CHAPTER 16

EPILEPSY AND OTHER SEIZURE DISORDERS

In contemporary society, the frequency and importance of epilepsy can hardly be overstated. From the epidemiologic studies of Hauser and colleagues, one may extrapolate an incidence of approximately 2 million individuals in the United States who are subject to epilepsy (i.e., chronically recurrent cerebral cortical seizures) and predict about 44 new cases per 100,000 population occur each year. These figures are exclusive of patients in whom convulsions complicate febrile and other intercurrent illnesses or injuries. It has also been estimated that slightly less than 1 percent of persons in the United States will have epilepsy by the age of 20 years (Hauser and Annegers). Over two-thirds of all epileptic seizures begin in childhood (most in the first year of life), and this is the age period when seizures assume the widest array of forms. The incidence increases again slightly after age 60. In the practice of pediatric neurology, epilepsy is one of the most common disorders. The chronicity of childhood forms and their persistence in patients of all ages adds to their importance. For all these reasons, every physician should know something of the nature of seizure disorders and their treatment. It is, however, notable that in striking contrast to the many treatments available for epilepsy, as pointed out by J. Engle, 80 to 90 percent of epileptics in the developing world never receive treatment.

Epilepsy was in the past defined as an intermittent derangement of the nervous system due to "an excessive and disorderly discharge of cerebral nervous tissue on muscles." This was the postulate, in 1870, of Hughlings Jackson, the eminent British neurologist, and modern electrophysiology offers no evidence to the contrary. The discharge may result in an almost instantaneous loss of consciousness, alteration of perception or impairment of psychic function, convulsive movements, disturbance of sensation, or some combination thereof. A terminologic difficulty arises from the diversity of the clinical manifestations. The term *convulsion*, referring as it does to an intense paroxysm of involuntary repetitive muscular contractions, is inappropriate for a disorder that may consist only of an alteration of sensation or consciousness. *Seizure* is preferable as a generic term, since it embraces a diversity of paroxysmal events and also because it lends itself to qualification. The term *motor* or *convulsive seizure* is therefore not tautologic, and one may likewise speak of a *sensory seizure* or *psychic seizure*. The word *epilepsy* is derived from Greek words meaning "to seize upon" or a "taking hold of." Our predecessors referred to it as the "falling sickness" or the "falling evil." Although a useful medical term to denote recurrent seizures, the words *epilepsy* and *epileptic* still have unpleasant connotations to the laity and should be used advisedly in dealing with patients.

Viewed in its many clinical contexts, the first solitary seizure or brief outburst of seizures may occur during the course of many medical illnesses. It indicates that the cerebral cortex has been affected by disease, either primarily or secondarily. Convulsive seizures by their nature, if repeated every few minutes, as in status epilepticus, may threaten life. Equally important, a seizure or a series of seizures may be the manifestation of an ongoing neurologic disease that demands the employment of special diagnostic and therapeutic measures, as in the case of a brain tumor.

A more common and less grave circumstance is for a seizure to be but one in an extensive series recurring over a long period of time, with most of the attacks being more or less similar in type. In this instance they may be the result of a burned-out lesion that originated in the past and remains as a scar. The original disease may have passed unnoticed, or perhaps had occurred in utero, at birth, or in infancy, in parts of the brain inaccessible for examination or too immature to manifest signs. It may have affected a very small or "silent" area in a mature brain. The increasingly refined techniques of magnetic resonance imaging (MRI) are now beginning to reveal small zones of cortical dysplasia and hippocampal sclerosis, both of which tend to be epileptogenic. Patients with such long-standing lesions probably make up the majority of those with recurrent seizures but are necessarily classified as having "idiopathic" or "cryptogenic epilepsy," because it is often impossible to ascertain the nature of the original disease and the seizures may be the only sign of brain abnormality.

There are other types of epilepsy for which no pathologic basis has been established and for which there is no apparent underlying cause except perhaps a genetic one. These epilepsies have been referred to as *primary*. Included in this category are hereditary forms, such as certain generalized tonic-clonic (grand mal) and "absence" seizure states. Some authors (Lennox and Lennox; Forster) have reserved the term *idiopathic* for recurrent seizures of these types.

CLASSIFICATION OF SEIZURES

Seizures have been classified in several ways: according to their supposed etiology, i.e., idiopathic (primary) or symptomatic (secondary); their site of origin; their clinical form (generalized or focal); their frequency (isolated, cyclic, or repetitive, or the closely spaced sequence of status epilepticus); or their electrophysiologic correlates. A distinction must be made between the classification of *seizures* (the clinical manifestations of epilepsy: grand mal, petit mal, myoclonic, partial, and others), considered below, and the classification of the *epilepsies*, or *epileptic syndromes*, which are disease constellations, most of which may manifest several seizure types. These are discussed later in the chapter.

The classification to be followed here was first proposed by Gastaut in 1970 and was then refined repeatedly by the Commission on Classification and Terminology of the International League Against Epilepsy (1981). This classification, based mainly on the clinical form of the seizure and its electroencephalographic (EEG) features, has been adopted worldwide and is generally referred to as the International Classification. A modified version of it is reproduced in Table 16-1.

