American Handbook of Psychiatry

EPILEPSY

NEUROPSYCHOLOGICAL ASPECTS

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Introduction

Epilepsy, as a state of disordered cerebral function, is derived from the Greek "epilepsia," meaning "a taking hold of or a seizing." Because of the existence of many kinds of seizures which appear in human disease under numerous and varied abnormal circumstances, designation as "The epilepsies" would be more appropriate.

The first definitive descriptions of both major and minor epileptic seizures are found in the Hippocratic writings of the fifth century B.C., *The Sacred Disease.* These actually localized the disturbances in the brain and revealed such aspects as the premonitory experiences or auras, the differentiation between so-called idiopathic and symptomatic epilepsy and the important influences of age, temperament, and menstrual cycles. These earliest considerations of human beings with epilepsy recognized the profound emotional experiences which in many different ways are associated with seizure phenomena. For example, in *The Sacred Disease* Hippocrates says:

Patients who suffer from this disease have a premonitory indication of an attack. In such circumstances they avoid company, going home if they are

near enough, or to the loneliest spot that they can find if they are not, so that as few people as possible will see them fall . . . Small children, from inexperience as being unaccustomed to the disease, at first fall down wherever they happen to be. Later, after a number of attacks, they run to their mothers or to someone who they know well when they feel one coming on. This is through fear and fright at what they feel, for they have *not yet learnt to feel ashamed.* [Sect. 15, p. 189]

Temkin quotes Herodotus as follows: "The great Persian king Cambyses suffered from birth with a certain great disease which some people call sacred and thus it would not be unlikely that if the body suffered from a great disease the mind was not sound either". Aretaeus of Cappadocia carried this point further in commenting upon certain personality characteristics of the epileptic: "They become languid, spiritless, stupid, inhuman, unsociable, not disposed to hold intercourse, nor be sociable at any period of life, sleepless, subject to many horrid dreams, without appetite and with bad digestion, pale, of leaden colour, slow to learn from torpidity of the understanding and of the senses."

The fact that epilepsy could be manifest by phenomena other than major convulsive movements was recognized relatively early. Bernard of Gordon in 1542 described such a situation: "As I have often seen that the attack was so short that the only thing necessary for the patients was to lean

against a wall or something similar and to rub his face, and it ceased. Sometimes, however, he didn't have to lean, he was seized by a confusion in the head, and darkness in the eyes, and feeling it beforehand, he said an "Ave Maria" and before it had finished, the paroxysm had passed. He spat once and it was all over, but it came frequently during the day. There are some people who after the paroxysm have absolutely no memory of their falling down or of their affliction, whilst there are others who remember and *feel ashamed."* Throughout the Middle Ages there was fixation on the relationship between epileptic phenomena and various magical, mystical, and religious philosophies. These led to the inappropriate reactions to the epileptic as being "possessed" and worsened the already existing fears, anxieties, and feelings of shame and inadequacy in the afflicted individual. Many of the present-day stigmas and the psychological and social problems of the epileptic patient have their origins in this unfortunate history.

Beginning with the Renaissance, increasing insight and medical understanding of epilepsy gradually developed, but it was not until the mid-nineteenth century with its anatomical and physiological approaches to the problem that the modern era began. Hughlings Jackson developed the first comprehensive understanding of seizure origin from an abnormal focus of excessive discharge of brain gray matter, with especially pertinent descriptions of the "dreamy state" and uncinated-temporal lobe seizure, differentiating these from major convulsive activity. Gowers, detailed the

extensive variety of clinical epileptic symptoms even further, and emphasized states which he regarded as in a “borderland” between actual epileptic seizure and certain psychological phenomena. Actually, it was gradually recognized, during the 19th century, particularly by workers in France, e.g., Falret, that psychological disturbances may occur in the epileptic subject as part of the seizure complex itself, i.e., ictal, or as an interictal disturbance involving various behavioral and cognitive functions. Disruptions of mental functions of severe degree such as psychoses were found, when brief and paroxysmal, to be ictal, but being more often of long duration, as part of an interictal state. The recognition of psychological precipitating factors both in a direct emotional or affective way, as in relation to various sensory stimuli, began in part with Richer of the Charcot school, leading to a differentiation between “hystero-epilepsy” and what could be called “actual” epilepsy. Problems still remain, however, in delineating the role of the epilepsy in relation to mental disorder, and in separating out factors due to specific brain lesion.

The twentieth century has seen extensive research in this field: in-depth studies of the life history of the patients; finer neuropathological, neurophysiological, and biochemical correlations; the use of electroencephalography in diagnosis and in studying, in a concomitant way, relationship between seizure discharges and psychological functions; neuropsychological tests of increasing sophistication in delineating specific

brain dysfunctions; antiepileptic drugs with increasing knowledge of their effects on seizures and mental functions correlated with blood levels; and, finally, the combined approaches of both medical-pharmacological and psychological-social management in the treatment of many epileptic patients, leading to rehabilitation and placement in an effective role in society.

Incidence

It has been difficult to determine an accurate epidemiology of epilepsy, particularly because of the increasing diagnostic awareness of the paroxysmal, but nonconvulsive, types of seizure disorders, especially those involving behavioral changes. The incidence may well be over l percent in the general population. Epileptic seizures appear in all age groups from the newborn to the elderly, but with different causes. There is a differential sex ratio of 140 males per 100 females. There are variations with different phenomena, for example the sex ratio with regard to the occurrence of chronic epileptic psychoses is about equal.

Only when seizures recur is the designation epilepsy appropriate. Not all epilepsy can be described in terms of convulsions, but the terms “fit,” “attack,” or “spell” are considered vague and inappropriate. Any disorder affecting brain function may result in seizures and the process must be considered in terms of various factors which may or may not be present in any individual instance, such as an anatomic substrate or actual physical lesion of brain tissue, the development of physiological disturbance, and biochemical and metabolic correlates. Genetic background and constitutional predisposition may be significant, and psychological determinants or “triggering” factors may be contributory.

Mechanisms and Etiology

Basic Mechanisms

Any neuron or aggregate of neurons may be made to discharge abnormally, by electrical stimulation, by alterations in basic metabolic environment, or by excitatory drugs. Thus, even a normal brain, may be made to develop either generalized or focal seizures. The various pathological disorders that produce recurrent seizures or epilepsy operate upon factors in terms of basic predisposition, specific abnormal process and precipitating or triggering circumstances. Certain regions of brain are considered seizure-sensitive, with low threshold and high susceptibility. These are especially related to motor and autonomic functions, such as motor cortex and the complex of the "limbic" system. The temporal lobe and its deeper limbic nuclear aggregates, the amygdala and hippocampus, are particularly involved in the development of seizures. Their vascularity is vulnerable to compression, and the neuronal structures in these regions are very sensitive to metabolic disturbance such as hypoxia. It is difficult to separate cause and effect in this regard, since structural lesions in these regions may be the result of seizure activity with secondary vascular insufficiency and hypoxia; however, such lesions, following severe convulsions or *status epilepticus* in infancy, may themselves become epileptogenic and lead to further "limbic" seizure activity.

Factors of age and development are important from the perinatal period onwards. There often is a little-understood delay between the event of a lesion (i.e., as due to trauma or encephalitis), and the appearance of seizure. Certain seizure types are more common in infants, e.g., massive spasms; petit-mal seizures appear in childhood after the age of four or five rather than later in life. The occurrence of seizures with high fever is almost exclusively a phenomenon of early childhood.

Seizure activity may develop from an abnormal focus or a number of foci or may be generalized from the onset, seemingly without focal origin. However, generalization of paroxysmal discharge throughout the brain may occur from a focus so rapidly that the focal origin may be obscured. Many patients with an epileptogenic cerebral lesion, especially in a temporal lobe, are in this category. Certainly, however, major convulsions caused by such metabolic distortions as hypoglycemia, hypocalcemia, water intoxication, or the withdrawal of sedative drugs are examples of those generalized from the onset. In these instances the initiation of the seizure may be in the subcortical mesodiencephalic nonspecific reticular systems, with diffuse propagation bilaterally into cerebral cortex, especially motor and autonomic pathways. The rapid loss of consciousness which occurs first and the marked amnesia for the seizure afterwards can be related to this type of patterned spread.

However, it is reasonable to consider, as did Jackson, that most other

seizures develop from a focus or aggregate of abnormally excitable neurons. The neuronal disturbances involved are those of intrinsic membrane instabilities related to both intra- and extracellular chemical derangements. These produce excessive paroxysmal potential discharges, spreading then through essentially normal neural pathways away from the focus. Thus, the clinical manifestations of a particular seizure state depend upon both the focus of origin and the region of brain involved in the propagated discharge.

However, epilepsy as a clinical phenomenon is a discontinuous process. Seizures of any type have varying periodicity in any particular patient and may relate to the sleep cycle, the menstrual cycle, or to unpredictable body rhythms. Certain seizures may occur one or more times a day in some subjects, but at much longer intervals in others. Yet, the clinical "interseizure" state may be characterized by more or less continually abnormal electrical activity as seen in the EEG. There are, therefore, two clinical states of the epileptic, i.e., the actual overt seizure or ictal disturbance, and the interictal state. Under certain circumstances the interictal state may be manifest by subtle difficulties in cerebral function, such as in memory processing and learning, or in behavioral distortions. Whether these, too, might be related to actual subclinical ongoing seizure or ictal discharge remains a problem for continued investigation (see below).

Much attention now is paid to "reflex" or sensory precipitating factors in

the production of seizures. These often are quite specific for individual patients such as light flickering, i.e., photic sensitive and TV epilepsy, visual patterns, reading, and sound (musicogenic).

Both physiological and biochemical processes must be considered not only in our understanding of how epileptogenic neurons develop, but of how such seizure activity ceases. A property of "neuronal exhaustion" may be physiological, yet in some way due to depletion of metabolic substrates, along with ionic shifts. Such a secondary clinical concomitant of generalized convulsive activity as apnea contributes to cerebral hypoxia, if not controlled. Actually cerebral blood flow does increase initially to meet cerebral oxygen demands during such seizures, decreasing only later if the seizure is severe and prolonged as in *status epilepticus.*

Etiology in Epilepsy

Idiopathic Epilepsy

Epilepsies, or recurrent seizures, appear in man in a great variety of situations, and consideration of etiology must involve factors which may be genetic and constitutional, or acquired and symptomatic. In individual patients certain precipitating or contributing factors, while not specifically causative, may be highly important. A major problem in the understanding of epilepsy by the patient, his family, and even the physician, is the failure to find

a specific cause, such as a structural or biochemical lesion, in a large number of patients (up to 75 percent). Even if such lesions are not found by the finest diagnostic techniques, it is indeed possible that a minute epileptogenic lesion could be present in a highly sensitive area of brain. One merely might consider the relatively high incidence of unrecognized encephalopathies in childhood associated with exanthema or head trauma to realize the possibility of production of such a lesion. Therefore, we can divide epileptics into two categories etiologically, the idiopathic and the secondary or acquired. Idiopathic epilepsy is diagnosed when no specific cause can be found. In acquired epilepsy such a cause is determined. Petit-mal epilepsy in childhood is regarded as the classic example of an idiopathic disorder, yet some cases are known to be associated with actual brain lesions.

The important question of genetics and heredity must be considered, particularly since it often plays a significant role in reactive psychological problems of the patient and his family. A genetically transmitted predisposition for seizure tendency is present in certain families, especially involving patients with onset of seizure in early life, as petit mal. There also are families with a high incidence of febrile seizures in infants. Even some familial focal patterning may occur. It has been determined that the relatives of some epileptic patients have a 3-5 percent incidence of epilepsy and an even higher incidence of electro-encephalographic abnormality. This is seen particularly in studies of monozygotic twins in whom such abnormalities may

reach a correlation of over 40 percent. There may be a constitutional susceptibility for seizure associated with a head injury or brain tumor. Yet, since epilepsy is a symptom often associated with other neurologic abnormalities such as motor disturbance and mental subnormality due to various underlying cerebral diseases, an inheritance pattern for such specific cerebral disease must be considered as well. In addition, there are a known number of indirect factors, nongenetic, such as cerebral birth trauma secondary to narrow maternal pelvis, which can be related to seizure incidence in siblings.

Acquired or Symptomatic Epilepsy

Any disease or structural abnormality of the brain may be associated with seizures, as well as other neurological dysfunctions including those producing perceptual and intellectual disorders. These are listed below.

Congenital malformations of the brain cause varying incidence of epilepsy, depending upon degree, location, and general genetic factors. These include microgyria, porencephaly, hemangiomas, and Down's syndrome. Multiple anomalies may be associated with maternal rubella. Prematurity, breech delivery, and neonatal asphyxia all may be important factors in epileptogenesis.

Acute, subacute, and chronic infections are productive of epilepsy both

during the active process and later due to residual lesions. The incidence of cerebral neurosyphilis has decreased. However, viral encephalitis, acute and subacute, is increasingly prominent. Certain of these, such as acute herpetic encephalitis, tend to localize in a temporal lobe.

Head injury is a major cause of acquired epilepsy, acutely and as a chronic residual effect. Posttraumatic epilepsy may develop within three years in up to 10 percent of cases after a closed head injury, and between 30 and 40 percent after open injuries. The seizure incidence depends upon the severity of the wound, dural penetration, and location.

Brain tumors (gliomas, meningiomas, metastatic) are associated with seizures, especially focal, in 30-40 percent of cases, the seizure being the first sign in 15-20 percent. The incidence is highest in supratentorial convexity tumors. Progression of symptoms from focal seizure to hemiparesis and organic mental dysfunction should be highly suggestive of tumor.

Cerebral vascular disease is a cause of epilepsy more frequently than usually realized, especially in older age groups. Seizures may occur in up to 25 percent of such patients due to localized vascular insufficiency and acute ischemic hypoxia, as well as secondary to the lesions of embolism, hemorrhage, and thrombosis. Prolonged syncope as in carotid sinus sensitivity and Adams-Stokes syndrome may develop into seizure. Diffuse

cerebral arteriosclerosis, often associated with hypertensive disease, can produce a syndrome of dementia and focal or generalized seizures.

