abnormal EEG's (53.4 percent) as in the control group (28.2 percent). When only epileptiform dysrhythmias were considered, the prevalence among the siblings of the centrencephalic group (46.2 percent) was three times as high as the control group (15.5 percent). It is of great significance that this difference is due almost entirely to the higher number of siblings with centrencephalic EEG abnormalities in the centrencephalic group (36.8 percent) than in the control group (8.7 percent).

In order to analyze the effect of age on the presence or absence of the centrencephalic type of EEG abnormality, the EEG's of the parents and siblings were grouped according to the age of the individual at the time that the record was obtained. Their findings clearly reveal that age has an important bearing on whether the EEG trait will be present since there is a definite peak for age 4½ to 16½ years. For this age group, approximately 45 percent of siblings tested had the centrencephalic EEG trait.

It would appear, therefore, that, if due allowance is given for the variability of age at onset of the centrencephalic type of EEG abnormality and also for its tendency to disappear in later years, the data which these investigators collected is compatible with the hypothesis that an autosomal dominant gene is responsible for the centrencephalic EEG. More recently, Metrakos and Metrakos have tested offsprings and nephews and nieces of centrencephalic patients, and the dominant hypothesis appears to be holding true.

Because of the strong evidence that an autosomal dominant gene was responsible for the centrencephalic EEG abnormality, Metrakos and Metrakos studied patients with "symptomatic" epilepsy resulting from definite neuropathology. In order to reduce, as much as possible, the tremendous heterogeneity of "symptomatic" epilepsy they chose to compare the prevalence of convulsions and/or cerebral dysrhythmias among the near relatives of hemiplegics having convulsions with that of near relatives of hemiplegics without convulsions. Their results clearly showed that the prevalence of individuals with convulsions was higher among all classes of relatives of the hemiplegics with convulsions

than among similar classes of relatives of the hemiplegics without convulsions. (The overall difference is highly significant for $P=0.001$). Furthermore, the prevalence of epileptiform dysrhythmias among the parents and siblings of hemiplegics with convulsions was higher than among the parents and siblings of the hemiplegics without convulsions. It is interesting that in another study, Glenting (1963) found that in patients with congenital spastic hemiplegia, genetic factors had some influence on the presence of intellectual retardation and seizures.

As part of their overall study, Metrakos and Metrakos also investigated the genetic aspects of febrile convulsions. A prospective longitudinal study has been made of 106 children whose first convulsion was labeled "febrile." Sixty-three percent of these have had additional convulsions since entering the group. Most of them have had their second convulsive episode within a year of their first. Of those with additional convulsions, 36 percent had convulsions other than febrile. Such a high percentage had subsequent convulsions not associated with fever that they wondered whether there actually is such a thing as a "simple febrile convulsion." Approximately 10 percent of the siblings of children whose first convulsion was febrile also had convulsions. The study of the electroencephalograms of children with febrile convulsions and of their siblings revealed that approximately 60 percent of the patients and 60 percent of their siblings had some form of EEG abnormality. This prevalence is at least twice that found in a control group.

In contradistinction to the work of Colver and Keridge (1962) these investigators did not find that birth order was a significant factor in the prevalence of epilepsy.

The work of Metrakos and Metrakos clearly indicate that there is an autosomal dominant gene responsible for the centrencephalic EEG abnormality. They also suggest that genetic factors are partly responsible for "symptomatic" or "acquired" epilepsy. Bray and Wisner (1962), after a study of children and their families, believe that the common form of focal epilepsy in children is transmitted as an autosomal dominant trait, and is not sex linked. The EEG trait and the associated seizure disorder express themselves with greatest frequency between the ages of 5 and 12 years.

Rodin (1963) has recently pointed out the familial occurrence of 14 and 6 per second positive spike phenomena. Schwartz (1962) has recorded the familial occurrence of photosensitivity. Evans (1962) and Caveness (1963) suggested that post-traumatic epi-

lepsy was more common in veterans with a positive family history of convulsions, and that there is a genetic factor in this disorder.

Rodin and Whelan (1960) found, in EEG studies, that there is a pronounced tendency to familial incidence of temporal abnormalities. More recently, Barslund and Danielsen (1963) reported on the occurrence of abnormal electroencephalograms in three families of monozygotic twins suffering from "cryptogenic" temporal epilepsy. In all three families, spike foci were found in the temporal region in near relatives of the twins, in the ascending and descending line, or there were reports of epileptic seizures. In all the cases studied, exogenous factors seem to have been less important than hereditary factors. In particular, there was nothing to suggest that birth trauma played any role. From these studies one is forced to conclude that genetic factors contribute to other types of epilepsy besides that with a bilaterally synchronous electroencephalographic abnormality.

Dr. Julius Metrakos summarized the findings of Dr. Katherine Metrakos and himself on the results of their genetic studies in epilepsy. In looking for genetic factors in "the epilepsies" their search led them to a consideration of three major categories of genes, each of which might contribute to an individual's resistance or susceptibility to convulsions. The three categories were: (1) cerebral disease genes or genes which produce such hereditary disorders as tuberose sclerosis, phenylketonuria, etc.; (2) threshold genes, the genes which enable one man to have a lower threshold for convulsion than another; therefore, one man will have convulsions associated with a specific disease, whereas the other will not; (3) epilepsy "per se" genes, or genes which may be etiologically linked with well-defined forms of epilepsy. They felt that one such gene had been isolated for centrencephalic epilepsy.

The parents of an epileptic child want to know the chances of the child's brother's or sister's developing epilepsy. Based on a study of the siblings of a convulsant group and a control group, Metrakos and Metrakos believed that the following statements could be made:

- (1) A sibling of a nonepileptic child has at least a 3 percent chance of having some type of convulsion.
- (2) Siblings belonging to a heterogenous group of convulsors have approximately a 10 percent chance of experiencing at least one convulsion.
- (3) A sibling of a child with a dominant cerebral disease has a modified 50 percent chance of having convulsions.

(4) A sibling of a child with a recessive cerebral disease has a modified 25 percent chance of having convulsions.

(5) The siblings of hemiplegics with convulsions have approximately a 6 percent chance of having some type of convulsion. (This risk is probably applicable to various forms of cerebral palsy or of "acquired" epilepsy.)

(6) The siblings of children whose first convulsions were febrile have a 10 percent chance of having convulsions. This risk is at least twice that of the control group.

(7) The siblings of a child with centrencephalic epilepsy have (a) a 50 percent chance of inheriting the dominant pathological gene and being, at least, a carrier; (b) approximately a 40 percent chance of having a demonstrable centrencephalic EEG pattern; (c) approximately a 15 percent chance of having at least one convulsion irrespective of etiology; and (d) approximately a 10 percent chance of having centrencephalic epilepsy.

It is apparent that much more work, unfortunately long and tedious, needs to be done to elucidate the role of hereditary factors in focal epilepsy, as demonstrated in the EEG, and epilepsy secondary to distinct pathological lesions of the brain at all ages.

Congenital Abnormalities

The literature is replete with references to congenital abnormalities associated with convulsions. The seizure is a symptom, and may occur with any structural abnormality of the brain. Seizures are common in children with porencephalic cysts, microcephaly, Arnold-Chiari malformation and so on. The teratogenic effects of drugs and radiation have caused an upsurge of interest in this field and may do much to prevent the related congenital abnormalities. Mental retardation and epilepsy are frequently a part of the total abnormality seen in children with chromosomal abnormalities. The most common, of course, is mongolism or Down's Syndrome. Whether convulsions will occur in these disorders depends on the extent of the abnormality and the activity of what Metrakos calls "threshold genes."

Antenatal Factors

Reference has been made to the effect of certain drugs taken in the early months of pregnancy and their roles in the production of congenital abnormalities. Some virus infections (Adams, et al. 1956), notably rubella (German measles), early in pregnancy are

known to cause severe multiple congenital malformations. Wolf and Cowan (1959) pointed out the role of syphilis, toxoplasmosis, cytomegalic inclusion disease, bacterial meningitides and meningoencephalitis, and other infections in the prenatal and perinatal periods as causes of damage to the central nervous system.

Improper implantation of the placenta may affect the growth and development of the foetus. Trauma from a blow to the lower abdominal region has been reported as a cause of cerebral damage and intrauterine convulsions (Ozan and Gonzalez, 1963). Severe toxemia or anoxia, regardless of the cause may affect the brain of the foetus and cause subsequent seizures. Lilienfeld (1954), in a study of 564 epileptic children, was able to demonstrate the important role that the complications of pregnancy and delivery played in the subsequent development of seizures.

Perinatal Factors

Birth trauma and asphyxia neonatorum are two of the most important causes of brain damage with subsequent epilepsy, mental retardation, and cerebral palsy. Although these disorders are mentioned separately, it is frequently impossible to separate one from the other. Extensive reviews by Ford (1960), Masland (1958), Dekaban (1959) and others are available. In the bibliography at the end of this section are listed some of the more significant studies of the roles of perinatal factors as causes of epilepsy.

The clinical findings and the cerebral pathology were presented, in a very careful review by Craig (1960), of newborn babies who had convulsions commencing within 10 days of birth. Three hundred seventy-four newborn babies were included in the study, of whom 158 died and came to autopsy. Craig pointed out how rarely a precise diagnosis could be made during life. Convulsions in the presence of unconsciousness, and of deepening cyanosis not responding to oxygen therapy suggest pressure on the mid-brain or brain stem caused by hemorrhage arising from a dural tear. An uncontrollable encephalopathic picture, punctuated by convulsive seizures, following difficult delivery of a large or postmature infant is suggestive of intracerebral and/or intracerebellar multiple perivascular hemorrhages. The dramatically sudden appearance in a premature child of violent, generalized convulsions, a bulging fontanelle, and an agonizingly piercing cry is in keeping with intraventricular hemorrhage. Otherwise, there is no clinical picture characteristic of intracranial pathology of a particular kind or with a particular anatomical location. Ter-

minal convulsions irrespective of their pathological explanation and of the maturity of the infant tend to be violent and general. In other circumstances convulsions encountered in small premature babies are generally of a subdued character.

Lubcheno and colleagues (1963) reported on 63 premature infants of low birth weights at 10 years of age. They found that one had petit mal seizures, one had temporal lobe seizures and six had "convulsions."

The work of Windle and his colleagues has led to a further understanding of the role of asphyxia in the newborn as a cause of cerebral damage (Windle, 1958; Ranck and Windle, 1959; Bailey and Windle, 1959), and the role that asphyxia plays in the production of kernicterus (Lucey, et al., 1964). They induced asphyxia neonatorum in monkeys near term for 11 to 16 minutes, followed by resuscitation. A common pattern of structural alteration was encountered in the nervous system of the asphyxiated monkeys. Nuclei were symmetrically affected; those most severely damaged were the nucleus of the inferior colliculus, gracile and median cuneate nuclei, roof nuclei of the cerebellum, ventral posterior group of thalamic nuclei and the globus pallidus, putamen and vestibular nuclei. The relation of lesions to vascular distribution was not apparent. Hemorrhages were seldom encountered.

Windle (1963) found that newborn monkeys need not be asphyxiated to the point of terminal apnoea in order to suffer structural brain damage. Asphyxia neonatorum requiring resuscitation of the offspring, which otherwise would die, was associated with a remarkably constant syndrome of bilaterally symmetrical, nonhemorrhagic lesions in thalamic and brain stem nuclei, mainly those of afferent systems. The monkeys in this second category were clearly retarded mentally, and demonstrated associated post-partum complications leading to neo-cortical atrophy, often of considerable magnitude. They were not only remarkably retarded, but also often palsied, epileptic, and in some instances even comatosed. Windle also found that increased intrauterine pressure in the monkey during prolonged labor led to fetal and post-partum depression. In this connection, cerebral cortical injury occurred in the absence of typical asphyxial lesions.

It is significant that asphyxia neonatorum, uncomplicated by trauma, causes diffuse symmetrical lesions. Ford (1960) points out that birth trauma causes a localized cerebral lesion, with asymmetrical paralysis and focal epileptic attacks usually beginning on the affected side. He found that the onset of convulsions was sometimes delayed until 10 or more years after birth.

Churchill (1959) found a high incidence (19.6 percent compared with 3.4 percent of the general population who are born by breech birth) of breech birth in patients who had epilepsy of the type associated with bilaterally synchronous spike-and-wave EEG disturbances. His studies suggest that breech delivery is an important factor in the pathogenesis of this disorder. Breech delivery did not seem to be an important factor, however, in the origin of focal cerebral seizures. This would suggest that the stresses and strains associated with breech delivery tend to damage the diencephalic region of the brain rather than the cortex or hippocampal region.

The role of birth order as a cause of cerebral injury at birth, and subsequent cause of epilepsy, has been a controversial subject. Colver and Kerridge (1962) studied 174 cases of central (21), focal (45), or undifferentiated epileptics who had suffered 10 or more "convulsion days" and concluded that, "it has been established beyond a reasonable doubt that epilepsy as defined above is more frequent in first than in second born children."

The findings of Metrakos and Metrakos (1963), however, do not substantiate this. The parity of 1,279 patients with epilepsy was considered from two points of view, birth order (pregnancies resulting in live infants only) and pregnancy order (all pregnancies irrespective of outcome). On the basis of the presence or absence of convulsions, as well as the electroencephalograms, the pregnancy order of nine groups of convulsant patients and two groups of nonconvulsant probands was analyzed. In none of these 11 groups was pregnancy order found to be other than randomly distributed. When live births only were considered, an analysis of the various convulsant and control groups failed to reveal any birth order effect. These investigators, failing to demonstrate one, suggested that profound conclusions based on the assumed association of birth order with epilepsy be withheld until such an association has been demonstrated.

Infectious Diseases

Infectious diseases of the nervous system and their relationships to epilepsy have been extremely well reviewed by Dekaban (1959) and Ford (1960). Convulsions may accompany any acute infection of the nervous system or may result from the damage done to the brain by the inflammatory process. The damage may be localized, as seen in a brain abscess, or diffuse as in a virus encephalitis.

Nyhan and Richardson (1963) recently reviewed the complications of meningitis. Convulsions may herald the onset of meningitis or may appear years after the illness. The seizure during the onset and acute course of the disease may be due to localized cortical, venous, or arterial occlusion; it may be due to the "toxic" state or the fever alone may precipitate the attack. Seizures of late onset are secondary to the meningo-cerebral cicatrix. They are often difficult to treat medically, and the diffuse nature of the scar makes it unlikely that they will be amenable to surgery.

Any child who has had bacterial meningitis—particularly influenzal—who fails to respond to antibiotics, and has a persistent fever and convulsions, should be suspected of having a subdural effusion. Investigation of the subdural space should be contemplated. An infant or young child who starts having convulsions, has a square looking head and signs of increased intracranial pressure, should be suspected of having a chronic subdural effusion. The mechanism by which collections of subdural fluid occur in a certain number of patients with meningitis is not clear. Gitlin (1955) determined immunochemically the concentrations of albumin and gamma globulin in patients with subdural accumulations of fluid in bacterial meningitis, following pneumoencephalography, and following trauma. In all three conditions the levels were quite similar, and in each, the ratio of albumin to gamma globulin in the subdural fluid was considerably higher than in the serum. The data suggested that the basic mechanism by which fluid accumulates in all of these conditions is an effusion of fluid through damaged or inflamed capillary walls.

The most common sequelae of viral encephalides are disturbances of movement, sleep, behavior, or intelligence, but seizures are not uncommon. The type of seizure depends somewhat on the degree of maturation of the brain. Myoclonic massive spasms, focal motor attacks, petit mal, or generalized convulsions have all been described.

Aguilar, and Rasmussen (1960) showed that focal cerebral seizures in children, and young adults who show evidence of deterioration, may be symptomatic of chronic encephalitis. The pathological changes include widespread perivascular cuffing, microglial activity, chronic leptomenigeal inflammation, vascular changes, gliosis, neuronal depopulation and, rarely, intranuclear inclusion bodies in neuroglial cells. The changes most likely represent a smoldering viral infection. Ultimate proof must rest upon serological and virus isolation studies.

Seizures are frequently the first manifestation of an acute brain abscess. Increased intracranial pressure, fever, a running ear, etc. may lead one to the correct diagnosis. However, apart from the signs of an expanding intracranial lesion there may be nothing to lead one to suspect an abscess. Many a surgeon has been surprised to find that what he thought was a tumor, was, instead, a localized abscess.

Tuberculomas of the brain are relatively uncommon in this country, but in races in which the nutrition is poor, the incidence of tuberculosis is high, and the natural immunity is low, calcified lesions of the brain are frequently found, indicating healed or healing tuberculosis. (Armstrong and Edwards, 1963; Tiberin and Beller, 1963.) Trichinosis has been shown to be a cause of seizures (Perot, et al., 1963). Stepien (1962) reported on 132 cases of cerebral cysticercosis, 37 percent of whom had convulsions. Twenty-two percent of the patients with cysticercosis studied by Lombardo and Mateos (1961) had convulsions.

Zeifert, et al. (1962), in a study of Western and St. Louis encephalides, failed to show a consistent correlation between followup electroencephalographic findings and the clinical status of the patient either during or after the acute illness. They suggested that the electroencephalogram did not necessarily reflect the effects of a viral encephalitis. Finley (In Smadel, et al., 1958) found that the sequelae in viral encephalitis consists of motor impairment, behavioral disorders, mental retardation, and convulsions. In children with severe damage, all types of sequelae occur. In the less severely damaged, one impairment may appear without the others. Children under 10 have a better chance of surviving the acute illness, but are more likely to have severe disabling residuals.

Febrile Convulsions

Febrile convulsions present a special problem in epilepsy. There are children who have convulsions associated with fever only. They have normal electroencephalograms between seizures, and appear normal on neurological examination. The attacks disappear as the child grows older. This is what may be called true "febrile convulsions." Unfortunately, many children who have their first seizure associated with a fever may have subsequent seizures not related to an elevated temperature, or they may have demonstrable cerebral abnormalities and fever tends to precipitate an attack. Metrakos and Metrakos found that of 106 children whose first convulsion was labeled "febrile," 63 percent had additional convulsions. Of those with

additional convulsions, 36 percent had convulsions other than febrile. They also showed that there was a strong genetic factor in "febrile convulsions." Approximately 10 percent of the siblings of children whose first convulsion was febrile themselves had convulsions. One is led to agree that "threshold genes" play a significant role in the occurrence of febrile convulsions.

A great deal of significant work has been done in this area (Lennox, M., 1947, 1949; Peterman, 1952; Fridericksen and Melchior, 1954; Schmidt and Ward, 1955; Millichap, 1959, 1960; Jennings, 1959; Millichap, Madson and Aledort, 1960). Problems still remain, however, which continue to be debated actively. How should one define "febrile convulsions"? Are they due to fever alone, in a patient with low threshold, or is there a toxic factor? In this connection the finding of Kowlessor and Forbes (1958) is significant that 42 percent of patients with shigellosis had a convulsion when their temperature reached 104.2° F., but only 11 percent had convulsions with a fever of 100.6° to 102.2° F. Fischler (1963) also found an increased incidence of convulsions in children with shigellosis. Prichard and McGreal (1958) suggest that it is the rate at which the body temperature rises, and not the infecting organism, which seems to be important in causing convulsions. Wegman (1939) working with kittens found that convulsions frequently occurred if the temperature was elevated rapidly, but rarely if the temperature rose slowly.

The manner in which the febrile convulsion is treated is also a very contentious problem. Some authors recommend no treatment for the first attack. Others use the EEG to help make a decision. Some treat the child with anticonvulsants and/or antipyretics whenever there is a fever. Others start regular anticonvulsant therapy and continue it for a year or more. There is no doubt that the attitude of the family physician or pediatrician, who sees many children with febrile convulsions, is different from that of the neurologist who sees only the patients with severe seizures which may have left a residual defect. Like so many problems in medicine, each case must be decided on its own merit.

The role that febrile convulsions, associated with excessively high fever may play in producing mental retardation, hemiplegia, or persistent epileptogenic foci warrants further study. Insufficient attention has been paid to the brain damage that excessive, prolonged fever and convulsions can cause. A temperature over 107° F. probably causes the convulsion. The combination of excessive temperature and convulsions, in turn,

produces focal or diffuse cerebral anoxia and irreversible brain damage (Fowler, 1957; Schmidt, 1958).

Toxic Factors

There are specific drugs known to affect the polarization of cell membranes sufficiently to produce convulsions. Pentylenetetrazol (metrazol) is the outstanding example. This is used as a means of activating electroencephalograms and provides a useful means of testing the anticonvulsant properties of certain drugs. There are many toxic substances that affect the brain sufficiently to produce convulsions. The mechanism varies with different groups of compounds or conditions. Some have a direct effect on the metabolic activity of the neurone and its conducting apparatus. Strychnine is an example of this. Others have a withdrawal effect. This is seen in alcoholism or certain types of drug addiction. Others exert an indirect effect, by causing an impairment of circulation as in lead poisoning.

Lyon, Dodge, and Adams (1961) describe a common neurological syndrome of children known as acute idiopathic or toxic encephalopathy; it consists of fever, convulsion, stupor or coma, decorticate or decerebrate postures, and respiratory embarrassment. These investigators reported on 16 fatal cases. In all except two cases, the syndrome was ingrafted on an evident febrile illness of variable type, the cause of which was seldom identified. Generalized convulsions were the dominant symptom, often ushering in the neurologic disorder and recurring throughout the acute phase of the illness. Lyon, Dodge, and Adams concluded that this was an acute encephalopathy, separable from a primary systemic electrolyte or fluid abnormality, arterial or venous thrombosis, meningitis, and encephalitis. In all probability it was closely related to febrile convulsions and febrile delirium. The fatal issue or permanent disability appeared to be determined by hypoxia or anemia of brain tissue. In other words, among several factors there are at least two operating in all the fatal cases: a primary one which is unidentified, possibly toxic; another which seems to be secondary and is hypoxic.

Inorganic Substances—Carbon Monoxide

The toxicity of carbon monoxide is due mainly to its much greater affinity for hemoglobin than oxygen. The carbon monoxide displaces the oxygen and forms a relatively stable compound, carboxy-hemoglobin, thus producing an anemic type of cerebral anoxia.

The pathology, well described by Meyer (1958), depends on the degree and length of exposure. In cases of mild exposure, recovery may be complete. In severe cases leading to death, extensive changes are seen in the cortex and basal ganglia. Infants are much more susceptible than adults. During the acute stage, coma may be preceded by vomiting, convulsions, and abnormal breathing. A considerable proportion of survivors have permanent neurological sequelae, including mental retardation, behavioral disturbances, disorders of locomotion, and epilepsy.

Metallic Substances—Lead

Lead poisoning is one of the most serious things that can happen to a child. It is most common between the ages of 1 and 3. Residual defects include epilepsy, mental retardation and behavioral disorders. Smith (1964) reported that 40 percent of his patients who had encephalopathy developed focal, generalized, or a combination of convulsive seizures as a sequelae. Most cases today are due to the inhalation of lead oxide from improper ventilation during the process of burning. Epidemics have occurred from the burning of battery boxes, and old wooden freight cars, broken up to be used as fuel. Ingestion of old lead paint is still a cause of lead poisoning. In the acute type convulsions, delirium and coma are often accompanied by papilledema and other signs of increased intracranial pressure. Popoff and his colleagues (1963) point out that the major effect of lead intoxication is the alteration of the small vessels producing cerebral swelling and oedema. The vessels of the cortex are affected in a similar fashion and to what may be a similar degree. The vascular changes are not limited to the small vessels but affect the larger veins as well. The venous walls are greatly thickened and are composed largely of fibroblasts and collagen fibers, arranged in a disorganized fashion. The pathological appearance suggests that vascular damage is the major factor in the cerebral disorder.

Alcohol

Alcohol, or the withdrawal from it, is one of the most common causes of convulsions after the age of 30. Rheinart (1961) found a 10 percent incidence of "rum fits" in an alcoholic population from a review of 200 consecutive patients admitted to a state mental hospital. He believed that the incidence actually is higher. On the other hand, Lennox (1941) studied the alcoholic histories of a large number of adult patients with epilepsy and found the incidence of heavy

drinking was no heavier in epileptics than in the general population. However, the patient who has some type of epilepsy, is more likely to have a seizure following even a modest amount of alcohol. The seizures occur, not during the period of ingestion, but in the first 48 hours following the cessation of drinking. Seizures are more likely to occur in patients who have been drinking excessively for a number of years. They may have a single seizure or bursts of seizures. The seizures are usually of the generalized tonic-clonic type. If they are focal seizures, some focal brain disease other than alcoholism should be suspected.