The strength of the International Classification lies in its easy applicability to patients with epilepsy and its universal adoption. The main value of classifying a seizure by its clinical and EEG features is the reasonable predictability of response to specific med-

Table 16-1
International classification of epileptic seizures

I. Generalized seizures (bilaterally symmetrical and without local onset)
  A. Tonic, clonic, or tonic-clonic (grand mal)
  B. Absence (petit mal)
    1. With loss of consciousness only
    2. Complex—with brief tonic, clonic, or automatic movements
  C. Lennox-Gastaut syndrome
  D. Juvenile myoclonic epilepsy
  E. Infantile spasms (West syndrome)
  F. Atonic (astatic, akinetic) seizures (sometimes with myoclonic jerks)
II. Partial, or focal, seizures (seizures beginning locally)
  A. Simple (*without* loss of consciousness or alteration in psychic function)
    1. Motor–frontal lobe origin (tonic, clonic, tonic-clonic; jacksonian; benign childhood epilepsy; epilepsia partialis continua)
    2. Somatosensory or special sensory (visual, auditory, olfactory, gustatory, vertiginous)
    3. Autonomic
    4. Pure psychic
  B. Complex (*with* impaired consciousness)
    1. Beginning as simple partial seizures and progressing to impairment of consciousness
    2. With impairment of consciousness at onset
III. Special epileptic syndromes
  A. Myoclonus and myoclonic seizures
  B. Reflex epilepsy
  C. Acquired aphasia with convulsive disorder
  D. Febrile and other seizures of infancy and childhood
  E. Hysterical seizures

ications and to some extent in prognosis. Basically, this classification divides seizures into two types—*partial*, in which a focal or localized onset can be discerned, and *generalized*, in which the seizures appear to begin bilaterally.

It is also useful clinically and etiologically to separate epilepsies that originate as truly generalized electrical discharges in the brain from those which spread secondarily from a focus to become generalized. The *primary generalized epilepsies* are a group of somewhat diverse, age-dependent phenotypes that are characterized by generalized 2.5- to 4-Hz bifrontally predominant spikes or polyspike-and-slow-wave discharges that arise without underlying structural abnormalities. In most instances, these individuals have normal intelligence. What is most significant is that a genetic component underlies many of these disorders (see below). By contrast, seizures that begin locally and evolve into generalized tonic-clonic seizures, termed *secondary generalized seizures*, generally have no such genetic component and are usually the result of underlying brain disease, either acquired or due to congenital malformations or metabolic defects. Quite often, the initial focal phase is missed, leading to misdiagnosis. Individuals with secondary generalized epilepsies tend to have more diffuse brain dysfunction and may have a progressive course. These seizures may be of different types, including atonic, myoclonic, and tonic-clonic seizures. An increasing frequency and severity of this group of disorders with age reflects the accumulation of focal insults from trauma, strokes, and other damage.

Partial or *focal seizures* are further classified as *simple* when consciousness is undisturbed and *complex* when consciousness is altered or impaired. Simple partial seizures are further classified according to their main clinical manifestations—motor, sensory, autonomic, or psychic. When one of these subjective manifestations precedes the progression of the attack to a loss of consciousness, it is referred to as an *aura* and has commonly been regarded as a premonitory sign or warning of the impending seizure. In reality, the aura represents the initial phase of a focal seizure; in some instances it may constitute the entire epileptic attack.

Generalized seizures are of two types—*convulsive* and *nonconvulsive*. The common convulsive type is the *tonic-clonic (grand mal) seizure*. Less common is a purely tonic, purely clonic, or clonic-tonic-clonic generalized seizure. The classic nonconvulsive generalized seizure is the brief lapse of consciousness or absence (*petit mal*); included also under this heading are minor motor phenomena such as brief myoclonic, atonic, or tonic seizures.

The classification of seizures and of the epilepsies is constantly being modified. In one of the latest versions, the so-called syndromic classification (*Epilepsia* 30:389, 1989), an attempt has been made to incorporate all of the seizure types and epileptic syndromes and to categorize them not only as partial and generalized but also according to their age of onset, their primary or secondary nature, the evidence of cortical loci of the epileptogenic lesions, and the many clinical settings in which they occur. This classification is semantically difficult and, in our view, too complicated as yet for general clinical application. Since many epileptic syndromes share overlapping features, it is often not possible to fit a newly diagnosed case of epilepsy into a specific category in this new classification (Manford et al). The commission is engaged in an extensive revision of terminology and classification in the field of epilepsy. Until this revision is widely adopted, we propose to begin our discussion with the 1981 classification of seizures, with certain modifications and additions, to be followed by a consideration of a number of well-defined epilepsies and epileptic syndromes.

In the discussions that follow, the various types of seizures are viewed largely in the context of the age at which they occur. An approximation of the distribution of the seizure types for each age epoch, obtained and aggregated from several sources, is shown in Fig. 16-1.

There has also been substantial progress in defining the molecular basis of familial and hereditary epilepsies over the last decade; it is highly likely that these new insights will lead to further modification of both the clinical classifications and the therapeutic management of the epilepsies (see further on).