Cerebral degenerative and demyelinating diseases have a significant incidence of seizures. This reaches 5 percent in multiple sclerosis. The incidence is relatively high in the presenile dementias (Alzheimer, Pick) with both myoclonic and generalized seizures.

Toxic and metabolic cerebral disorders are associated with both seizures and encephalopathy (dementia, stupor, precoma, coma). Various drug intoxications as with alcohol, barbiturates, and other sedatives or tranquillizers produce seizure induction usually in a withdrawal phase, within forty-eight to seventy-two hours, often with delirium. Carbon monoxide intoxication, hypoxia, water intoxication, lead poisoning, hypoglycemia, hypocalcemia, and porphyria may cause seizures in individual instances.

In many cases a combination of factors may be playing a role, such as genetic predisposition, a toxic metabolic disturbance, a focal brain lesion, vascular insufficiency and a nonspecific trigger such as an emotional crisis or a flickering light. Each patient, therefore, must be evaluated diagnostically from many different aspects in order to establish etiology on the different levels leading to appropriate total therapy.

Clinical Epileptic Manifestations with Emphasis on Neuropsychological Phenomena

Generalized Seizures

Major or Grand Mal Epilepsy

Within the major generalized seizure, a complex series of events occurs which the patient usually does not remember. A description must be obtained from witnesses, especially experienced, if possible, since details are extremely important, particularly in relation to establishing focal origin or in differentiation from a major hysterical state.

Such seizures usually start with a prodromal phase lasting minutes or even hours, with a change in emotional reactivity or affective responses, such as the appearance of increasing tension or anxiety, depression or elation. This initial phase may be difficult to recognize, and more often the onset of the seizure is regarded as the aura. This usually is a brief sensory experience directly related to the locus of origin of the seizure. Frequently experienced auras are a sense of fear and dread, a peculiar upper visceral epigastric sensation welling up into the throat, an unpleasant odor, various formed and unformed visual and auditory hallucinations and peculiar sensations in an arm or leg. At times, localized movements of an extremity or portions of the face precede the generalized seizure. The aura, as the initial phase, may allow

distinction between seizure generalized from the start or generalized with focal onset. The convulsion itself often begins with sudden vocalization (the "epileptic cry"), loss of consciousness, tonic extensor rigidity of trunk and extremities, then clonic movements, impaired breathing with brief apnea, cyanosis, and stertor. Incontinence of bladder and bowels, biting of the tongue and inside of cheeks ensue in the clonic phase. Examination may reveal marked pupillary inequality and extensor plantar responses. After some minutes the excessive motor activity ceases, breathing becomes more normal and consciousness gradually returns. However, a postictal state is frequently present with confusion, general fatigue, headache, and at times residual neurologic signs, such as hemiparesis, sensory disturbances, and dysphasia. Postictal paralysis (Todd's paralysis) may last from several minutes to hours after the seizure. In general, there is complete amnesia for the major events of the seizure, with the exception of possible recollection of the prodromal phase and the aura. Knowledge and familiarity of this entire sequence of events will help the physician to distinguish between actual epileptic seizure and "functional" seizurelike states.

The EEG pattern associated with generalized seizure, during the seizure itself, is difficult to distinguish from movement artifact, but otherwise may be seen to consist usually of bilateral discharges from all areas with patterns of high amplitude spikes and slow waves. These discharges may be present intermittently in the interseizure state. However, between seizures many

patients (up to 25 percent) may have an EEG characterized by nonspecific generalized slow wave changes or even essentially normal patterns. Localized slow waves or discharges are suggestive of a focal cerebral lesion.

Generalized seizures appear in all etiologic circumstances and in all age groups. The frequency may vary greatly, with about 20 percent of patients only having nocturnal convulsions. In females, a cyclic occurrence may appear with the menses. The designation "fragmentary seizure" may be utilized for the occurrence of brief phases of the generalized complex, i.e., only auras (frequent epigastric "butterflies") or brief, abortive movements and disturbance of consciousness. These may occur in some patients during therapy with anticonvulsant drugs and relatively incomplete control.

Petit Mal Epilepsy

The seizure of "absence," a minor form of "generalized" epilepsy, is characterized primarily by a brief lapse of consciousness usually lasting 5-10 sec. but occasionally up to 30 sec. The petit-mal seizure ordinarily appears in childhood, with onset between the ages of three and ten years. Usually no specific cause is found, and this form of epilepsy is regarded as classically idiopathic. It tends to diminish in incidence after puberty and persistence into adult life is unusual, being quite infrequent after the age of thirty. In rare instances a specific brain lesion, such as a frontal calcified tumor or diffuse

lipidosis, has been reported with petit mal.

Clinically, the patient is seen to have a sudden cessation of activity and to stare, without any gross movements. However, blinking of the eyelids is common and occasionally slight deviation of the eyes and head, along with brief minor movements of the lips and hands may occur. When more complex behavior alterations with motor acts are present, the pattern should be regarded as a brief automatism or minor motor seizure. The term “akinetic attack” refers to a generalized seizure with simple falling and loss of consciousness. It may be accompanied by an absence seizure and minor movements, but usually there is but a marked diminution of general postural tone. Afterwards, the patient recovers normal posture and mental clarity, though there may be a slight period of confusion.

The electroencephalographic correlate of petit-mal or absence seizure is a rhythmic 3-Hz. spike-and-wave discharge appearing from all regions synchronously both during and between seizures in about 85 percent of patients. Usually a discharge of more than two seconds is associated with a clinical seizure. Akinetic and myoclonic seizures may be associated with atypical spike-wave discharges, often slower than 3 Hz.

Photic sensitivity is present in a number of patients and may be familial. Flickering light at 12-14 Hz- most commonly triggers these seizures. In some

patients, mere exposure to bright sunlight may precipitate seizures; in others the flickering of a television screen is effective. The phenomenon of self-induction of seizure appears in this context, the patients inducing absence seizure by looking at a light and passing a hand in front of the eyes. Self-induced television epilepsy has been described. Apparently, in these instances, a peculiar pleasurable sensation accompanies the experience of the seizure. The incidence of absence attacks varies from very few, often in the morning, to a great many, up to 100 or more per day ("pyknolepsy"). As the frequency increases, the child may develop difficulties in continuing certain tasks and in developing complex learning functions, since there may be a defect in memory patterning induced by the absence. The designation "petit-mal status" or "absence status" refers to many such attacks occurring close together in time, lasting from minutes to several hours and producing clouding of consciousness with marked confusion and disorientation. Close observation may reveal minor twitching of the eyelids and upper limbs along with a dull facial expression. The state is associated with prolonged EEG discharge of the 3-Hz. spike-wave type as well as more irregular complex slower and faster components with polyspikes. Instances of even more prolonged mental dullness with profound psychic disturbances, a change in personality, motor agitation, dreamy states, delusion and "dementing" syndrome have been found associated with this type of EEG abnormality.

Myoclonic seizures as related seizure phenomenon in this group may be

localized or generalized and when severe are often associated with impairment of consciousness. They involve sudden integrated contractions of a single muscle or many muscle groups producing relatively simple arrhythmic jerking movements of one or many joints or a body segment. They can exist as an independent entity, as a phenomenon preceding a generalized seizure, usually with a build-up in severity, or in association with petit mal absence. They often are sensitive to sensory influences and may be precipitated by light or sound stimuli, change in posture or movement of a limb, by drowsiness or an emotional upset. In some instances cerebellar dysfunction with ataxia may be present in an associated syndrome. The myoclonus epilepsy of "Unverricht" refers to generalized myoclonus and mental deterioration due to a diffuse degenerative metabolic disorder. Myoclonic seizures associated with other signs of diffuse cerebral dysfunction (confusion, stupor, dementia) occur in uremic encephalopathy, subacute encephalitis, Creutzfeldt-Jakob chronic viral encephalitis, and cerebral lipidoses.

A severe myoclonic seizure disorder appearing in the first eighteen months of life and usually associated with general cerebral deterioration and marked mental retardation is called infantile massive spasms or jackknife seizure. The infant develops marked flexion spasms of head, neck, and trunk, and extension of legs and arms. This probably is the most common major seizure pattern in infancy. Some known causes of this disorder are

phenylketonuria, tuberous sclerosis, Down's syndrome, bilateral subdural hematoma, and marked porencephaly. However, the cause is often not determined.

The EEG correlates of myoclonic seizures usually are synchronous 2-3 Hz. spike-wave complexes in bursts, with clear EEG patterns interspersed. The massive spasm seizures are more associated with hypsarrhythmia, or relatively asynchronous, asymmetric slow spike-wave and slow-wave discharges.

Perceptual Functions during Seizures and EEG Discharges

A relatively controllable way of evaluating perceptual abilities during epileptic activity has been to study the ability of patients to perceive and react during overt electroencephalographic discharges. Because the petit-mal absence type of epileptic seizure has a high degree of correlation (over 85 percent) with the typical 3 Hz. paroxysmal spike-and- wave activity in the electroencephalogram, such studies were first carried out in subjects with this disorder. Initially, Schwab was able to demonstrate that patients with petit-mal seizures displayed a disturbance in response to auditory stimuli; the responses were delayed during attacks lasting about five seconds, and in those lasting more than eight seconds no response occurred. This was regarded as due to the distorted awareness or "unconsciousness" caused by

the petit-mal seizure. Since that time, there have been a number of other investigations of this phenomenon of delayed or disturbed reactivity correlated with electroencephalographic discharges in subjects with petit mal and other forms of epilepsy. This subject is of great importance in our understanding of psychological disturbances in epilepsy and will be discussed in some detail.

A high degree of variability has been reported, but the experimental designs themselves have been very different, particularly in the types of tests performed by the subject. Not all investigations utilized tests of actual perceptual functions, although many cognitive elements were involved. Kooi and Hovey studied the performance of standard psychological tests (i.e., Wechsler-Bellevue, particularly picture completion and digit symbol) during continuous EEG recording of patients with mainly grand-mal or psychomotor epilepsy, but with intermittent bilateral spike-wave discharges in the EEG. The test performances always were impaired, often with nonanswer responses during the EEG discharges. Similar results were reported by Davidoff and Johnson. Visual motor continuous-performance tests showed greater deficiencies during suppressed or flattened periods in the EEG, in an unusual study by Prechtl et al. Courtois et al. reported an unequal affection during petit-mal attacks of somatosensory modalities, i.e., light touch most readily, then passive movement, and pain perception least. Goode et al. and Mirsky and Van Buren have demonstrated that patients with petit-mal

epilepsy performed more poorly on a test of sustained attention, i.e., the continuous-performance test, than did patients with focal motor epilepsy. This test utilized a repeated specified visual signal, and it was found that the ability to execute the simple repetitive discriminative response was lost if the stimulus fell within a burst of spike-and-wave activity in the electroencephalogram. Actually, the interpretation of the mechanism of this disturbance still is not definite because it may be due (as Mirsky and Tecce have emphasized) to reduced sensory input or reduced perception, to weakened motor effective capacity, to temporary impairment of the central integrative or decision-making process, to temporary forgetting of the task instructions, or to a combination of these factors. Mirsky and Van Buren suggested that both input and output might be affected by whatever produces the spike-and-wave discharge, although reduced input or reduced perception seemed to be more obviously disturbed than a weakened or reduced output. Thus, in the sensory task the subject was presented with a visual auditory stimulus with the instruction to hold it in mind until questioned by the examiner. When stimuli were presented during the spike-and-wave burst and the patient questioned a few seconds later, recall was severely impaired; the degree of impairment was generally less than that seen with the ordinary continuous-performance test. However, the interpretation of this as a "purely" sensory perceptive impairment remains equivocal. The patient may have registered the stimulus, but it may have been expunged from his

memory by the physiological phenomenon manifested by the spike-and-wave burst. Alternatively, it may not be possible under these conditions to maintain a stimulus trace without some initial subvocal verbalization or rehearsal; there may be a subtle but important motor component even in this pure sensory perceptive task. It should be mentioned that these workers found that electroencephalographic bursts which were symmetrical, regular, and bilaterally synchronous tended to produce more deficit in these tasks than other less extensive EEG discharges. The interjected problem of memory disturbance has been emphasized by the work of Hutt et al., who showed that children with light-sensitive epilepsy demonstrated impaired recall of digits during bioelectric paroxysms in the EEG evoked by stroboscopic light stimulation.

Further analysis of this phenomenon has been carried out by Tizard and Margerison. They showed that patients with petit-mal epilepsy worked more slowly during the performance of various tests and made more errors during electroencephalographic spike-wave discharges. Even very brief bursts of one to one-and-one-half second's duration, without overt behavioral accompaniments, were shown to be associated with significantly slowed response times. The psychological tests utilized by these workers were simple, repetitive, and continuous, and involved responses to various perceptual stimuli, such as auditory, visual, and tactile. The auditory stimuli were of both numbers and tones, the visual stimuli were of different

combinations of numbers of lights and colors, and the tactile stimuli were those of a tickling stimulus applied to the hand. In six patients studied, all but one had an amnesia for the events occurring during clinical attacks or correlated electroencephalographic discharges. Even this patient, however, had some disturbance of recall. All of the patients exhibited defects in performance in all tests during the discharges. The phenomenon was not regarded as one merely of a loss of "consciousness" during spike-wave discharges of sufficiently long duration. When the discharge lasted longer than six to eight seconds, the disturbance of performance was much greater; however, the important finding in this study is the demonstration of disturbed performance during the very brief discharges of around one to two seconds in duration, even though no clinical seizure or other behavioral abnormality was observed. The implication from all of these studies is that both perception and memory are disturbed during even brief seizure activity, and that both of these processes probably interact in developing the actual experience of the subject.