Seizures frequently occur at the onset of delirium tremens. Victor and Adams (1953) found 30 patients with seizures among 101 consecutive patients with delirium tremens. Isbell, et al., (1955) showed that symptoms such as nausea, vomiting, tremor, hallucinations, and delirium tremens are precipitated by a reduction in the blood alcohol level. The symptoms of delirium tremens and convulsions are closely related, and the severity depends on the length of time and the amount of alcohol taken before withdrawal. Many authors state that the withdrawal symptoms are due to malnutrition and vitamin deficiency. It has been shown (Victor and Adams (1953)), however, that the symptoms occur despite the ingestion of an adequate diet and supplemental vitamins throughout the period of intoxication and withdrawal. Pluvinaige and Lelus (1962) demonstrated a pyridoxine deficiency in 113 cases of alcoholism, although there was no correlation between this and the severity of the clinical picture. It has also been shown (Oura, et al., 1963) that alcohol administered to rats causes an increased excretion of pyridoxine, thiamine, and several other vitamins. For the present, it must be stated that the exact biochemical phenomena associated with the alcoholic withdrawal syndrome is not known.

Drugs

There are groups of compounds which have a stimulating effect and others that have a depressant effect on the nervous system. Given in sufficient dosages, CNS stimulants will produce convulsions. Goodman and Gilman (1955) have reviewed the action of such drugs as picrotoxin, pentylenetetrazol (metrazol) nickethamide, strychnine and camphor. In proper dosages these drugs are used as stimulants or as a means of activating the electroencephalogram. Experimentally, they can produce convulsions in animals, and are thus used for testing anticonvulsants. The CNS depressants in therapeutic doses generally raise the convul-

sive threshold. In massive "suicidal" doses, convulsions may occur, but these may be a secondary effect from anoxia rather than a direct effect of the drug. Withdrawal symptoms occur following prolonged use of the CNS depressants, especially in the withdrawals of barbiturates.

It has been suggested that convulsant drugs act by inhibiting the production, or blocking the action, of an inhibitory substance—perhaps related to gamma amino-butyric acid—and, in turn, affecting sodium transport, by decreasing the sodium ratio, across neuronal membranes. CNS depressants may work in an opposite fashion and withdrawal convulsions may occur in the period of adjustment until a normal hyperpolarized state of the neuronal membranes could be reestablished. A greater understanding of the mode of action of these compounds should be sought.

Allergic Reactions

It is not an uncommon story that a child receives a "booster shot" for typhoid, poliomyelitis, diphtheria, pertussis, etc., (Byers & Moll, 1948) and shortly thereafter has a convulsion that may leave a residual hemiparesis. This may be transient or permanent. It is highly probable that there is a vascular occlusion associated with the hemiparesis. Some of these have been demonstrated by arteriography; however, more frequently than not, nothing abnormal is seen. It has been postulated that there is some type of allergic reaction, causing localized vascular spasm or occlusion, that accounts for the hemiparesis, and the convulsion is secondary to the encephalomalacia. Another suggestion is that the hemiparesis is a post-ictal Todd's paralysis, due to "exhaustion" of the involved area of the cortex. Regardless of the pathogenesis, such phenomena do occur and constitute a calculated risk in any program of mass immunization (Miller and Stanton, 1954; Park and Richardson, 1953). Acute allergic encephalopathies, with convulsions and coma, have been known to occur following the ingestion of antibiotics, including sulpha drugs and penicillin. Not infrequently, a similar state is seen following certain of the exanthemata. It has been called encephalitis, but actually is more likely to be an allergic encephalopathy. The response to steroids may be very dramatic.

Pregnancy

Over the years the myth has evolved that the patient with epilepsy has more seizures during pregnancy, and that pregnancy should be avoided because defec-

tive children are likely to be born. In view of the obscurity in the literature, in 1938, Baptisti reviewed the problem and reported on a study of 37 patients. He concluded that epilepsy has no appreciable effect on the course or termination of a pregnancy, and in the majority of the patients, the pregnancy did not affect the epilepsy. Convulsions do occur during pregnancy and in the postpartum period. There may be an increase or decrease in frequency of seizures in an established epileptic. The pregnancy and the associated metabolic disturbances may initiate seizures in a latent epileptic, or seizures may result from another complication of the pregnancy, such as eclampsia, brain tumor, or postpartum cortical venous thrombosis. The possibility of pseudoeclampsia should be born in mind. Robb (1955) cites a case of a woman admitted as an emergency patient because of continuing convulsions. She was near term, had the marked facial changes of advanced pregnancy, and seemed confused. A tentative diagnosis of eclampsia was made; however, her urine was normal and there was no oedema. Further questioning revealed that she was severely retarded mentally with seizures. She was treated with anticonvulsant medication and delivered spontaneously.

Huhmar and Järvinen (1961) are of the opinion that, during pregnancy, an epileptic state may be aggravated by the physiologic water retention and other metabolic changes. They studied 96 women with epilepsy during pregnancy or during the puerperium. Epilepsy preceded gestation in 59 cases, and 10 women had initial symptoms of epilepsy during intervals between pregnancies. Epilepsy unrelated to toxemia became manifest in 18 women during pregnancy or delivery. Symptoms originated during the puerperium in nine cases, and possibly were caused by thrombosis of the cerebral veins. Obvious worsening was observed in 70 percent of the women with serious epilepsy; 42 percent in those with moderate disease, and 17 percent in slight cases. These findings are not universal. Many patients with epilepsy have been free of seizures during pregnancy. Others who have been under good control have continued control, provided they have continued to take their medications. Occasionally, a patient may stop her medication for fear of affecting the foetus, but anticonvulsants used today do not have a teratogenic effect.

It is clear that the relationship between epilepsy and pregnancy requires further clarification.

Trauma or Physical Agents

Trauma

Acute craniocerebral injuries constitute a prime cause of symptomatic epilepsy. Seizures may occur in the acute phase of the injury due to direct cerebral trauma. They may occur in a convalescent or late stage due to a meningo-cerebral cicatrix, or they may result as a secondary effect as, for example, seizures secondary to a subdural hematoma.

The wars in Europe and Korea have provided an opportunity to study post-traumatic epilepsy due to penetrating and non-penetrating injuries. In a 5-year followup of 820 brain-wounded patients, Russell and Whitty (1952) found 43 percent were affected by seizures. In a series of 286 patients followed by Watson (1952), 36 percent had seizures within 2 years of receiving the wound and 41.6 percent within 3 years.

In 1930, Credner presented his findings on 1990 German cases of war injuries with head trauma. Over half had been followed continuously for 5 years or more. Of the total cases, post-traumatic epilepsy was reported in 38.2 percent. Ascroft, in 1941, reviewed, from the records of the British Ministry of Pensions, 317 cases of gunshot wounds of the head. After a 7- to 20-year followup, post-traumatic epilepsy, as adjudged by one or more seizures, was reported in 34 percent.

Quadfasel and Walker (1947) reported, from 246 cases of penetrating wounds of the head, that patients with infected, penetrating wounds of the parietal region were more prone to develop epileptic seizures. Walker (1957) followed 244 men of this group for a 10-year period. During that time, 19 died. Of the surviving group, 46 percent had no attack for 2 years, and 36 percent had no seizure for 5 years. The number with major attacks fell from 78 in the first year to 18 in the 10th year. Walker also showed that the mental status of 213 patients correlated closely with their work status. The employed numbered 14 percent if the I.Q. was below 90; 53 percent if it was from 90 to 110, and 84 percent if it exceeded 110. Many of the unemployed were seizure-free and were not neurologically impaired. They suffered from a much more complex disability than hemiplegia or epilepsy; i.e., a chronic post-traumatic syndrome of insufficient drive, intellectual or physical, which prevents an adequate adjustment to their disabilities.

Walker and Jablon (1959) reported on a study of U.S. veterans who were head injury casualties from World War II. These investigators examined 739

men 7 to 8 years after their injuries and found the overall incidence of post-traumatic epilepsy, based on one or more attacks, was 28 percent. Caveness (1963) followed 356 veterans of the Korean War for a period of 8 to 11 years. Of these, 197 received missile and 159 nonmissile injuries. Of the total, 109 men had one or more seizures that were classified as focal, focal and general, or general in pattern. The initiation of attacks ranged from the first day until the ninth year. Half of the men with seizure had their first attack within 6 months of injury, and four-fifths within 2 years. Early attacks occurred in an equal proportion of men irrespective of mode of injury, but after the first month the significantly greater proclivity for the missile-injured to have fits became apparent. The incidence for the missile-injured was 42.1 percent as compared with 16.4 percent for the nonmissile-injured men. The greater the brain damage, with or without penetration of the dura, the greater the incidence of seizures. If the site of impact was in the parietal region, the susceptibility to attack was greater than if the injury was elsewhere. Although the character of the injury played a significant part in the onset of attacks, there was no correlation between the cessation of attacks and the mode, site, or severity of the injury. The frequency of attacks was higher in those with persistent attacks. Caveness found little correlation between the use of the anticonvulsants and the cessation of seizures.

As part of the Korean Study, Caveness (1961) reported on the sequelae of cerebral concussion. Patients included were those who had a delayed loss of consciousness or profound confusion, a loss in consciousness of under 1 hour, or a loss in consciousness of more than an hour but less than 6 hours. The assumption of complete recovery depended on the clinical course and laboratory findings in the acute phase of injury. For practical reasons transient, minimal, neurological signs were permitted, such as nystagmus or bilateral pyramidal tract signs of short duration. Cerebral concussion as defined occurred in 29.7 percent of 407 men. It was followed by a neurological deficit of 2.9 percent, post-traumatic epilepsy in 11.9 percent, post-traumatic syndrome in 35.9 percent, and social and economic failure in 21.9 percent.

Paillas and his colleagues (1962) studied 216 cases of post-traumatic epilepsy, 50 of which followed open head injuries and 166, closed head injuries. The incidence of epilepsy in open head injury could reach 37 percent and in closed injuries, 9.4 percent. They found post-traumatic epilepsy more frequently in men than in women, and stressed the possibility that alcohol

could be an aggravating factor. With carefully controlled medical therapy, clinical cure could be expected in 50 percent. Surgical therapy was carried out on 30 selected patients with satisfactory results.

Jennett (1962) reviewed in great detail epilepsy as it develops in patients after blunt head injuries. The incidence of early epilepsy was studied in 1,000 consecutive admissions for head injury to the Accident Service in Oxford. To study the character of early epilepsy, further cases were added from Oxford, as well as cases from Manchester and Cardiff. The incidence of late epilepsy was determined by following a selected number (315) of patients seen in the acute stage of injury. This group consisted of 75 patients in the inclusive series with early epilepsy, plus 240 from the 1,000 series who did not have early epilepsy. This yielded 58 cases of traumatic epilepsy of late onset. The total number of patients with post-traumatic epilepsy studied was 381, but 40 of these had seizures in the early and late stages of the study and, therefore, appeared twice. Jennett's careful analysis was summarized as follows:

(1) Epilepsy in the first week after injury occurs in less than 5 percent of patients admitted to hospital; its importance is that it presages late epilepsy.

(2) Late traumatic epilepsy (after the first week) occurs in about 5 percent of all blunt injuries followed for more than 4 years, but the risk varies widely in different types of cases.

(3) Between a quarter and a third of patients who have had early epilepsy, and a similar proportion of those with intracranial hematoma, develop late epilepsy.

(4) Depressed fracture increases the risk of epilepsy only in adults in whom the dura is penetrated, or who have had early epilepsy, or in whom the post-traumatic amnesia (PTA) has exceeded 24 hours. The risk in such cases is over 50 percent, but the risk in the remaining fractures is only 3 percent.

(5) The risk of epilepsy is about 1 percent for all injuries uncomplicated by early epilepsy, hematoma, or depressed fracture, even when the PTA is of more than 24 hours' duration.

(6) Although just over half the patients with late epilepsy have the first seizure within a year of injury, the onset is delayed beyond the fourth year in more than a quarter of the cases.

(7) Traumatic epilepsy is often severe and persistent, regardless of the kind of injury it follows or the length of the interval between injury and onset of seizure.

(8) A normal, or an abnormal but nonepileptic EEG is common at any time after injury in patients who develop late epilepsy, and is, therefore, of no help in predicting the likelihood of this complication.

The factors that determine the development of post-traumatic epilepsy are outlined by Walker (1962). Of the intrinsic factors he suggests: (1) hereditary predisposition, (2) prenatal, natal and post-natal conditions causing brain damage, (3) childhood neurologic afflictions; and (4) systemic disorders. Extrinsic factors may include: (1) location of cerebral injury, (2) severity of brain damage, (3) complications of the wound and healing. It is clear that there are other factors besides the brain injury that contribute to post-traumatic epilepsy. There are background factors, such as heredity or other illnesses, and precipitating factors, such as television, alcohol, or emotional disturbances.

Other forms of physical trauma to the brain can cause epilepsy. Mawdsley and Ferguson (1963) report that epilepsy, along with other neurological disorders, occurs in boxers. Subdural hematomas present a special problem. Cole and Spatz (1961) reviewed 50 patients and found that 42 percent of them had seizures. The occurrence of seizures was not related to age, past history of convulsive disorders, or prognosis. When the seizure was unilateral, it almost always was contralateral to the hematoma. They considered it significant that seizures did not appear to offer evidence against the diagnosis of chronic subdural hematoma. The first symptoms of infantile subdural hematoma are irritability, convulsions, and vomiting (Ingraham and Matson, 1944; Christensen and Husby, 1963). The mechanism of seizure production could be due to localized cerebral ischemia, as suggested by Penfield and Jasper, or to direct cortical damage which is frequently an accompaniment of subdural hematoma.

Anoxia and Hyperthermia

Two other physical agents should be considered as causes of epilepsy: excessive heat and severe anoxia. It is probable that they are both indirectly related in their abilities to cause brain damage. It has also been suggested, with some justification, that hyperthermia may play a role in the remarkable brain destruction seen after severe convulsions in infants and in children. Gorin and his confreres (1963), reviewing 12 cases who showed signs and symptoms of "heat stroke," warned against the dangers of serious neurological sequelae. The hyperthermia is secondary to excessive

environmental temperature and dehydration, and it compounds the cerebral anoxia that accompanies severe and prolonged convulsions.

Other forms of anoxia, such as occurs in cardiac arrest or near drowning, cause cerebral destruction which may or may not be followed by recurring seizures.

The changes in the brain metabolites in anoxia are very similar to those occurring during convulsions: There is a decrease in the brain glucose, glycogen and high energy phosphate bonds and an increase in lactic acid, adenosine diphosphate (ADP), and inorganic phosphate. There is also a decrease in the acetylcholine content, a liberation of ammonia, and a redistribution of sodium and potassium in the nerve cells and extracellular fluid (Richter, 1960). Convulsions are commonly accompanied by anoxemia due to impairment of the respiration, and the observed changes in brain metabolites during convulsions might, therefore, be attributed to the incidental lowering of the oxygen tension in the blood. From the observations of Gurdjian and his colleagues (1947), it appears that moderate anoxia increases the irritability of the brain, whereas severe anoxia decreases it, and that an adequate oxygen level is one of the necessary conditions for convulsive activity to take place. Further evidence suggests that acute anoxia causes convulsions by releasing the lower centers from cortical inhibition, whereas severe anoxia inhibits convulsions by depressing the activity of the lower, as well as the higher, centers of the brain. It has been shown also that the oxygen consumption of the brain varies with changes in temperature. Increasing the temperature of the body up to 43° C. increases the oxygen consumption. The effects of temperature on convulsive activity are clearly complex; they may be expected to depend in part on the release of the lower centers through impairment of cortical control, and partly on the combination of an increased oxygen demand by the neuron at a rising temperature with the increased oxygen requirement for convulsive activity.

Circulatory Disturbances

Vascular disorders are seldom mentioned as a cause of epilepsy, and yet it is well known that anything that interferes with cerebral circulation and causes neuronal anoxia will cause seizures. Indeed, many thoughtful clinicians have attempted to explain all seizures on the basis of a circulatory disturbance.

Impairment of cerebral circulation, either of a generalized nature as seen in syncope due to a fall in blood

pressure, or localized cerebral ischemia secondary to spasm or occlusion of a cerebral artery, may lead to an epileptic seizure. Whether cerebral ischemia, either generalized or localized, will precipitate a seizure depends on the severity of the ischemia on the one hand, and the susceptibility of the brain to seizure activity on the other. Seizures are frequently due to the localized cerebral ischemia related to migraine. They are seen in the patient who faints on the "sight of blood." They are frequently the first sign of a cerebral hemorrhage. It is not uncommon for a patient who has had a cerebral vascular occlusion from an embolus or thrombosis subsequently to develop convulsions. Probably local or diffuse anoxia affects the stability of the neuronal membrane and causes excessive depolarization as well as a disturbance in the ionic balances across the neuronal membrane. The end result is a focal or generalized epileptic discharge and a seizure.

Cerebral arteriosclerosis frequently is stated to be the cause of epilepsy (Kehrer, 1963). This is not too difficult to comprehend if the patient has had a known vascular infarct sufficient to cause symptoms. In the patient over 50 years of age with a lowered threshold for seizures, because of alcoholism, genetic factors, or other reasons, the small unrecognized cerebral infarct may be sufficient to cause epilepsy. White and his associates (1953) studied 107 patients who had an onset of seizures after the age of 50. They concluded that cerebrovascular disease was the cause of seizures in the majority of instances. Furthermore, their followup studies supported the concept that tumors were present in only a small group. Woodcock and Cosgrove (1964) studied 93 patients whose seizures started after the age of 50, and were able to follow up 80 of them. Of these 80, 29 had intracranial tumors. Of the 51 remaining, 20 were reported as being atherosclerotic, 10 had a variety of known diseases, and 21 had no obvious cause for the seizures. The possibility still remained that some of the last group could have had atherosclerosis or a very slowly growing tumor.

From the days of Gowers, "Faints or Fits" has been a subject that has intrigued the experts, and has led to a voluminous, if somewhat inconclusive, literature. Gastaut and his conferees recently have done much to elucidate this difficult problem. Penfield has suggested that seizures may result from fluctuating ischemia at the margin of a focal cerebral cicatrix. The whole problem of anoxia at a neuronal level, and its ability to cause a synchronous epileptic discharge, warrants further study.

Metabolic and Nutritional Disorders

The importance of metabolic and nutritional disorders as a cause of epilepsy has been known for a long time. It is only recently, however, that any real knowledge of the role they might play has been demonstrated. A good example is pyridoxine or vitamin B₆ deficiency or dependency. It has been shown that pyridoxine plays an important role in the production of gamma aminobutyric acid, GABA, an inhibitory substance, the lack of which interferes with the sodium ratio, and permits seizures to take place. Disorders of electrolyte and water balance are closely related to seizures in infancy during periods of hydration and dehydration, and are undoubtedly related to the shift of sodium and potassium across cell membranes. One is reminded of the hydration test to bring out abnormalities in the EEG or to precipitate a convulsion, as a means of studying the seizure pattern. Physicians continue to advise patients against drinking too much water. The roles of acid-base equilibria, and water and salt balance have been reviewed by Tower (1960) Wolfe and Elliott (1962). Electrolyte disturbances are not the prime cause of epilepsy. In mild forms they may help precipitate an attack in a predisposed individual, whereas in severe forms, as shown by Dodge and his colleagues (1960), actual brain damage may take place and be a further contributing factor.

It is not uncommon for newborn children with seizures to have a low serum calcium. The seizures may stop with the administration of calcium in one way or another. These children may subsequently be found to be retarded mentally, but it is never known whether the hypocalcemia was primary or secondary.

Epilepsy frequently occurs in chronic hypocalcemia, and the seizures frequently show features of tetany, as seen in hypoparathyroidism and pseudo-hypoparathyroidism. Glaser and Levy (1960) point out that in hypoparathyroidism the seizure states usually are associated with paroxysmal abnormalities in the EEG characterized by slow theta and delta waves, spike discharges varying in frequency from 1½ to 4 per second, and single and multiple spiking. Usually the treatment of the underlying disorder by the administration of calcium salts, vitamin D, and other phosphaturic agents, relieves the seizure state and improves the electroencephalogram. However, the time sequences of return of the serum calcium level to normal, and the disappearance of seizures and EEG abnormalities, are not always parallel. Others have pointed out the role of hypoparathyroidism in the production of seizures, intracranial calcification, and slow but progressive de-

mentia (Bronsky, 1958; Melchior, et al., 1960; Sugar, 1953; Tiberin and Beller, 1963).

Magnesium is known to be an important intracellular cation, and magnesium deficiency in man is associated with muscular weakness and hyperirritability. Efforts have been made to relate epilepsy to a deficiency of magnesium, but to date, the relationship remains obscure.

Back, Montgomery and Ward (1962) described five infants with gastroenteritis who had tremor, muscular rigidity, twitches, and convulsions associated with low levels of serum magnesium. Three of the children were frankly malnourished. Serum calcium levels were normal in all and parental calcium was without therapeutic effect in three cases. On the other hand, magnesium administration in all five cases induced remission of the neurological disorder.

Disorders of Carbohydrate Metabolism

Newborn children having seizures are frequently found to have a low blood sugar. Brown and Wallis (1963) reported, in a series of newborn infants, that the babies were below expected birth weight and nearly all showed gross malnutrition. They postulated that intrauterine malnutrition predisposes to neonatal hypoglycemia because the baby has been depleted of fat and glycogen stores which are readily exhausted. Those babies who were treated inadequately either died or suffered from brain damage. Those who were treated early and vigorously with intravenous glucose and a high calorie diet recovered completely. Haworth and his colleagues (1963) reported on six infants who appeared normal at birth but who developed apnea, irritability, lethargy, and muscular twitchings between 24 and 72 hours of age. Blood sugar levels were 10 mg. per 100 ml. or less. The condition was self-limited in all cases, although two showed evidence of permanent brain damage. It is possibly significant that four of the mothers had a toxemia, and three babies were premature. The recognition and treatment of hypoglycemia in the underweight newborn baby is one way of preventing brain damage in the newborn. It is probable that in some instances the prolonged intrauterine malnutrition has already caused irreversible cerebral changes.

Etheridge and Millichap (1963) studied the role of hypoglycemia in children with primary cerebral lesions. They concluded that in a relatively large percentage of patients with cryptogenic hypoglycemia, seizures associated with low levels of blood sugar may be caused primarily by a maldevelopment or other lesion of the

brain. There was a surprising lack of correlation between the occurrence of seizures and the degree of hypoglycemia, which suggested that the seizures were not due to the hypoglycemia, but were related more to the brain defect.

Hypoglycemia may be a familial condition. Dekaban, et al. (1962), reported on five siblings with this disorder. They pointed out that the age of onset is usually during early infancy, and mental retardation frequently results. Epileptic attacks, perspiration, limpness, and coma are the most common clinical findings during the episodes of marked hypoglycemia. Treatment of this variety of familial idiopathic hypoglycemia consists of frequent carbohydrate feedings, and in severe cases, administration of glucocorticosteroids or corticotropin for a prolonged period of time. In general, there is a tendency towards spontaneous improvement after 5 to 6 years of age. If early and adequate control of the hypoglycemia is not established, permanent cerebral changes will most certainly occur.

The essential amino acid l-leucine, was first shown by Cochrane (1960), to be a causative agent in provoking hypoglycemia in infants. His studies suggested that the cause was primarily extrapancreatic.

Some authors have suggested that the effect was due to an increased production of insulin, and others believed that inhibition of hepatic glucose output was the mode of action (Wohltmann, et al., 1961; McKendrick, 1962; Pensuwan, 1963; Floyd, et al., 1963).

Islet cell tumors of the pancreas, found in children and adults, may be a baffling cause of syncopal attacks, convulsions and weakness. A careful history, defining the relationship of the attacks to meals, is frequently the most important factor in making the diagnosis; however, provocative tests, such as starving, may help clarify the nature of the problem (Hardy, 1963).