GENERALIZED SEIZURES

The Generalized Tonic-Clonic Seizure (Grand Mal)

As has already been pointed out, it is important, whenever possible, to distinguish between a primary (generalized) type of seizure, with widespread EEG abnormalities at the onset, and a secondarily generalized type, which begins as a focal or partial seizure and then becomes generalized.

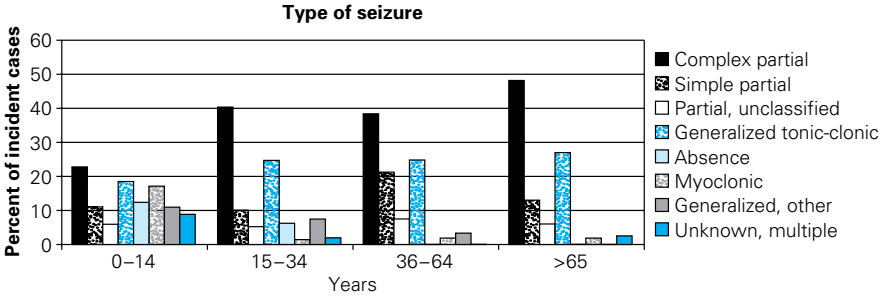

Figure 16-1. The distribution of the main types of epilepsy by age. Apparent is the overrepresentation of absence and myoclonic seizures in childhood and of complex partial seizures in older individuals. (Adapted from Hauser and Annegers and the texts of Engel and of Pedley.)

The patient sometimes senses the approach of a seizure by one of several subjective phenomena (a *prodrome*). For some hours, the patient may feel apathetic, depressed, irritable, or, very rarely, the opposite—ecstatic. One or more myoclonic jerks of the trunk or limbs on awakening may herald a seizure later in the day. In more than half the cases, there is some type of movement for a few seconds before consciousness is lost (turning of the head and eyes or whole body or intermittent jerking of a limb), although the patient fails to form a memory of this and such information is obtained only from an observer. Abdominal pains or cramps, a sinking, rising, or gripping feeling in the epigastrium, pallor or redness of the face, throbbing headache, constipation, or diarrhea have also been given prodromal status, but we have not found them consistently enough to be helpful.

Most often, the seizure strikes "out of the blue," i.e., without warning, beginning with a sudden loss of consciousness and fall to the ground. The initial motor signs are a brief flexion of the trunk, an opening of the mouth and eyelids, and upward deviation of the eyes. The arms are elevated and abducted, the elbows semiflexed, and the hands pronated. These are followed by a more protracted extension (*tonic*) phase, involving first the back and neck, then the arms and legs. There may be a piercing cry as the whole musculature is seized in a spasm and air is forcibly emitted through the closed vocal cords. Since the respiratory muscles are caught up in the tonic spasm, breathing is suspended, and after some seconds the skin and mucous membranes may become cyanotic. The pupils are dilated and unreactive to light. The bladder may empty at this stage or later, during the postictal coma. This is the tonic phase of the seizure and lasts for 10 to 20 s.

There then occurs a transition from the tonic to the *clonic phase* of the convulsion. At first there is a mild generalized tremor, which is, in effect, a repetitive relaxation of the tonic contraction. It begins at a rate of eight per second and coarsens to four per second; then it rapidly gives way to brief, violent flexor spasms that come in rhythmic salvos and agitate the entire body. The face becomes violaceous and contorted by a series of grimaces, and often the tongue is bitten. Autonomic signs are prominent: the pulse is rapid, blood pressure is elevated, pupils are dilated, and salivation and sweating are abundant; bladder pressure may increase sixfold during this phase. The clonic jerks decrease in amplitude and frequency over a period of about 30 s. The patient remains apneic until the end of the clonic phase, which is marked by a deep inspiration. Instead of the whole dramatic sequence described above, the seizures may be abbreviated or limited in scope by anticonvulsive medications.

In the terminal phase of the seizure, all movements have ended and the patient lies still and limp, in a deep coma. The pupils, equal or unequal, now begin to contract to light. Breathing may be quiet or stertorous. This state persists for several minutes, after which the patient opens his eyes, begins to look about, and is obviously bewildered and confused and may be quite agitated. The patient may speak and later not remember anything that he said. Undisturbed, he becomes drowsy and falls asleep, sometimes for several hours, then sometimes awakens with a pulsatile headache. When fully recovered, such a patient has no memory of any part of the spell but knows that something has happened because of the strange surroundings (in ambulance or hospital); the obvious concern of those around him; and a sore, bitten tongue and aching muscles from the violent contractions. The latter, if violent enough, may crush a vertebral body or result in a serious injury; a fracture, periorbital hemorrhages, subdural hematoma, or burn may have been sustained in the fall.