In many instances similar impairments of cognitive functions may be present between bursts of paroxysmal EEG discharge, implying a more persistent disturbance of integrating cerebral circuits. Another clinically highly significant observation, often of practical significance in patient management, is the frequently found suppression or limitation of paroxysmal seizure activity (especially petit mal) during states of attention, stimulation,

concentration, and motor activity, particularly during periods of interest and high motivation (See references 29, 40, 41, 83, 90, 94, and 134). However, periods of inactivity, boredom, and irritability may trigger even more seizures. The use of EEG telemetry on patients, especially school children in various task settings is increasing our information and understanding of such psychological factors in the triggering of epileptic discharges in the EEG and actual seizures.

Sensony-Evoked Potentials during Epileptic Discharges

Disturbances of sensory perception already described as occurring in epileptic patients and often correlated with electroencephalographic discharges vary from simple to complex, and clearly involve different portions of the sensory perceiving and analyzing cerebral structures. The epileptic discharges may involve only certain systems or portions of systems and produce the changes that vary in their complexity of expression. Not all neuronal populations seem to participate fully in the different kinds of seizure activity, even those characterized by the generalized high-amplitude synchronous discharging seen during prolonged absence attacks.

Attempts have been made to study these phenomena by investigating cerebral sensory-evoked potentials in epileptic subjects in the interseizure state and during epileptic discharges. Cernacek and Ciganek found a

decreased amplitude of the earlier components of visual-evoked responses, i.e., presumably that portion related to primary receiving activity, and an increase in certain of the later secondary waves (especially their wave V), in patients in the interseizure state. This effect was more pronounced at lower frequencies of stimulation than at higher. Photogenic epileptic subjects did not differ from those with psychomotor and grand-mal epilepsy. Potentials from occipital cortex were not specifically enhanced. However, Gastaut et al. studied hemianopic subjects with visual epileptic seizures in the blind field and found, from the involved occipital regions, higher amplitude late components of visual-evoked responses. Similarly, Bacia and Reid described an increase in amplitude of somatosensory-evoked potentials on the side of the epileptogenic focus in patients with focal epilepsy. They did not elicit altered responses in patients with "centrencephalie" epilepsy, with a prolonged high amplitude after discharge phenomenon. Gastaut and Regis found the greatest changes in photosensitive generalized epileptics, with markedly increased secondary components (especially wave V) being evoked, correlated with the degree of photic sensitivity and seizure frequency. In general, similar findings were reported by Morocutti and Sommer-Smith, Hishikawa et al., and Green. The enhancement of the secondary component of the evoked response is thought to be due to the related phenomena of neuronal facilitation and recruitment at subcortical and cortical levels, greater postinhibitory rebound, and hypersynchronization of neuronal

activity in cortical areas associated with epileptogenic activity.

Visual-evoked responses have been studied during physiological sleep in “centrencephalie” epileptics. During the slow wave (first and second phases), the responses are similar to those in the waking state with greater amplitude of later components. In the paradoxical or REM sleep the responses show less reactivity and late waves of longer duration and later peaking in amplitude.

Rodin et al. investigated visual-evoked potentials during epileptic discharges characterized as “petit-mal status,” classical petit mal seizure, and tonic seizure with unresponsiveness. Evoked responses were “suggestively present” in three subjects during grand-mal seizure discharges. The evoked potentials were present in relatively unchanged fashion during petit-mal seizure induced by bemigride activation. At times “some change in latencies” during seizure activity was reported, but a quantitative analysis of these data was not given. During grand-mal-seizure activity in man the elements of evoked visual response were distinguishable during tonic and clonic phases, but not clearly in the immediate postictal phase; this latter deficit was related to hypoxia. These investigators also showed that photic responses could be evoked unchanged from cat cerebral cortex during seizure discharges produced by bemigride administration. The evoked responses could be elicited immediately postictally in these experiments. The animals were

receiving artificial respiration and, therefore, the factor of hypoxia probably did not play the apparent significant role that it did with humans. The authors emphasized the importance of the elicitation of evoked responses during the clonic portions of seizure activity, and suggested that a process of generalized inhibition probably was not playing a significant role during such an epileptic phase.

Mirsky and Tecce have conducted more elaborate investigations of visual-evoked potentials during electroencephalographic spike- and-wave activity in man. They demonstrated that the enhancement of the voltage of the evoked potential was least evident from the parietal-occipital region and more prominent from the anterior region, an effect which seemed to mirror the distribution of voltages of the spike-wave discharge itself, which is maximal in the frontal and less pronounced in the posterior region. Also, the form of the average evoked potential appeared to be influenced by the particular part of the spike-wave complex within which the stimulus was administered. However, the nature of these changes is not clear. These investigators also studied visual-evoked potentials during spike-wave discharges produced by the administration of chlorambucil to monkeys. This substance produced epileptiform activity thought to be similar to that associated with petit-mal absence in man. In these experiments, visual-evoked potentials were recorded during the spike-wave discharges; however there was an apparent reduction in amplitude of the potentials from areas

associated with visual perception in the monkey including optic nerve and chiasm, lateral geniculate, and occipital cortex. The reduction in evoked potential amplitude was absent from regions usually not associated with visual functions, such as the midline thalamus, frontal cortex, and pons. In fact, there was probably an enhancement of the potential from these regions. These results suggested to Mirsky and Tecce that "if the size of the evoked potential reflects the amount of sensory information being transmitted, then there is actually less visual input (as seen in visually related structures) during spike and wave activity." The interpretation of the enhancement, if it be such, in nonvisual areas is problematical: "It may reflect differential inhibitory and/or disinhibitory effects during spike and wave seizure activity or some effect which serves to compensate for reduced information flow in the primary receptor." The other question suggested by this work is related to the influence on the evoked visual potential of the specific period in the development in the spike-and-wave burst into which the stimulus falls. These authors indicate that there are behavioral data to suggest that the period just prior to the appearance of the epileptiform burst is deleterious to performance in any continuous-performance test and that absence-seizure phenomenon may antedate the appearance of the paroxysmal burst in the electroencephalogram.

Focal or Partial Seizures

Focal or partial seizures are characterized by manifestations indicating involvement of a specific region of brain, and therefore usually represent an acquired epilepsy. Rapid secondary generalization of seizure may develop from a focus, but more usually the attack remains limited. Although any region of cortex or subcortex may develop excitatory seizure activity, certain regions are more frequently involved. Total loss of consciousness is uncommon, but usually there is some altered conscious awareness with varying degrees of amnesia for the events of the seizure. This is particularly true when portions of the limbic system (i.e., hippocampus and amygdala) and associated diencephalic structures are involved in seizure production.

The EEG concomitants of focal seizures including the psychomotor-temporal-limbic variety are characterized by discharges of spikes, complexes, and slow waves localized from the particular region involved in at least 75 percent of instances. Frequently, however, the discharges may be bilateral and asynchronous, representing transmission and diffusion of the focal abnormalities. This is especially true in the EEGs of children with focal seizures. Also, at times, deeply situated lesions produce only minimal or no significant scalp-recorded electroencephalographic abnormality. In adults, recording during sleep may evoke focal discharges, especially from patients with temporal-lobe limbic seizures.

Focal motor seizures are produced by lesions in any of the motor regions

of the brain, especially the motor (pre-RoIandic) cortex. The classic Jacksonian motor seizure begins as a repetitive movement of a distal portion of an extremity, such as fingers or toes, and then spreads by a march of clonic contraction up the extremity toward the trunk. Consciousness seldom is altered unless spread occurs contra-laterally. Focal motor seizures may affect speech production with even an arrest of speech.

Focal sensory seizures may be Jacksonian with lesions in the sensory (post-Rolandic) cortex producing a march of abnormal sensations, such as numbness and tingling, spreading up an extremity. Seizures derived from other sensory and receptive analyzing areas contain more complex visual, auditory, olfactory, gustatory, and vertiginous components in varying degrees of organization (see below).

Autonomic seizures are produced from cerebral foci associated with autonomic functional representation, such as deep temporal-limbic or diencephalic-hypothalamic. Many of the symptoms are associated with other focal or generalized seizures, but, especially in children, they may exist more or less by themselves as paroxysms of abdominal pain, sweating, piloerection, incontinence, salivation, and fever.

Psychomotor-temporal-lobe (limbic) seizures represent the most prominent and common form of focal or partial epilepsy. The temporal lobe

and its deeper nuclear masses, the amygdala and hippocampus and their associated limbic structures, as indicated previously, are particularly vulnerable to many pathological processes from the perinatal period onwards throughout life. Such seizures may represent at least 25 percent of all seizures in childhood and well over 50 percent in adult life, often coexisting with grand-mal seizures. In over 60 percent of cases a definite structural lesion may be found, secondary to trauma, encephalitis, ischemia, hypoxia, or tumor (vascular malformation, hamartoma, glioma). The latter may be so small as to escape detection by neurodiagnostic radiological methods and may only be found within a temporal lobe resected for intractable incapacitating seizures. Even when focal frontal lesions or diffuse cerebral disease are present, for example, it is likely that clinical manifestations are evoked by propagation of the discharge through temporal-limbic structures."

The most simple, but relatively rare, type of temporal-lobe seizure is manifest by a paroxysmal dysphasic speech disturbance when the dominant lobe is involved. This is usually an inability to form speech components, but may be experienced as a blocking of the ideation necessary to produce speech. It has been associated with visual hallucinations.

The clinical manifestations of psychomotor-temporal-limbic seizures are characterized by an initial aura most frequently consisting of anxiety and visceral symptoms, especially a peculiar epigastric sensation welling up into

the throat. (See references 8, 30, 31, 45, 51, 63, 93, 118, and 171). This is followed by an alteration—not a loss—of consciousness, associated with many varied, complex mental states and automatic somatic and autonomic motor behavior. These phenomena are associated with at least a partial amnesia, particularly for automatisms. Recollection of sensory experiences of an aura, or of certain perceptual distortions early during the seizure, may be obtained.

During the seizure itself, there is often arrest or suspension of ongoing activity at first, then simple movements such as lip-smacking, chewing, swallowing, sucking, and aimless motions of the arms and legs. These are followed by repetitive stereotyped automatisms of varying complexity and involving partially purposeful or inappropriate and bizarre behavior. The latter can be associated with the environment and occasionally influenced by psychological factors related to unresolved conflicts. For example, one of our patients recited the “Apostles Creed” during his seizure. The activities in this phase of the seizure may merge into normal behavior.

The occurrence of olfactory hallucinations— usually unpleasant—associated with lesions of the mesial portions of the temporal lobe, the uncus, was called “uncinate” seizure by Jackson, who also described the “dreamy” state of the patient during the seizure, occasionally prolonged postictally. He also reports the complex case of a physician with a temporal-lobe lesion who

was, however, capable of organized, appropriate activity, i.e., examination of a patient, diagnosis, and prescription, with no recollection of these activities.

In children with this type of seizure there is emphasis on visceral manifestations with expressions of hunger, nausea, retching, vomiting, and abdominal pain. Spitting automatism is an unusual expression of temporal-limbic seizure. Epileptic laughter or gelastic epilepsy may be part of this complex.

Destructive, aggressive behavior occasionally occurs, but is not usually purposeful (See references 31, 34, 43, 147, 157, and 164). The possibility of paroxysmal, ictal violence leading to homicide is a problematic matter still under intensive investigation. The implication of actual temporal-lobe seizure in a specific directed violent attack remains difficult to prove.

Affective disturbances, particularly expressions of fear, anger, and depression may be present ictally. Occasionally, prolonged fuguelike states with running or wandering about may last many minutes. A fugue of longer duration with the patient moving some distance and with amnesia for the experience is more likely a postictal automatism.

During many seizures of this type, patients are involved in experiential hallucinations, both visceral and auditory, as well as interpretive illusions involving their own bodies or the immediate environment (i.e., micropsia,

macropsia). These symptoms are frequently associated with ideational blocking and forced thinking. Common symptoms are the peculiar experiences of false familiarity with places and people (deja vu), thoughts (deja pen-see), and voices (deja entendu).

Ictal Perceptual Disturbances in Limbic Epilepsy

Ever since the fundamental descriptions of Jackson and Gowers the occurrence of perceptual disturbances during epileptic seizures has been studied particularly in patients with psychomotor-psychosensory seizure complex originating from the temporal lobes or limbic system as listed in Table 13-1. There have been many clinical investigations of these ictal perceptual phenomena, with striking instances of both correlation and noncorrelation with either focal or generalized electroencephalographic discharges. However, it is well known that scalp electroencephalographic recordings may give only incomplete or occasionally no reflection at all of abnormal discharge activity present in deep cerebral nuclear structures.

Table 13-1. Perceptual Disorders in Limbic Epilepsy

SOMATIC	VISCERAL
Olfactory	Gastric, epigastric
Visual	nausea
illusions	hunger
deja vu	thirst
hallucinations	Abdominal

Auditory	Pharyngeal
illusions	Precordial
deja entendu	Respiratory
hallucinations	Genital, urinary
Vestibular	Vasomotor
vertigo	
movement	
loss of equilibrium	
Gustatory	
Somesthetic sensations of	
face (nose, mouth)	
half of body	
extremities	

To circumvent this problem, Penfield and his group in many thorough and sustained investigations, have utilized electrical stimulation of temporal-lobe structures in conscious patients to reproduce the psychological disturbances experienced ictally. Similar methods and results have been described by others. Penfield has classified the disordered perceptual phenomena as follows:

1. Psychical hallucinations or experiential seizures: the recall of past experiences in detail, with all the imagery that fell within the patient's attention at the time.

2. Psychical illusions: misrepresentations or altered interpretations of present experience, better called illusions of comparative interpretation or interpretive illusions. These are quite common, appearing in at least one third

of the patients studied, either spontaneously as part of the seizure or as a result of temporal-lobe stimulation. During the illusory experience there is no depersonalization or loss of identity; although a voice may sound remote or a room may appear distorted and unfamiliar, the patient is usually able to distinguish reality from unreality.