Hypoglycemia is also seen in hypopituitarism and hypoadrenalism (Dunlop, 1963), and may contribute to the production of seizures. A "hereditary intolerance" of the ingestion of fructose, resulting in hypoglycemia, has been reported. Froesch, et al. (1963), suggest an enzymatic defect, which inhibits the release of hepatic glucose, as the cause of the hypoglycemia. Not all cases reported were associated with seizures. Hypoglycemia may also follow sudden withdrawal of alcohol in the chronic alcoholic, or following an alcoholic debauch, and may be a contributing factor in the "withdrawal seizures."

Convulsions may occur in diabetes, particularly in the labile diabetic. This is seen in infantile diabetes where there are wide oscillations in blood sugar levels.

Brain damage may result, in turn, and cause further seizures. Improvement in both behavior and control of the diabetes may result from the addition of anti-convulsants to the diabetic regime (Fabrykart and Pacella, 1948). The incidence of arteriosclerosis is high in diabetes. This, combined with fluctuating blood sugar, may be the cause of seizures in the elderly.

Disorders of Protein Metabolism

Each year new diseases are discovered in which there is an inborn error of protein metabolism, usually associated with progressive cerebral deterioration, mental retardation, convulsions, and frequently leading to death. The most common is phenylketonuria; others include alkaptonuria, albinism, Hartnup disease, and maple-syrup-urine disease, cystinuria, Fanconi syndrome, etc. (See Watts, 1962.)

Phenylketonuria has been most carefully studied not only because it is more common than the others, but also because the progressive mental deterioration can be prevented with proper diet. This disorder is characterized by the excretion of phenylpyruvic acid in the urine, and is due to a metabolic error contingent on the recessive inheritance of a defect in an enzyme that converts phenylalanine to tyrosine. Pathologically, there is, according to Alvord and his colleagues (1950), a marked lack of myelination of the nervous system involving principally the optic, cortico-ponto-cerebellar, and perhaps other tracts in the central and peripheral nervous systems. Other abnormalities such as gliosis and increased fat about the blood vessels may be present. The findings vary somewhat with the age of the patient. Poser and van Bogaert (1959) suggest that the disease, neuropathologically, should be classified with the leukodystrophies and the cerebral lipoidoses in the general group of demyelinating diseases.

Young children with phenylketonuria frequently have seizures, usually in the form of infantile spasms. Paine (1957) found a 26 percent incidence of seizures in the patients he surveyed. Epilepsy was more common in the most severely retarded patients, but frequently ceased with advancing age. In the majority, the age of onset was under 18 months. Low and his colleagues (1957), in studies of the young age group, found hypsarhythmia and multiple seizure foci on electroencephalography. As the children grow older, seizures tend to change from the myoclonic type of infantile spasms to tonic-clonic convulsions, and their EEG's tend to show focal or generalized spike discharges. Of 23 patients, seven had spike-and-wave complexes similar to those found in petit mal epilepsy.

Eight of the patients had EEG examinations while undergoing treatment with a phenylalanine restricted diet. There was a beneficial effect on the seizures as well as on the electroencephalograms.

Acute intermittent porphyria is another inborn error of metabolism in which there is a genetic defect in enzymatic biosynthesis of porphyrins. The disorder is characterized by excretion in the urine, both during the acute attack and often during remission, of large amounts of porphobilinogen. Prominent signs and symptoms are abdominal pains, polyneuritis, mental disturbances, convulsions, and excretion of dark brownish-red urine. Attacks may be precipitated or made worse with barbiturates, and other drugs must be used to control seizures. The mental changes in this disorder may be very baffling, and many patients are suspected of malingering for some time before the true nature of the disorder is discovered. If the condition is suspected, repeated examinations of the urine should be made.

An acute attack may be accompanied by a spreading and complete paralysis, similar to a Guillain-Barré syndrome, and lead to death. Indeed, in all cases of Guillain-Barré syndrome, the urine should be tested for porphyrins. (Watson, 1954; Aldrich, et al., 1955; Sunderman and Sunderman, 1955; Waldenstrom, 1957). The EEG changes in intermittent porphyria are non-specific with high voltage and show activity during the acute exacerbations of the disease. Pathologically the most common finding is a demyelinating peripheral neuropathy, with diffuse neurone changes mainly in the anterior horn cells. Other nonspecific parenchymatous changes are described throughout the nervous system (Dow, 1961). Convulsive seizures and gross EEG changes are a common accompaniment of many biochemical defects in nerve cell metabolism, including acute intermittent porphyria.

Disorders of Fat Metabolism

Among the inborn errors of fat metabolism, amaurotic family idiocy (Tay-Sachs disease) is the most common. Seizures may occur in the course of any of the lipid storage diseases, but they seem particularly prominent in amaurotic idiocy. The type of seizure varies with the age of the patient. Because of the early onset, infantile myoclonic seizures are most common, but if the age of onset is later, then typical petit mal seizures may occur with a characteristic wave-and-spike type of EEG abnormality. Andermann, et al., have recently had a patient with the juvenile type in

whom petit mal attacks preceded any other symptoms by many months.

The relationship of epilepsy to amaurotic family idiocy and other lipoidoses has been reviewed recently by Edgar and Post (1963). Reference should also be made to the "studies in Tay-Sachs disease" by Gomez and his colleagues (1963).

Recent studies by Andermann, Fawcett and Owen have demonstrated usefulness of rectal biopsies as a means of establishing the diagnosis. Carefully done as a major procedure, this technique has been known to be safe, effective, and much easier than a cerebral biopsy.

Pyridoxine (Vitamin B₆) Dependency

Following an epidemic of convulsions in children which was found to be due to a milk preparation deficient in pyridoxine, it became fashionable to administer pyridoxine in all cases of infantile convulsions. This led to the description of Hunt and his colleagues, in 1954, of a case of pyridoxine dependency. Since then, many more isolated cases of pyridoxine dependency have been reported, and recently the condition has been described in siblings (Scriver, 1960; and Waldinger and Berg, 1963). It is apparent that seizures may occur in infants from a deficiency of pyridoxine in the diet, resulting from either (1) an inborn error of metabolism, (2) a dependency developed from a high intake of pyridoxine by the mother before the birth of the child. Using the tryptophan loading test, abnormalities in tryptophan metabolism, which is dependent on vitamin B₆ may be detected by studying the urinary excretion products.

The excretion of Xanthurenic acid after tryptophan loading reflects impairment of a vitamin B₆-dependent enzyme which is distributed in liver and kidney (Neister, 1957) and is used as a test of vitamin B₆ co-enzyme deficiency. (Bessey, et al., 1957; Coursin, 1964).

It has been shown that gamma-aminobutyric acid, an inhibitory substance, can be derived from glutamate by a pyridoxine-dependent decarboxylase. Reduction of gamma-aminobutyric acid (GABA) in the brain increases its irritability, and the seizure threshold is lowered.

More convincing evidence for a relationship between glutamic acid metabolism and seizure activity is provided by studies of the convulsant hydrazides. The most potent convulsant is theocarbohydrazide. Seizures produced by this can be controlled by the administration of pyridoxine. It has been suggested that

the action of these convulsants is limited to the metabolic reactions of pyridoxine. It has also been suggested that the convulsant action of topically applied penicillin is related to a local pyridoxine deficiency due to a release of penicillamine and subsequent reaction with pyridoxine. The evidence for a defect of glutamic acid metabolism in pyridoxine deficiency, whether nutritional or antimetabolic, is convincing. However, the connection of this kind of defect and decreased GABA levels with neuronal excitability is not clear cut (Wolfe and Elliott, 1962).

These problems tend to stress the need for a better understanding of the chemical reactions of the brain which predispose and lead to convulsions.

Endocrine Disorders

The role of the endocrines in the epilepsies is essentially one of modifying the seizure threshold of the brain. Some hormones are capable of activating seizures, and others, of suppressing them. Adrenocorticotrophic hormone and cortisone have been shown to arrest myoclonic seizures in the infant. Woolley and Timiras (1962) demonstrated, in animals, that testosterone could have either a convulsant or an anticonvulsant effect on brain function, depending upon several factors, such as the dose of the hormone or the age of the animal. As one would expect, these hormones play definite roles in the maturing brain. Lennox (1960) demonstrated the importance of puberty and the first menstruation in the development of epilepsy. It is well known that young women are more prone to seizures during the premenstrual period (Laidlaw, 1956; Logothetis, et al., 1959). The sexual cycle of the mature human female involves interactions among the pituitary gonadotropins, follicle-stimulating and luteinizing hormone, and the ovarian steroid hormones, principally estradiol and progesterone. The lowered threshold for seizures during the premenstrual period has been attributed to the decrease in progesterone levels following atrophy of the corpus luteum. The exact roles of these hormones at a neuronal level are not known, but it is suspected that they may be related to a change in the sodium ratio in favor of intracellular sodium.

In some endocrine disorders, the change in seizure threshold is due, not to the increase or decrease in the particular hormone, but rather to indirect effects. An outstanding example is the effect of islet cell tumors, which secrete insulin, and, in turn, cause hypoglycemia and seizures. Another example is the effect of hypo-

parathyroidism on calcium metabolism which, in turn, produces cerebral excitability and seizures.

Although seizures are more common in disorders of the pituitary-thyroid-adrenal axis, the main interest is the effect of hormonal changes on excitation and inhibition of neurones and their abilities to produce seizures. A better understanding of the roles these hormones play in the developing brain, and its day-to-day and month-to-month metabolism, would be very valuable to the improvement of the treatment of epilepsy, particularly epilepsy of infancy and childhood.

Convulsions are a fairly common occurrence in Addison's disease (Storrie, 1953; Dunlop, 1963). Experimental animals, as well as humans, with adrenocortical insufficiency exhibit spontaneous seizures during crises. The seizures have been attributed to a reactive hypoglycemia; however, some studies suggest that there are other factors involved and that the problem should be studied further. The brain of the adrenalectomized animal exhibits an increased concentration of intracellular sodium, a decreased ratio of extracellular to intracellular sodium concentration, and a decreased turnover of sodium. The total brain potassium concentration is unchanged, but the ratio of intracellular to extracellular potassium is decreased, and the turnover is unquestionably increased (Woodbury, 1958). In the adrenalectomized animals, the inability of the brain actively to pump sodium results in brain electrolyte changes associated with increase in brain excitability. Additionally, Woodbury and Vernadakis (1958) found that adrenalectomy caused a marked decrease in certain amino acids of the brain, particularly gamma-aminobutyric acid (GABA). This is of interest because of the role GABA seems to play in inhibition.

The relationship of the endocrine glands to the nervous system recently has been reviewed in an article by Reichlin (1961), which has an extensive bibliography. The Association for Research in Nervous and Mental Disease (1963) soon will publish more information regarding this relationship. Reference should also be made to the reviews by Woodbury, 1958, on the relationship of the adrenal cortex to the central nervous system, and by Way and Sutherland (1963) on pharmacologically active brain substances and their relationships to endocrine effects.

Neoplasms

It has been said that anyone over the age of 20 having a seizure for the first time should be considered as a tumor suspect. This is true, but it should be also

be remembered that brain tumors are common in children and a convulsion may be their first manifestation. Seizures from other causes are so common in children that one is likely to forget the possibility of a tumor. Generally, in this age group, tumors manifest themselves with focal signs, such as ataxia, hemiparesis, focal convulsions, or signs of increased intracranial pressure.

Backus and Millichap (1962) reviewed 291 consecutive children seen for intracranial tumors. The ages ranged from 2 months to 14 years. Forty-three percent of the tumors were supratentorial and 57 percent were infratentorial. Seizures occurred in 17 percent of the total group. Sixty-two percent of the patients with supratentorial tumors had seizures whereas only 38 percent of those with infratentorial tumors had seizures. The average time from the onset of seizures to clinical diagnosis was 3 months in patients with infratentorial tumors, and 2 years in others. The seizures were the initial sign in 21 patients.

In determining the cause of the severe increased intracranial pressure, with separation of the sutures, a ventriculogram or some other type of contrast study usually is necessary to distinguish tumors from tuberculous meningitis, lead poisoning, or subdural hematomas. A common cause of acute increased intracranial pressure, with or without focal signs, is leukemic infiltration of the meninges. This presumably is related to the success of treatment for the condition elsewhere in the body.

As one advances into the older age groups, tumors become a more prominent cause of epilepsy. Sumi and Teasdall (1963), in a review of 150 patients with focal seizures, found a 1 to 2 ratio in vascular to tumor pathology under the age of 50, but over the age of 50, it was 2 to 1. Meningiomas accounted for 34 percent of the tumors causing focal seizures. Astrocytomas, or oligodendrogliomas, accounted for 23 percent, metastatic for 17 percent and glioblastomas for only 9 percent. Generally, benign tumors, such as meningiomas, are more likely to produce seizures in their course of expansion before other signs or symptoms appear. In the more rapidly growing tumors, such as glioblastomas the onset of seizures is likely to coincide with the appearance of other clinical signs (Zander, 1962). In a study of 182 supratentorial meningiomata, DeVet and Ponsen (1962) found the preoperative incidence of seizures was 54 percent; this was reduced to 46 percent after surgery. Forty-two percent of patients who did not have seizures before operation developed them postoperatively. These investigators also noted that seizures were more likely to be the presenting symptom

if the meningioma was on the convexity, the base of the middle fossa, or parasagittal region (incidence was 50 percent) than if the tumor was on the olfactory groove or lesser wing of the sphenoid (33 percent).

Woodcock and Cosgrove (1964) reviewed 93 patients with seizures, starting when the patients were 50 years old or more, and were able to follow 80 of them. Of these 80, 29 had intracranial tumors. All those with primary intracranial tumors had some focal feature, either a type of clinical seizure, neurological sign, or electrographic abnormality, although five contrast studies were initially negative. Of the 29 patients with cerebral tumors, 22 had electrographic changes suggestive of destructive lesions. The investigators concluded that if there were focal features to the seizure pattern, and abnormalities in the neurological examination or electroencephalogram, then pneumoencephalography or other contrast studies were advisable to aid tumor diagnosis. In patients without any focal features to the seizures, contrast studies were unlikely to show a space-occupying lesion, and might even miss a small tumor. In such cases, Woodcock and Cosgrove suggest a careful followup and review of the neurological and electroencephalographic status at various intervals is of great importance. In their studies approximately one-third of the patients followed were found to have cerebral tumors. It appears that the majority of patients whose seizures begin past the age of 50 do not have cerebral tumors. Of these, a large proportion were atherosclerotic and others had miscellaneous diseases associated with their seizures. In 25 percent, no definite cause was found for the attacks, despite a 5-year followup. These findings support those of White and his colleagues (1953) who concluded that cerebrovascular disease was the cause of seizures in the majority of patients over the age of 50; and the followup studies support the concept that tumors are present in only a small group.

Penfield and Jasper (1954) reviewed 703 expanding intracranial lesions of all types. In addition to neoplasms, they included brain abscesses, tuberculomas, and extra- and intra-cerebral hematomas. There were 164 infratentorial tumors. The incidence of epileptic seizures was almost zero; some 20 percent had small attacks of a myoclonic, syncopal, vertiginous, or parasthetic nature. Of the supratentorial tumors, there were 49 in the region of the pituitary. Only four of this group of patients had seizures. It was apparent that intrasellar tumors do not produce seizures unless the tumor has escaped from the sella and is large enough to press upon the brain. Of the remaining

group of patients with supratentorial neoplasms, there were 51 percent epileptiform seizures among those having intracerebral tumors, and 62 percent among those having extracerebral tumors. Penfield also found that there was a lower incidence of seizures among patients with tumors situated deep within the hemisphere and which did not come to the surface enough to be assigned to one lobe or the other. Penfield and Jasper point out, like others, that whether an intracranial tumor produces seizures depends upon the location of the tumor, its nature, and its chronicity. They have done a very complete and careful analysis of this problem and reference should be made to the original work.

Hereditary and Degenerative Disorders

Epilepsy is a frequent manifestation of all of the hereditary and degenerative disorders. The type of seizures is dependent more on the age of the patient, and degree of maturation of the brain, than on the nature of the degenerative processes. Since many of these disorders first manifest themselves in infants and young children, myoclonic seizures are frequently the outstanding feature of the disease. There is no typical electroencephalographic pattern for the leukodystrophies, either as a whole or for a specific type. The EEG abnormality becomes severe early in the course, and shows a progressive deterioration with diffuse slow waves, fluctuating spikes, and suppression bursts at one time or another. Although the course of the disease is not altered, myoclonic seizures are reported to respond to ACTH.

In many of the disorders there may be an inborn error of metabolism which has not yet been identified. In some, seizures are more common than others. For example, they are a constant and extremely difficult problem in dysnergia cerebellaris progressiva whereas in Friedreich's ataxia or ataxia telangiectasia, they are much less common.

Epilepsy and trigeminal neuralgia are found in patients with multiple sclerosis. Drake and Macrae (1961) found 13 out of 289 patients with multiple sclerosis who had seizures. The seizures were commonly focal and transient, occurring often at a time of relapse, although they also could be generalized and chronic. The electroencephalogram was abnormal in two-thirds of the cases with both focal and generalized abnormalities. Ashworth and Emery studied 159 patients with multiple sclerosis, 29 of whom had epilepsy. In nine of these, seizures were the presenting symptom, although eight of the nine had abnormal signs on physical examination. They, too, found that the attacks

might remit or continue on for years, but that they responded satisfactorily to anticonvulsant drugs.

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CLASSIFICATION OF THE EPILEPSIES

Just as there are many causes of epilepsy, there are also many different types of seizures. Indeed, one author wisely suggested that there are as many types of seizures as there are regions of the brain, and an attempt to distinguish each of them would be quite hopeless. Although there is some truth in this, a classification of the various types of seizures should be established for several reasons. First, so that those working in the field may use the same terms for specific types of seizures. Secondly, to provide uniformity in reporting individual cases. Thirdly, to correlate medication with specific types of seizures. Fourthly, so that the relationships may be ascertained between certain types of seizures and known physiological or pathological changes.

The type of classification would, of necessity, vary with the need. For example, in a study designed to test the anticonvulsant properties of drugs, it may be sufficient to divide seizures into major or minor. Attendants watching the patients can determine, and record, whether an attack is "major" or "minor." On the other hand, a study designed to evaluate abnormalities in the temporal lobe, leading to surgical exposure and cortical and depth electrode studies, would require a detailed classification of the seizures if any meaningful relationship is to be made.

Another problem in the classification of seizures is to know what point in the sequence of the attack is to be used for classification. Many patients have prodromal symptoms. Mothers recognize irritability or behavioral changes in children that herald the onset of an attack by several hours. The "aura" may indicate in which part of the brain the seizure originates. The patient may see flashing lights, smell a bad odor, have an unusual sensation in a hand, and so on. It is not entirely clear whether this should be considered as the onset of the attack and used for the classification.

An aura may develop and the attack spread into a generalized tonic-clonic seizure. There is a question, whether this attack should be classified according to the aura, or be called a generalized tonic-clonic seizure. The patient may be left with a postictal aphasia, following a generalized seizure, indicating a focal cerebral lesion. The same question arises.

Certain types of seizures are known to originate in specific areas of the brain. For example, attacks of automatic behavior generally originate from within the temporal lobe. There has been a tendency to classify them as "temporal lobe" epilepsy, thus introducing anatomical factors into a descriptive classification. Others have used electroencephalographic abnormalities loosely to describe seizures. It may be true that "spike and wave" abnormalities are associated with absence attacks, however not all apparent absence attacks show a spike and wave abnormality on the EEG, and a patient can have a burst of spike and wave activity without having a demonstrable attack.

Another possible way of classifying seizures is according to age. The newborn tends to have focal myoclonic types of attacks. The infant between 6 months and 3 years tends to have myoclonic seizures, with massive spasms, myoclonic jerks or akinetic attacks. As the child gets older, absence attacks appear, and gradually change to a more mature adult type of generalized tonic-clonic convulsion. Of course, generalized convulsions can appear at any age, depending on the site of origin of the attack and the ability of the seizure to spread within that particular patient.

Old terms have been perpetuated and tend to detract from an accurate descriptive classification. The term "grand mal," generally refers to a generalized tonic-clonic seizure, but one finds it being used for most any type of major attack. The term "Jacksonian seizure" may refer to any type of focal attack with a unilateral motor component. "Petit mal" continues to be

a very useful and meaningful term, but it is not as descriptive as "absence," or "loss or diminution of consciousness without motor component." The term "status epilepticus" intimates a continuing generalized tonic-clonic convulsion. Actually, this seldom occurs, and most continuing attacks have a focal component, or they are recurring generalized tonic-clonic seizures with, or without, return to consciousness. It is difficult to part with old friends, but the time has come for these terms to be discarded.

These are some of the problems associated with the classification of seizures. Masland (1960) reviewed the problem and the various classifications that have been proposed by distinguished workers such as Penfield and Jasper, McNaughton, Gastaut, and Symonds. The attempt by Symonds to divide the problem according to clinical, anatomical, physiological (EEG), pathological and therapeutic aspects has many merits. In our present state of incomplete knowledge, such a classification may be revised as indicated.

For some years, at the Montreal Neurological Institute, an attempt has been made to classify seizures according to their anatomical site of origin, their cause, and the pattern of the attack. These were coded, where possible, according to the numbers of the *Standard Nomenclature of Diseases and Operations*. Certain new numbers had to be created for types of seizures not included in this volume. The anatomical and etiological aspects presented no particular difficulty, but for reasons mentioned above, the symptomatic classification was never completely satisfactory.

The classification of seizures to be suggested here does not answer all of the problems, but it is an attempt to provide a workable description and to separate some of the various components of seizures. Thus, they may be related to sites of origin in the brain, maturation of the brain, physiological disturbances, causes, and responses to medication.

Symptomatic Classification of Seizures

I. Generalized convulsion

- A. Tonic-clonic
- B. Tonic
- C. Clonic
- D. Myoclonic
 - 1. Myoclonic jerks
 - 2. Atonic (Salaam or drop fit)
 - 3. Massive spasms

II. Unilateral convulsion

III. Loss or diminution of consciousness without gross motor component.

- A. Absence—simple
- B. Absence with minor motor accompaniment
- C. Absence with automatism
- D. Absence status

IV. Localized onset, with or without loss of consciousness (based on initial event)

- A. Motor
 - 1. Focal motor (with or without spread)
 - 2. Masticatory
 - 3. Vocalization
 - 4. Adversive
 - 5. Tonic postural
- B. Sensory
 - 1. Somatic
 - 2. Visual
 - 3. Auditory
 - 4. Olfactory
 - 5. Gustatory
 - 6. Vertiginous
 - 7. Abdominal
- C. Aphasic
- D. Automatism (apparently integrated purposeful activity with amnesia)
- E. Psychical (delusions, hallucinations, forced thinking)
- F. Autonomic

V. Unclassified

Duration of Seizures

- I. Very brief (of the order of 1 second)
- II. Brief (of the order of 10 seconds)
- III. Long (of the order of 1 minute or more)
- IV. Prolonged or continuing (of the order of 1 hour or more)

Precipitating Factors

- I. Visual stimuli
- II. Auditory and vestibular stimuli
- III. Olfactory stimuli
- IV. Tactile stimuli
- V. Emotional or psychic disturbances
- VI. Sleep
- VII. Miscellaneous Stimuli

Postictal Phenomena

- I. Confusion
- II. Paresis
- III. Aphasia

- IV. Amnesia
- V. Headache
- VI. Sleep

Associated Disorders

Behavioral Disorders Associated with Epilepsy

- I. Schizoid reaction
- II. Manic or depressive reaction
- III. Reactive neurosis
- IV. Behavior disorder
- V. Mental retardation
- VI. Specific learning disorder

Related Paroxysmal Disorders

- I. Migraine
- II. Syncope
- III. Narcolepsy and cataplexy
- IV. Hysteria
- V. Vertigo and giddiness (including Meniere's syndrome)
- VI. Breath holding spells
- VII. Paroxysmal abdominal pain
- VIII. Trigeminal neuralgia
- IX. Other

Patterns of Attacks

A patient seldom has only one type of attack, of the same pattern, duration and severity. Consequently, it is preferable to describe the components of an attack. For example, a patient might start having a focal motor attack which spreads to become a generalized tonic-clonic convulsion, lasting 5 minutes, and followed by a postictal paresis. This would be described as a focal motor seizure which became generalized, tonic-clonic, of long duration with postictal paresis.