Each of these phases of the generalized tonic-clonic seizure has its characteristic EEG accompaniment. Initially, movement artifacts obscure the EEG changes; sometimes there are repetitive spikes or spike-wave discharges lasting a few seconds, followed by an approximately 10-s period of 10-Hz spikes. As the clonic phase asserts itself, the spikes become mixed with slow waves and then the EEG slowly assumes a polyspike-and-wave pattern. When all movements have ceased, the EEG tracing is nearly flat for a variable time, and then the brain waves resume their preseizure pattern.

Convulsions of this type ordinarily come singly or in groups of two or three and may occur when the patient is awake and active or during sleep, or frequently when falling asleep or awakening. Some 5 to 8 percent of such patients will at some time have a prolonged series of such seizures without resumption of consciousness between them; this is called *convulsive status epilepticus* and demands urgent treatment. Sometimes the first outburst of seizures takes the form of convulsive status.

Few clinical states closely simulate a grand mal convulsion, but several are worthy of mention. One is a clonic jerking of the extended limbs (usually less severe than those of a grand mal seizure) that occurs with vasodepressor syncope or a Stokes-Adams attack. In contrast to an epileptic type of EEG, the brain waves are slow and flat during the jerking movements. A rarer phenomenon that may be indistinguishable from a generalized convulsion occurs as part of basilar artery occlusion (Ropper). This presumably has its basis in ischemia of the corticospinal tracts in the pons; a similar ischemic mechanism in the cortex has been invoked for "limb-shaking TIAs" (transient ischemic attacks), in which there are clonic movements of one limb or one side of the body during an episode of cerebral ischemia. Hysterical (nonepileptogenic, "psychogenic") seizures, as discussed further on, are often difficult to distinguish from a true seizure. Rarely, in adults, an attack of panic (page 438) or the rare entity of rapid-eye-movement (REM) sleep

behavior disorder (page 343) may resemble a seizure. In infants, a breath-holding spell may resemble the tonic phase of a generalized seizure.

Idiopathic Nonconvulsive Seizures (Absence, Petit Mal)

In contrast to major generalized seizures, absence seizures (formerly referred to as *petit mal* or *pykno-epilepsy*) are notable for their brevity and the paucity of motor activity. Indeed, they may be so brief that the patients themselves are sometimes not aware of them; to an onlooker, they resemble a moment of absentmindedness or daydreaming. The attack, coming without warning, consists of a sudden interruption of consciousness, for which the French word *absence* ("not present," "not in attendance") has been retained. The patient stares and briefly stops talking or ceases to respond. Only about 10 percent of such patients are completely motionless during the attack; in the remainder, one observes a brief burst of fine clonic movements of the eyelids, facial muscles, or fingers or synchronous movements of both arms at a rate of three per second. This rate corresponds to that of the EEG abnormality, which takes the form of a generalized three-per-second spike-and-wave pattern (Fig. 2-3*E*, page 26). Minor automatisms—in the form of lip-smacking, chewing, and fumbling movements of the fingers—are common during an attack but do not assume prominence. Postural tone may be slightly decreased or increased, and occasionally there is a mild vasomotor disorder. As a rule, such patients do not fall; they may even continue such complex acts as walking or riding a bicycle. After 2 to 10 s, occasionally longer, the patient re-establishes full contact with the environment and resumes preseizure activity. Only a loss of the thread of conversation or the place in reading betrays the occurrence of the momentary "blank" period (the absence). In many such patients, voluntary hyperventilation for 2 to 3 min is an effective way of inducing absence attacks.

Typical absence seizures constitute the most characteristic epilepsy of childhood; rarely do the seizures begin before 4 years of age or after puberty. Another attribute is their great frequency (hence the old term *pykno*, meaning "compact" or "dense"). As many as several hundred may occur in a single day, sometimes in bursts at certain times of the day. Most often they relate to periods of inattention and may appear in the classroom when the child is sitting quietly rather than participating actively in his lessons. If frequent, they may disturb attention and thinking to the point that the child's performance in school is impaired. Such attacks may last for hours with no interval of normal mental activity between them—so-called *absence* or *petit mal status*. Small, subtle three-per-second myoclonic movements are the only motor display (myoclonic petit mal), and are accompanied by a continuous three-per-second spike-wave abnormality in the EEG. Most cases of absence status have been described in adults with frontal lobe epilepsy (see below). Such attacks may begin or end with a generalized tonic-clonic seizure or a burst of seizures.

Absence may be the only type of seizure during childhood. The attacks tend to diminish in frequency in adolescence and then often disappear, only to be replaced in many instances by major generalized seizures.

Absence or Petit Mal Variants To be distinguished from typical absence seizures are varieties in which the loss of consciousness is less complete or in which myoclonus is prominent, and others in which the EEG abnormalities are less regularly of a 3-per-second spike-and-wave type (they may occur at the rate of 2 to 2.5 per second or take the form of 4- to 6-Hz polyspike-and-wave complexes). *Atypical petit mal* is a term that was coined to describe long runs of slow spike-and-wave activity, usually with no apparent loss of consciousness. External stimuli such as asking the patient to answer a question or to count will interrupt the run of abnormal EEG activity.