The perceptual illusions have been classified further as follows: (1) auditory illusions, with sounds seeming louder or clearer, fainter or more distant, nearer or farther; (2) visual illusions, with objects appearing clearer or blurred, nearer or farther, larger or smaller, fatter or thinner, and so forth; and (3) illusions of recognition, the present experience seeming familiar, strange, altered and unreal. This includes the experience of the deja-vu phenomenon. Less common illusions of perception are those of an increased awareness of surroundings, illusions of alteration and speed of movement and vestibular-visual disturbances in which objects appear tilted, along with vertiginous sensations.

Penfield and his group found that auditory illusions could be produced by cortical temporal-lobe stimulations bilaterally, but visual illusions mainly from stimulations of the minor hemisphere. The latter finding may be correlated with a number of psychological studies which were able to show evidence of impaired eye-hand coordination, with difficulties in such tests as trail making and picture completion, particularly in cases with epileptic

dysfunction of the nondominant temporal lobe.

Peculiar illusions of familiarity or of strangeness of the environment also are frequent in these patients, and are predominantly associated with epileptic discharge or electrical stimulation from the minor hemisphere. Distortions of the body image involve experiences of feeling disconnected, fragmented, malformed, or incomplete. A sensation of fear also is frequently associated with perceptions of peculiar bodily sensations involving thoracic and abdominal structures. Often feelings of lonesomeness, sorrow, absurdity, and disgust have been recounted, but it is remarkable that pleasant sensations are extremely rare.

In general, it is felt by these workers that the temporal-lobe functions involved are largely devoted to comparative interpretations of perceptions of the present environment and the analysis of the components of the different sensory perceptions, comparing them with previous experiences; these functions of analysis and comparison then transmit the experience into consciousness of the present and immediate significance. These functions become altered during states of seizure, producing the perceptual disturbances as experienced by the patient. Penfield has used the term “interpretive cortex” as applied to these regions of temporal lobe.

The disturbed perceptions in experiential hallucinations derived from

temporal-lobe epileptic activity occur also in at least 10 percent of patients. These are similar to “flashback” phenomena which are past experiences and happenings incorporated into the patient’s seizure pattern. They are more usually produced by stimulation of the involved cortex and only relatively infrequently are recalled otherwise by the subject. The phenomenon varies from fragmentary to extensive elaboration of various sights, sounds, and other perceptual experiences along with accompanying emotions, and the patient usually recognizes these as coming from his past. Again, these states appear almost twice as frequently in association with lesions of the nondominant temporal lobe as compared with the dominant; auditory experiences are about half as common as visual. Most such responses have been produced by stimulations of the lateral and superior surfaces of the first temporal convolution, and some can be produced by stimulations of the medial border of the hippocampal gyrus. The hallucinations involving somatic sensory perceptions are often associated with epigastric and other general visceral sensations and it is not unusual for some patients to have an abortive attack consisting of visceral experience alone. In many cases there is an association with sensory or psychic precipitation as a form of reflex epilepsy. For example, attacks beginning with hand tingling may in some instances be precipitated by touching the hand, and certain attacks with visual hallucinations by utilizing light stimuli. There may be a lower threshold and a facilitation for these phenomenon in epileptogenic cortex involving these

functions.

The effects of seizure activity on perceptual functions and memory processes reach profound complexities in relation to the temporal-lobe-limbic epilepsies. It does seem likely that abnormal bioelectrical excitatory states developing in and propagating through limbic-system structures can interfere with perceptual functions of patients during overt clinical seizure, but also in apparently interseizure states (see below) with no overt seizure actually observable or experienced (i.e., subictal excitation).

Cortical sensory-evoked potentials during experimental limbic seizures have been studied. Flynn et al, reporting a series of experiments on the performance and acquisition of a conditioned avoidance response during hippocampal after-discharge in cats, noted, in passing, that the potentials evoked by the clicks which preceded the shock continued to arrive at the cortex during the seizure. Experiments carried out by Prichard and Glaser utilized auditory click and visual flash stimuli evoking cortical potentials in cats, unanesthetized and with chronically implanted electrodes, during sleep, wakefulness, and bilateral limbic seizures. The seizures were induced by stimulation unilaterally across amygdala and hippocampus, which produced propagated bilateral seizure activity. The evoked cortical potentials to both auditory and visual stimuli during such seizures were of normal configuration and amplitude and were undistinguishable from those recorded during the

waking state. There were no significant changes in the evoked responses even during marked behavioral limbic seizures characterized by behavioral changes in the animal which included alterations in posture, facial twitching, pupillary dilatation, drooling, and some vocalization. There were no differences either behaviorally or with regard to the evoked potentials whether stimulation was begun with the animals awake or asleep. These results indicated that during widespread limbic seizures the auditory and visual systems were in a functional state, at least with regard to the pathways generating the evoked potential to these sensory stimuli, similar to that present during wakefulness. The findings are consistent with clinical observations that some patients with psychomotor epilepsy can perform certain complex integrated acts involving perception during their seizures (even though the perceptions may be distorted), and with the studies of Flynn et al. that cats could perform a conditioned leg withdrawal after a training period in which the conditioned stimulus was paired with an unconditioned stimulus only during hippocampal after-discharge. Further investigation, with patients in a clinical setting, is necessary in this area.

Thus, it does seem clear that under certain conditions sensory information presented to the brain only during limbic seizures can influence both immediate and subsequent behavior, and that such seizures need not disturb the occurrence in the cortex of the usual configuration of potentials evoked by auditory and visual stimuli. On the other hand, the fact that

psychomotor epileptics are almost always at least partially amnesic for their seizures implies a defect of storage, if not of actual reception of sensory information, and the performance of certain previously conditioned responses actually may be disrupted during limbic seizures. All these clinical and experimental observations do present the consideration of a boundary between what a brain can do and what it cannot do during seizure discharge occurring in the involved cerebral structures, such as those regarded to be within "limbic," "centrencephalie," or other epileptogenic aggregates. The actual anatomical and physiological substrates finally responsible for the perceptual distortions are less clear. The more precise definition of these boundaries in both electrophysiological and behavioral terms, along with the correlation with the nature and extent of seizure activity, are among the avenues to a clearer understanding of epileptic processes in man.

The Interseizure State

The intellectual performance and behavior of a patient with epilepsy between obvious clinical attacks, whatever the type, characterize the interseizure or interictal state. (See references 12, 25, 27, 32, 37, 42, 52, 58, 65, 68, 7 1 , 84, 95, 96, 1 17 , 12 1 -12 3 , and 154). Generalizations are difficult, but since the etiology is specific in up to 25 percent of cases, certain points may be made. The interseizure disorder in a patient with a progressive degenerative cerebral disease, encephalitis, or an expanding brain tumor who

develops changes in behavior, personality and intellectual-cognitive functioning is probably not due to any seizure activity but to the underlying brain disease. This applies as well to the child with extensive cerebral damage or malformation.

However, the larger group consists of patients with seizures and an otherwise presumably normal functioning brain at onset. A major question, then, concerns the potential influence of the recurrent seizure state (clinical and subclinical) upon total brain functioning. In the past, much attention was paid to the possibility of a specific personality distortion in epileptic patients, stated to be manifested by excessive irritability, arrogance, paranoid ideation, religiosity, and often social withdrawal. This led to the persistence of inappropriate restrictive actions by society and to general stigmatization. However, the severe emotional problems and disturbances in the patients have been found to develop most often as a reaction to such restrictions— to the presence of an uncontrollable, overwhelming seizure disorder, and also, at times even more common, intrafamilial denigration. Severely neurotic, maladjusted behavior then developed into the so-called "epileptic personality," which is just a collection of secondary reactive psychological phenomena. In Taylor's sample of 100 patients with temporal lobe epilepsy, only thirteen were considered psychiatrically normal; thirty were diagnosed "neurotic;" forty-eight "psychopathic" (e.g., aggressive, immature and inadequate, paranoid, antisocial, cyclothymic, schizoid, or sexual

deviationist); sixteen "psychotic" (with eight of "schizophreniform psychosis," five with paranoid-hallucinatory psychosis, and one each with abrupt onset catatonic psychosis, "organic" psychosis, or simple schizophrenia). Two children were called "psychotic." Other patients were described as showing psychomotor retardation in depressive psychosis. In twelve cases two diagnoses were made. Five patients had an "epileptic personality," in one instance prior to onset of florid psychosis. Thus, practically all types of mental disorders may accompany epilepsy. The specific relationships between the two conditions require detailed psychiatric analysis by careful psychological testing, especially of cognitive neuropsychological components. These evaluations have practical therapeutic significance, since increasing psychological difficulties often lead to increased seizure activity more difficult to control. Yet, upon reviewing large populations of epileptic patients, one finds that most do have, or are capable of, normal behavior and intellectual functions, and can develop controlled personality characteristics which can lead to appropriate, effective adjustments in society. History and the literature is replete with descriptions of such individuals contributing to our civilization in all walks of life.

A significant number of patients with frequent recurrent generalized seizures, especially *status epilepticus* and excessive numbers of absences, and particularly those with psychomotor-temporal-limbic seizures, may develop disturbances of cognitive intellectual functions, including memory and

learning, and, at times interictal severe behavioral disorders and psychotic states (See references 12, 14, 18, 20, 24, 27, 32, 37, 52, 54, 62, 68, 77, 87, 117, 122, 128, 137, 161, and 172). The actual definitive role of the seizure disorder itself and its potential specificity in relation to these developments is difficult to analyze. The effects on mental function of prolonged administration of anticonvulsant drugs, and their resulting folate deficiency remain to be clarified (See references 15, 16, 57, 96, 133, and 137). In many patients, secondary social and psychological factors assume primary importance with the production of withdrawal, depression, neurotic symptoms and apparent impairment of intellectual performance of varying severity. Severe hyperkinetic states may develop in epileptic children.

As described above, frequent absence attacks may interfere with tasks requiring repetition and which may be involved in learning and memory processing. This is unusual in most children with petit-mal seizures; in general, they have no significant intellectual difficulties or personality disturbance.

Certain patients with frequent grand-mal and/or psychomotor-temporal-lobe seizures may develop a slowly progressive intellectual disturbance. How often this occurs is not yet determined, nor is the general distribution of these difficulties known. In some instances the chronic effects of drugs such as phenobarbital and diphenylhydantoin may be important. In

clinical experience these changes in overall brain functioning may be quite subtle in the early years of the epileptic disorder in a particular patient, and would be most recognizable in individuals of high intellectual attainment. There is increasing evidence that progressive damage in, or disturbed function of, certain susceptible brain areas, particularly in the deep temporal regions, occurs in association with poor seizure control (and perhaps increasing dosages of medication) over a period of several years (i.e., "epileptogenic encephalopathy"). The mechanism of this process is not clear; a concept of "consumptive hypoxia" of overactive cells leading to neuronal cell loss has been invoked. In these patients, appropriate neuropsychological tests reveal progressive impairment of concentration and attention, memory defects, word finding distortions and subtle losses in ability to associate and to track patterns (i.e., perceptual disorders). However, it must be emphasized that the majority of patients with epileptic seizures under adequate control escape these difficulties and retain normal intellectual function.

Neuropsychological Testing in Epilepsy

The effects of epileptic activity, both in the ictal and interictal states, on intellectual performance, learning and memory, have not yet been clearly elucidated (See references 18, 21, 24, 33, 65, 71, 87, 93, 100, 103, 128, 144, 145, 153, and 172). Perhaps more important to the patient is the fact that anticonvulsant drugs still are administered over a long period of time without clear knowledge of effects on such functions. Most studies thus far have used a standard intelligence test such as the WAIS (Wechsler Adult Intelligence Scale), to provide for some measure of mental status, together with the Minnesota Multiphasic Inventory (MMPI), or, in earlier years, the Rorschach test, as an estimate of personality traits. These tests of relatively random populations of patients have demonstrated that there is a tendency for the distribution of simple scores, especially in clinic groups, to be skewed towards the lower end of the scale. Some authors have shown a discrepancy between verbal and performance IQ figures, and have attributed the finding to "organicity." A few longitudinal studies indicate that this finding may be true only for the patient at that particular time of testing. There is a lack of good controlled testing, with age, sex, seizure history and frequency, anticonvulsant drug levels and types, etc., taken into account.

More specific neuropsychological testing, using the more subtle techniques devised for the assessment of localized brain damage, can aid

understanding of the epileptic patient at two levels. The first is a knowledge of the general intellectual level, specific impairment associated with focal dysfunction, learning and memory difficulties—often consequences of poor attention and concentration —which may give invaluable help in vocational guidance and specialized teaching. The epileptic is often an "underachiever," since much school time may be missed and social factors make job finding difficult. It also can be important to find out how anticonvulsant drug therapy is influencing mentation, especially since many such drugs have a sedative effect. Thus, Cereghino and Penry note that brain damage may make the patient susceptible to "mild depression and impairment of performance secondary to drug administration (that) may go unnoticed." One hopes that neuropsychological tests not only are able to "notice" such impairments, but also help balance the effects of maximum seizure control against possible dulling of intellect due to drug effects, by reassessments at different doses of the drugs. The now available sophisticated measures of anticonvulsant blood levels may not be relevant unless an overall measure, at the same level of sophistication, of the efficacy of the drug can be made. There has been but one such controlled (but acute) study relating impairment in perceptual-motor behavior distortion to blood phenobarbital level; a detailed study of chronic effects needs to be performed with this and other drugs such as diphenylhydantoin.

The other level at which neuropsychological testing can function has

been developed within the last thirty years. The neuropsychologist is concerned with the relationship between psychological function and cerebral structure. The effects on behaviour of localized lesions in the cerebrum have been studied extensively, in the hope that this will lead to a better understanding of the functions of these areas. The interpretation of these studies is always subject to the limitations imposed by looking at a malfunctioning system in order to understand the normal. However, any theory of brain function must be able to account for changes observed during pathological behaviour. Thus, the closer study of psychological function in the epileptic—especially with focal seizures—may lead to a better idea of how the brain functions.