Since each item is a separate entity, an individual number can be given respectively. The classification can thus be used in conjunction with various types of information storage systems, and easily retrieved. One of the main reasons for attempting to classify each patient's seizures is to be able to store this information in a uniform manner and to retrieve it at any time. This classification has already proven to be very useful as a means of storing and retrieving medical literature related to any one of the different types of seizures. At the National Institute of Neurological Diseases and Blindness a "peek-a-boo" system is in use which has proven to be highly satisfactory.

The Aura

The aura is generally considered to be the onset of an attack. It is the first warning to the patient that an attack is about to begin. Young children are usually unable to describe an aura, but may run to their mother in fear. As they grow older, they frequently can describe the warning. The type of aura depends, of course, on where the attack originates in the brain. A sensation in the hand experienced in seizures starting in the parietal lobe, the bad smell so often experienced by patients with tumors in the temporal lobe, the "déjà vu" phenomena seen in seizures originating in the temporal lobe, and so on, all constitute aura. Some of the best descriptions of auras are those of Penfield (Penfield and Jasper, 1952) when he reported on the feelings of patients during cortical stimulation. The stimulation, if near the crucial epileptogenic area, might start a seizure. The patient would describe the initial feelings and the events as the attack spread. By recording directly from the cortex, the attack could be followed as it spread across the cortex. It might stop or develop into a generalized tonic-clonic convulsion. Although one must be very cautious in relating a certain type of aura to specific areas of the brain, careful questioning of the patient is most essential in any examination, and may be a major factor in revealing the site of origin of the attack.

The Tonic-Clonic Convulsion

A tonic-clonic convulsion starts usually with the tonic phase. The patient falls to the ground, becomes unconscious, and develops generalized tonic stiffness of the body. The head is retracted, the arms flexed, legs extended, and the muscles of the trunk are in spasm, so that respirations cease. The purest example, if there is such a thing, is seen in patients receiving electrical shock treatment for mental disorders. Here, the aura is eliminated; there is no buildup to the seizure. With the shock, the tonic phase of the seizure starts. After a varying period of time, the clonic phase begins. This consists of alternate periods of spasm and relaxation of muscles so that clonic movements of the face, trunk, and extremities develop. During the clonic phase, the patient may bite his tongue or become incontinent of urine or stool; breathing is labored or jerky, and at times it may appear as if breathing has stopped completely. Cyanosis may be profound.

In the normal course of events, the motor component of the seizure subsides and the patient gradually regains consciousness. The muscle tone is, then, generally poor. The patient may complain of fatigue or

headache, experience difficulty speaking, or have some residual paresis. The naturally occurring tonic-clonic seizure is similar to this with the exception that the onset is more prolonged.

The hysteric or skillful malingerer may be able to simulate a true attack in a very real manner. If having an attack provides a means of gain for the patient, if there is no incontinence, tongue biting, nor other injury, if there are no reflex changes, or if the patient seems to be conscious during a generalized attack, then one must suspect that it is not a genuine epileptic attack but, rather, of psychogenic origin.

During a generalized tonic-clonic seizure, the EEG reveals a bilaterally, synchronous, symmetrical pattern. There are rhythmic spikes interrupted by slow waves during the clonic phase. Matsumoto and Ajmone-Marsan, by means of intracellular microelectrode studies in cats, were able to show that during the tonic phase, the neuronal membrane potential markedly decreases, and rhythmical oscillations, usually with active potentials, appear above a sustained, excessively depolarized potential level. The clonic phase corresponds to a slow repolarization process, and the end of the episode seems to be due to inactivation, rather than to true membrane hyperpolarization. Some neurones appear to be activated only in the later phases of the seizure.

Myoclonic Seizures

Myoclonic seizures refer to a series of involuntary shocklike contractions of a group, or groups, of muscles, or a "spasm" of the whole body. They may be restricted to one somatic region or appear throughout many areas of the body. They may be restricted to one somatic region or appear throughout many areas of the body. The myoclonic jerk may be single or repetitive for a varying period of time. Swanson and his colleagues (1962), in their excellent review, point out that the clinical picture implied by the term myoclonus is characterized by great variation in its degree of organizational complexity, and represents a wide spectrum of altered excitability at different levels or organization within the neuraxis. When the alterations occur predominantly at cerebral levels, they are called seizures; when motoneurons are involved, fasciculations are said to result; and when the origin is in the brain stem or spinal cord, the term myoclonus is used. There is a growing body of evidence which suggests that the increased excitability results from removal of some inhibitory mechanism in the pools of motoneurons and

interneurones, and that the brain stem and spinal cord are the sites of this unstable repetitive neuronal firing. The resulting clinical disorder appears to be dependent upon the predominant site of involvement: midbrain, brain stem, spinal cord, or all three. Higher structures may influence myoclonus, but they are not essential for its occurrence. The degree of maturation of these structures, phylogenetically older than the forebrain, is important in the susceptibility to myoclonic epilepsy. A great variety of pathological conditions will produce myoclonus, particularly in those disorders involving the neuraxis diffusely, and are related to the degree of maturation of the spinal cord, brain stem or midbrain. The newborn infant has localized myoclonic jerks. With increasing age, "infantile massive spasms" and "salaam" or "drop fits" appear, indicating a higher level of origin. The massive spasm consists of a sudden spasm of the body, extension of the legs, flexion of the head and neck, and the arms extended upwards. The atonic attack, or "drop fit," is expressed by a sudden loss of tone and the child is suddenly thrown to the ground. It is not clear whether there is a positive contraction which "throws" him down, or whether it is the sudden and complete loss of tone. The children frequently injure themselves. When sitting in the high chair, for example, they frequently strike their faces on the tray. Protection with some type of helmet may sometimes be required.

Unilateral Convulsions

The French school has emphasized the importance of unilateral seizures. Certainly, they do occur (Gastaut, 1963). Whether they should be considered as a separate class of seizures, or purely as a focal seizure that does not spread to involve the opposite hemisphere, is a moot point. There is a serious form of seizure seen in children involving one side only, which frequently leaves the child with a hemiparesis of a transient or permanent nature. It may or may not be associated with demonstrable vascular occlusion.

Gastaut suggests that unilateral attacks are, in fact, generalized attacks, predominantly or solely unilateral, but sometimes with an alternative distribution of seizure pattern. All forms of generalized seizures can occur in this way, thus producing (1) hemigrand mal or unilateral major seizures, (2) "hemitonic attacks," (3) "hemiclonic attacks," and (4) petit mal with unilateral myoclonus or amyotonus (Faidherbe, et al., 1962).

Absence Attacks

There are four types or degrees of absence attack: Simple, with minor motor accompaniment, with automatism, and absence status. The term "petit mal," like "grand mal," in itself is not very descriptive. It has come to mean a particular type of attack in which there is a sudden transient loss of consciousness without any convulsive activity. It is of short duration, lasting 5 to 20 seconds. During the attack, the patient has a blank stare, does not fall, and may not move. It is a state of "suspended animation." Unfortunately, the term "petit mal" is used by many physicians to mean any attack which is not a generalized tonic-clonic seizure. The term "absence" is more descriptive, and is preferable to "petit mal." The least complicated is described as absence-simple. Parents describe the attacks well when they say the child for a few seconds is "dans la lune," or "day dreaming." Often parents think nothing of these attacks, and they may go unnoticed for months or years. If the attacks create a problem, particularly in school, or the child has a tonic-clonic seizure, then they are brought to the attention of the physician.

Absence with minor motor accompaniment is a second type of "petit mal" seizure. The eyes may blink, or deviate, the head may turn a little, the lips smack, or stereotyped movements of the hands may be seen.

Absence with automatism is a third type of minor attack (Penfield and Jasper, 1954). This is really a prolonged attack. If it lasted for only a minute or two, and the patient moved around in a "daze," it has been called a "petit mal automatism." If the attack persisted for many minutes, or even hours, it was generally referred to as "petit mal status" (Tucker and Forster, 1950). The term "absence-status" is preferred. It is highly probable that some of these attacks in children originate deep within the temporal lobe, and with the passage of time, the typical picture of epilepsy originating in the temporal lobe will evolve.

For the most part, during an observable absence attack the patient is unconscious. During this time the electroencephalogram reveals a burst of spike-and-wave activity which is characteristic of this disorder. However, a patient can have short bursts of spike-and-wave activity on the EEG for which no clinical abnormality can be seen. Also in absence-status, when there is continuous spike-and-wave activity being recorded, patients have been known to be conscious, able to talk, despite drowsiness, dysarthria, and ataxia.

It has been postulated, on good evidence, that absence attacks originate in the diencephalon, and that

the spike-and-wave activity is a response of the cortex to a stimulus originating from the deeper structures of the brain. The work of Jasper and Droogleever-Fortuyn (1947), Pollen, et al. (1963), Guerrero-Figuero, et al. (1963), tend to substantiate this.

The problem is more complex than this, however. The degree of maturation of the brain is undoubtedly an important factor. Guerrero-Figuero and his colleagues were able to produce experimental "petit mal" only in kittens up to 30 days of age. Older kittens did not develop the pattern. Absence attacks tend to occur in children after the age of 3, and unless there is a specific cause, they tend to disappear. This is not true in all cases, by any means, as pointed out by Holowatch, et al. (1962), and Currier, et al. (1963).

The problem of the prognosis in this type of minor seizure warrants further study. Absence attacks are seen in children where there is a strong hereditary background and no known pathology. They are seen also in children with a Sturge-Weber syndrome, who have a focal cerebral lesion, and in juvenile forms of Tay-Sachs disease where there is diffuse lipoidosis. Surely the only common factor in these three different types of pathology is the state of maturation of the brain.

One of the characteristic features of absence attacks is the ease with which attacks may be precipitated by hyperventilation and blowing off carbon dioxide. They are also common when the child is hungry and has a low blood sugar. They are more common in the early hours of the morning and less common during active exercise. Children may play at dangerous games, ride bicycles (not that it is recommended) and have no trouble, but then sit down in school and have one attack after another.

Seizures of Localized Onset With or Without Loss of Consciousness

Any of the following types of seizures may remain localized in one region of the brain, and manifest themselves by the single component, or they may spread to other regions of the brain and develop into a generalized tonic-clonic convulsion.

Motor

The classical Jacksonian form of epilepsy is one which originates in one part of the motor area of the cortex and spreads to involve the rest of the motor strip. The attack starts with tonic or clonic movements of part of the arm or leg, usually peripherally, and spreads to involve the rest of the body.

Other focal motor seizures are known as masticatory when the attack starts with chewing movements, and vocalization, if the attack starts with a cry and progresses to a complete tonic and clonic attack. Another focal motor attack is the adversive seizure. Here there is a turning of the eyes, head, and body away from the side of the brain which is firing. The tonic-postural seizure is one in which the attack starts with tonic posturing of an arm or leg which may also indicate the site of origin of the attack.

Sensory

A sensory attack involves some part of the brain where sensations of various types are appreciated. It may be somatic, visual, auditory, olfactory, vertiginous, or abdominal. Frequently in young children, the origin of the attack is not appreciated. The child will express fear or anxiety, or run to a parent. It is not until the child matures and can describe the sensation that one can appreciate the truly focal nature of the attack.

Aphasic Attacks

Many patients describe clearly how they are unable to talk at the onset of an attack. Postictal aphasia is also frequent. One has to distinguish a true aphasia from a dysarthria which may follow an attack and be part of the general picture of confusion that exists. One must also distinguish the aphasia that accompanies a seizure from the aura of a migraine attack. Frequently in patients having their first attack of migraine, the aura is a more frightening thing to the patient than the headache which follows.

Automatism

Attacks of automatism, or automatic behavior, consist of apparently purposeful activity for which the patient subsequently has no memory. The actual activity, which may be conditioned by the immediate environment, may be complicated activity, or it may be a simple form of repetitive activity such as picking at clothes and so on. Attacks have been described of prolonged periods of confused activities in otherwise healthy individuals. EEG examinations may reveal continuous epileptic activity arising from a temporal lobe. Attacks of automatism are generally considered to originate in the temporal lobe, particularly from the hippocampal region, but they can originate also from other regions of the brain. For this reason, it is not wise to refer to them all as "temporal lobe seizures."

Psychical.

Psychical seizures consist of a sudden onset of delusions, hallucinations, forced thinking, "déjà vu" phenomena, and so on. They have been described in great detail by Penfield. He has been able to reproduce the attacks by stimulating the epileptogenic cortex usually in the temporal lobe. The attacks must be intermittent and must be distinguished from delusions and hallucinations of the continuous nature seen in schizophrenia. The outstanding feature of the epileptic attack is its intermittent nature, with interictal periods of normal behavior. As has been noted, a seizure may last for a long period of time, producing prolonged abnormal behavior. The EEG is of great help in distinguishing a seizure originating in the temporal lobe from truly psychotic behavior in a schizophrenic.

Autonomic

Many seizures are accompanied by disturbances of the autonomic nervous system. Such things as sweating, piloerection, salivation incontinence, abdominal cramps, laughter or crying, Penfield described as "diencephalic autonomic epilepsy." It is probable that these seizures originate in, or near, the hypothalamus.

It is relatively easy to classify and define the various types of seizures. It is a different and much more difficult problem to classify the seizure of a particular patient. The lack of opportunity to witness the onset, the inability of the patient to describe the onset, the changing pattern, and variability often combine to make it impossible to determine specifically the type of seizure a patient is having. Many times one can merely describe what is seen and then try to classify it. The seizure should be classified as a symptom and not as an anatomical diagnosis, as is suggested by "temporal epilepsy," or an electroencephalographic diagnosis, as is suggested by "wave-and-spike attacks" or "hypsarhythmic attacks." Having described and classified the attack, one can attempt to correlate it with a possible anatomical site of origin, the etiology, and the abnormalities in the EEG.

Duration of Seizures

There has been some confusion in trying to classify seizures according to different stages of their evolution or varying periods of duration. Such terms as "focal continuing," "petit mal status," or "status epilepticus," indicated a prolonged or continuing attack, whereas "petit mal" and "grand mal" generally indicated an isolated short attack. The possibility of indicating

the duration as: (1) very brief (in the order of 1 second); (2) brief (in the order of 10 seconds); (3) long (in the order of 1 minute or more); (4) prolonged or continuing (in the order of an hour or more) is recommended.

Precipitating Factors

Seizures may be precipitated by many different types of stimuli. Children with light sensitive epilepsy may voluntarily induce seizures by passing their fingers between their eyes and a bright light. There is a recent report of a man who has seizures when he hears certain church bells. There are the so-called musicogenic epilepsy, television epilepsy, reading epilepsy, arithmetic epilepsy, olfactory epilepsy, and so on. A distressing form is the sudden myoclonic attack occurring in children when spoken to suddenly and harshly. Epilepsy that is brought out by these mechanisms is referred to by some as "reflex epilepsy." This indicates that the seizure is a response to a stimulus—in a susceptible brain. Most seizures probably have some precipitating, or triggering factor. Rather than referring to them as a separate type of epilepsy, it is better to classify the precipitating stimuli. There is probably a common mechanism, acting through thalamic nuclei, which initiates the chain of events leading to a seizure. The following division has proven useful as a means of separating the various precipitating factors as they appeared in the literature: (1) visual stimuli, (2) auditory and vestibular stimuli, (3) olfactory stimuli, (4) tactile stimuli, (5) emotional and psychic disturbances, (6) sleep, (7) miscellaneous stimuli.

That seizures can be evoked has been known for a long time. Hydration and pitressin were once used to bring out seizures. They were used before the development of the electroencephalogram. The procedure was difficult for everyone involved and seldom used.

Hyperventilation was known to blow off carbon dioxide, and change the pH of the blood. It had an uncanny ability of precipitating absence attacks in children. With the advent of the EEG, hyperventilation proved to be a very useful means of bringing out abnormalities in the record, particularly in patients with absence or tonic and clonic attacks originating in the diencephalic region. The next step was to use convulsive drugs for this purpose. Pentylenetetrazol (metrazol) was being used to induce convulsions in patients with various psychoses. By giving the drug slowly, it was found that the EEG could be activated, latent epileptogenic foci made to fire, and thus epileptogenic areas of the brain demonstrated without causing a convulsion.

This was followed by a recognition of the importance of sleep as a means of bringing out abnormal activity on the EEG. About the same time photic stimulation with a flashing stroboscopic light was also found to be a very useful method of activating an EEG.

With the increase in sophistication of the EEG, these activating procedures have been developed to a fine degree. Many different types of activating procedures are now used, such as fasting, intravenous glucose, convulsant drugs, noises, lights, reading, sudden shocks, hyperventilation, sleep, intravenous sedatives, etc., each one tailored for the patient's needs. Apart from their value as research tools, activation procedures help the clinician determine whether the periodic attacks a patient has are epileptic. They are of value in distinguishing various types of epilepsy, may suggest a diagnosis of the underlying condition, and serve to clearly define epileptogenic foci which might be amenable to surgery.

This subject is extremely important in the understanding of epilepsy, and reference should be made to original articles. (Allen, 1954; Andermann, et al., 1962; Cobb, 1947; Forster, et al., 1949; Lang and Urban, 1962; Rothova and Roth, 1963).

Inhibition of Seizures

It is appropriate to discuss, at this point, the voluntary inhibition, or arrest, of seizures. The ability of a patient to arrest a seizure is possible only if there is an aura which precedes loss of consciousness. Paulson (1963) studied a group of 112 patients, of whom almost one-third believed they could occasionally voluntarily inhibit seizures after the aura began. The problem of inhibition of seizures was of interest to Hughlings Jackson and Gowers. Both reported cases where seizures starting in extremities could be arrested by ligatures or massage. Symonds (1959) stated that 53 of 100 cases he had seen could inhibit seizures by means of some mental or bodily activity.

The exact mechanism of the voluntary suppression of seizures is not known, although many theories have been propounded, based on isolated observations related to inhibition in the cortex, activation of the ascending reticular system, etc. It is known that epileptic discharges are less frequently seen in the EEG in patients who are aroused or attentive. Absence attacks are less frequent during periods of activity. Stevens (1962) showed that some stimuli of known frequency, used to evoke abnormal EEG potentials, activated the electroencephalograms of patients with one type of epilepsy, whereas the same stimuli caused

suppression in other patients with a different type of epilepsy. Those working with epileptic patients in rehabilitation centers maintain that work and contentment are important factors in the prevention of seizures. The problem of the natural inhibition, or control, of seizures is an important one with far-reaching consequences, and warrants further study.

Postictal Phenomena

Headache, drowsiness, fatigue, and muscular aches frequently persist after the cessation of a convulsion. There are other more specific phenomena which persist, thus suggesting that the function of one area of the brain is depressed. Following a prolonged seizure, confusion may be present and suggests a slowness on the part of the diencephalon to return to normal function.

Paresis of part of the body may persist for several hours, or days, after a seizure. This is referred to as Todd's paralysis. Frequently there is a story of a child having an inoculation or a fever associated with a unilateral convulsion which is followed by a transient hemiparesis. Sometimes the paresis does not disappear completely. Gastaut and his conferees have described this in great detail (1962). The explanations for this postictal paralysis have been many and varied. It is probable that the loss of neuronal function is related to anoxia. The increased demand for oxygen created by the fever and the excessive neuronal activity, combined with the asphyxia caused by the tonic contraction of the respiratory muscles is one explanation. Another is that the seizure is a result of a vascular spasm or occlusion, and the damage is done before collateral circulation can be developed. Elderly patients may have a profound and lasting Todd's paralysis after a seizure. Indeed, it may be impossible to distinguish the hemiparesis from a cerebrovascular occlusion. It is only the next day, when the paralysis is all gone and the patient is well and wondering what all the fuss is about, that one can be sure the paralysis was secondary to the seizure. The profound loss of function in the patient with arteriosclerosis probably is related to the inability of the vessels to dilate as readily as in younger patients. Recovery is possible because there was no major vascular occlusion and the neurones were able to build up their energy stores.

For similar reasons, seizures involving the dominant hemisphere may leave the patient with a transient aphasia. The aphasia will vary, depending upon the area of the cortex involved, and is likely to change rapidly. This makes it difficult to decide exactly what type of aphasia it is. Care should be taken not to con-

fuse the aphasia with dysarthria, which is a transient phenomenon that follows most major attacks and has no localizing value except to indicate that the diencephalon and brain stem were involved.

The amnesia which follows an attack also varies, depending upon the severity of an attack. If a patient has no warning of a pending seizure, he may have a severe tonic and clonic attack. The only way he will know that he has had a seizure, however, is that he has bitten his tongue or has been incontinent.

For many patients, this amnesia is a blessing. For others it constitutes a real problem. Some are unable to accept the fact that they have attacks, or that the seizures are severe. They insist on doing things which may be dangerous. It is often impossible to distinguish the amnesia, which is part of an attack of automatism and automatic behavior originating in the temporal lobe, from postictal amnesia. In these seizures they may be the same.

Behavior Disorders Associated with Epilepsy

The greatest problem that confronts the patient with epilepsy may not be the convulsions, but the effect of the pathological lesion which causes the attacks on his intelligence and personality. The effect may be direct and cause mental retardation, or it may be indirect and cause a reactive neurosis or behavior disturbance. Superstition, fear, and prejudice continue to be very powerful in harming the epileptic in the eyes of himself and others. It is not infrequent that the medication given to control the seizures is a direct cause of overactivity, impulsive acts, drowsiness, or other behavior disorders.

The current literature on the relationship to schizophrenia, manic-depressive psychosis, reactive neuroses, behavior disorders, mental retardation and specific learning problems has been reviewed and a limited bibliography presented. Limitations of time have not permitted a complete review of this aspect of the epilepsy problem.

Related Paroxysmal Disorders

A thorough study of the epilepsies should include a consideration of related paroxysmal disorders: migraine, syncope, narcolepsy and catalepsy, hysteria, vertigo (including Meniere's syndrome), breath-holding spells, paroxysmal abdominal pain, and trigeminal neuralgia. Although a detailed review of these disorders has been prohibited in this paper because of unfortunate time limitations, bibliographies of each, therefore, are included.

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DIAGNOSIS

The diagnostic evaluation of a patient presenting with the complaint of convulsions or seizures, regardless of the type, is based on sound medical practice. A careful history is taken, and a physical examination and indicated laboratory studies are conducted.

The History

The technique of taking histories varies from doctor to doctor and from patient to patient. The procedure used for an infant is different from that of a child, and that for a child is different from that for an adult. Whether the facts are obtained from the parents, the patient, or both, the basic formula remains the same.

Complaints

The "complaints," which constitute a description of the attacks, are generally presented first and lead to a "history of the present illness."

History of the Present Illness

This phase of the history is concerned particularly with localizing the site of origin of the attacks in the brain and evaluating the patterns of the seizure activity.

It starts with a description of the first attack and the events leading up to it. This is followed by a description of each subsequent attack or, if they are very frequent, any different types of attacks. Attention is paid to the following aspects:

a. *Pattern of the Attack.* Every effort should be made to get a sufficiently accurate description of the attack to permit classification of seizure. The physician must determine such questions as whether there was an aura or warning, what happened during the attacks and what happened after the attack.

b. *Frequency of the Attacks.* The frequency of attacks is noted, both on and off medication.

c. *Time of Day.* The relationship of attacks to sleep, meals, or specific times during the day is noted.

d. *Precipitating Factors.* Unless specific questions are asked, the fact that certain stimuli can precipitate an attack may be missed.

e. *Related Events.* Hunger, fatigue, menses, recent intake of alcohol, watching television, painful stimuli, etc., should be considered.

f. *Response to Medication.* The types and amount of medication, as well as length of time each has been taken, and any unusual reaction to the medication is noted.

g. *Other Complaints.* The development of other complaints and their relations to the seizures is noted. If the seizures are a response to some other medical condition, special attention is given in obtaining the history of this aspect.

Family History

The importance of an accurate and detailed family history cannot be overemphasized. Particular care must be taken if the history is to be used for genetic research or genetic counseling. Often there is an apparent "negative family history" and, yet, further questions may reveal the story of febrile convulsions or "fainting attacks" within the family.

Past History

This starts with a description of the pregnancy, birth, and early development, and may be obtained from different sources. Many children with seizures are retarded. Note should be made of when the child passed the developmental "mile stones," and of the school progress. From the history and the examination, the physician must develop his own impression of the child's intelligence, and decide whether further psychological evaluation is indicated.