About one-third of children with absence attacks will, in addition, display symmetrical or asymmetrical myoclonic jerks without loss of consciousness, and about half will also at some time have major generalized (tonic-clonic) convulsions. As described further on, a common and relatively benign variety of myoclonic seizure occurs in late childhood and adolescence (*juvenile myoclonic epilepsy*).

In sharp contrast to the aforementioned epilepsies is a form that has its onset between 2 and 6 years of age and is characterized by atonic, or astatic, seizures (i.e., falling attacks), often succeeded by various combinations of minor motor, tonic-clonic, and partial seizures and by progressive intellectual impairment in association with a distinctive, slow (1- to 2-Hz) spike-and-wave EEG pattern. This is the *Lennox-Gastaut syndrome*. Often it is preceded in earlier life by infantile spasms, a characteristic EEG picture (3-Hz "hypsarrhythmia"), and an arrest in mental development, a triad sometimes referred to as the *West syndrome* (see further on). The early onset of atonic seizures with abrupt falls, injuries, and associated abnormalities nearly always has a grave implication—namely, the presence of serious neurologic disease. Prematurity, perinatal injury, and metabolic diseases of infancy are the most common underlying conditions. This is essentially a symptomatic generalized epilepsy, in contrast to the foregoing idiopathic types. The Lennox-Gastaut syndrome may persist into adult life and is one of the most difficult forms of epilepsy to treat.

The notion that absence, myoclonic, and akinetic seizures constitute a petit mal triad, as originally proposed by Lennox, has been generally abandoned. Akinesia (motionlessness) is not unique to any seizure type. The typical absence, with or without myoclonic jerks, rarely causes the patient to fall and should be considered a separate entity because of its relative benignity.

Myoclonic Seizures

The phenomenon of myoclonus has already been discussed in Chap. 6, where the relationship to seizures was indicated. Characterized by a brusque, brief, muscular contraction, some myoclonic jerks are so small as to involve only one muscle or part of a muscle; others are so large as to implicate a limb on one or both sides of the body or the entire trunk musculature. Many are brief, lasting 50 to 100 ms. They may occur intermittently and unpredictably or present as a single jerk or a brief salvo.

As mentioned earlier, an outbreak of several small, rhythmic myoclonic jerks may appear with varying frequency as part of absence seizures and as isolated events in patients with generalized clonic-tonic-clonic or tonic-clonic seizures. As a rule, these types of myoclonus are quite benign and respond well to medication. In contrast, *disseminated myoclonus (polymyoclonus)*, having its onset in childhood, raises the suspicion of acute viral encephalitis, the myoclonus-opsoclonus-ataxia syndrome of Kinsbourne, lithium or other drug toxicity, or, if lasting a few weeks, subacute sclerosing panencephalitis. Chronic progressive polymyoclonus with dementia characterizes the group of juvenile lipidosis, Lafora-

type familial myoclonic epilepsy, certain mitochondrial disorders, or other chronic familial degenerative diseases of undefined type (paramyoclonus multiplex of Friedreich, dyssynergia cerebellaris myoclonica of Ramsay Hunt). In middle and late adult years, disseminated myoclonus joined with dementia usually indicates the presence of so-called Creutzfeldt-Jakob disease (page 653) and rarely of Alzheimer disease. A few late-onset cases of *Lafora disease* have been reported (Messouak et al), but this remains mainly a childhood process, autosomal recessive in transmission, characterized by a triad of progressive dementia, myoclonus, and episodes of generalized seizures, some of which are visual in nature. Intraneuronal cortical inclusions of amyloid are found, and similar inclusions are found in muscle, liver, and skin (polyglucosan body disease is another process associated with these changes). Myoclonus is usually the main manifestation of juvenile myoclonic epilepsy, as discussed below. Uremia at any age gives rise to myoclonus, twitching, and sometimes seizures. The large number of diseases causative of myoclonus and seizure disorders are discussed in Chaps. 33, 37, and 39.

Juvenile Myoclonic Epilepsy This is the most common form of idiopathic generalized epilepsy in older children and young adults. It begins in adolescence, typically about age 15, with a range that essentially spans all of the teenage years. The patient comes to attention because of a generalized seizure, often upon awakening or because of myoclonic jerks in the morning that involve the entire body; sometimes absence seizures are prominent. The family reports that the patient has occasional myoclonic jerks of the arm and upper trunk that become prominent with fatigue, during early stages of sleep, or after alcohol ingestion. A few patients in our experience have had only the myoclonic phenomena and rare absence seizures that persisted unnoticed for years. The EEG characteristically shows bursts of 4- to 6-Hz irregular polyspike activity. A linkage has been established to chromosome 6 in some cases of this illness and in some other forms of juvenile-onset epilepsy, but no mendelian pattern of inheritance has been established. The disorder does not impair intelligence and tends not to be progressive, but a proclivity to infrequent seizures usually continues throughout life. Valproic acid in particular and some other anticonvulsants have been highly effective in eliminating the seizures and myoclonus; they should be continued indefinitely.