A clearer idea of the effects of repeated focal and generalised seizures on the specific areas involved, as well as on the ability of other areas of the brain to compensate, may be found. How far does such interruption of normal function give rise to permanent malfunction? How much compensation takes place in such a situation? To what extent does a faulty input (perceptual disorders in all modalities, often interrupted by ictal behaviour) give rise to faulty output and inappropriate responses, seen as personality disturbances? Does the clue to abnormal behaviour lie in the study, in particular, of temporal-lobe or limbic epilepsy? Do changes in EEG activity, such as spike-wave discharges, correlate with changes in mental activity? Does good seizure control prevent intellectual deterioration, as has been suggested in some

studies (see above), or is some other variable more important?

The solution to these and many other problems may be found in part by the application of neuropsychological measurement in which specific tests for focal dysfunctions, using knowledge acquired through the study of localized cerebral lesions, may lead to a better understanding of brain function, and the means to achieve better treatment of the epileptic. A brief comment concerning these tests follows. As has been noted previously,-in most studies in which the psychological aspects of epilepsy have been commented upon, the Wechsler Adult Intelligent Scale (WAIS) and Wechsler Memory Scale have been used. Neither of these two tests really gives a good indication of more subtle disturbances in brain function. The WAIS is a battery of tests in which two IQ scores are obtained, one verbal and one performance. A simple statement of these two scores, or one of the "full scale IQ" which is a combination of the two, may obscure specific deficits. Thus, individually lower scores on one of the subtests may show only in the overall figure, without making it clear where the lower figure arose. Memory and concentration difficulties may lower some scores, particularly on arithmetic and digit span, not necessarily a purely verbal loss. Likewise, some of the tests on the performance scale (which ostensibly measures nonverbal, nondominant-hemisphere abilities) are not purely nonverbal or not purely performance verbal, thus rendering the distinction between the two IQ scores less significant. There is no valid reason why a lower score on the

performance scale should mean “organicity” as has been stated by some authors. The WAIS has two “hold” tests, vocabulary and picture completion, from which an estimate of deterioration can be computed. But the bluntness of the total scores as instruments for measuring specific deficits may be the reason for the discrepant findings obtained with the use of the WAIS to distinguish groups of epileptics from each other and from control groups. It is not a test battery which enables one to show objectively, that which has been noted clinically.

Attempts to measure brain damage by the application of such tests have not been very useful, since there is an underlying assumption that Lashley’s law of mass action stands, and is mensurable. It is, however, possible to measure some aspect of intelligence commensurate with Spearman’s g factor. The discrepancy between scores on a standardized vocabulary test (such as the WAIS or the Mill Hill), and the score on Raven’s matrices, may give a good basic idea of dementia. Vocabulary tests reflect acquired information, and are held to be good indicators, together with education and job history, of the level which an individual can attain. Raven’s matrices[2] are held to measure a subject’s ability to “develop a systematic method of reasoning,” not subject to previous training, cultural background, etc. Such a test can provide a useful baseline from which specific difficulties can be assessed, and some idea of the degree of dementia can also be found.

Memory and Temporal-Lobe Epilepsy

It has been shown repeatedly that the temporal lobe and related structures are involved in memory (See references 13, 26, 28, 105, 146, and 169). Not only has it been shown that bitemporal lobectomy produces a dense amnesia, both retrograde and anterograde (as in the well-known case of H.M.) but much attention has been given to laterality effects. Thus, anterior lobectomy in the dominant hemisphere for speech, causes a lasting impairment in memory for verbal material. This is independent of whether the presentation be auditory or visual, and also of the recall technique used. Removal of the nondominant hemisphere, or damage to it, gives an impairment in memory for visual material, such as places, faces, nonsense designs, and music, i.e., material that is not easily coded verbally. A double dissociation effect between visual perception and visual memory has also been demonstrated in the nondominant hemisphere. Apart from simple free recall experiments using verbal and nonverbal material, more complex paradigms using learning also show laterality effects. Left-temporal lobectomized patients show a deficit on Hebbs Digit Sequence task, right-temporal lobectomized patients do not.

Experimental psychologists have also studied the various components of memory, three of which are now generally distinguished: (l) immediate or iconic memory having very limited capacity and a rapid decay of the stored

material of about one second; (2) short-term memory (STM) or primary memory, having a trace of slightly longer but still limited duration (20-30 sec.) and with a slightly larger capacity; and (3) long-term memory (LTM) or secondary memory, in which a stable trace or engram exists and may remain permanently. Evidence exists that the anatomical localization of these memory systems may be different. Thus the amnesic syndrome, characterized by severe LTM loss in the presence of intact immediate and STM and intellect, is thought to be a concomitant of bilateral lesions of the diencephalon, thalamus, and hippocampus structures closely related to the temporal lobe. A situation in which STM, particularly for auditorally presented material, is grossly impaired in the presence of intact LTM has been described. The critical lesion is thought to be in the dominant parietal lobe, in the region of the supra-marginal and angular gyri.

It thus is clear that the temporal lobes are important to the proper functioning of memory in man, as shown by a fairly extensive literature concerning subjects with brain lesions. It is, therefore, surprising that the problem of memory impairment in patients with epilepsy, especially temporal-lobe epilepsy, has not yet been analyzed in the same depth, even given the evidence that lack of any structural damage to the temporal area is not always evident. Milner has pointed out that care must be taken to distinguish between impairment of memory and impairment of attention or vigilance. Thus “absence” in petit mal may be interpreted later as producing

memory loss, and generalised intellectual impairment may appear to the patient as memory loss. Given that such situations exist, there remains a need to study the memory problems that may be associated with epilepsy. Examples of dense amnesia seen after bitemporal lobectomy for epilepsy (H.M.), or in one case after right-temporal lobectomy have been studied. The episodes of deja vu in temporal-lobe epilepsy have been interpreted as abnormal activity in the temporal lobe, giving rise to a false sense of memory, analogous, perhaps, to Penfield's stimulation studies.

There have been studies of memory impairment in epilepsy, and many workers have sought to find both the differentially affected temporal-lobe epileptic, and the predicted laterality effects. Thus, Horowitz and Cohen in a follow-up study of patients after surgery for temporal-lobe epilepsy, did not find any consistent memory impairment (using the Wechsler memory scale and Benton visual retention test, amongst other general tests of intellectual performance such as the WAIS). They do not accept the view that psychologists are able to demonstrate laterality effects, and argue that temporal lobectomy merely leads to impairment of "organization."

Serafetmides and Falconer studied thirty-four patients with right anterior temporal-lobe ablations and showed that only two had some brief postoperative memory impairment; six had persistent memory deficits, but the authors state that "the type of memory deficit did not correlate with the

more formal psychometric test results." They suggest that these six subjects must have had bilateral temporal-lobe dysfunction. Meyer studied similar patients and found that nondominant lobectomies produced no change, and that dominant lobectomies produced auditory verbal learning difficulties. Many studies have made comparisons between various types of seizure patients. Guerrant et al. found no overall significant differences in any of their groups of grand mal, petit mal and psychomotor (temporal-lobe) epileptics, with respect to memory functioning, using the memory span for objects and the Wechsler memory scale.

Mirsky, Primac et al. found no significant group differences on memory tests between subjects with temporal-lobe epilepsy (TLE) of a focal and nonfocal nature. Scott, Moffett et al. tested subjects with and without epilepsy, matched for age and IQ and found no differences in their performance on nonverbal tests in three modalities. Quadfasel and Pruyser predicted a greater impairment in verbal skills and some memory difficulty in patients with TLE, and Fedio and Mirsky and Dennerll demonstrated some laterality effects in TLE patients.

Thus there is some confusion as to the precise nature of the memory impairments in the epileptic patients. Memory tests have not differentiated adequately between STM (short term memory) and LTM (long term memory) components; indeed, there is little indication that very remote memory has

been tested at all. Although some studies have considered laterality effects, more subtle tests have not been used. Thus, the use of tests of nonverbal memory cannot be described as such, unless it is clear that no verbal labels can be applied to the stimulus to be remembered, at least during the time of presentation to the subject. Horowitz is of the opinion that no gross differences between right and left foci in the temporal-lobe epileptic have yet been demonstrated. It has yet to be proved definitively that the lack of differentiation in these studies is a result of test inefficiency, or whether temporal-lobe disturbances in epilepsy really do produce a different type of dysfunction from other types of lesions, where perhaps the disturbance may be more continuous. Lack of direct information about the true origins—i.e., perhaps subcortical—of discharges in many patients with temporal-lobe epilepsy adds to the difficulties.

It has been noted that there is often a discrepancy between the observed clinical findings, the patient's subjective impression of memory impairment, and psychological test findings. Since memory is so vital an element in adequate functioning, good evaluation is important. More discriminating tests, such as have been employed in other memory studies, may improve the evaluation of this function in epilepsy. There is also a need for more careful control of other influences, such as anticonvulsant levels, seizure frequency, and the overall psychological state of the patient (i.e., level of anxiety, depression, etc.).

Interictal psychotic states can develop, especially in certain patients with psychomotor-temporal lobe epilepsy, and may be correlated with long-standing disturbances in intellectual function, particularly in perceptual-cognitive areas. The overall incidence of psychosis is relatively small and difficult to determine, yet significant; if psychotic states in epileptic patients are considered as the starting point of any study of this problem, then it is likely that their coincidence is not just a matter of chance (See references 14, 27, 37, 54, 121, and 152).

A fluctuating episodic behavioral and personality disorder other than actual seizure can exist in a patient. At times an alternation between seizure and overt psychosis can be observed, especially in patients under medication. However, it is often difficult to distinguish an ictal or postictal psychotic episode from an interictal state. Ever since the midnineteenth century, so-called acute epileptic psychotic reactions have been recognized as part of what is now regarded as the psychomotor-temporal-lobe seizure complex, and more prolonged psychotic disturbances with schizophreniclike manifestations have been differentiated from actual seizure in some patients. Epileptic "furor," fugue, twilight and depersonalization phenomena have been described in both settings.

The electroencephalogram has aided somewhat in these considerations. Confusional states have been found to be more common in patients with

bilateral spike-wave discharges and prolonged petit-mal seizures. More complex psychotic disturbances of schizophreniclike qualities in patients with psychomotor seizures have been found with unmodified EEG rhythms, desynchronization of the EEG, “forced normalization” with disappearance of abnormal discharges or a reinforced temporal abnormality.

The interictal psychotic states may appear early in the history of the patient, even at the onset of seizures, but more often some years later varying from six to 14 years. The psychotic episodes may last from one to many days. Reactions are paranoid, depressive, confusional, and hallucinatory along with bizarre behavior. Episodes of self-mutilation have been reported. There usually is little or no occurrence of otherwise goal-directed destructive, violent behavior in these patients and no indications of major withdrawal or atavistic mechanisms. Affect is often warm and appropriate with much reality testing, a major difference from schizophrenic psychosis occurring in other spontaneous circumstances. Affective flattening is unusual. Catatonic disorders appear, but are usually transitory. Religious preoccupations are frequent, as well as related obsessional activities. Impulsive, compulsive eating and drinking may occur. Somnambulism has been reported. In some patients, acute disorganization of verbal productions is present along with bizarre distortions and many somatic delusions. Pregnancy fantasies have existed in some females. Diminished libido and sexual functions are found in some patients with temporal-lobe epilepsy Hypersexuality is unusual. Sexual

deviation, such as fetishism, has been reported in association with temporal-lobe epilepsy, relieved, in one instance, by temporal lobectomy.

Over half the patients have fluctuating memory disturbances with mild to moderate impairment, difficulty in attention and concentration and disorientation to time. Extreme confusion occasionally appears, often lasting several hours and not associated with the usual manifestations of seizure with motor-sensory or visceral components. Partial to complete amnesia, often for the psychosis, suggests subclinical “seizure” activity; in some of the cases with confusion, bilateral EEG discharges suggesting subcortical origin may be correlated.

Psychological testing of such patients requires not only scoring, but also observation of performance and response. There is evidence of loss of trains of association along with word finding and tracking difficulties, vacillation of alertness, and fluctuation in the accuracy of perceptions. Looseness of associations without bizarre content or mode of thought is common, along with indications of concreteness. However, there is usually no clear sign of autism or withdrawal; many patients make continued attempts to be in contact with reality. There are usually no signs of archaic thinking or autistic fantasy elaboration as would be found in more typical schizophrenic subjects.

Mild to moderate memory disturbances are frequent in these patients,

with both retention and recall difficulties in both short- and longterm memory. Mere scoring of IQ levels is not very meaningful. Many patients express concern over problems in the clarity of their thinking and make concerted efforts to control, restrict, and contain emotions and actions in order to become clear, accurate, and realistic. Misperceptions and arbitrary thought processes usually involve relatively benign, neutral content, although themes of religiosity are frequent. A degree of word-finding difficulty is often apparent, and distinct dysphasia is occasionally present (in over 10 percent of Slater's cases). Flor-Henry and others have emphasized the correlation of dominant temporal-lobe focal involvement and schizophreniclike psychosis in these patients. Some patients experience weakness of spatial orientation and fluctuating motor incoordination. Difficulty in arithmetic is sometimes present.

The paranoid elements involve projection of thoughts and feelings, but well-organized delusions of persecution, for example, are relatively uncommon. Indications of contamination and feelings of depersonalization and unreality are frequent. Disturbances of body image involve feelings of being disconnected, fragmented, malformed, awkward, or incomplete.

Most epileptic patients with interictal psychosis are found to have psychomotor temporal-lobe seizure disorders. The classification of the seizure disorder must be on the basis of the clinical signs, not of the EEG,

since the latter might show fluctuating bilaterality of discharge. The onset of the psychotic reaction does not appear to be clearly related to specific psychological triggers in many instances, but often does follow increasing buildup of tension and anxiety. Gradual intellectual disorganization, often subtle at first, may initiate the process. Some patients remain in an impulsive, aggressive, unstable, obsessional state without actual psychotic break. It should be stated that the actuality of a "true" or non-directly related schizophrenia could develop in patients with epilepsy, but the above described schizophrenialike phenomena are qualitatively different.