A record is made of any untoward response to vaccination or other immunizing procedures. Any accidents, serious illnesses, or hospitalizations are noted. Particular attention is paid to any past or present behavioral or emotional disturbances. This may be the only clue to an organic disorder of the brain.

In an adult, habits of drinking, taking drugs, smoking, sleeping, working, and so on may provide important information. One needs to determine whether there is anything in the past history to suggest organic deterioration which might point to a brain tumor, a subdural hematoma, or cerebral arteriosclerosis.

A review of systems, or functional inquiry, is an essential part of the history. Often an adult will admit to headaches, whereas only a specific question will reveal impotency. An inquiry into possible allergic or hematological disorders is essential. Also, a careful inquiry into the social and emotional backgrounds of any patient with seizures, may prove important to the success of therapy.

There are no shortcuts to a careful history, but once obtained it provides a useful and important document for the future.

Laboratory Examinations

Although some laboratory tests are described as "routine," and are requested with the vague hope that some unusual finding may be revealed, this should not be the case. Rather, laboratory tests should be requested with a definite purpose in mind and a knowledge of what useful information may be revealed by the test. An initial evaluation generally includes the following:

- (1) Urinalysis.
- (2) Hemogram.
- (3) X-rays of skull.
- (4) EEG.
- (5) Psychological evaluation.
- (6) Social evaluation.

Urinalysis

In the young child, urinalysis may reveal evidence of a latent nephrosis, and thus may influence one's decision regarding medication. In the older patient the possibility of diabetes increases. Patients taking trimethadione or paradione should have periodic urinalyses to exclude a toxic nephrosis. It is also a wise precaution to advise parents to watch for swelling of the ankles or unusual increase in weight in the child.

Special urinary studies may be conducted to detect abnormalities of protein metabolism, such as phenyl-

ketonuria or metachromatic inclusion bodies in the presence of undiagnosed encephalopathies.

Hematological Studies

A red, white, and differential cell count, and hemoglobin estimate are requested to reveal evidence of anemia or other blood dyscrasia. These also provide a baseline for repeat studies during the time the patient is on medication. If diabetes, or any other metabolic disorder, is suspected, appropriate blood chemistry studies are requested.

Radiological Investigations

X-rays of Skull

Cranial X-rays are an essential part of the investigation of any patient with epilepsy. Some radiologists prefer multiple projections at different tangents; others prefer stereoscopic films in the beginning followed by special projections as indicated.

Of particular significance is an asymmetry of the skull, especially in the region of the middle fossa. Thickness of one side of the calvarium may indicate smallness of the cerebral hemisphere on that side. Abnormal positions of the pineal or glomus bodies of the choroid plexuses may indicate an expanding intracranial lesion, or contracture due to cerebral atrophy. Abnormal intracranial calcifications may indicate a tumor, tuberose sclerosis, Sturge-Weber syndrome, an old tuberculoma, or other disorders. Signs of increased intracranial pressure, such as erosion of the sella turcica, or separation of the sutures, may provide other clues to the cause of the seizures.

X-rays of the Chest

Any patient who might possibly have a metastatic tumor warrants an X-ray of the chest. In infants and children, X-rays of the chest may reveal evidence of a nutritional disorder or lead poisoning in the long bones, or pulmonary disease, and should be considered in the diagnostic procedure.

Pneumoencephalography and Ventriculography

A pneumoencephalogram is a technique for outlining the brain and ventricles by radiography. The CSF in the subarachnoid space and ventricles is replaced with air or oxygen, and the different refractive index of the gas compared to that of the brain enables the gas filling the spaces to be demonstrated. In the

event of increased intracranial pressure, it may be safer to perform a ventriculogram. Here the gas is injected directly into the ventricle. The indications for, and information derived from, these procedures have been described well by Davidoff and Dyke, and others. Should an expanding intracranial lesion be suspected as a cause of seizures, then some form of contrast studies should be considered, whether it be a pneumoencephalogram, ventriculogram, arteriogram, or a radioactive isotope study. The decision will depend on the nature of the problem. Like any test of this type, it is important to consider what useful information may be obtained before it is undertaken.

Castorina and McRae (1963) reviewed the X-ray findings of 100 patients with temporal-lobe epilepsy who were operated on and found not to have a tumor or angioma. About 15 percent had asymmetry of the vault and/or base of the skull. About 80 percent showed radiologic signs of hypoplasia, or atrophy of the lobe or hemisphere which produces the seizures. Of particular value was the combination of relative smallness of the ipsilateral middle fossa and relative enlargement of the ipsilateral temporal horn.

Arteriography

Arteriography is a technique for outlining the vessels of the brain with a contrast medium. Injections may be made directly into the carotid or vertebral arteries, or indirectly from catheters inserted into the brachial or femoral arteries. Arteriography has proven to be an extremely useful procedure in demonstrating brain tumors, subdural hematoma, and vascular abnormalities. Although it is of less value as a diagnostic procedure in epilepsy, it is useful to help rule out tumors or vascular abnormalities. It is also useful in demonstrating vascular occlusions in the unexplained hemiplegia associated with convulsions frequently seen in children.

Electroencephalogram

The development of the electroencephalogram (EEG) has provided the clinician with the most remarkable means of evaluating the patient with epilepsy. It is a means of amplifying the electrical activity of the brain, and recording it continuously on paper. When large numbers of neurones discharge together in synchrony, sufficient voltage is developed on the surface of the brain to be detected on the scalp. In a premature child, when the cortical connections are not developed and the cortex is less mature than the deeper structures, impulses originating in the

mesencephalon and in the diencephalon may be recorded through the scalp. However, as the cortex matures, all impulses originating in deep structures must be "filtered" through and modified by the neurones of the cortex. The EEG, as recorded through the scalp, gives only a gross picture of the neuronal activity of the brain. The electrocorticogram can more accurately localize areas of abnormal activity on the surface of the brain, but it still only indirectly reveals the site of origin of deep-seated epileptogenic activity. Newer depth electrode studies have been remarkably successful in localizing the origin of epileptogenic activity, particularly in the temporal lobe and hippocampal region.

Seizures are due to synchronous firing of a large group of neurones and, despite its limitations, the EEG has a remarkable ability to localize their sites of origin. Over the years, normal controls have been developed for the human at all ages, under a variety of physiological states of wakefulness and sleep. EEG recordings have been made in nearly every disease or functional disorder of the nervous system. The correlation of the EEG recordings with pathological findings in disease states, as well as experimental studies, has augmented the ability of the electroencephalographer to relate the EEG findings to specific pathology. Nevertheless, it should be remembered that widely divergent pathology may give identical EEG recordings.

The EEG is of greatest value in the study of epilepsy. In patients, particularly children, for whom one cannot obtain a good history, the EEG helps to establish the clinical diagnosis, and sometimes is of value in suggesting a pathological diagnosis. It may be of value as an indicator of the severity of the disorder. This is particularly true in some of the infantile encephalopathies. The EEG is of value in distinguishing hysteria or syncope from a true convulsive disorder. It also may be helpful in determining whether therapy is indicated. The child who has a normal EEG following his first febrile convulsion is likely to be observed over a period of time without treatment. The child who has an abnormal EEG following such an incident is more likely to be started immediately on prophylactic medication.

It would be inappropriate here to describe the technique of recording or how to interpret the EEG. These have been presented elsewhere in great detail, and advances have been recorded in journals and textbooks. A limited bibliography is presented, however, to provide the reader with information covering major works or recent reviews on the subject.

Reference should be made to activation procedures. In the early days of electroencephalography, attempts were made to activate epileptogenic areas of the brain by hydration. Since then, several methods of activation have been developed. The simplest is that of hyperventilation, which is of particular value in patients with a bilaterally synchronous abnormality on the EEG, or in "absence" or "petit mal" attacks. The convulsant, pentylenetetrazol (metrazol), given slowly intravenously in subconvulsant doses during the time of the recording, has proven to be a useful means of activating the EEG. However, the danger of precipitating a major tonic-clonic seizure must be anticipated and precautions taken. EEG studies during various phases of sleep have proven to be a very useful way of searching for epileptic activity. Sleep studies now are almost a standard part of any EEG study.

Intermittent photic stimulation also has proven itself a useful method of activation. With a stroboscopic light, the patient is confronted with intermittent light flashes of a high intensity. The parieto-occipital EEG is altered in all patients with this procedure, but high-voltage activity may be initiated in other regions in those patients sensitive to this type of stimulation. It is significant that certain patients can bring on attacks by waving their hand between their eyes and a bright light. Others have attacks when watching television. Some patients have been known to have seizures during periods of hypoglycemia. For this reason, observations are carried out during periods of fasting or following the administration of insulin. Intravenous administration of glucose may be used to abolish abnormal activity. Other types of activating procedures are used, but these are usually developed for patients whose attacks are brought on by unusual stimuli. Such things as musigenic epilepsy, reading epilepsy, tactile epilepsy, etc., are included here.

The advances which have taken place in the surgery of epilepsy have been dependent upon the ability to localize the site of origin of the epileptogenic focus with the EEG. With each advance in EEG technology, the selection of patients for surgery and the surgical results have improved. With a better understanding of the EEG, as recorded through the scalp, combined with depth electrode studies, one can look forward to even better selection, and further improvement in the results.

A word of caution is essential, however. Kellaway expressed it well when he said, "The electroencephalogram should not be considered a means of obtaining a 'penny-in-the-slot' diagnosis." In the first place, the test is expensive for the average patient, and secondly,

too many tests are ordered unnecessarily before careful consideration is given to what useful information might be obtained. The EEG gives a picture of the electrical activity of the brain as it is reflected through the cortex. It is rarely diagnostic in itself, but when combined with the clinical history and findings, may make a complete diagnosis possible.

Implanted Electrodes

Depth electrode studies have proven to be a useful diagnostic tool in certain patients with EEG abnormalities originating in the temporal lobes.

Crandall and his colleagues (1963) reported on a group of eight patients with apparently independent bitemporal spiking EEG activity. By means of stereotactically implanted electrodes in the amygdala, pes-hippocampi, and hippocampal gyri, bilaterally, they were able to show that in six of the eight patients the disorder was primarily unilateral since one site demonstrated greater activity and lower threshold for after-discharges, reproduced the typical seizure on electrical stimulation, and was pharmacologically activated. Temporal lobectomy in these patients resulted in relief from seizures.

Angeleri, et al., (1964) reviewed their results of prolonged implantation of electrodes in regard to the electrical activity and reactivity of the rhinencephalic, parahrinencephalic, and thalamic structures in man. They performed simultaneous deep cerebral recordings in 94 cases of neuropsychiatric patients, of whom 32 had epilepsy, 56 had extrapyramidal synchrony, 4 had schizophrenia, and 2 had severe psychasthenia with associated motor manifestations. They pointed out that our knowledge of the clinical syndrome of epilepsy originating in the temporal lobe is now fairly accurate, nevertheless, our understanding is less clear in regard to the physiopathological phenomena which cause the syndrome and the structures that are directly or indirectly involved. Also, the mechanism of transmission of epileptic discharges from one sector of the brain to another is a complicated problem which remains to be solved. From the studies of Angeleri and his colleagues, they concluded the following:

(1) It now appears to have been adequately demonstrated that the hippocampal-amygdalar structures are of predominant importance for the precipitation and maintenance of epileptic attacks, particularly of temporal lobe origin, and also of the so-called centrencephalic forms. Either by synergic activity, or separately, these structures may be regarded as the "starter" of the temporal attacks; they may play a

very important role in the preparation of particular functional conditions of the neopallium which facilitate the occurrence of generalized attacks of the tonic-clonic type. Studies carried out in electrophysiological laboratories cannot contribute data comparable to that obtained by recording and stimulating in epileptic subjects.

(2) The relations between the convulsive electrical activity of the rhinencephalic structures and activities of the same type from the neopallium are rather complicated, but it may be stated that there is dissociation between the attacks originating from these two structures.

(3) The importance of the rhinencephalic system in the genesis of the changes in so-called centrencephalic epilepsy is strongly confirmed by their experiments but it has proved rather doubtful whether the thalamus is also concerned in these abnormal manifestations.

(4) Their observations, during stimulation of rhinencephalic structures, of the appearance of after-discharges in these structures contain clues which are useful in correlating the electrical aspects of temporal attacks and the accompanying clinical phenomena.

Finally, they again stressed the importance and value of depth electrode recordings and stimulation studies in patients with epilepsy as compared to animal studies.

Radioactive Isotope Studies

The use of radioactive isotopes as a means of localizing epileptogenic lesions has not proven to be of value, even though changes in permeability of blood vessels to fluorescein, at areas of epileptogenic activity, have been demonstrated. In definitive lesions, such as tumors, this technique has been valuable.

Intracarotid Injection of Sodium Amytal

In patients being considered for surgical excision of an epileptogenic area, it is important to know what hemisphere subserves speech. In a right-handed person, speech is almost invariably in the left hemisphere; however, the opposite is not true for left-handed people (Wada and Rasmussen, 1960). The carotid amytal test, as originally described by Wada, has proven to be a useful means of determining the dominant hemisphere for speech, particularly in left-handed patients when operation is being considered in the left hemisphere. The test is performed by injecting sodium amytal into one carotid artery and recording the ability of the patient to perform voluntary movement with the arms and legs on the side opposite

the injection while replying to "aphasia" tests. If the speech area is not located in the hemisphere on the side of the injection, a contralateral hemiparesis will develop, but no aphasia.

Psychological Evaluation

In an infant and preschool child one can follow with gross tests the mental development of a child including the time the child sits, walks, talks, and so on. When a child with epilepsy approaches the school age, a careful psychological evaluation should be conducted. The difficulties that these children have revolve around frequently impaired intellect and difficult behavior. One should have a clear picture of a child's intellectual potential, and be able to transmit this to both the parents and teachers. The same can be said about patients with seizure problems attempting to obtain work. Frequently they cannot hold a job because of their intelligence or difficulty in getting along with their fellow workers. Vocational guidance specialists have been of great help in seeing that a man is not asked to do more than he is capable, and in interpreting the ability of patients to employers.

The role that psychological studies can play in evaluating the effect of lesions in the temporal lobe on intellect, hearing, and memory, is described well by Milner and others. Reference should be made to the original articles.

Social Background

Social service workers play an essential role in a convulsive disorder clinic. They can help the patient and the physician with many problems. They investigate the social environment of a patient, and frequently determine why a particular patient is not responding well. They interpret the nature of the problem to both the patient and his family. They can offer advice with schooling and employment problems, and be of very practical help in many instances. With the guidance of the neurologist or psychiatrist, the social worker can do much to assist in the emotional life and adjustment of the patient with seizures.

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PATHOLOGY

Pathological lesions have been described for different types of epilepsy; however, the pathology of idiopathic epilepsy continues to be somewhat obscure and it is not clear whether the lesions found are the result or the cause of seizures. Scholz (1951) reviewed the pathology of epilepsy. More recently, Meyer (1958) presented a general analysis of the described pathology including his own work, particularly in relation to the temporal lobe.

The oldest and most familiar lesion seen in epilepsy is sclerosis of Ammon's horn. Many of the earlier investigators reported that Ammon's horn sclerosis occurred in approximately 50 percent of epileptic brains, and was usually unilateral, or, if bilateral, was more marked in one hemisphere. It was observed not only in cases of "idiopathic" but also of "symptomatic" epilepsy. It has been found even in the brains of patients who had not suffered from convulsions. Spielmeyer (1927), and later Scholz, confirmed and expanded the earlier findings. They provided clear evidence that the sclerosis was due to vascular disturbances and/or anoxia. Pathological lesions have been found in the cortex and subcortical regions in epileptic patients, but they have also been found in patients who did not suffer from epilepsy. There is some question as to whether such lesions are directly related to, or caused by, the convulsions.

Most of the pathological findings reported are clearly the consequence of disturbance of the blood circulation and/or lack of oxygen. They are identical with those considered to be attributable to anoxia.

Spielmeyer suggested that disturbance of vasomotor regulation, and in particular angiospasm, caused the necrosis. He, therefore, postulated angiospasm as a possible cause of the convulsion. Some investigators have suggested that angiospasm may play a role in the causation of convulsions. Others (Meyer, 1939), however, using histological techniques similar to that of

Scholz, were unable to confirm the finding of anaemia preceding the onset of a seizure.

Similar problems exist with regard to the pathology of epilepsy originating in the temporal lobe. Earle, Baldwin, and Penfield (1953) claimed that "incisural sclerosis" was the most common cause of temporal lobe epilepsy. This change was noted in 100 out of 157 patients who had been operated on at the Montreal Neurological Institute. The extent of this sclerosis ranged from involvement of a single gyrus to that of the entire temporal lobe. The apex and the anterior part of the hippocampal gyrus, with the uncus and amygdaloid nucleus, were the most frequently involved. The lesion was presumed to be the result of the herniation of the temporal lobe, or more strictly its most medial and inferior parts, into the tentorial openings during the head molding phase of parturition. Such herniation occurs at a time when the temporal lobe is poorly developed and thus particularly susceptible to damage through local anoxia following the compression of the anterior choroidal and posterior cerebral arteries against the tentorial edge.

Sano and Malamud's (1953) clinical, pathological, post mortem studies revealed 29 of their 50 cases of epilepsy had Ammon's horn lesions. After excluding severely demented cases unsuitable for clinicopathological analysis, they found that all cases with clinical temporal lobe symptoms had Ammon's horn sclerosis and/or traumatic frontotemporal lobe lesions. Stauder, in 1935, found Ammon's horn sclerosis in 36 of 53 cases of epilepsy. Thirty-three of the 36 cases with temporal lobe lesions had clinical symptoms suggestive of the type of epilepsy usually associated with the temporal lobe. None of the 17 cases with normal Ammon's horn showed clinical signs of temporal lobe involvement. Meyer studied the patients who had had an anterior temporal lobectomy by Mr. Murray Falconer. The incidence of sclerosis of Ammon's

horn in their cases was just over 70 percent, followed closely by lesions of the uncus (64 percent), and to a lesser degree, lesions of the amygdaloid complex. (Meyer, et al., 1954).

The results of these studies suggest that lesions in and near the hippocampal gyrus play an important part in the mechanisms of many seizures of the temporal lobe type. Ammon's horn, the uncus, and parts of the amygdaloid complex may be of considerable importance as general activators of brain function (Green and Arduini, 1954; Feindel and Gloor, 1954). They may also play a role as part of the so-called visceral brain, or participate in the cerebral control of emotions and emotional expression (Papez, 1937 and Kluver and Bucy, 1939). Lesions in these structures could thus account for the autonomic and emotional features of temporal lobe seizures.

The concept that incisural sclerosis is a result of a molding of the head at birth, as proposed by Earle and his colleagues, is at variance with the hypothesis that Ammon's horn sclerosis is caused by seizures and related to vascular spasm.

The most recent report by Falconer and his colleagues (1964) is a review of 100 patients operated on between 1951 and 1960 for epilepsy originating in the temporal lobe. Forty-seven patients showed evidence of mesial temporal sclerosis. Their evidence suggested that patients with this type of lesion generally had seizures dating from infancy or childhood. There was frequently a history of difficult birth (28 percent), and the seizures were first precipitated by fever. Although no wholly satisfactory explanation was forthcoming to explain the origin of the mesial temporal sclerosis, these investigators were of the opinion that hypoxic episodes in infancy and early childhood played a more important role than birth trauma. There were 21 patients with small cryptic tumors. Some had dual pathology, so that there were 18 small glial formations or tumors, 3 small capillary angiomas, 1 dermoid cyst, 1 parasitic cyst, and 1 lesion suggesting tuberose sclerosis. The rest of the patients, some 32, were those with miscellaneous focal lesions and equivocal lesions.

The investigators found that the small cryptic tumors tended to be situated in, or around, the amygdala rather than the hippocampus, while among others, mesial temporal sclerosis almost invariably involved the amygdala. In view of this, as well as physiological data, these workers believed the amygdala has a more important role in the production of clinical seizures than has the hippocampus (Ammon's horn).

Penfield and Jasper (1954) present, clearly and concisely, the pathology seen in focal epileptogenic lesions. They point out that there are common features in all these atrophic epileptogenic lesions. In all, there was an area of grey matter in which the circulation was imperfect. There was found in all those studied carefully, evidence of periodic closure of minute blood vessels sufficient to produce progressive punctate injury or destruction. In cases of most such lesions, the evidence indicated that the point of departure for epileptogenic discharge was either an area of grey matter obviously abnormal, or an area of grey matter not obviously abnormal, but influenced in an abnormal manner by an adjacent lesion of the brain.

Penfield also found that within or at the periphery of an epileptogenic lesion is a zone in which recurring ischemia is produced in minute areas, due to periodic impairment of bloodflow through one or another of the small local blood vessels. A localized anoxia acts as an irritant in the sense that greater activity occurs in local neurones. They suggest that this increased local ganglionic activity is reflected in the fluctuating increases of electrical potential, which may be detected by the electroencephalograph even through skull and scalp. The recorded waves are apt to be brief and of high amplitude, which gives to them a "spike" or "sharp" waveform. This irritative and stimulative effect of ischemia varies, but continues locally for years. During this time the area of brain tissue probably atrophies very gradually but continuously, and the frontier of maximum irritation may thus undergo progressive advance.

The investigators also showed that the epileptic focus, when clearly outlined, is objectively abnormal as well as physiologically abnormal. They concluded that the various types of lesions, expanding or atrophic, produce continuing or recurring ganglionic ischemia. They, thus, proposed the hypothesis that this mild or recurrent chronic ischemia is irritating to nerve cells, and that it is the cause of epileptic discharge.

Although the pathological lesions seen in many conditions which cause convulsions are known, the exact nature of the pathological lesion at the site of the origin of the attack is still obscure. Penfield and Jasper, as indeed have others, suggest that the epileptogenic area is due to localized neuronal ischemia. This may be the case and may account for the changes seen in the hippocampal region of the brain in epilepsy originating in the temporal lobe. It is not, however, established whether the pathological lesions seen there are the primary cause of the convulsions, or whether

they are secondary to ischemia which takes place before, during, or after the actual attack. It is clear that further work, including experimental and carefully controlled clinical, electrographic, and pathological studies, is necessary.

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TREATMENT

Introduction

"The patient is not concerned with what is causing his fits; he wants them stopped" (Houston Merritt).

The patient's plea for direct clinical action is readily appreciated by his doctor. The most direct approach one can make toward the successful treatment of the epilepsies is to determine and treat, if possible, the primary underlying cause of the attack. The second approach is to control or prevent the symptomatic seizures by the use of anticonvulsants and other drugs, and occasionally by surgery. The third major aspect of the treatment of epilepsy is an understanding of the total problem, of the patient as a person, his emotional life, and the relationship to his environment.

Seizures are, in a sense, a physiological disturbance. They can be elicited in normal brain by chemical or electrical stimulation. In abnormal brain tissue, as a rule, the threshold for seizures is lower, and attacks are more readily produced by chemical or electrical stimulation. In the normal brain there is a certain stability between the processes of excitation and inhibition. However, in a seizure, generally it is considered that the balance is lost in favor of excitation. Current investigation suggests that convulsive activity is not an enhancement of the normal excitation of neurones but a partial, or complete, block of normal inhibition. A biological abnormality of some neurones is thought to underlie the initiation of a gradually increasing depolarization in their dendritic fields, so that minimal stimuli may initiate a seizure discharge. In any case, therapy is directed at increasing the stability of the neuronal tissue. A seizure originating in an area of abnormal cerebral tissue may remain localized or it may spread to involve normal brain cells. If the spreading electrical activity is sufficiently extensive, the

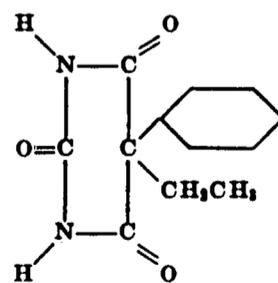
whole brain and spinal cord become involved and a tonic-clonic seizure ensues.

Factors such as blood sugar level, blood gas concentration, body fluid, plasma, pH, body temperature, endocrine disturbances, nutritional deficiencies, specific metabolic disorders, etc., are known to influence the development and spread of a seizure.