PARTIAL OR FOCAL SEIZURES

As indicated earlier, the International Classification divides all seizures into two types—generalized (described above), in which the clinical and EEG manifestations indicate bilateral and diffuse cerebral cortical involvement from the onset, and focal or partial (more recently termed *localization-related*), in which the seizure is often the product of a demonstrable focal lesion or EEG abnormality in some part of the cerebral cortex (or perhaps in the diencephalon). As noted, partial seizures vary with the locale of the lesion and are conventionally divided into two groups, *simple* and *complex*, depending on whether consciousness is retained or impaired. Simple partial seizures most often arise from foci in the sensorimotor cortex. Complex partial seizures most often have their focus in the temporal lobe on one side or the other, but a frontal localization is also well known. The sites of the offending lesions and the types of seizures to which they give rise are listed in Table 16-2. These relationships are so helpful in diagnosis that they should be familar to all neurologists.

Table 16-2
Common seizure patterns

CLINICAL TYPE	LOCALIZATION
Somatic motor	
Jacksonian (focal motor)	Prerolandic gyrus
Masticatory, salivation, speech arrest	Amygdaloid nuclei, opercular
Simple contraversive	Frontal
Head and eye turning associated with arm movement or athetoid-dystonic postures	Supplementary motor cortex
Somatic and special sensory (auras)	
Somatosensory	Contralateral postrolandic
Unformed images, lights, patterns	Occipital
Auditory	Heschl's gyri
Vertiginous	Superior temporal
Olfactory	Mesial temporal
Gustatory	Insula
Visceral: autonomic	Insular-orbital-frontal cortex
Complex partial seizures	
Formed hallucinations	Temporal neocortex or amygdaloid-hippocampal complex
Illusions	
Dyscognitive experiences (déjà vu, dreamy states, depersonalization)	
Affective states (fear, depression, or elation)	Temporal
Automatism (ictal and postictal)	Temporal and frontal
Absence	Frontal cortex, amygdaloid-hippocampal complex, reticular-cortical system
Bilateral epileptic myoclonus	Reticulocortical, frontocentral

SOURCE: Modified by permission from Penfield and Jasper.

Frontal Lobe Partial Seizures (Focal Motor and Jacksonian Seizures)

Focal or partial motor seizures are attributable to a discharging lesion of the opposite frontal lobe. The most common type, originating in the supplementary motor area, takes the form of a turning movement of the head and eyes to the side opposite the irritative focus, often associated with a tonic contraction of the trunk and limbs on that side. This may constitute the entire seizure, or it may be followed by generalized clonic movements; the extension of the seizure may occur just before or simultaneously with loss of consciousness. On the other hand, a lesion in one frontal lobe may give rise to a major generalized convulsion without an initial turning of the head and eyes. It has been postulated that in both types of seizure, the one with and the one without turning movements, there is an immediate spread of the discharge from the frontal lobe to integrating centers in the thalamic or high midbrain reticular formation, accounting for the loss of consciousness.

Seizures that begin with forceful, sustained deviation of the head and eyes, and sometimes of the entire body, are referred to as

versive or *adversive*. Since the turning movements are usually to the side opposite the irritative focus (sometimes to the same side), *contraversive* and *ipsiversive*, respectively, would be preferable terms. Nonforceful, unsustained, or seemingly random lateral head movements during the ictus do not have localizing value. The same is true for the head and eye turning that occurs at the end of the generalized tonic-clonic phase of versive seizures (Wylie et al). Contraversive deviation of only the head and eyes can be induced most consistently by electrical stimulation of the superolateral frontal region (area 8), just anterior to area 6 (see Fig. 22-1). Less dependably, the same movements can be obtained by stimulating the more anterior portions of the frontal cortex, or the supplementary motor area, and the temporal or occipital cortex—presumably through propagation of the ictal discharge to the frontal contraversive area. In seizures of temporal lobe origin, early in the seizure, there may be head turning ipsilaterally followed by forceful, contraversive head (and body) turning. These head and body movements, if they occur, are preceded by quiet staring and other automatisms.

The *jacksonian motor seizure* begins with a tonic contraction of the fingers of one hand, the face on one side, or the muscles of one foot. This transforms into clonic movements in these parts in a fashion analogous to that in a generalized clonic-tonic-clonic convulsion. Sometimes a series of clonic movements of increasing frequency build up to a tonic contraction. The movements may remain localized or spread ("march") from the part first affected to other muscles on the same side of the body. In the latter, or "classic," jacksonian form, which is relatively uncommon, the seizure spreads from the hand, up the arm, to the face, and down the leg; or, if the first movement is in the foot, the seizure marches up the leg, down the arm, and to the face, usually in a matter of 20 to 30 s. Interestingly, spontaneously occurring focal motor seizures, e.g., those beginning in the toes or fingers, may sometimes be arrested (inhibited) by applying a ligature above the affected part or, in the case of focal sensory seizures, by applying a vigorous sensory stimulus ahead of the advancing sensory aura. Rarely, the first muscular contraction is in the abdomen, thorax, or neck. In some cases, the one-sided seizure activity is followed by turning of the head and eyes to the convulsing side, occasionally to the opposite side, and then by a generalized seizure with loss of consciousness. Consciousness is not lost if the sensorimotor symptoms remain confined to one side.