Taylor has recently emphasized that, from the clinical point of view, the epileptic schizophrenialike psychoses emerge as a group of disorders following largely on psychomotor-temporal-lobe epilepsies involving mainly the left temporal lobe either alone, or as part of a more generalized seizure disorder, emerging mainly in the second and third decades, where mesial temporal sclerosis is an improbable pathological substrate, to which females are more prone, but in whom half the risk to psychosis is past by the twenty-fifth year. Of interest is the increasing evidence that a number of cases of childhood psychosis or "autism" follow episodes of infantile epilepsy, especially of the myoclonic spasm type.

The therapeutic implications of these considerations are yet to be fully realized. It might be expected that a psychotic reaction associated with a

seizure disorder would regress as seizures respond to treatment. Although this does happen, the interictal behavioral disturbance occasionally persists and may increase as seizures are controlled. Anticonvulsant drugs are to be used, and the administration of certain psychotropic drugs such as "alerting" phenothiazines (i.e., flu-phenazine) might be helpful. In selected cases with intractable seizures and well-defined focus, temporal lobectomy has produced some improvement in "schizophrenic" symptoms, but this is unpredictable and does not correlate well with the response of the seizures.

Clinical Evaluation of the Patient

The patient with epilepsy should receive a thorough diagnostic evaluation in order to determine the relative significance of the possible etiologic factors as well as precipitating circumstances. This requires thorough history taking, physical, medical, and neurologic examinations, and selected laboratory investigations with particular reference to blood chemistry studies, cerebrospinal fluid analyses, and electroencephalography; special radiologic studies may be required. The collected data may lead to the diagnosis of either a specific medical illness associated with seizures or a focal cerebral lesion.

History

In order to establish whether recurrent seizures are being experienced, a careful history should contain detailed descriptive material, usually from sources other than the patient. Eye-witness accounts are helpful. As much recollection as possible should be obtained from the patient, particularly of experiences of the aura or the onset of the seizure. The patterning or course of events during and after seizure episodes should be documented with special attention to phenomena which might be of localizing significance. Other information of great importance with regard to treatment concerns the circumstances under which the seizure occurs, e.g., time of day or night, frequency of attacks, and the influence of medication, menstrual cycle, pregnancy, food intake, sound or light stimulation, intake of alcohol, and psychological stress. Additional indications of neurologic disturbance should be described, e.g., headache, hemiparesis, hemisensory symptoms, dysphasia, and visual difficulties, especially loss of acuity and hemianopsia, and vertigo.

A family history may reveal data of importance, particularly with regard to susceptibility to seizure. In a significant number of families a history of febrile seizure in early childhood may be obtained, as well as seizures of both generalized and focal types extending into later life. In addition, since a number of genetically determined cerebral disorders may be associated with seizure as well as other neurologic abnormalities, the family history may include phenomena other than seizures as indications of brain disorder related to structural or metabolic abnormalities.

The general medical history is significant, since seizure may be associated with cardiovascular disease, various blood dyscrasias, and metabolic and endocrine disorders; for example, the history of neoplasm anywhere in the body is important, since a focal seizure may be the first manifestation of a cerebral metastasis.

The past medical and developmental history of the patient is of great significance in attempting to determine etiology; information concerning pregnancy, delivery, the neonatal period, and the developmental neurological milestones should be obtained. The position of the child on the developmental scale should be determined, particularly with regard to motor and intellectual skills. Past history should also include information regarding head injuries, reactions to immunizations, childhood diseases such as measles, mumps, and chickenpox, and any severe illness with delirium or coma that might be considered related to an encephalitis. A history of exposure to toxic substances is important, as well as the possibility of drug intake, particularly in adults suspected of taking barbiturate or tranquilizing drugs.

A detailed survey of the patient's social development and behavior in and out of the family setting is relevant, including an evaluation of intellectual performance at school and vocational performance. Attention should be paid to alteration in any of these phases of existence in relation to seizure

occurrence, as well as between seizures, and also to possible effects of medication on seizure incidence or behavior.

Physical and Neurological Examination

Clinical examination of patients with seizures may not reveal significant physical or neurologic abnormality in 75 percent or more of cases. However, thorough physical examination is necessary to establish whether a general medical disorder is present; even examination of the skin may produce the requisite information for diagnosis of tuberous sclerosis, neurofibromatosis, or cerebral hemangioma. Examination of the lungs may provide the background for consideration of metastatic tumor or abscess; evaluation of the peripheral circulation and blood pressure may give indication of the possibility of the various types of cerebral vascular lesions, or aid in differential diagnosis of syncope and seizure.

The neurological examination serves two functions: (1) to give indication of general cerebral disorder, and (2) to demonstrate whether focal signs are present, indicative of a localized cerebral lesion. Neurological examination at the time of or shortly after a seizure may be important, since hemiparesis and related signs may be revealed. Psychological testing may be useful in the assessment of general intellectual status, possible deterioration from a previously higher level of functioning, and the possibility of focal

cerebral damage. As discussed previously, the WAIS and Wechsler Memory Scale give a very broad idea of the patient's functioning, but more careful evaluation of learning, memory, and perception is needed to distinguish subtler disturbances, as discussed above. The Rorschach and other projective tests have been used to demonstrate both "organicity" and the epileptic personality, but doubt has been cast on the validity of such techniques for this purpose. Attention should be paid to the patient's performance during these tests as well as to the actual scores.

Laboratory Investigations

Each patient with recurrent seizures, regardless of age, should be subjected to selected laboratory investigations at least once during the course of his history, particularly if changes in seizure patterns or neurologic signs develop. There are no routines, but at different age levels certain tests are more apt to produce results leading to specific etiologic diagnosis. In addition, certain studies are necessary for the evaluation of the general health of the patient and in following the effects of medication which may be toxic to various body systems. Aside from electroencephalographic abnormalities, there are no abnormal laboratory findings characteristically associated with the seizure process. Urinalysis is important to determine the state of kidney functioning, which, if abnormal, may preclude the use of certain drugs or may suggest a specific diagnosis. Similarly, a complete blood count is necessary,

particularly if a blood dyscrasis is suspected. Severe seizure states, such as *status epilepticus,* may be associated with proteinuria, leukocytosis, and fever as secondary manifestations. In certain instances, special blood chemistry studies are important, e.g., blood sugar and glucose-tolerance test in the diagnosis of hypoglycemia and in the evaluation of a difficult-to-control diabetic. Determinations of serum calcium are necessary in the evaluation of infants and young children with seizure states, since hypocalcemia may cause generalized seizures, distinct from tetany. Evaluation of serum electrolytes and acid-base balance is extremely important in the study of both children and adults with metabolic encephalopathies and seizures in various disorders of the kidney, liver, heart, and lungs. As yet, no specific patterns of electrolyte distortion are associated with seizures, but at times variations in these can be so correlated. Determination of serum enzymes is mainly important in establishing the presence of general medical disorders, and serologic tests are helpful in the diagnosis of past infectious states.

The cerebrospinal fluid is apt to be normal except in a minority with certain neurological disease. Following severe seizures there may be a slight increase in cerebrospinal fluid protein and white cell counts, but this is usually transitory. In structural neurological disorders with concomitant seizures, the protein or pressure or both may be persistently elevated and the diagnosis is then dependent on other tests, such as contrast radiologic studies. Chronic infection of the nervous system can be associated with

increase in white cell count in the cerebrospinal fluid, and occasionally the presence of cerebral neoplasm may be shown by neoplastic cells in the fluid, diagnosed by cell block and appropriate histologic examination.

Radiologic Studies

All patients should have an X ray of the skull and chest. The plain X-ray film may show abnormal calcifications and shift of the pineal or other signs of increased intracranial pressure. The X ray of the chest is of two-fold importance: (1) in the evaluation of any anomalous cardiopulmonary status in an adult or a child; and (2) to reveal possible primary tumor in an adult.

The so-called contrast radiological studies of the intracranial contents are extremely useful diagnostic procedures, but since they have a certain morbidity they must be selected with great care and be performed when they can be expected to be most informative. Certainly, such procedures must be considered when there is suspicion of a focal intracranial lesion.

If there is increased intracranial pressure, particularly if there may be a lesion involving the posterior fossa, ventriculography may be the procedure of choice; however, this procedure generally gives incomplete information with regard to the subarachnoid spaces. Ordinarily, if the pressure is normal, a fractional pneumoencephalogram gives more information with regard to a lesion occupying space in the brain substance or distorting the ventricular or

subarachnoid system. In addition, the presence of focal brain atrophy may be shown by differential enlargements of specific spaces such as the temporal horns of the ventricles.

Cerebral arteriography is useful in patients with and without evidence of increased pressure, and may give important information, particularly if there are focal or lateralizing signs. Abnormal vascular patterns are found in particular types of tumors, intracranial hematomas, and vascular malformations; the location of vascular occlusions may be found by arteriography as well. There are instances when such studies are negative but reveal a lesion when repeated later; occasionally such tests may be worthwhile in initial base-line investigations of a case.

The use of brain scanning with radioactive isotopes requires more evaluation, but there is increasing regard for these procedures as a means of determining the presence of certain types of tumors, either single or multiple, and of vascular lesions. In some instances a negative brain scan may eliminate the necessity, for the moment, of a contrast radiological procedure. Also, a significantly lateralized pickup in scanning may indicate the preferred side for an arteriogram, an indication which otherwise might not be clear from the neurological evaluation and the EEG.

Electroencephalography

The various electroencephalographic correlates of the different types of seizures have been described above. The EEG, however, must be regarded only as an indicator of a certain kind of cerebral activity determined by the recording method using electrodes upon the scalp. This is important to realize, since the EEG from a patient with known seizures of any type might be normal, as it is the case in a single-sample recording in 25 percent of such patients. Depth electrode recording techniques have shown that, in some of these instances, there may be abnormal discharges in the deeper structures such as the amygdala and hippocampus, while the electrical activity of the cortex shows no change. The EEG; therefore, has limited diagnostic applications, and it must be considered only as a reflection of certain cerebral functions to be correlated with other information obtained from physical and neurological examinations. The electroencephalographic findings are of varying usefulness in the diagnosis of epilepsy, depending on their nature and the circumstances under which they are obtained.

The EEG may be utilized as an aid in the confirmation of the presence of a seizure state, particularly if paroxysmal discharges are recorded during and correlated with a seizure; for example, in the petit-mal absence, up to 85 percent of children have the typical 3 Hz. spike-and-wave discharges both between and during seizures. In addition, these may be precipitated by overventilation and light stimulation. The EEG may merely contain generalized nonspecific slow-wave discharges, which may be considered only

as an indicator of cerebral dysfunction, but not necessarily of a definite seizure disorder. Focal slow-wave abnormality is suggestive of a localized structural lesion and indicates the need for further investigations. In certain forms of focal epilepsy the EEG may show focal discharges of spikes, sharp waves, and complex components indicative of the epileptogenic nature of the focus. However, in some of these instances such abnormality might be transmitted from deeper, even centrally disposed, lesions.

In most laboratories of electroencephalography the procedure includes recordings in the waking state and during hyperventilation. Frequently, however, attempts are made to provoke generalized and focal paroxysmal discharges by means of sleep, sensory stimulation with light or sound, or certain metabolic and pharmacologic adjuvants. The EEG during sleep is useful to demonstrate focal discharges in patients with psychomotor-temporal-lobe epilepsy. Such discharges are increased during sleep in 50-75 percent of adults. The results in children are less definitive; in 25-35 percent of young patients the temporal activity becomes more prominent during sleep. However, in some patients sleep tends to produce increased bilaterality of abnormal temporal discharges. The use of sphenoidal electrodes is occasionally helpful in lateralizing temporal-lobe discharge, particularly when patients are being evaluated for surgery. At times barbiturate-induced fast-wave activity is found to be less marked in the involved temporal lobe. Photic stimulation detects patients with light-sensitive epilepsy and occasionally

evokes lateralized discharges in patients with a sensitive focus.

There have been many attempts to alter the electrical activity of the brain in susceptible patients by inducing metabolic changes, such as hydration, following an injection of vasopressin or the induction of hypoglycemia with small doses of insulin. Various stimulant drugs have been used, e.g., pentylenetetrazol and bemegride. All of these methods, particularly the use of drugs, may precipitate paroxysmal discharges as well as clinical seizures; the latter are usually generalized, but occasionally activation of a focus occurs. Attempts to measure seizure discharge threshold have been largely unsuccessful because of great variability; in addition, many otherwise normal subjects respond to these procedures with seizure activity. For these reasons this approach is not recommended for general use in the diagnosis of an epileptic state. Occasionally, however, it may be desirable to view in detail the clinical phenomena of the seizure and to determine focal components either in the EEG or clinically. At times this can be accomplished by the administration of a controlled dose of a seizure-producing drug.

The degree of electroencephalographic abnormality, especially in its paroxysmal characteristics, may be regarded as an objective indicator of the severity of a particular seizure state in a patient; this may fluctuate with the clinical behavior of the seizure disorder. However, the use of the EEG to follow patients with epilepsy is limited since in many instances some degree

of electroencephalographic abnormality persists even when seizures are controlled. This occurs most often in patients with psychomotor-temporal-lobe epilepsy and least often in children with petit-mal and myoclonic seizures.