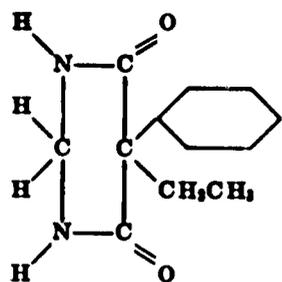
Other factors such as hyperventilation, flickering lights, sudden noises, pain, and even emotional disturbances may precipitate an attack. When planning treatment, these factors, and, indeed, the whole patient and his environment should be considered.

Anticonvulsant Drugs

The first significant advance in the medical treatment of epilepsy was the discovery by Sir Charles Locock in 1857 (Lennox, 1960), of the value of bromides as anticonvulsants. The report in 1912, by Alfred Hauptmann, on phenobarbital as an anticonvulsant was the next important step forward. The structural formula of phenobarbital, or "luminal" as it was called, is:



Most anticonvulsants which have been developed since phenobarbital was discovered have been structurally related to it. Primidone for example has dropped an oxygen atom in favor of two hydrogen atoms:



The structural relationships of the various anticonvulsants are described exceedingly well by Goodman and Gilman (1955).

In 1937, Merritt and Putnam found that diphenylhydantoin had a remarkable ability to prevent electrically induced convulsions in cats. This compound had little sedative effect, was safe, and soon became widely used as a good anticonvulsant in man. Following this, hundreds of drugs were tested on electrically or chemically induced seizures. A few have been proven to be valuable in preventing or controlling various types of seizures. Unfortunately, however, all have some sedative effect and varying degrees of toxicity which have limited their usefulness.

The modes of action of anticonvulsants, their absorption, distribution, excretion, and chemical action on the neurone were reviewed in 1959 by Woodbury and Esplin. Their research was related particularly to diphenylhydantoin and acetazoleamide as examples of drugs acting in somewhat different manners to affect the sodium ratio across the cell membrane and to improve neuronal stability.

Absorption, Distribution, and Excretion

Diphenylhydantoin has been shown to be absorbed from the intestines into the bloodstream. Some is excreted, unchanged, by the salivary glands; some, probably in pancreatic and intestinal secretions. It is believed that only the liver is able to metabolize diphenylhydantoin. It is then excreted in the bile. The vast majority of the metabolites are reabsorbed by the intestine and finally excreted in the urine. Since the major metabolic product, 5-phenyl-5- (p-hydroxyphenyl) hydantoin, does not possess significant anticonvulsant properties, it is tentatively concluded that diphenylhydantoin is the active anticonvulsant agent. The fact that diphenylhydantoin is excreted unchanged by the salivary glands suggests that the hypertrophy of the gums, seen in patients on relatively large doses of the drug, is due to a local action of the drug. The hirsutism and thickness of the skin and subcutaneous tissues of the face, seen in children who have received the drug in large doses for long periods of time, may be due to local action of the drug or to a secondary stimu-

lating effect on the pituitary and adrenal glands. Diphenylhydantoin has been shown to increase the adrenal weight and the output of adrenal cortical steroids (Woodbury, et al., 1958).

Phenobarbital is converted to an inactive derivative by hydroxylation, and therefore, like diphenylhydantoin, the drug itself is considered to be the active anticonvulsant. (Mark, 1963).

Trimethadione, on the other hand, is converted to demethylated trimethadione which both retains anticonvulsant properties itself, and enhances the anticonvulsant properties of the drug. Paramethadione acts somewhat similarly.

The anticonvulsant actions of mephobarbital and primidone can be partly accounted for by their conversion to phenobarbital. Mesantoin is converted to nirvanol, a compound which has anticonvulsant properties. The roles which these drugs play as anticonvulsants before they are converted are not completely known. Most anticonvulsants are converted in the liver; however, acetazoleamide is excreted essentially unchanged in the urine.

The Evaluation of New Drugs

The clinical toxicity or undesired side effects of a drug include a large variety of reactions which may be divided into four general classes: (1) Overdosage, (2) exaggerated secondary effects, (3) hypersensitivity, and (4) "true toxicity." The side effects resulting from deliberate or accidental overdosage can be serious. Occasionally a patient may prove to be unusually susceptible to dosages which are normally considered within the therapeutic range. The second class of side effects includes those due to the secondary properties which are an inherent part of every drug. It is hoped that the secondary properties are of such a low order of activity that the side effects will not be evident at the therapeutic dose level. The third class of side effects, hypersensitivity, includes a variety of reactions due to sensitization of some patients with certain drugs such as penicillin. The fourth class includes side effects produced by the "true toxicity" which is a secondary attribute of the drug. This activity can be subtle or delayed, and thus may not be revealed in the relatively short-termed studies employed in the initial investigations.

Preclinical Investigations

Peck (1964), at a symposium on drug safety, outlined the preclinical investigations necessary to establish the safety of a new drug and to define its toxicologi-

cal attributes. These investigations include the single dose studies, and both short-term and long-term toxicity studies. A number of collateral observations and tests, consisting of physical examination, hematological, liver and kidney function tests, and extensive post portem examinations, may be included in the subacute and chronic toxicity experiments. In acute toxicity studies, a drug is administered to two or more species of animals, by different routes, in single doses which are large enough to be in the lethal range. Subacute and chronic toxicity studies, which usually are conducted in two or more species of animals, differ primarily in the duration of the treatment, the number of animals used at each dosage level, and the number of levels employed.

In addition to noting the therapeutic effect of the drug, the absorption, metabolism, and excretion of the drug are studied in the preclinical investigation. The effect on normal metabolism and any specific actions on tissue or organ systems are determined in the basic studies. Knowledge of the long-term effects is acquired through subacute and chronic administration of the drug to animals. Also, post portem studies should be conducted as an integral part of the subacute and chronic toxicity experiments. Furthermore, investigations should be carried out to determine the effect of the drug on the reproductive cycle or on fetal development. These studies should be designed to evaluate the drug's effect on fertility, implantation of the ovum, development of the embryo and fetus, resorption, abortion, delivery, number of live births, size of litters, teratogenesis, viability of the newborn, growth of the young, and quality of the mother's milk.

The results of adequate biochemical and metabolic studies, however, may permit the development of more meaningful experimental designs for toxicity studies. Thus, the safety of drugs may be determined more satisfactorily by an expansion of pharmacological and metabolic studies than by an extension of the toxicity studies. There may be certain compounds for which long-term toxicity studies will be necessary to evaluate their safety; however, in many instances shorter toxicity studies should be adequate.

Clinical Investigations

Kohlstaedt (1964), in his contribution to the symposium on drug safety, stated that the initial clinical trial is a crucial matter in the development of a new drug. The risk inherent in its first use in man, and the need to obtain a true evaluation of its actions before large sums of money are invested in materials, make it im-

perative that the initial trial be a well-controlled study. The investigation should be conducted by a physician who is trained in this form of clinical research, and performed in an environment that permits accurate observations. Years of effort in research and testing which may have preceded the first clinical trial will have been wasted if the first tests in man are not appraised accurately.

The preclinical data may indicate the nature of any hazard the drug might present in man. The possible hazards of the drug must be weighed against its beneficial effects on the patient directly, and the opportunity to add to the physician's armamentarium. Kohlstaedt points out that although the difference between the quantity of a drug that will kill half the animals (LD_{50}) and the amount that will give the desired effect in half of the animals (ED_{50}) is important, it is not enough on which to base the decision as to whether or not a new drug should be tried in man. It is generally accepted that a new drug should have been administered in large amounts (much more than the amount estimated as necessary to obtain the desired response) for at least 30 to 60 days, to two or more species of animals before the first dose is given to a human subject.

In March of 1953, new regulations issued by the Food and Drug Administration made it mandatory to submit to that agency a complete report on the nature of the drug, its composition and properties, the method of preparation, tests for quality control, and the results of all preclinical tests in animals as well as *in vitro* studies. The plan for the proposed clinical trial must be outlined and the investigator must sign a form indicating that he is aware of the new regulations and will abide by them. Also, his qualifications as an investigator must be on file with the sponsor of the program. Recent legislation and the accompanying regulations of the FDA have served to discourage physicians who were interested in the clinical testing of new drugs. As a result, competition is rapidly increasing for the services of competent investigators who have adequate research facilities.

There is a need for research units which provide the proper environment and personnel competent to conduct initial clinical trials. These units could be established in academic centers with large outpatient clinics that would provide a reservoir of patients and normal subjects for tests. In addition to a hospital ward, it is essential that the unit include laboratories for chemical and bacteriological tests.

If preclinical testing has been thorough and animals have been closely observed, a great deal of useful infor-

mation will be available for guidance in selecting the amount of the first dose to be given to man. Nevertheless, it is important to remember that it is never safe to extrapolate the dose from animal to man. If the difference between LD_{50} and ED_{50} is small, then the first dose in man should be very much less than would be estimated from experience in animals. After the quantity to be given is selected, the amount is administered to one patient. If no undesirable effects occur, the same amount is given to a second and then a third patient. Provided that there have been no untoward symptoms, the first subject then receives a larger dose, but the increment should be small. During an initial trial the cardinal principles for safety are to begin with a small dose, increase it gradually, and keep the patient under constant surveillance. This procedure is continued until the desired effect is obtained, until untoward symptoms occur, or until as much as 1 or 2 gm. have been given and no activity is noted. Larger amounts are seldom practical by the oral route of administration. When single doses have been shown to produce satisfactory responses in several subjects and the duration of effect has been determined, the same dose of the drug may then be given at regular intervals.

The elimination of bias is essential in all stages of clinical trial, but it is especially important in the early stages of evaluation. Kohlstaedt outlines the methods used to eliminate a biased experiment.

When sufficient data have been collected to establish that a drug is active in man, it is necessary to increase the amount given so that a "dose response" can be developed. The next step is a comparison with a known drug. Again, experimental design becomes very important. The patient will serve as his own control in the "crossover" type of study. Randomization must be planned, and such devices as the "Latin Square" are employed to be sure that the new drug is given prior to the control drug as many times as it is administered after the control substance. When patients with disease are used as subjects, a known drug is usually used for control, but when normal subjects are participating, the use of a placebo and double-blind techniques are essential.

It is always desirable to perform a battery of liver, kidney function, and hematological studies before beginning the initial clinical trial. These tests should be repeated at intervals after a dosage schedule has been established. The initial clinical trial is considered complete when dose response has been established and definite activity has been demonstrated. The entire procedure is usually finished within 30 days. The

second phase of clinical trial is then ready to be undertaken.

If the acute trials are encouraging, a limited number of patients can be subjected to continuous treatment for a period of 3 to 6 months under the direction of a single qualified clinical pharmacologist, preferably the investigator who carried out the short-term trial. The investigator will be less inclined to publish prematurely if he is not competing with others for priority. If severe toxicity does not occur in the small series, the long-term trial can be extended and additional investigators enlisted in the study. These various steps represent a routine sequence that has been recognized as good practice for many years.

Freis (1964) reviewed the problems of evaluation of toxicity evaluation in long-term clinical trials. He points out that if a new agent appears to be safe and effective after 3 or 4 months of treatment in a limited number of patients, a well-designed double-blind study should then be undertaken utilizing larger numbers of patients. The double-blind technique is valuable not only in evaluating the incidence of side reactions, but also in judging drug effectiveness.

The target organs affected by toxic drugs usually are the liver, kidneys, and bone marrow. Sensitivity reactions, such as dermatitis and arthritis, also are common. Routine laboratory procedures should be carried out before treatment and at regular intervals during treatment. The appearance of toxicity should not, in itself, be a reason for discarding a new drug since it may be sufficiently valuable therapeutically to justify a measure of risk.

Long-term evaluation of a new drug is more difficult than the assessment of acute effects. Short-term studies usually permit frequent and close observation of the patient, and medication is dispensed by professional personnel in a hospital or clinic. During long-term evaluation, the patient cannot be seen at frequent intervals. Faithful adherence to the prescribed schedule of medication depends on the reliability of the patient whose cooperation may be lost during a prolonged therapeutic trial. Ingestion of medications may then become sporadic or even nonexistent.

It is rarely possible for a single investigator to observe or recognize every toxic reaction or to judge the effectiveness of a new drug under all possible conditions.

To compensate for unpredictable variations which may lead to an inaccurate and too limited evaluation of a new drug, the scope of the study must be extended to include a number of investigators working in different localities. The final evaluation of the usefulness

of a new agent, however, will depend, for various reasons, on the judgment of clinical practice. A drug which is valuable in the hands of the expert may be too difficult for the physician in general practice to manage. A serious toxic reaction may occur so rarely or in such a limited portion of the total population that it may not become apparent prior to its release for general use.

A new therapeutic agent is said to be good or bad in comparison with presently available therapy. The standard of merit for a new drug is based on effectiveness plus ease of administration, minus toxicity, and tolerance. To determine the true value of a new drug, studies must be designed which provide an unbiased comparison with placebos or an established drug, or both. The number of defaulters must be minimal, and the patients treated should be of sufficient number and variety to form a representative sample of the population suffering from the particular disease being treated.

The ideal anticonvulsant should be capable of preventing an epileptic discharge, regardless of its pathological or neurochemical background. The drug should develop the stability of cerebral tissue to withstand the normal provoking factors and be effective in all locations in the nervous system. It should be non-sedative, well tolerated, and devoid of untoward effects on vital organs and functions. When taken orally, its effect should be of long duration, in order to maintain a fairly stable level in the body. It is no secret that such a compound does not exist, and thus the search for new compounds must continue.

When a new drug is prepared with anticonvulsant properties, it is subjected to a series of tests designed to measure its efficiency and toxicity. The anticonvulsant properties are tested by measuring the ability of the drug to raise the threshold for minimal (clonic) seizures or to modify the pattern of maximal (tonic-clonic) seizures in animals. (Swinyard, 1949). A second method is to test the ability of the drug to protect the animal from seizures produced by convulsant drugs such as pentylenetetrazol (metrazol). A third method, although less popular, is utilizing mice subject to audiogenic seizures. A fourth method is to produce epileptogenic lesions in animals, and to test the ability of the anticonvulsant to prevent seizures and suppress abnormal electrical activity in the EEG.

If by these tests, the compound appears to have good anticonvulsant activity, it is then tested in humans. There are different stages of testing, the object being to determine as quickly as possible whether the drug has good potential. It is desirable to determine early

if a drug, for one reason or another will not be useful, and thus avoid long, expensive, and ultimately useless trials.

After the initial toxicity studies are completed, an effective dosage is determined. This is done by standard methods of gradually increasing the dose until sedative or toxic effects appear, and then by establishing a dose somewhat less than this. At the same time, blood and urine are examined for any signs of immediate toxicity.

When a dose is established, testing can advance to patients with epilepsy. Gruber and his colleagues (1962) have developed a method of screening prospective drugs efficiently and quickly. Working with institutionalized epileptic patients having frequent seizures, usually due to an organic lesion of the brain, the effectiveness of the new drug can be easily and accurately compared to the effectiveness of known anticonvulsants, such as diphenylhydantoin, phenobarbital, primidone, etc. This method, however, does not appear to be a good one for screening drugs designed to control petit mal seizures. Furthermore, the stage of chemical and physiological development of the region of the brain from which the seizure originates may be a more important factor in this method of screening than the type of seizure.

Compounds also have been tested in psychiatric patients by measuring the ability of the drug to inhibit convulsions induced by electric shock given for therapeutic purposes. This method has many obvious disadvantages.

If the compound is shown to have good anticonvulsant properties, then groups of patients are tested under controlled conditions to determine further the consistency and reliability of the effects, and to check for slowly developing toxicity or other side effects. If the drug passes these tests, then it can be released for double-blind testing under conditions such as those used by Forster and his collaborators.

Mode of Action

To understand the action of drugs on the central nervous system it is important to understand its functional organization. There is a phylogenetically old diffusely projecting system and a phylogenetically new discretely projecting system. The organization of function and behavior is more generalized in the older structures; thus, the spinal cord, the oldest structure, is concerned with general behavior patterns, such as walking and gross reflex patterns. The brain stem, containing the reticular substance, is the next step in

phylogeny, and mediates the coordination of generalized functions such as arousal, attention, orientation, and integration of movement. The archicortex and diencephalon, which are the next to develop phylogenetically, integrate basic survival behavior, such as flight-fight, sexual behavior and consumatory activity. The neocortex is the most recent phylogenetic development and it coordinates the highly specialized functions, such as discrimination, object identification, and decisionmaking. (Siminoff, 1963).

At the various levels, each system makes two types of synaptic connections with the efferent portion of the reflex arc. The first is the axosomatic ending which acts primarily to pass the activity along the reflex arc. The other, the axodendritic ending, acts, by long-term depolarization to modulate the activity of the effector neurone. Each level relays activity up and down the central nervous system and there is considerable interplay between levels. As one ascends, the axodendritic endings become more numerous and the modulating system becomes more important.

Drugs, depressing axodendritic endings, block generalized functions such as arousal, wakefulness, and orientation, and thereby produce unconsciousness. At therapeutic doses which do not affect transmission through the reflex pathways, these drugs, such as anaesthetics and barbiturates, depress neocortical structures. The degree of depression depends on the type and dose of the drug. The anticonvulsants block only the abnormal spread of activity through the axodendritic networks of the neocortex. It is probable that a drug such as diphenylhydantoin exerts its greatest effect on the neocortex and prevents the spread of focal seizures, whereas trimethadione has a greater effect on the phylogenetically older diencephalic structures. This would explain their abilities to control different types of seizures.

The work of Esplin (1957) suggests that anticonvulsant drugs influence neuronal processes which underlie transmission at various sites. Esplin and Laffan (1957) showed that the effects of diphenylhydantoin and trimethadione act on the stellate ganglion in the identical manners in which they act on the spinal cord. This may also explain the ability of diphenylhydantoin to affect trigeminal neuralgia.

Woodbury and Esplin (1959) suggest that trimethadione exerts its anticonvulsant action by reducing transmission during repetitive discharge; diphenylhydantoin decreases spread of seizure discharge by depressing posttetanic potentiation (P.T.P.); and acetazoleamide reduces the intensity of seizure discharge by

depressing certain pathways in which the safety factor for transmission is low.

Diphenylhydantoin has been shown to enhance the activity of the neuronal sodium pump and increase the ratio of extracellular to intracellular sodium concentration. This probably increases the membrane potential which, in turn, would be expected to reduce the amplitude of the positive after-potential (Woodbury and Esplin, 1960). Acetazoleamide also acts by increasing the sodium ratio but in a somewhat different manner. It inhibits carbonic anhydrase, and reduces the rate at which H_2CO_3 is dehydrated. The increased H_2CO_3 within the neurone results in a lower steady-state concentration of sodium within the neurone and a higher gradient of sodium across the cell membrane.

Tuttle and Preston (1963) suggest that there is an apparent relationship between the complexity of the neural pathway and the demonstration of an effect of diphenylhydantoin. They felt that interneurons may be of considerable importance in explaining the actions of the drug. Any condition which modifies the repetitive activity of the interneurone (Frank and Fuortes, 1956) would have a marked effect on the level of background facilitation and inhibition in motoneurone pools. There is evidence that diphenylhydantoin is particularly effective, not only in depressing repetitive discharge but also in depressing the response of nervous tissue to repetitive stimulation (Korey, 1951; Esplin, 1957; Morrell, et al., 1958). Tuttle and Preston's work suggests that diphenylhydantoin depresses interneuronal activity and has a generalized depressing influence on both suprasegmental facilitatory and inhibitory pathways. The latter is affected quantitatively to a greater extent.

Those working in the field are the first to point out the gaps in our knowledge of the actions of anticonvulsants. They are acutely aware of the need for more complete knowledge of the functions of neurones, including their axons, dendrites, and synapses. A great deal of excellent research has been conducted which has yielded isolated information on the electrical activity and chemistry of the neurone. It seems clear that when all the pieces of this puzzle are available, many factors will be found to contribute to a seizure, and anticonvulsant drugs will be shown to operate at different levels.

Other Factors Contributing to Action of Anticonvulsants

Whether a discharge will spread further in the neuronal network of the nervous system depends on

the intensity of the original stimulus, the organization of excitatory and inhibitory synaptic junctions in the network, and the state of irritability of the individual neurones. It is the latter that is of particular concern in considering the possible action of anticonvulsant medication.

Toman and Goodman (1947) showed that an important factor in determining seizure thresholds is the concentration of electrolytes in the extracellular fluid and the intracellular fluid volume, which is undoubtedly related to sodium ratio. At the same time they showed that seizure threshold is reduced when body temperature is lowered, and increased when body temperature is increased.

Electrical stimulation of the brain causing a convulsion has been shown by Richter and Crossland (1949) to be followed by a rapid decrease of the acetylcholine content of the brain to half the normal level. This is attributable primarily to a rapid release of the acetylcholine bound in the nerve endings, followed by rapid breakdown of the free acetylcholine by cholinesterase, and the escape of parts of the free acetylcholine into the bloodstream and cerebrospinal fluid. Convulsions induced with pentylenetetrazol also cause a fall in acetylcholine content of the brain (Stone, 1957).

It is well known that acute anoxia can cause convulsions and reduce the threshold in animals for seizures induced electrically by strychnine or by other convulsant drugs. On the other hand, severe anoxia can reverse this effect (Richter, 1960). Moderate anoxia increases the irritability of the brain, and severe anoxia reduces it. It has been suggested that acute anoxia causes convulsions by releasing lower centers from cortical inhibition, while severe anoxia inhibits convulsions by depressing the activity of the lower centers as well. It is clear that in order to have a convulsion an adequate oxygen level is necessary. It should also be noted that the oxygen consumption of the brain varies almost linearly with the temperature, and the effects of anoxia are reduced under hypothermia (Schneider, 1957). Richter (1960) points out that the effects of temperature on seizure activity are complex; they depend in part on the release of lower centers, through impairment of cortical control, and partly on the combination of an increased oxygen demand of the neuron to a rising temperature and the increased oxygen requirement for convulsive activity.

Age is also an important factor in seizure threshold. Seizures are 10 times more common in the infant than the adult. As an infant grows, the pattern of attacks changes. Many investigators have demonstrated that

the changes are related to the physical and chemical maturation of the brain. For example, Purpura, et al. (1959), have shown that inhibitory synaptic activity is relatively underdeveloped in the immature animal. It has also been shown that as the brain matures, there is an increase in gamma-aminobutyric acid. Changes in enzymes in the brain associated with age also influence seizures. Millichap (1957) observed a relationship between the susceptibility to maximal (tonic) seizures and the level of carbonic anhydrase activity in the brain of rats and guinea pigs. He concluded that brain carbonic anhydrase is of functional significance in the general spread of the seizure discharge and in the production of a maximal convulsion. Seizure susceptibility is reduced by carbonic anhydrase inhibitors such as acetazoleamide. In addition to changes in enzymes, there are significant changes with age in the acetylcholine content of the brain (Richter and Crossland, 1949) and in the development of the blood brain barrier.

It is well known that the hormones from endocrine glands have an ability to affect the nervous system. Severe adrenal insufficiency in man is accompanied by a slowing of the electroencephalogram. This is restored with the administration of cortisone. Mental changes associated with steroid therapy are common. Torda and Wolff (1952) and Torda (1953) showed that a single administration of ACTH causes an increase in acetylcholine and ammonia content of the brain. ACTH may precipitate seizures in patients with a previous history of seizures (Dorfman, et al., 1951; Soffer, et al., 1950). It has been established that certain steroids from the adrenal cortex in part regulate salt and water metabolism and protein, fat and carbohydrate metabolism. Shifts in sodium and potassium balance associated with changing quantities of adrenal hormones are important in the regulation of excitability of nerves and synaptic conduction.

Hodgkin and Katz (1949) showed that the resting nerve membrane is more permeable to potassium than sodium. However, the active, conducting membrane is more permeable to sodium than potassium. They give evidence to show that the action potential is due primarily to the movement of sodium. The nerve message, itself, is subject to modification by both sodium and potassium gradients across the nerve membrane. This phenomenon suggests the importance of homeostatic regulation of these cations for normal function of the nervous system, including synaptic conduction.

The adrenocortical hormones act to restore normal brain excitability regardless of the direction in which

the deviation lies. Woodbury, Timiras, and Vernadakis (1957) showed that the primary effects of deoxycorticosterone acetate (DCA) and 17-hydroxycorticosterone acetate (Cortisol) on brain activity are related to their influences on active sodium transport in the brain. DCA, which acts like diphenylhydantoin, stimulates the active transport of Na from cells which, in turn, decreases brain excitability. A single dose of DCA causes an increase in electroshock seizure threshold (E.S.T.), an increase in brain concentration of glutamic and aspartic acids, and a decrease in brain concentration of glutamine and asparagine. In contrast, a single dose of Cortisol causes a decrease in E.S.T., an inhibition of active Na transport, and an increase in intracellular brain Na concentration and brain excitability.