Following convulsions that have a prominent focal motor signature, there may be a transient paralysis of the affected limbs. This "Todd's paralysis" persists for minutes or at times for hours after the seizure, usually in proportion to the duration of the convulsion. Continued focal paralysis beyond this time usually indicates the presence of a focal brain lesion as the underlying cause of the seizure. A similar phenomenon is found in cases of focal epilepsy that involve the language, somesthetic, or visual areas; here the persistent deficit corresponds to the region of brain affected.

The high incidence of onset of focal motor epilepsy in the face, hands, and toes is probably related to the disproportionately large cortical representation of these parts. The disease process or focus of excitation is usually in or near the rolandic (motor) cortex, i.e., area 4 of Brodmann (Figs. 3-3 and 22-1); in some cases, and especially if there is a sensory accompaniment, it has been found in the postrolandic convolution. Lesions confined to the motor cortex are reported to assume the form of clonic contractions, and those confined to the premotor cortex (area 6), tonic contractions of the contralateral arm, face, neck, or all of one side of the body. Tonic elevation and extension of the contralateral arm ("fencer's posture") and choreoathetotic and dystonic postures have been associated with high medial frontal lesions (area 8 and supplementary motor cortex), as have complex, bizarre, and flailing movements of a contralateral limb, but this always raises the suspicion of hysterical seizure. Perspiration and piloerection occur occasionally in parts of the body involved in a focal motor seizure, suggesting that these autonomic functions have a cortical representation in or adjacent to the rolandic area. Focal motor and jacksonian seizures have essentially the same localizing significance.

Seizure discharges arising from the cortical language areas may give rise to a brief aphasic disturbance (*ictal aphasia*) and ejaculation of a word, or, more frequently, a vocal arrest. Ictal aphasia is usually succeeded by other focal or generalized seizure activity but may occur in isolation, without loss of consciousness, in which case it can later be described by the patient. Postictal aphasia is more common and has much the same localizing value. Vocalization at the onset of a seizure has no such significance. These disturbances should be distinguished from the stereotyped repetition of words or phrases or the garbled speech that characterizes some cases of complex partial seizures or the postictal confusional state.

As pointed out by Manford and colleagues, relatively few focal seizures can be localized precisely from clinical data alone. However, when combined with scalp and intracranial EEG recording and MRI, the data are reasonably accurate.

Somatosensory, Visual, and Other Types of Sensory Seizures

Somatosensory seizures, either focal or "marching" to other parts of the body on one side, are nearly always indicative of a focus in or near the postrolandic convolution of the opposite cerebral hemisphere. Penfield and Kristiansen found the seizure focus in the postcentral or precentral convolution in 49 of 55 such cases. The sensory disorder is usually described as numbness, tingling, or a "pins-and-needles" feeling and occasionally as a sensation of crawling (formication), electricity, or movement of the part. Pain and thermal sensations may occur but are exceedingly rare. In the majority of cases, the onset of the sensory seizure is in the lips, fingers, or toes, and the spread to adjacent parts of the body follows a pattern determined by sensory arrangements in the postcentral (postrolandic) convolution of the parietal lobe. If the sensory symptoms are localized to the head, the focus is in or adjacent to the lowest part of the convolution, near the sylvian fissure; if the symptoms are in the leg or foot, the upper part of the convolution, near the superior sagittal sinus or on the medial surface of the hemisphere, is involved.

Visual seizures are relatively rare but also have localizing significance. Lesions in or near the striate cortex of the occipital lobe usually produce elemental visual sensations of darkness or sparks and flashes of light, which may be stationary or moving and colorless or colored. According to Gowers, red is the most frequently reported color, followed by blue, green, and yellow. These images may be referred to the visual field on the side opposite of the lesion or may appear straight ahead. If they occur on one side of the visual field, patients perceive that only one eye is affected (the one opposite the lesion), probably because most persons are aware of only

the temporal half of a homonymous field defect. Curiously, a seizure arising in one occipital lobe may cause momentary blindness in both fields. It has been noted that lesions on the lateral surface of the occipital lobe (Brodmann's areas 18 and 19) are likely to cause a sensation of twinkling or pulsating lights. More complex or formed visual hallucinations are usually due to a focus in the posterior part of the temporal lobe, near its junction with the occipital lobe, and may be associated with auditory hallucinations. The localizing value of visual auras has been confirmed recently by Bien and colleagues in a group of 20 surgically treated patients with intractable seizures. They found that elementary visual hallucinations and visual loss were typical of occipital lobe epilepsy but could also occur with seizure foci in the anteromedial temporal and occipitotemporal regions.

Auditory hallucinations are infrequent as an initial manifestation of a seizure. Occasionally a patient with a focus in one superior temporal convolution will report a buzzing or roaring in the ears. A human voice, sometimes repeating unrecognizable words, or the sound of music, has been noted a few times with lesions in the more posterior part of one temporal lobe.