Differential Diagnosis

The implications of a diagnosis of an epileptic disorder are so significant both medically and psychologically that the diagnosis must be positive and specific, excluding other disturbances characterized by similar transitory abnormalities of neurological function that are not seizures. Consciousness may be disturbed episodically by limitations of cerebral blood flow, either generally or locally, e.g., in instances of cerebral vascular insufficiency and syncope of various types, particularly the vasodepressor form. Disturbances of cerebral circulation occur frequently in older age-groups; there is usually evidence of hypertension and cerebral arteriosclerosis. Periodic blackouts and general confusional states may result from basilar artery insufficiency; however, there are usually other signs of brainstem and cerebellar dysfunction. Patients with deficient carotid circulation may have transitory hemiparesis and hemisensory disturbances along with dysphasia. Electroencephalographic findings of paroxysmal discharge may suggest the presence of a seizure state; however, rhythmic discharges may be related to lesions of vascular origin in the upper brainstem. The differential diagnosis in

these patients involves careful evaluation of the history and general medical state of the patient; arteriographic confirmation of a vascular lesion may be necessary.

Syncopal episodes may resemble akinetic or minor motor seizure; actually, prolonged syncope can develop into convulsions due to the persistence of cerebral ischemia and hypoxia. The patient with syncope usually has some indication of disturbed vasomotor reactivity with excessive sweating, pallor, and tachycardia. Specific precipitating factors often are present, such as fear or other psychological upset; the confusion, headache, and drowsiness which occur after a generalized seizure do not usually appear. During a simple syncopal episode the EEG consists of diffuse asynchronous slow waves without paroxysmal or focal discharges.

Various disturbances of consciousness, from confusion to coma, may be produced by metabolic disturbances not necessarily leading to seizures. These conditions are important in the differential diagnosis, since in specific instances of metabolic encephalopathy seizures may be only a minor clinical concomitant, and the overall distortion of general cerebral function may be of major concern. These clinical abnormalities appear in hypoglycemia, hyponatremia, kidney failure with uremia, hepatic insufficiency, and pulmonary insufficiency (with hypoxia and hypercarbia). The EEG in these states contains generalized, often intermittent, intermediate (4-7 Hz.) and

very slow waves (1-3 Hz.). Rhythmic components (such as the triphasic complexes in hepatic encephalopathy) may be present, but paroxysmal discharges are unusual unless actual seizures are occurring. Hypocalcemia, as in hypoparathyroidism, may produce tetanic spasms throughout the somatic musculature; occasionally these may be unilateral and suggestive of localized seizure, but consciousness is not lost and actual clonic contractions do not occur. However, as mentioned previously, hypocalcemia may precipitate actual convulsive seizures. Fluctuating distortions in behavior are also characteristic of many endocrine disorders, e.g., hypoadrenalism and hyper-adrenalism, hypopituitarism and hyperpituitarism, and myxedema. In none of these states are seizure disorders particularly prominent.

Certain psychogenic disorders may resemble epileptic states and be difficult to distinguish from them. Hysterical "seizures" may occur independently, but are occasionally seen in patients with known seizures, i.e., so-called liystero-epilepsy. The clinical problem in these patients is often difficult to solve because of the interrelationships between the seizure state and the reactive development of the psychological disturbance. The hysterical seizure is not associated with neurological signs of reflex abnormality; the EEG contains no paroxysmal discharges. The hysterical seizure pattern is bizarre and not a stereotyped tonic-clonic movement sequence, and self-injury does not occur during, or as a result of, the hysterical seizure. The postictal states of confusion, headache, and drowsiness are absent. The

diagnosis of hysterical seizure requires careful psychiatric evaluation because of the deep-seated and severe neurotic process involved. Similarly, certain hysterical or psychotic fugue disturbances and dissociative reactions may need to be distinguished from psychomotor-temporal-lobe seizures.

Treatment

The treatment of a patient with an epileptic disorder must take into account not only the patient and his disorder, but also his family and life situation. Much depends on the diagnostic evaluation and the etiology or precipitating factor. This can be clearly defined where a metabolic disturbance is obvious, e.g., in a hypoglycemic or hypocalcemic patient cured of seizures by administering glucose or calcium. Operable cerebral tumors represent another such situation. However, in many cases of acquired epilepsy the cause of the seizure cannot be treated directly, and symptomatic therapy with anticonvulsant drugs together with the total management of the patient are necessary. This may be true even in certain cases in which the precipitating factor is known, e.g., an anticonvulsant drug may be temporarily necessary in hypocalcemia, since a delayed response to calcium may be present. Seizures may continue even after surgery for a brain tumor due to postoperative scarring or incomplete excision. Immediate specific therapy is not always indicated in patients with acquired epilepsy. Only a limited number of patients with posttraumatic epilepsy are amenable to surgery for a

localized meningo-cerebral scar. For these reasons, only a relatively small number of patients with seizures do not require anticonvulsant drugs and a general psychosocial rehabilitative program.

Medical Therapy with Anticonvulsant Drugs

Drugs commonly used in the treatment of epilepsy are listed in Table 13-2 together with recommended dosage, indications, and toxic effects.

Table 13-2. Medical Therapy in Epilepsy: Anticonvulsant Drugs

Bromides	
Daily dosage	Adults: 1.0-3.0 g. (not recommended for children)
Symptoms	All types of seizures, especially grand mal and psychomotor; may be combined with hydantoins
Toxic effects	Drowsiness, dulling, rash, psychosis; *rarely used now.*
Celontin (methsuximide)	
Dose 0.3 g. capsule	
Daily dosage	Children: 0.6 g.; adults: up to 1.5 g.
Symptoms	Petit mal, psychomotor seizures, myoclonic seizures, massive spasms
Toxic effects	Ataxia, drowsiness, rarely blood dyscrasias, anorexia
Dexedrine (dextroamphetamine)	
Dose 5 mg.	

	tablet; 10 and 15 mg. spansules
Daily dosage	Children: 5-15 mg.; adults: 15-50 mg.
Symptoms	Hyperkinetic behavioral disturbances in children, narcolepsy, to counteract sedative effects
Toxic effects	Anorexia, irritability, sleeplessness

Diamox (acetazolamide)

Dose	250 mg. tablet
Daily dosage	Children: 0.75-1.0 g.; adults: 1.0-1.5 g. Use intermittently, as an adjuvant in all types of seizures, especially those in females related to menstrual cycles; tolerance may develop
Toxic effects	Anorexia, acidosis, drowsiness, numbness of extremities, rare blood dyscrasia

Dilantin (diphenylhydantoin)

Dose	0.03 g. and 0.1 g. capsules; 0.05 g. tablet; 0.25 g./ml. suspension; 0.1 g. in oil capsule; 0.25 g. ampul for parenteral use
Daily dosage	Children: 0. 1-0.3 g adults: 0.3-0.6 g. Effective blood level 10-20 μg/ml.
Symptoms	Grand mal, psychomotor, and focal seizures; most useful in combination with phenobarbital or primidone
Toxic effects	Rash, fever, gum hypertrophy, gastric distress, diplopia, ataxia, hirsutism (in young females); drowsiness uncommon; lymphadenopathy, rare megaloblastic anemia, secondary folate deficiency, “encephalopathy,” hepatitis rare, aplastic anemia, agranulocytosis rare

Gemonil (metharbital)

Dose	0.1 g.
Daily dosage	Children: 0. 1-0.3 g.; adults: 0.3-0.6 g.
Symptoms	Mainly in children with petit mal, myoclonic seizures, massive spasms, occasionally in grand mal
Toxic effects	Drowsiness, rash

Mebaral (mephobarbital)

Dose	0.03 g., 0.1 g. tablets. Demethylated to phenobarbital.
Daily dosage	Children: 0.06-0.3 g; adults: 0.3-0.6 g.
Symptoms	Grand mal, petit mal, psychomotor, focal seizures; most useful in combination with hydantoins
Toxic effects	Drowsiness, irritability, rash

Mesantoin (methylphenylethylhydantoin)

Dose	0.1 g.
Daily dosage	Children: 0.1-0.4 g.; adults: 0.4-0.8 g.
Symptoms	Grand mal, psychomotor, focal seizures
Toxic effects	Rash, fever, drowsiness, ataxia, gum hypertrophy, (less than dilantin), neutropenia, agranulocytosis, aplastic and megaloblastic anemia.

Milontin (methylphenylsuccinimide)

Dose	0.5 g. capsules; 250 mg./4 ml. suspension.
Daily dosage	Children: 0.25-1.5 g.; adults: 2.0-4.0 g.
Symptoms	Petit mal, myoclonic, akinetic seizures, occasionally psychomotor seizures

Toxic effects	Nausea, dizziness, rash, hematuria (may be nephrotoxic)

Mysoline (primidone)

Dose	0.25 g. tablets; 250 mg./5 ml. suspension
Daily dosage	Children: 0.25-1.0 g.; adults: 0.75-2 g. The daily dosage should be built up very slowly. Blood levels: therapeutic range 5-15 /μg/ml.
Symptoms	Grand mal, psychomotor, focal seizures, occasionally petit mal; useful in combination with Dilantin
Toxic effects	Drowsiness, ataxia, dizziness, rash, nausea, leukopenia rare

Paradione (paramethadione)

Dose	0.15-0.3 g. capsules; 0.3 g/ml. solution.
Daily dosage	Children: 0.3-1.8 g.; adults: 1.2-2.4 g.
Symptoms	Petit mal, myoclonic and akinetic seizures, massive spasms, occasionally psychomotor seizures (in children); often useful in combination with Dilantin and phenobarbital; somewhat less effective and less toxic than Tridione
Toxic effects	Rash, gastric distress, visual symptoms (glare, photophobia), neutropenia, agranulocytosis

Peganone (ethylphenylhydantoin)

Dose	0.25-0.5 g. tablets
Daily dosage	Children: 0.5-1.5 g.; adults: 2.0-3 g.
Symptoms	Grand mal, psychomotor, focal seizures
Toxic effects	Similar to Dilantin but less severe; may be substituted for Dilantin, but is generally less effective

Phenobarbital

Dose	0.015, 0.030; 0.060, and 0.1 g. tablets; 4 mg./ml. elixir. Therapeutic blood level 10-30 /μg/ml.
Daily dosage	Children: 0.45-0.1 g.; adults: 0.1-0.3 g.
Symptoms	All seizure states; grand mal, petit mal, psychomotor, and other focal; most useful in limited dosage in combination with other drugs such as Dilantin
Toxic effects	Drowsiness, dulling, rash, fever; irritability and hyperactivity in some children

Phenurone (phenacemide)

Daily dosage	Children: 0.5-2.0 g.; adults: 1.5-3.0 g.
Symptoms	May be effective in all types of seizures, especially focal temporal-lobe or other psychomotor seizures; should be used only in very resistant cases
Toxic effects	A *highly* toxic drug, producing liver damage, agranulocytosis, psychotic reactions, and rashes

Tridione (trimethadione)

Dose	0.15 g. tablet; 0.3 g. capsule; 0.15 g./4 ml. solution
Daily dosage	Children: 0.3-1.8 g.; adults: 1.2-2.4 g.
Symptoms	Petit mal, myoclonic and akinetic seizures, massive spasms, occasionally psychomotor seizures (in children); often useful in combination with Dilantin and phenobarbital
Toxic effects	Rash, gastric distress, visual symptoms (glare, photophobia), neutropenia, agranulocytosis

Zarontin (ethosuximide)

Dose	0.25 g. capsule

Daily dosage	Children: 0.75-1.0 g.; adults: 1.5 g.
Symptoms	Petit mal seizures (the drug of choice, now); use with Dilantin in mixed seizure states
Toxic effects	Blood dyscrasias (pancytopenia, leukopenia), dermatitis, anorexia, nausea, drowsiness, dizziness, euphoria; disturbance of mental functions reported in some patients

The following drugs may be used in the emergency treatment of status epilepticus:

Drug	Dose
Sodium phenobarbital:	0.25-0.50 g., IV
Sodium amytal:	0.25-0.50 g., IV
Paraldehyde:	3.0 -5.0 g., IV diluted in saline, or 10-20 ml. IM
Dilantin sodium: (parenteral prep.)	0.25 g., IV or IM (to 0.5 g./24 hours)
Valium (diazepam):	10 mg., IV

More general anesthetics, such as ether, avertin, and xylocaine, have a limited usefulness in treatment of status epilepticus. Careful nursing and attention to fluid and electrolyte balance, airway, cardiac, and renal functions, and temperature control are essential. Adrenocorticotrophic hormone (ACTH) and adrenocortical steroids are used as anticonvulsants in treating massive spasm epilepsy in infancy associated with the "hypsarhythmic" electroencephalogram. A "ketogenic" diet may be helpful in certain children

and young adults, with intractable seizures.

The basic mechanisms of anticonvulsant drugs are not clearly understood. Most such drugs are neuronal depressants with certain variations in action. The hydantoin drugs have been found to reduce the synaptic activity of posttetanic potentiation; the oxazolidine (trimethadione) drugs decrease transmission during repetitive stimulation. Increased stabilization of excitable neuronal membranes probably takes place by action upon electrochemical characteristics involved in ion permeability and membrane polarization. These stabilizing effects presumably decrease the activity of the abnormal hyperexcitable neuronal aggregates in an epileptogenic focus and, more importantly, generally prevent the spread of discharge through normal neuronal circuits.

While there are many anticonvulsant drugs, none is capable of total seizure control in all patients. However, careful selection and utilization in each individual case often leads to optimal results. Each physician should learn to use a number of these drugs and to recognize disturbing side effects as early as possible. Periodic blood counts, urinalyses, and liver-function tests are necessary during administration of many of these drugs.

The majority of the anticonvulsant drugs are administered to achieve a desired effect and the dosage must be increased to the point of tolerance

without untoward toxic reactions. Blood levels should be followed (see Table 13-2). It is best to start with a drug of choice; however, a single drug does not usually achieve the desired degree of control and a second may be necessary; two drugs may be indicated initially in patients with two different types of seizure, e.g., grand mal and petit mal. The process may require weeks of adjustment and during this time the patient's and family's cooperation in reporting effects on seizure frequency or side reactions is most important. Frequent changing of drugs is to be avoided.