Woodbury, et al., (1957) were also able to show that the recovery process, which restores normal function following excitation such as seizure, requires energy; this is intimately associated with changes in carbohydrate metabolism, particularly blood glucose. Glycogen stores in the brain are small, and the chief energy substrate is blood glucose. Any procedure or substance which influences blood sugar level will effect the recovery process, provided the agent does not also interfere with the utilization of glucose by the brain. Woodbury's group was able to correlate the blood sugar level with the duration of postictal depression which follows maximal electroshock seizures in rats in their studies, but recovery from postictal depression was not related to brain excitability or brain electrolyte metabolism.

They were also able to show that diphenylhydantoin activates the pituitary-adrenal and the pituitary-thyroid systems, and that the hormones released by such activation tend to counteract the anticonvulsant effect of the drug. Thus, they were able to demonstrate further that adrenocortical hormones tend to restore normal brain activity, regardless of the direction in which the deviation lies.

The whole story on the role of the influence of adrenocortical hormones on brain function and metabolism is not completely understood. It is clear, from the manner in which these hormones influence infantile myoclonic seizures, that their role is an important one, but further studies related particularly to the developing brain are needed.

The Anticonvulsant Treatment

The anticonvulsant compounds are the backbone of treatment of the epilepsies, and the prevention of con-

vulsions. The decision of when to start a patient on medication is an individual one. It will depend on the circumstances and the results of the investigation. A child who has had one seizure associated with a febrile illness, and who has a normal electroencephalogram, may be observed instead of administering immediate medication. On the other hand, if there is a positive family history, or some positive signs of postictal paralysis, then drug therapy should be started. In an older person, a single seizure may herald a tumor. Complete investigation is indicated, and prophylactic anticonvulsants are a wise precaution.

There are some 15 to 20 anticonvulsants which have proven useful; however, the majority of patients are treated with some combination of phenobarbital, diphenylhydantoin, primidone, and trimethadione. Probably 75-80 percent of patients are well controlled with these drugs alone.

Treatment is generally started with one drug, and the dosage is slowly increased until the seizures are controlled or toxic symptoms develop. If the patient is admitted in status epilepticus or has had a prolonged seizure, it is well to start him on immediate large doses of intramuscular phenobarbital, but as soon as possible oral phenobarbital and diphenylhydantoin should be substituted. As the seizure comes under control, the phenobarbital can be reduced. In such a case, one is likely to continue with both drugs and slowly regulate them. Most patients require a combination of drugs. The time the drugs are taken is also of some importance. It is easier and more convenient to take them at mealtimes and at bedtime. Ordering medication at odd hours is to be discouraged since it is too easy for the patient to forget. It is probable that drugs which are absorbed and excrete slowly, and which do not show a great fluctuation in blood level, could be given twice a day; however, the general tendency is to order them with meals, and to add a drug with a greater sedative effect such as phenobarbital, at bedtime.

Buchthal, Svensmark, and Schiller (1960) studied serum levels of diphenylhydantoin and correlated them with the pharmacological effect. Clinical improvement in patients with grand mal epilepsy treated orally required a serum level of 10 μ g/ml-20 μ g/ml of the drug which corresponded to a dosage of 4-7 mgm/kg of body weight, and required 6 to 10 days of oral administration. It took some time to reach a steady concentration. With a daily oral dose of 5 mg/kg body weight, it took about 1 week for the serum concentration to reach a maximum. The same serum level was obtained whether the total daily dose was administered

in one or in three doses. To maintain a stable serum concentration, administration of the drug at 12-hour intervals is preferable to once a day. They showed that the fall in 12 hours is insignificant, so that three or four daily doses are probably unnecessary.

Buchthal and his colleagues were also able to show that pronounced side effects from diphenylhydantoin did not occur with serum levels below 30 $\mu\text{g}/\text{ml}$, but were present in half the patients with serum levels of 30–60 $\mu\text{g}/\text{ml}$.

Unless there is a toxic or allergic reaction to a drug, it should not be discarded until proven to be of no benefit in maximal tolerable doses. The tendency to switch from one drug to another, before the first one has been tested adequately, should be avoided.

The importance of taking medication regularly and the dangers of precipitating status epilepticus by sudden withdrawals should be stressed to the patient or his parents.

The decision of when to stop medication is a difficult one. As a general rule medication should be continued for 1 to 3 years after the last seizure. Some older patients who have had one or two occasional seizures after having a long free period, and stopping medication, probably should continue medication indefinitely. In some of the younger children who are taking a toxic drug, especially those with petit mal, one may wish to try discontinuing medication even before a seizure-free year is passed. The length of time the child had the attacks and the EEG help in making the decision. In patients approaching puberty, it is better to continue medication until puberty is completed.

The possibility of the development of blood dyscrasia, hepatitis, or nephrosis should be considered in patients receiving trimethadione, paramethadione, mesantoin, phenurone, and ethyl-methyl-succinimide. To detect and prevent serious suppression of hemopoiesis, white blood counts should be made before starting treatment and again every 2 weeks until maintenance dosage is established. Such counts should be repeated monthly for 1 year, and every 3 months for the balance of treatment. If neutrophils drop to between 2,500 and 1,600 per cu. mm., counts should be made every 2 weeks, and medication should be stopped if the count goes below 1,600.

The following anticonvulsants are those most commonly used in the treatment of epilepsy. Detailed descriptions of their structure and pharmacology can be found elsewhere (Goodman and Gilman, 1955; Lennox, 1960; Gunn, Gogerty, and Wolf, 1961).

Many other drugs have been discovered and tested clinically, but for reasons of their sedative effects, tox-

icity, or their poor abilities to control seizures, their use has been discontinued. Some reached the stage of being assigned names; others were merely given numbers.

Some of the most commonly used anticonvulsants are:

- Celontin (methsuccinimide).
- Desoxyn (methamphetamine hydrochloride).
- Dexedrine (dextroamphetamine).
- Diamox (acetazoleamide).
- Dilantin (diphenylhydantoin).
- Elipten (aminoglutethimide).
- Gemonil (metharbital).
- Librium (chlordiazepoxide).
- Mebaral (mephobarbital).
- Meprobamate.
- Mesantoin (3-methyl-5, 5-phenyl-ethyl-hydantoin).
- Milontin (methylphenylsuccinimide).
- Mysoline (primidone).
- Paradione (paramethadione).
- Paraldehyde.
- Phenobarbital (ethyl-phenyl-barbituric acid).
- Peganone (ethotoin).
- Phenurone (phenacemide).
- Tridione (trimethadione).
- Zarontin (ethyl-methyl-succinimide).

ANTICONVULSANTS CURRENTLY AVAILABLE

Celontin: (Methsuccinimide)

Indications: May be effective in mixed seizures, automatism, akinetic or myoclonic seizures.

Dosage:

15–20 mg per kg per day.

600 mgm per day for adults.

Preparations: 300 mg capsules (Parke Davis).

Toxicity: Drowsiness, ataxia, rash.

Remarks: Worthwhile to try this drug if others fail.

Desoxyn: (Methamphetamine hydrochloride)

Indications: Absence and akinetic attacks. Counteracts sleepiness and effective in narcolepsy.

Dosage: 2.5 mgm–10 mgm per day.

Preparations:

2.5 mgm tablet (Abbott).

5 mgm tablet.

5, 10, 15 mgm gradument.

2–5 mgm tsp. of elixir.

Toxicity: Anorexia, irritability, insomnia.

Remarks: May be used in place of Dexedrine.

Dexedrine: (Dextroamphetamine)

Indication: See Desoxyn.

Dosage:

0.25 to 0.75 mgm per kg. per day.

10 mgm 3 to 5 times daily for adults.

Preparations: 5 mgm tablets (Smith Kline and French).

Toxicity: See Desoxyn.

Remarks: This drug is sometimes effective when other drugs fail. It may be helpful in postencephalitic seizures or behavior disorders. It may also be used in combination with other drugs to counteract the sedative effect.

Diamox: (Acetazolamide)

Indications: May be tried in all types of seizures. More effective in minor seizures in children.

Dosage:

15 to 90 mg. per kg. per day.

250 mgm, 3 to 6 times a day.

Preparations:

250 mg. tablets (Lederle).

500 mgm amp. i.v. or i.m.

Toxicity: Loss of appetite, acidosis, numbness.

Remarks: This drug is more likely to be effective in children in attacks precipitated by hyperventilation, and in women who have seizures in the premenstrual period. It is used to supplement other medication.

Dilantin: (Diphenylhydantoin)

Indications: Any seizure with the exception of absence, myoclonic or akinetic attacks.

Dosage:

3-8 mgm per kg. per day.

100 mgm 3 times a day in adults.

Preparations:

50 mgm infatabs (Parke-Davis).

30 and 100 mgm capsules.

100 mgm per tsp. suspension.

100 mgm delayed action capsule.

It is also prepared in combination with other drugs.

Phelantin capsules:

diphenylhydantoin 100 mgm.

phenobarbital 30 mgm.

desoxyephedrine HCL 2.5 mgm.

Mebroin (Winthrop) tablets:

diphenylhydantoin.

60 mgm.

mebarol 90 mgm.

Toxicity: Gingival hypertrophy, nystagmus, ataxia, diplopia, rash, tremor, nausea and vomiting, hirsutism.

Remarks: A very effective drug used singly or in combination; usually phenobarbital. A rash may appear soon after it is started, ataxia is seen with overdosage, and gum hypertrophy and hirsutism after prolonged usage. It is a safe drug.

Elipten: (Aminoglutethimide)

Indications: Useful as adjuvant.

Dosage: 750 mgm per day in adults (Ciba).

Preparations: 125 and 250 mg. tablet.

Toxicity: Drowsiness, irritability.

Remarks: Has not proven to be too effective. It is relatively new and still requires further trial.

Gemonil: (Metharbital)

Indications: Myoclonic seizures, or seizures due to organic brain damage.

Dosage:

5 to 15 mg. per kg. per day.

100 to 300 mgm per day in adults.

Preparations: 100 mgm tablet (Abbott).

Toxicity: Drowsiness, irritability, rash.

Remarks: Is not as satisfactory as other drugs.

Librium: (Chlordiazepoxide)

Indications: May be effective in mixed types of seizures. Useful in patients with behavior disorders.

Dosage: 15 mg. to 60 mg. per day.

Preparations: 5 mg., 10 mg. and 25 mg. capsules (Roche).

Toxicity: Drowsiness.

Remarks: Reports have been conflicting as to merits as anticonvulsant. Useful in behavior disorders. (Livingston et al., 1961, and Watson, et al., 1964).

Mebaral: (Mephobarbital)

Indications: Same as phenobarbital.

Dosage:

2-8 mg. per kg. per day.

100 mgm 1 to 6 times a day (adult).

Preparations: 30, 50, 100 mgm tablets (Winthrop).

In combination with diphenylhydantoin (see Dilantin).

Toxicity: Drowsiness, irritability.

Remarks: This drug metabolized to phenobarbital and anticonvulsant activity has been attributed to this.

Meprobamate:

Indications: Absence attacks, convulsive equivalents occasionally in myoclonic seizures.

Dosage:

20-40 mg. per kg. per day.
400 mgm 3 to 5 times a day in adults.

Preparation: 200-400 mgm tablets (Equanil—Wyth).
(Miltown—Ayerst).

Toxicity: Drowsiness.

Remarks: Not very effective as an anticonvulsant, but useful to control hyperactive behavior.

Mesantoin: (3 methyl-5, 5-phenyl-ethyl-hydantoin)

Indications: Same as diphenylhydantoin.

Dosage: 100 mgm 3 times a day for adults.

Preparations: 100 mg. tablet—(Sandoz).

Toxicity: Rash, fever, leukopenia and agranulocytosis, ataxia.

Remarks: to detect and prevent serious suppression of hemopoiesis, white cell counts should be made before starting treatment and every two weeks until maintenance dosage is established. Thereafter, monthly for one year, and every three months for the balance of treatment. If neutrophils drop to between 2500 and 1600/cu.mm. counts should be made every two weeks. Stop medication if count drops to 1600. The patient or parents should be warned. No patient should be given mesantoin if he has had it before and stopped. Hypertrophy of the gums will occur with this drug, so it should not be substituted for diphenylhydantoin for this reason. This is a good anticonvulsant, but the fear of fatal agranulocytosis has limited its use.

Milontin: (Methylphenylsuccinimide)

Indications: Absence, akinetic, and myoclonic seizures.

Dosage:

20-40 mg. per kg. per day.
0.5 gm. 3 times a day.

Preparations:

0.5 gm. capsules (Parke Davis).
250 mg. 1 tsp. suspension.

Toxicity: Drowsiness, headache, slightly nephrotoxic.

Remarks: May be useful when other medications fail or in combination.

Mysoline: (Primidone)

Indications: Generalized and focal seizures and automatism.

Dosage:

12 to 25 mg. per kg. per day.
250 mgm 3 to 6 times daily.

Preparations:

250 mgm tablets (Ayerst).
50 mgm tablets.
250 mgm per tsp. suspension.
125 mgm flavored tablet (in Canada).

Toxicity: Drowsiness, ataxia, anorexia, irritability vertigo, nausea, vomiting, rash.

Remarks: This drug must be started slowly. It is safe, and has good anticonvulsant properties. It metabolized to phenobarbital, but is felt to have anticonvulsant properties of its own. It may be used simply or in combination.

Paraldione: (Paramethadione)

Indications: Absence, akinetic and myoclonic attacks.

Dosage:

20-50 mg. per kg. per day.
900 to 1800 mgm per day for older child.

Preparations:

150 mgm capsules.
300 mg. capsules.
300 mgm/cc elixir (drops).

Toxicity: Same as trimethadione.

Remarks: Said to be less effective and less toxic than trimethadione. Same precautions should be taken as with mesantoin and trimethadione.

Paraldehyde:

Indications: Useful in status epilepticus.

Dosage: 5-15 cc per rectum. May be mixed with olive or mineral oil.

Preparations: Bottles and 5 cc ampoules.

Toxicity: Can cause muscle necrosis and i.m. use should be avoided.

Phenobarbital. (Ethyl-phenyl-barbituric acid)

Indications: Any type of seizure.

Dosage:

1-5 mg. per kg. per day.
7-15 mgm 3 times a day in infants.
30 mg. 2-3 times a day in children.
60 mg. 1-3 times a day in adults.

Preparations:

15, 30, 60, 100 mgm tablets.
15 mg. per tsp.—elixir.
60, 120 mg. ampoules for i.v. or i.m. use.

Toxicity: Drowsiness, hyperirritability in children, ataxia.

Remarks: Apart from bromides, this is really the first anticonvulsant discovered. It is still one of the safest, and the best, but is limited by its sedative effect, and its ability to produce behavior disturbances in children.

Peganone: (Ethotoin)

Indications: Same as diphenylhydantoin.

Dosage:

250 mg. 3 times a day.

500 mg. 2 times a day.

Preparations: 250 and 500 mgm tablets (Abbott).

Toxicity: Drowsiness, ataxia, diplopia, tremor, rash.

Remarks: Worthwhile trying if other preparations fail.

Phenurone: (Phenacemide)

Indications: In seizures originating in the temporal lobe, when other medications fail.

Dosage:

20-35 mg. per kg. per day.

500 mgm 2-4 times a day in adults.

Preparations: 0.5 gm. tablets (Abbott).

Toxicity: Rash, anorexia, nausea, vomiting, hepatitis, personality change and blood dyscrasia.

Remarks: Same precautions should be taken as with Mesantoin plus Urobilinogen tests monthly. The incidence of hepatitis is high which has limited its use.

Tridione: (Trimethadione)

Indications: Absence, akinetic and myoclonic attacks.

Dosage: 20-50 mg. per kg. per day.

Preparations:

300 mgm capsules (Abbott).

150 mgm tablets.

150 mgm per tsp. solution.

Toxicity: Rash, leukopenia, agranulocytosis, photophobia, irritability and nephrosis.

Remarks: Same precautions should be taken to prevent blood dyscrasia as for Mesantoin. Monthly urinalysis should also be done for six months, and the child watched for sudden increase in weight or swelling of the ankles.

Zarontin: (Ethyl-methyl-succinimide)

Indications: absence, akinetic and myoclonic attacks.

Dosage: 250-500 mg. 3 times a day.

Preparations: 250 mg. capsules (Parke Davis).

Toxicity: Drowsiness, nausea, vomiting.

Remarks: Has proven to be useful in minor types of attacks in children.

Toxic Effects of Anticonvulsants

The acute psychosis and severe repulsive pustules seen on the skin of patients taking prolonged overdosage of bromides made the advent of phenobarbital a welcome event. However, many physicians today still resort to bromides when all other measures fail. Phenobarbital proved to be an excellent anticonvulsant, and still is probably the most useful and safest known. Many patients prefer not to take it during the day because of its sedative effect, and parents welcome a change from phenobarbital since it tends to produce hyperactivity and behavior disorders in children. Overdosage will cause ataxia, but this is easily remedied by adjusting the dose. There is considerable danger of precipitating status epilepticus by sudden withdrawal of phenobarbital in a patient who has been receiving it for a long time. If the drug is to be stopped, it should be done slowly. Severe and fatal exfoliative dermatitis has been reported (Welton, 1950, and Snedden and Leishman, 1952), but this is unusual considering the tons of phenobarbital consumed annually. Care should be taken to keep the drug from the reach of young children. The most common cause of death from phenobarbital is a suicidal overdose.

The most serious toxic effect from the newer anticonvulsants is suppression of bone marrow activity leading to blood dyscrasias such as aplastic anemia with pancytopenia, thrombocytopenia, leukopenia, or agranulocytosis, erythroid hypoplasia with pancytopenia, hemolytic anemia and megaloblastic anemia (Best, 1963). Such disorders have been reported following the prolonged use of acetazoleamide, diphenylhydantoin, Mesantoin, primidone, trimethadione, paramethadione, phenacemide, mephobarbital, ethotoin, and ethyl-methyl-succinimide. The subject has been well reviewed by Robins (1962) and Long, Childress, and Bond (1963), Benians and Hunter (1957), Mann and Habenicht (1962), Robins (1962), and Underwood (1956). The exact mechanisms of suppression of hemopoiesis is not known. The majority of cases have developed secondary to the administration of methylphenylethyldantoin (Mesantoin) and trimethadione, but it is suggested that most of the anticonvulsant drugs could have potential toxic effects on bone marrow. Treatment has varied from simple withdrawal of the anticonvulsant medication

to simultaneous treatment with vitamin B₁₂, folic acid, and other hematinic agents.

Other undesirable, but not fatal, side effects have been reported with diphenylhydantoin and methylphenylethylhydantoin (Mesantoin). These include hypertrophy of the gums, (Francis and Melville, 1958), hirsutism, lymphadenopathy simulating Hodgkin's disease (Doyle and Hellstrom, 1956), and a syndrome simulating lymphosarcoma (Saltzstein and Ackerman, 1959; and Rosenfelt, 1961).

Robinow (1963) suggests that some of the untoward reactions to diphenylhydantoin and related anticonvulsant drugs present themselves as allergic or hypersensitive disorders. They may resemble serum sickness; they can produce widespread lymphatic hyperplasia, featuring lymphadenopathy and hepatosplenomegaly; or they may mimic as erythema multiforme, periarteritis, nodosa, or lupus erythematosus. Robinow also suggests that symptoms can be controlled with corticosteroids or, more satisfactorily, by a combination of small doses of corticosteroids with small doses of 6-mercaptopurine (also Jacobs, 1963).

Gingival hyperplasia is a common complication of prolonged diphenylhydantoin or Mesantoin therapy. The problem has been carefully reviewed by Francis and Melville (1958). The clinical picture is described well by Gardner and his colleagues (1962). The actual cause is not known. The excretion of dilantin, unchanged, in the saliva is probably a significant factor. Mild cases of gingival hyperplasia can be treated by changing to a different drug. In severe cases, gingivectomy makes a remarkable change in the patient's appearance and comfort.

The use of phenacemide is limited because of its known effect on the liver. Craddock (1955) points out that, of the commonly used anticonvulsants, phenacemide is the only one proved to cause severe toxic effects on the normal human liver. He suggests that the drug should be used only as a last resort in "psychomotor seizures" if other drugs, such as Mesantoin, fail.

Toxic effects by anticonvulsants, particularly trimethadione and paramethadione, have been reported on the kidney. (Wren and Nutt, 1953; Finkel and Israels, 1959; Barnett, et al., 1948; Denhoff and Lauffer, 1950). The nephrotic syndrome included edema, albuminuria, and decreased plasma albumin. The diagnosis is easy with examination of the urine, but parents should be advised to watch for swelling of the ankles or sudden unexplained increase in weight. The condition has been known to recur. So the offending drug should not be used again. Treatment

is withdrawal of the anticonvulsant and corticosteroids.

There are other undesirable side effects of anticonvulsants such as dizziness, photophobia, drowsiness, and rashes which occur usually with the initiation of treatment. Often they can be controlled by starting with small doses and gradually increasing until a therapeutic level is reached.

Other Drugs and Hormones

Tranquilizers

Variable reports have been made on the value of such drugs as reserpine, phenothiazines (chlorpromazine, promazine, compazine, trilafon, pacatal), and other ataractic drugs in epilepsy. Some authors report increased incidence and others a decreased incidence of seizures. It is the general experience that they are not very effective as anticonvulsants, but in some instances are useful to control associated behavior disorders (Gunn, Gogerty, and Wolf, 1961). Initial reports on sulthiame (ospolot) suggest that it has good anticonvulsant properties, but the side effects limit its use. (Sutherland and Bowman 1963; Griffiths and Sylvester, 1964).

Good results have been reported with the use of Tegretal (G 32833); side effects were rare, and it is said to have a remarkable effect on personality and behavior (Lorge 1963).

ACTH and Cortisone

Adrenocorticotrophic hormone (ACTH) and cortisone have proven to be useful in the treatment of myoclonic seizures of infancy and occasionally in petit mal seizures. The effectiveness seems to be related to the age of the child, the degree of maturation of the brain, and the type of seizure. Children in the younger age group, regardless of the pathology—whether phenylketonuria, inclusion body encephalitis or cause unknown, have responded to such treatment and seizures have been controlled. All authors emphasize that this type of treatment does not have any effect on the mental retardation associated with these disorders. At first, the hormones were given in myoclonic epilepsy after anticonvulsants had been tried. Many physicians now start the hormones at once in an attempt to control the attacks and prevent further cerebral deterioration in those children who do not have a progressive degenerative disease. Frequently, the seizures do not stop and anticonvulsants are added. It is difficult to assess the effect of therapy since this type of attack tends to stop spontaneously as the child matures (Bray,

et al., 1961; Martinez-Lage, et al., 1962; Stamps, et al., 1959).

Millichap and Bickford (1962) described 21 patients with infantile spasms and hypsarrhythmia treated with ACTH or cortisone, or both. The ACTH was given by intramuscular injection in a dose of 20 units daily for an average of 5½ weeks. The dose of cortisone was gradually reduced from 3 mg. to 1 mg. per lb. body weight during a period lasting for an average of 6 weeks. The frequency of seizures was reduced in 52 percent of the cases and the electroencephalogram became normal, or was improved, in 44 percent. This improvement seemed to be unrelated to the causation but was far more often seen in babies under 1 year than in older children. The longer the interval between the onset of the seizures and the start of treatment, the less was the likelihood of a favorable response.

Matthes and Mallmann-Muhlberger (1963) treated 70 children suffering from massive spasms with ACTH or cortisone and followed them for 1 to 3 years. A therapeutic response was obtained in 74 percent of the patients treated with hormones. This was better than in the control group treated with anticonvulsants. Although the steroids seemed to produce an earlier reversal of any pathological processes, however, they apparently had little effect on the ultimate prognosis.