Unfortunately, there is no specific anticonvulsant drug for each type of seizure. However, there is one major therapeutic axiom; the petit-mal absence does require a special anticonvulsant drug, either a succinimide (Zarontin) or an oxazolidine (trimethadione). Ethosuximide (Zarontin) is generally the drug of choice for this seizure state. This group of drugs is not effective in the treatment of major generalized seizures; conversely, the hydantoins are not generally effective in petit mal. Some authors state that the drugs effective in petit mal may worsen a generalized seizure state and vice versa; adequate evidence for this generalization has not been reported to date.

Generalized seizures, grand mal, and minor motor seizures are best treated with diphenylhydantoin sodium and phenobarbital. Initially, either drug may be administered to patients with infrequent attacks, but generally

the combination of diphenylhydantoin and phenobarbital will achieve control of seizure in up to 85 percent of patients. Dosages should vary as indicated in Table 13-2. The average dose of diphenylhydantoin is 0.3-0.4 g. per day, usually administered as 0.2 g. in the morning after breakfast and 0.2 g. after dinner. The use of diphenylhydantoin has been enhanced by the determination of blood levels of the drug. The effective therapeutic range is between 10 and 20 μg/100 ml. Toxic effects usually appear at levels above this. The dosage of phenobarbital is initially 60 mg. at bedtime, with 30-mg. increments during the day if necessary; dosage is limited by its sedative effect.

Patients with psychomotor-temporal-lobe epilepsy are often more difficult to control. In these instances many trials may be necessary; the best results are to be expected with diphenylhydantoin and either phenobarbital or primidone. Although in some clinics the latter two drugs are used together, their sedative effects combine to make such administration difficult. Actually a significant amount of primidone is metabolized into phenobarbital. When employing primidone it is very important to start with doses ranging from 50 to 125 mg. per day, increasing slowly at weekly intervals to a maximum of 0.75 or 1.0 g. per day. If untoward side effects occur with diphenylhydantoin, substitution with the less reactive ethylphenylhydantoin is sometimes successful, although this drug has a weaker anticonvulsant effect. Mephenytoin and phenacemide are useful in difficult cases, but must be

utilized with extreme care because of their high toxicity.

Occasionally, a paradoxical reaction to diphenylhydantoin occurs, at a time when a high or toxic blood level is reached, or, in some instances, even at a level regarded as nontoxic but relatively high for the particular patient. This clinical state is characterized by a lapse of seizure control with actual increase in seizures, worsening of the EEG with increased paroxysmal discharges and background slow waves, and a dulling of perceptual-cognitive functions (with poor school or work performance, for example). Occasionally, focal neurological signs, such as hemiparesis, appear. There may be no usual "toxic" signs of diphenylhydantoin excess such as nystagmus or ataxia. Photic stimulation or other "alerting" stimuli may actually reduce the EEG phenomena. The term "diphenylhydantoin encephalopathy" has been applied to this state, but the mechanism of its production remains unclear. It is clinically significant, and can be treated by reduction of dosage.

Disturbances of intellectual function, along with psychotic states, reported in children treated with ethosuximide have been difficult to evaluate in relation to the seizure process and interictal state.

Certain stimulating drugs such as the amphetamines may be useful adjuncts in the therapy of certain patients, particularly to counteract sedative effects of phenobarbital or primidone without interfering with anticonvulsant

action.

It is of interest that certain drugs interfere with the metabolism of diphenylhydantoin and increase its blood levels; these include dicoumarol, phenylbutazone, disulfiram, *p*-aminosalicylate, and isoniazid.

Acetazolamide is (Diamox) an important adjuvant in some patients with any type of seizure state, since it seems to have a general effect upon hyperexcitable cerebral neurons because of its inhibition of carbonic anhydrase or production of an acidosis. Since tolerance develops, the drug should be administered intermittently; it is occasionally useful, for example, in helping to control seizures occurring prior to or during the menstrual cycle. Under these circumstances acetazoleamide is administered for a week before and during the menstrual period. Some patients require its administration continually; tolerance does not develop in all patients.

The results of drug therapy are difficult to predict. With careful attention to individual details and general patient management, the patient with occasional generalized and psychomotor seizure can achieve effective control of seizure frequency. In children with petit-mal absences, the results are generally quite satisfactory. There are in each group of patients, however, a refractory number with increasing psychological and social problems as the years go by. This is the group which requires frequent changes in drugs and in

which side effects become most troublesome.

Problems relating to drug withdrawal appear when patients achieve complete seizure control for a number of years; after two years the question of drug withdrawal is usually raised. However, in most adults with grand mal and psychomotor epilepsy, continued therapy is necessary. In relatively few patients can drug withdrawal be accomplished even after freedom from seizures for three to five years; seizures usually recur. As has been pointed out, the EEG may remain abnormal in clinically seizure free patients, indicating seizure potentiality; and even in cases in which the EGG reverts to normal, drug withdrawal may be unsuccessful.

However, a calculated risk of drug withdrawal should be considered in some patients, since successful withdrawal could represent an important psychological achievement. Drug withdrawal should be attempted extremely carefully with small decrements over many weeks. Drug withdrawal can be expected to be more successful in children with controlled petit-mal epilepsy, particularly since there is a natural tendency for petit mal to diminish with age and maturity. However, in some of these patients generalized convulsions appear even after the absences have ceased.

Dietary Treatment

In general, there are no dietary restrictions for the patient with

epilepsy, nor is there a specific diet capable of aiding most patients. However, a diet high in fat content producing significant ketosis, i.e., the "ketogenic diet," is occasionally helpful in young children, particularly those with intractable absences and minor motor seizures. Anticonvulsant drugs usually have to be continued and the diet is difficult to maintain because of its lack of appeal.

Psychological Therapy and Sociological Management

Even though drugs may achieve a significant degree of seizure control in individual patients, there are many problems related to the life and adjustment of the patient that need additional management. These are generally less marked when the seizures are under control, and require greater attention when seizures create continued problems. There are certain patients, particularly some children and adults with psychomotor-temporal-lobe seizures, who develop increased personality and behavioral disorders after seizure control; the reasons for this are not clear. In many patients, the coexistence of seizure and personality problems requires a combination of medical anticonvulsant therapy and psychologically oriented management.

Although many anticonvulsant drugs have sedative properties, these usually are not used directly. The so-called tranquilizing drugs have limited usefulness in the management of seizure patients. Chlordiazepoxide and

diazepam may reduce disturbed behavior, particularly in children. The phenothiazine drugs have variable effects; the alerting phenothiazine, fluphenazine, is of some use in controlling abnormal behavior in certain patients with psychomotor seizures. However, other drugs in the chlorpromazine group are known to provoke paroxysmal discharges in the EEG and seizures.

In most patients there is a direct interplay of emotional disturbances with clinical seizure activity; patients in a state of psychological turmoil have increased seizure susceptibility and often require greater amounts of anticonvulsant drugs. The achievement of psychological adjustment often reduces seizure frequency and intensity, and lessens drug requirement. This fact must be considered in relation to the individual patient, the age, family, and social circumstances. Family understanding is of primary importance, since the child with seizures must live, insofar as possible, as a normal individual within home and school settings. A great problem, still to be overcome, is the stigma attached to epilepsy and the lack of understanding which exists not only among people in general but in relation to various restrictive legal and social practices. Most children with seizures can attend schools and vocational programs successfully; most adults with seizures can develop productive careers and engage in activities, such as marriage, childbearing, obtaining an education, driving an automobile, traveling, and working successfully in business and industry; while so engaged they can and

should be protected by insurance and workmen's compensation programs. Only few patients require a protected environment in schools or "colonies" specifically developed for the epileptic. Even these should not be institutions in which many hundreds of epileptic patients are kept under essentially custodial care. Special treatment units or "colonies" in Great Britain, Holland, Denmark, and France are relatively small and homelike; they are designed to provide care for usually small numbers of patients at a time, involved in intensive programs of medical therapy, psychological management, education, and vocational training. From these units increasing numbers of adequately controlled patients are sent out into the general community where they can live well-adjusted and productive lives.

There are only a few occupations contraindicated for patients with a tendency toward seizures; these include activities of potential danger to either the patient or others, e.g., work requiring climbing to great heights, using heavy power equipment, or perhaps dangerous chemical substances; there may be exceptions in individual cases.

There is no medical reason to restrict driving an automobile if the patient has been seizure-free for at least two years. Furthermore, the work records of many patients with a history of seizures show that they are seldom involved in industrial accidents because they realize how important it is to their welfare to be most careful.

In a family situation, therefore, the person with epilepsy must be accepted on as normal a basis as possible; restrictive situations must be minimal, if needed at all, and a regular program of education and vocational planning should be developed. School officials frequently need appropriate orientation; most children and young adults with seizures are accepted without question by their associates.

In individual instances, both informal and formal psychotherapeutic measures can be undertaken in order to reduce emotional disturbances. The role of the family physician is all-important; often he alone can judge the problems in a family, school, or social setting and can, by his guidance and understanding, help the patient and his family overcome the feelings of despair, anxiety, fear, and self-consciousness that interfere with everyone's normal adjustment. It is only when anxieties and depressive tendencies develop into more severe reactions, associated with perhaps paranoid states, increased withdrawal, and excessive obsessional tendencies, that more intensive psychiatric treatment may become necessary. Occasionally, it is found that brief periods of appropriately oriented hospitalization with psychotherapy can help readjust or control such patients. This may also be required to evaluate the intensity of the psychological disturbance and the apparent intellectual difficulties that may be interfering with the patient's performance. Adjustment of drug schedules may be carried out at the same time. With increased experience even the child with epilepsy and behavioral

disorder can be cared for best if he can attend a normal school with an understanding environment and, in addition, be associated with a clinical outpatient service in which the functions, of the physician and social service department work together with the child and the family. It is becoming less necessary to arrange for either home tutoring or placement of such children into special schools or other facilities for the maladjusted.

"Conditioned Inhibition" or "Desensitization" Therapy

There has been much interest, in recent years, in attempting to reduce or control seizures, particularly those triggered by sensory or reflex stimuli, by "desensitization" techniques. Whether these represent "true conditioning" in the Pavlovian sense remains problematic. However the results have sometimes been interesting and therapeutically successful. Olfactory stimuli have been known to arrest uncinate seizures since the time of Jackson, and were studied in detail by Efron. Forster and his group have been involved in a number of "conditioning" therapeutic trials in patients with various kinds of sensory or reflex-induced epilepsies (reading, photic, audiogenic, especially musicogenic). These phenomena have led to experimental studies as well. In specifically selected patients, therefore, such techniques, utilizing the known stimulus in a "desensitization" or "conditioning" paradigm, may lead to effective therapy.

Surgical Therapy

There is no question that a patient with a lesion such as a brain tumor should be considered for operation, regardless of the state of the seizures. Surgical intervention with removal of a focus of abnormal discharge is considered an appropriate treatment for certain patients who have intractable focal epilepsy, after adequate trial of intensive medical care. The evaluation of such a patient, therefore, must consist of careful medical and neurological studies which should include a psychological consideration, since rehabilitation may be affected by the procedure. A focally discharging area should be determined by serial electroencephalographic studies as being fixed, and the region of brain considered for excision must be such that the patient will not be left with a severe speech, memory, or other neurological deficit.

Patients so evaluated often do not have obvious brain tumors, but the epileptogenic region involved as the discharging focus may contain a small tumor, a vascular lesion, or a scar secondary to trauma or previous encephalitis. This approach has been particularly used in patients with focal motor seizures, especially psychomotor-temporal-lobe or limbic seizures. It must be realized that even though many patients are considered for surgical therapy, few are chosen; the number of surgically treated epileptic patients is still only in the hundreds. Yet, the occasional patient carefully selected for

such surgical therapy may achieve significant control of seizures. In some series good results have been reported in up to 50 percent; unfortunately, this means that an equal number are not better controlled postoperatively. In some cases, however, less anticonvulsant medication may be required. Occasionally, generalized seizures appear instead of previous psychomotor-temporal-lobe seizures. In most of these patients it would seem that the regions of brain involved are too widespread for limited excisions to be practicable. A small number of patients have experienced relief from severe personality disturbances, particularly aggressive psychotic behavior, but the surgical intervention usually has not been primarily directed toward this end. Bilateral operations on the temporal lobe have only limited effectiveness and may produce severe memory disturbances. The use of stereotaxic neurosurgical techniques to destroy epileptogenic regions deeply seated in brain, i.e., amygdala and hippocampus, has been recommended, particularly for certain patients with psychomotor-temporal-lobe epilepsy where there is such evidence from depth electroencephalographic studies. In a small number of carefully selected children with severe infantile hemiplegia, intractable convulsions, and behavior disturbance, cerebral hemispherectomy has been performed with improvement in seizure state and behavior despite the persistence of neurologic disability.

Concluding Remarks

Much more must be learned about the natural history of the epileptic in order to evaluate thoroughly the different therapies. The question of treating the young child who has had a single febrile convulsion is typical of the problems involved. There is accumulating evidence that recurring seizures (especially with *status epilepticus*) do produce cerebral damage which may eventually cause clinical neurological dysfunction and further severe seizures. On the other hand, many infants and young children have one or a few seizures and then no more.

Proper medical therapy adequately controls most seizure states in over 60 percent of patients and partially controls an additional 25-30 percent. The drugs involved are decreasingly toxic, although anticonvulsant medication remains essentially nonspecific and broadly directed against mechanisms of neuronal hyperexcitability that are little understood. The remaining intractable patients may be considered for surgical therapy; such procedures are applicable, however as stated, to only a very small selected group. Surgical therapy is effective in only about 50 percent of those chosen. It is hoped that combined physiological and biochemical studies of disturbed cerebral and general bodily functions in epilepsy will lead eventually to more rational and effective therapy.

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Notes

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2 Raven’s matrices consists of a graded series of patterns in which one part is missing and the correct missing part is chosen by the subject from a collection of six (or later in the test eight) alternatives. At its simplest, the task requires only matching a pattern, but at its most complex, the grasp of a subtle relationship between the parts of the system is required.