These and other recent reports confirm the opinion that the hormone treatment of massive spasms has a beneficial effect on both the incidence of the seizures and the EEG abnormalities, but the chances of preventing mental deficiency are poor. This may not be surprising in a group of such varied causation, where the clinical and EEG findings seem to be related more to the patient's age than to any other factor. If brain damage is preventable by treatment with steroids, as, for example, in seizures due to encephalomyelitis following inoculation, early treatment then becomes a matter of great urgency. If the clinical picture is associated with undoubted mental deficiency or neurological disease before the onset of the seizures, it would seem reasonable to try anticonvulsants first, and resort to steroids only if the anticonvulsants fail. The sudden onset of massive spasms in an otherwise healthy baby should be considered and treated as an emergency.

Procaine and Lidocain (Xylocaine)

Experimentally, French, et al., (1957) have shown that procaine given intravenously is capable of preventing seizures. Clinically, lidocaine has been found to be effective in aborting status epilepticus and some

focal seizures; however, its use is limited (Bohn, et al., 1959).

Quinacrine (Atabrine, Mepacrine)

Reports have appeared in the literature on the favorable use of quinacrine (Evans, 1962 and Sibley, et al., 1962) and chloroquine (aralen) (Vasquez, et al., 1959) in the treatment of children with resistant petit mal. The daily dose of quinacrine recommended is 50 to 100 mgm daily. With this, the skin becomes yellow and the eyes may also be stained. Apart from the staining of the skin, however, the drug has a low toxicity in the dose range employed and should be useful in some cases with resistant petit mal seizures.

Dietary Treatment

In the Hippocratic collection of medical writings it is suggested that epilepsy be treated, not by magic but by diet and drugs. From that time until the present, diet has played a role in the treatment of epilepsy, even though, for the most part, there was little rationale. Because of the noted effect of fasting on epilepsy, Wilder (1921) suggested that ketone bodies, produced during starvation, might be anticonvulsant, and he proceeded to develop a diet which would produce ketosis. Since then, others have used this ketogenic diet in certain types of epilepsy and reported considerable success. Recently, Keith (1963) has reviewed his experience with the diet. He has given a careful review of the rationale and the results, and also prepared a manual of instructions. Patients on the diet generally continue to take anticonvulsant medication. Keith suggests that patients diagnosed as idiopathic might be expected to respond more favorably than those who are known to have an organic lesion. Nevertheless, the type of epilepsy most likely to respond to the diet is not clearly defined. Livingston found the diet most effective in children from 2 to 5 years of age and in patients with minor motor seizures. Dietary treatment must be reserved for patients who do not respond to regular drug therapy since the difficulty in preparing the diet, the cost, and the natural dislike for the diet on the part of the patient, make it extremely difficult to carry through with any degree of success.

Surgical Treatment

It was the concept of John Hughlings Jackson that epileptic attacks originate in nerve cells of the brain, and that the pattern of the seizure depends on the

anatomic location of these cells, which led Sir Victor Horsley, on May 25, 1886, to operate on a young Scot. The patient was 22 years old, and since the age of 15 had been having focal seizures resulting from a compound fracture of the skull when he was 7. The scar was removed, the wound healed, and the seizures ceased.

Other operations followed, and in modern medicine the surgical treatment of epilepsy has been a means of helping many hundreds of patients whose seizures had not responded to medication. The historical development of this form of therapy is completely covered by Penfield and Jasper (1954) in their classical volume *Epilepsy and the Functional Anatomy of the Human Brain*. Indeed, no one has done more than these two colleagues to develop the surgical treatment of epilepsy to the fine point it is at today. Penfield's object was to eliminate the seizures, but he took advantage of the opportunity to study the human brain. Penfield made many discoveries and encouraged others to study the basic function of the brain as related to epilepsy.

It is recognized that some patients with epilepsy do not respond to medication. If, after adequate trials on medication and careful diagnostic evaluation, the patient meets the necessary criteria, then surgical exploration should be offered to the patient. The amount of the brain to be removed depends on the degree of abnormality, as evaluated preoperatively, and the findings by electrocorticography on exposure of the cortex. It may be small and localized; it may be a whole lobe; or in exceptional circumstances, a whole hemisphere. Not every patient who fails to respond to medical therapy is a candidate for surgery. Indeed, relatively few of them are.

Rasmussen (1963) on the basis of his experience with the surgical treatment of epilepsy outlines clearly and concisely what could be called the rationale for this type of treatment:

(1) Epilepsy is basically an abnormality in seizure threshold.

(2) This abnormal seizure threshold, or abnormally high seizure tendency, may reside in more or less restricted areas of the brain, and removal of most or all of this area may reduce the seizure tendency permanently to the level of the normal brain.

(3) Limited removal of part of an epileptogenic area seldom results in a satisfactory reduction of the seizure tendency.

(4) When the majority of this epileptogenic area is removed, a residual seizure tendency, if it is small enough, often disappears progressively during the early postoperative months or years.

(5) An epileptogenic area, particularly when it is large, may have various levels of epileptogenicity within it and the area of lowest seizure threshold gives the local sign to the habitual seizure patterns. Removal of this area lets the epileptogenicity of the adjacent areas become manifest clinically and in the **EEK**.

(6) A local epileptogenic area may induce epileptogenic activity in other areas of the brain which is dependent on the primary area and may decrease progressively and disappear sooner or later after removal of the primary area.

(7) Active and extensive epileptiform activity may interfere with the function of the rest of the brain, and removal of the offending area may result in improved brain function even though a considerable amount of functioning brain tissue is removed.

(8) The cicatrix of the surgical excision rarely becomes epileptogenic, suggesting that a sizable population of nerve cells must be injured, as a general rule, to provide a substratum for the later development of an epileptogenic lesion, and cortical removals carried out with scrupulous care to preserve untraumatized and normally vascularized pial surfaces at the margins of the excision wherever possible, rarely, if ever, produce this substratum."

Indications

The indications for the surgical treatment of epilepsy are as follows:

(1) The clinical seizure pattern should indicate a discharging lesion in accessible or excisable cortex.

(2) Serial electroencephalography should localize a cortical epileptogenic lesion.

(3) A cortical pathological lesion should be suggested by the clinical and laboratory evidence as the cause of the seizures.

(4) Intensive and methodical treatment must have been tried and shown to be unable to stop the seizures or rehabilitate the patient.

(5) The mental status of the patient must be adequate to offer hope of rehabilitation in the event that the seizures are stopped, or controlled by surgical treatment.

(6) The area of abnormality of the brain is not one, which if removed will leave the patient with a serious speech defect or other neurological deficit.

(7) The patient should be of such an age that recovery is not likely to occur spontaneously.

Investigation

A patient being considered for operation is usually referred because of the lack of response to medication. Investigation starts with a careful general and neurological history and examination. Some reliable person should witness the attacks. Blood and urine studies are conducted in search of a medical disorder that might contribute to the seizures. X-rays of the skull are taken to detect signs of asymmetry, or previous injury, intracranial calcification, pineal shift, or other abnormalities. Repeated EEG's are performed with, and without, activation procedures. Implanted electrode studies may be of great value. A pneumoencephalogram is usually performed. An arteriogram may be indicated to detect signs of a vascular abnormality. Intracarotid sodium amytal tests confirm the side of the brain harboring speech. Psychological studies establish a baseline, and also help localize the site of the abnormal brain. A psychiatric evaluation reveals the personality, and a social evaluation indicates the background or environment from which the patient comes and to which he will return. It is apparent that the preoperative evaluation of an epileptic is a complicated team effort. Although the ultimate decision rests with the surgeon, he is wisest who consults with all of the members of the team, seeking their help and advice. The success of the operation depends, to a large measure, on the care with which patients are selected.

Results

Following the 1914-18 war, Otfried Foerster, in Breslau, started to excise brain scars from patients who had received cranial wounds during the war. By 1928, when he was visited by Wilder Penfield, he had performed about 100 such operations. Foerster and Penfield (1930) reported on 12 suitable cases, 10 of which could be followed up. All of them had remained attack free for a period varying from 20 months to 5 years, with two exceptions: patient number 7 had had one attack 4 years after operation, and patient number 11 had begun to have minor seizures at the end of 3 years.

In 1941 Penfield and Erickson reported on patients operated on between 1929 and 1939 at the Montreal Neurological Institute. Forty-three percent of them were scored as successful. In a second series, between 1939 and 1944, Penfield and Steelman (1947) reported that 56 percent of the cases of cortical excision could be placed in the successful group. A third

study (Penfield and Flanigin, 1950) reported on temporal lobe excisions done between 1939 and 1949. Fifty-three percent were classed as "undoubted success," and in another 25.4 percent the procedure was considered "worthwhile" by the patient and the doctor, which left only 21 percent with slight or no improvement. Subsequent followup on the complete series showed that approximately 40 percent of patients with temporal lobe seizures can be cured by appropriate surgical excision. However, this is not a complete statement of the benefits, nor is it an adequate evaluation of the results of operation. Many patients have significant reduction in seizure tendency without being completely free of attacks. The rehabilitation of many patients, from a social and economic point of view, is most important and is often dramatic, despite the occurrence of an occasional seizure.

French (1958) reported on 25 patients with temporal lobe seizures in which a uniform type of surgical excision of the major portion of the temporal lobe was performed. Seventy-nine percent had a cessation of the psychomotor seizures during a followup period of from 2 to 7 years. Fifty percent of patients were completely free of seizures, and 50 percent continued to have either major or minor seizures originating other than in the temporal lobe.

Fenyés, Zoltan, and Fenyés (1961) reported on 34 patients operated on for epileptogenic lesions deep in the temporal lobe. Followup studies revealed the results were good in 56 percent and poor in 44 percent. Lack of improvement after surgery was reported in no more than 20 percent of cases. Fenyés' group concluded that the operation was worthwhile even in cases with slight improvement.

Twelve patients with epilepsy and psychosis, in a group of 100 who had anterior temporal lobectomies, were reported on by Serafetinides and Falconer (1962). They noted that the epilepsy preceded the psychosis, usually by many years. Five patients were rendered completely seizure free, five had been greatly benefited, and the remaining two improved at least 50 percent in regards to their epilepsy. The acute confusional states disappeared with the seizures. The same improvement was not seen in the schizophrenic-like states, which persisted, although with the improvement in the epilepsy they may have become less florid. The relationship between the epilepsy and the psychosis remained unsettled.

The problem of the surgical therapy of patients' temporal lobe seizures and bilateral EEG abnormalities, is discussed by Bloom, Jasper, and Rasmussen

(1960). They found that unilateral temporal lobectomy in these 29 patients produced complete, or nearly complete, relief of seizures in 24 percent, whereas in patients with unilateral temporal EEG abnormality, two patients out of three received similar benefit. Brain injuries, either at birth or postnatally—the two most common causes of temporal lobe seizures, may cause various degrees of injury and result in epileptogenicity in both temporal lobes. When unilateral temporal lobectomy eradicates a major portion of the epileptogenic activity, a satisfactory relief of seizures may result in some cases, despite some persisting epileptiform activity in the EEG from either the operated or unoperated temporal lobe, or in both.

In a comprehensive review of the surgery of epileptogenic lesions of the temporal lobe, Green and Scheetz (1964) report on 78 patients treated by excision of part of the temporal lobe for "psychomotor" epilepsy. Chronic atrophic lesions were found in 64.2 percent (hippocampal sclerosis being the most common by 2½ times), neoplasms in 17.9 percent, and no demonstrable lesion in 17.9 percent of the patients. Operative morbidity and mortality indicate six instances of transient complications and six instances of permanent complications (four patients with upper-quadrantic field defect, one with hemiplegia and hemianopsia, and one operative fatality due to hemorrhage and massive pulmonary edema). The operative mortality was 1.3 percent; 17 of the 78 patients were reported as dead because of factors unrelated to surgery. The most common of these factors was recurrent tumor (10 patients). In 60 patients with psychomotor epilepsy, the effects of anterior temporal lobectomy on the control of seizures, behavioral abnormalities, and social and economic rehabilitation were as follows: 11.7 percent no longer have seizures, warnings, or require medication; 56.6 percent have marked reduction in seizures and medication; 31 percent have not changed appreciably; and none is worse. Each of the 60 patients was dependent and nonproductive prior to surgical treatment; thirteen were psychotic. Now, 60 percent are independent, productive, and self-supporting; 11.6 percent are partially self-supporting; and 28.4 percent remain dependent and nonproductive. Green and Scheetz attribute the remarkable social and economic rehabilitation which has been achieved by 36 of their 60 previously disabled patients (60 percent) to a combination of factors, including (1) elimination of significant reduction of seizures and medication in 68.3 percent of their patients; (2) direct alteration of a portion of the anatomic substrate of behavior (limbic and reticular systems) by means of removal of the temporal

lobe; and (3) the improved psychological state associated with the patient's feeling of increased security.

All authors report that temporal lobectomy is a safe procedure as far as life is concerned, but transient or permanent complications are reported. Penfield, Lende, and Rasmussen (1961) describe a "manipulative" hemiplegia, associated with a homonymous hemianopsia, following temporal lobectomy in 8 cases of a series of 168. In all but one of the eight cases the complication occurred when the excision of epileptogenic tissues extended across or mesial to, the fissure of Sylvius. They felt it was due probably to interference with the anterior perforating arteries as they leave the middle cerebral artery supplying the cortico-spinal tracts and the optic radiation. Green and Scheetz (1964) describe similar complications.

Note should also be made of the report of Paillass and his conferees (1963) on the results of temporal lobectomies performed on 60 patients (two of whom were subjected to bilateral lobectomy) in an attempt to suppress refractory epileptic attacks. A study of mental alterations yielded different results according to whether bilateral or unilateral lobectomy had been performed. Bilateral resection caused deficiencies of memory and intelligence, although there was some improvement in character. After unilateral resection, intelligence, on the whole, was unchanged so far as psychometric studies indicated. Preoperative mental disorders generally showed improvement: Considerable improvement of character disturbances in 25 cases out of 33, no change in 8 cases, and only 1 case appeared to be worse. Seven out of 14 patients with depressions showed improvement. Mental coherence, on the other hand, was scarcely influenced; deficiencies of memory, connected with recent events, were present in varying degrees in 7 out of 58 patients who had unilateral lobectomy. The rhinencephalic lesion appeared to be the cause, rather than the destruction of the temporal neocortex. Improvement in character associated with suppression or attenuation of the attacks, and the absence of deficient intelligence after the operation accounted for the parallel improvement in social behavior.

Following Krynauw's description in 1950 of the removal of one cerebral hemisphere for the treatment of infantile hemiplegia, there have been many reports on hemispherectomy (Ransohoff, 1955; French, et al., 1961). Everyone agrees that there are some patients who can benefit by such a procedure, although the initial reports of improved intelligence have been questioned. Rasmussen and Gossman (1963) suggest the ideal patient for this procedure is one who has

(1) intractable seizures arising from a cerebral hemisphere badly damaged at birth or in infancy, with resulting hemiplegia and homonymous hemianopsia; and (2) sufficiently good function in the rest of the brain so that a socially useful individual can be expected if the seizures are stopped. If discrete individual finger and toe movements are lacking, as a general rule removal of the hemisphere will not significantly increase the motor deficit, and spasticity may be decreased. In some of these patients, behavioral disturbances are almost as distressing and incapacitating as the seizures. Hemispherectomy often, but not always, brings about striking improvement in this sphere.

The possibility of using stereotaxic techniques to obliterate areas of the brain exhibiting epileptogenic activity has been suggested. Baird, Spiegel, and Wycis (1960), Bancaud (1959) and Riechert and Hassler (1957) have utilized the stereotaxic technique primarily in patients with temporal lobe epilepsy, and also to investigate some specific structures in the depth of the temporal lobe. The results have not been satisfactory in terms of control of temporal lobe seizures. Narabayashi, et al. (1963), report on stereotaxic amygdalotomy performed unilaterally in 39 patients and bilaterally in 21 patients. Forty-six of the patients were classified as having clinical epilepsy, most of which were of grand mal type with some psychomotor or combined types. In 85 percent the operation resulted in a marked reduction in the emotional excitability, and in the normalization of the patient's social behavior and adaptation. There was relatively little change in the seizure patterns, themselves, in those patients who had an associated epileptiform disorder.

A new form of stereotaxic treatment of major convulsions has been proposed by Jinnai and Nishimoto (1963). Based on their studies of the "conduction pathways of epileptic convulsion," and the importance of the FOREL-H field, they felt that if this region could be destroyed, major convulsive seizures could be stopped. Using stereotaxic techniques and a mixture of oil and wax or electrocautery, 43 operations were carried out on 22 patients. There was a complete cessation of grand mal attacks in eight cases; preoperatively, two of them had several attacks daily. A decrease in grand mal seizure was noted in four cases. An alleviation was noted in seven cases. There was no effect in three cases, including a case in which only a one-sided operation was performed. Postoperative followup varied from 69 to 200 days. There was no detectable change in the EEG between the pre- and post-operative state. The procedure was aimed pri-

marily at interrupting major convulsions, but there were some unexpected results. The alleviation of the major attacks was accompanied by an "absence" or by an abortive episode, such as a shortening of the unconscious period associated with a little muscle twitching. The authors believed that lesions in the H fields of FOREL may interrupt not only the convulsive pathways, but also such reverberating circuits as those in the reticular formation of hypothalamus, and in this way cause a shortening of the unconscious period. This pioneer work will have to be evaluated carefully, particularly to determine what effect it has on the patient's intelligence and mentality.

Turner (1963) found that lobotomy of the temporal lobe isthmus in the roof of the descending horn greatly improved psychomotor attacks as well as the temperamental disturbances of uncontrollable rage and fear, and to some extent also improved "grand mal." Although this type of surgery has not proved itself, as yet, further investigation is indicated.

One could briefly summarize the "surgical therapy" of epilepsy by stating that there are some patients with focal cerebral lesions, particularly in the temporal lobe and hippocampal region who fail to respond to medication, but who will benefit by surgical excision of the cicatrix. The success of the operation depends to a great extent on the proper selection of patients. Young children, for the most part, should not be operated on, for several reasons: there is a good chance that as they grow older, the seizures will come under control. The areas of abnormal electrical activity in children tend to shift with maturation of the brain. As reported by Vitale (1963), surgical excision is likely to be disappointing. Finally the practical difficulties of doing a long procedure under local anaesthesia in a young child, are considerable. There are exceptions of course. Young children with continuing focal seizures have been helped by discrete cortical excision, and children with intractable seizures and hemiplegia, as described above, have benefited by hemispherectomy.

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PROGNOSIS

Judging from the limited amount of information available, one might conclude that the natural history and prognosis was not an important aspect of the epilepsy problem. Nothing could be further from the truth. The first question parents ask, and the most difficult to answer is prognosis—will he get better.

Lennox (1960) presented an optimistic outlook when he stated, "Probably the majority of young children subject to metabolic epilepsy or febrile convulsions would recover even without the benefit of medicines. This opinion is formed because many relatives of patients have had only a few seizures, or had them for only a brief time, in childhood. Cases that arise from a damaged brain do not fare so well; but under experienced treatment, most children can be substantially freed of attacks." Most clinicians would agree that the majority of children who have had one or more seizures, with or without medication, will recover. If it were not so, the statement that seizures are 10 times more common in children than in adults, could not be made.

Although Livingston (1963) was not in a position to publish exact data, he estimated that complete control of seizures occurred in 60 percent of patients seen in his clinic. In another 25 percent, seizures were reduced in frequency to the extent that they probably would not significantly handicap the patient. In the remaining 15 percent, seizures were refractory to all forms of antiepileptic therapy.

When predicting the outcome of seizures in an individual patient, one must consider the family history, any known cause, the type of seizures, duration of the disorder, presence of precipitating factors, and other less tangible factors such as the attitudes of the patient and his relatives, and the emotional and social environment of the patient. It is easy to see why "prognosis" is such a difficult subject.

Neonatal Convulsions

Neonatal convulsions regardless of causative factors, have a serious significance for prognosis. Craig (1960) reported on 374 infants who had convulsions within 10 days of birth; 158 of these died for various reasons, and of those who survived a large percentage showed some type of "intracranial disturbance." Graham and Prichard reported a 6-year followup study of 278 children who had neonatal convulsions. Sixty-three infants died in the first 3 months. Of the survivors, 75 had some disability such as cerebral palsy or mental retardation. The 140 remaining were considered normal. Del Mundo and Robb (1964) found that the chances of there being permanent brain damage was great in newborn infants with convulsions, particularly if there were other abnormal neurological signs. These papers substantiate the general opinion, that one must give a very guarded prognosis in any child having convulsions in the newborn period.

Myoclonic Epilepsy

Myoclonic epilepsy (massive infantile spasms, drop fits, etc.) generally has a poor prognosis, depending upon the pathological nature of the cerebral lesion. The seizures may be arrested or controlled with ACTH or adrenocortical hormones, but the associated mental retardation is not alleviated. Frequently, motor and mental development has been retarded, but unrecognized before the onset of seizures. There are patients, however, whose development has been normal before myoclonic seizures start, but who subsequently decline mentally. The attacks may "burn themselves out" and the child left seriously retarded, without the basic cause ever being discovered. Such things as a period of hyperpyrexia, anoxia, hypoglycemia, cardiac arrest, a very severe nocturnal seizure may be suspected later, but cannot be proven. At present there is no way

of predicting what the outcome will be in a child who has developed myoclonic seizures. The prognosis should be guarded.

Febrile Convulsions

Convulsions due to fever alone rarely cause any irreversible brain damage. Although they may recur with fever, generally the children grow into adulthood free of epilepsy. If the child has a cerebral lesion, or a low threshold for seizures, however, and the fever precipitates the attack, the prognosis is different. The EEG may help separate the two, but usually time alone, determines the differentiation. M. A. Lennox (1947) studied 153 children with febrile convulsions. Males outnumbered females two to one. There was a family history of convulsions in 44 percent. Sixty-five percent had their first febrile convulsion between the ages of 1 and 3. Only 25 percent of the children had one attack. Severe convulsions occurred in 35 percent. At the same time, Lennox studied another group of 52 children in whom the initial convulsion occurred with fever but who later developed recurrent convulsions with or without fever. In these children there was a higher incidence of abnormal births as well as a higher percentage with a family history of epilepsy.

In spite of this work, and the work of Fridericksen and Melchior (1954), Schmidt and Ward (1955), Fowler (1957), Prichard and McGreal (1958), Millichap, et al. (1960), and others, the real significance of febrile seizures remains unknown. They have been described as a benign event, but as a result of the seizure or some other associated disorder, a severe and prolonged attack may cause profound and permanent cerebral damage. Thus, the ability to predict the outcome in a child who has one febrile seizure is poor.

Absence Attacks

It is the general opinion that most patients with petit mal seizures will recover as they grow older. A certain number of these will begin at puberty to have grand mal attacks, but this is the exception rather than the rule. Recent studies suggest that this is not altogether true. Lees and Liversedge (1962), from a study of 132 patients, indicated that the prognosis could not be considered very favorable. Currier, et al (1963) followed 32 patients who had a presenting complaint of petit mal seizures with EEG verification after an average interval of 18 years. Thirteen of the patients continued to have petit mal seizures at

the time of the followup study, although the frequency and duration of the seizures was greatly reduced. Five patients had petit mal and grand mal attacks, two patients had grand mal attacks, alone, and 12 patients were free of seizures at the time of followup. A total of 12 of the 32 had experienced grand mal after the onset of the petit mal, and in five of these, the seizures had stopped spontaneously or were under complete control with medication. None of the patients developed psychomotor seizures. Favorable prognostic signs included early onset (between 3 and 10 years), no more than 10 petit mal spells a day when at their maximum, positive family history, normal mentality, and normal neurological examination.

Holowach, et al. (1962), reviewed the life histories of 88 children with petit mal epilepsy. They concluded that the condition was not necessarily benign nor unaccompanied by cerebral pathological changes affecting mentality and personality. It is significant that 10 percent of their patients had brain damage of recognized etiology: one congenital microcephaly, one tuberosc sclerosis, one Sturge-Weber Syndrome, one craniosynostosis, one neonatal intracranial hemorrhage and four postencephalomyelitis. Also 24 percent of their patients were retarded.

These findings suggest that there is no such thing as "pure" petit mal, but, like myoclonic epilepsy, it is the response of the brain at a particular stage of maturation to a genetic defect. The prognosis will depend, not on the pattern of the attack, but, rather, on the basic pathophysiological lesion behind it.

Post-traumatic Epilepsy

The prognosis of post-traumatic epilepsy is dependent upon many factors, both intrinsic and extrinsic. The problem has been reviewed in the section on Etiology—Trauma.

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