Vertiginous sensations of a type suggesting a vestibular origin may on rare occasions be the first symptom of a seizure. The lesion is usually located in the superoposterior temporal region or the junction between parietal and temporal lobes. In one of the cases reported by Penfield and Jasper, a sensation of vertigo was evoked by stimulating the cortex at the junction of the parietal and occipital lobes. Occasionally with a temporal focus, the vertigo is followed by an auditory sensation. Giddiness, or light-headedness, is a frequent prelude to a seizure, but this symptom, as discussed in Chap. 15, has so many different connotations that it is of little diagnostic value.

Olfactory hallucinations are often associated with disease of the inferior and medial parts of the temporal lobe, usually in the region of the parahippocampal convolution or the uncus (hence Jackson's term *uncinate seizures*, pages 199 and 398). Usually the perceived odor is exteriorized, i.e., projected to someplace in the environment, and is described as disagreeable or foul, though otherwise unidentifiable. *Gustatory hallucinations* have also been recorded in proven cases of temporal lobe disease (see page 201) and with lesions of the insula and parietal operculum; salivation and a sensation of thirst may be associated. Electrical stimulation in the depths of the sylvian fissure, extending into the insular region, has produced peculiar sensations of taste.

Vague and often indefinable *visceral sensations* arising in the thorax, epigastrium, and abdomen are among the most frequent of auras, as already indicated. Most often they have a temporal lobe origin, although in several such cases the seizure discharge has been localized to the upper bank of the sylvian fissure; in a few others, the focus was located in the upper or middle frontal gyrus or in the medial frontal area near the cingulate gyrus. Palpitation and acceleration of the pulse at the beginning of the attack have also been related to a temporal lobe focus.

Complex Partial Seizures (Psychomotor Seizures, Temporal Lobe Seizures)

These differ from the major generalized and absence seizures discussed above in that (1) the aura (i.e., the initial event in the seizure) may be either a focal seizure of simple type or a hallucination or perceptual illusion, indicating (usually) a temporal lobe origin, and (2) instead of a complete loss of control of thought and action, there is a period of altered behavior and consciousness, for which the patient is later found to be amnesic.

Although it is difficult to enumerate all the psychic experiences that may occur during complex partial seizures, they may be categorized into a somewhat arbitrary hierarchy of illusions, hallucinations, dyscognitive states, and affective experiences. Sensory illusions, or distortions of ongoing perceptions, are the most common. Objects or persons in the environment may shrink or recede into the distance, or they may enlarge (micropsia and macropsia), or perseverate as the head is moved (palinopsia). Tilting of the visual environment has been reported. Hallucinations are most often visual or auditory, consisting of formed or unformed visual images, sounds, and voices; less frequently, they may be olfactory (usually unpleasant, unidentifiable sensations of smell), gustatory, or vertiginous. The term *dyscognitive* state refers to feelings of increased reality or familiarity (déjà vu) or of strangeness or unfamiliarity (jamais vu) or a sense of depersonalization. Fragments of certain old memories or scenes may insert themselves into the patient's mind and recur with striking clarity, or there may be an abrupt interruption of memory. (See Gloor for a more detailed description of the experiential phenomena of temporal lobe epilepsy.) Associated epigastric and abdominal sensations have been alluded to above.

Emotional experiences, while less common, may be dramatic—sadness, loneliness, anger, happiness, and sexual excitement have all been recorded. Fear and anxiety are the most common affective experiences, while occasionally the patient describes a feeling of rage or intense anger as part of a complex partial seizure. Ictal fear may have no apparent connection to objective experience and is generally not related to the situation in which the patient finds himself during the seizure.

Each of these subjective psychic states may constitute the entire seizure (simple partial seizure), or some combination may occur and proceed to a period of unresponsiveness. Patients call these "auras," but they represent electrical seizures and have the same significance as a motor convulsion. The motor components of the seizure, if they occur, do so during the latter phase and take the form of automatisms such as lip-smacking, chewing or swallowing movements, salivation, fumbling of the hands, or shuffling of the feet. Patients may walk around in a daze or act inappropriately (undressing in public, speaking incoherently, etc.). Certain complex acts that were initiated before the loss of consciousness—such as walking, chewing food, turning the pages of a book, or even driving—may continue. However, when asked a specific question or given a command, the patients are obviously out of contact with their surroundings. There may be no response at all, or the patient may look toward the examiner in a perplexed way or utter a few stereotyped phrases. In a very small number of patients with temporal lobe seizures (7 of 123 patients studied by Ebner et al), some degree of responsiveness (to simple questions and motor commands) is preserved in the presence of prominent automatisms such as lip-smacking and swallowing. Interestingly, in this small group of partially responsive patients, the seizures originate in the right temporal lobe.

The patient, in a confused and irritable state, may resist or strike out at the examiner. The *violence and aggression* that are said to characterize patients with temporal lobe seizures usually take this form of nondirected oppositional resistance in response to restraint during the period of automatic behavior (so called be-

cause the patient presumably acts like an automaton) or, more often, in the postictal period. Unprovoked assault or outbursts of intense rage or blind fury are very unusual; Currie and associates found such outbursts in only 16 of 666 patients (2.4 percent) with temporal lobe epilepsy. Penfield once commented that he had never observed a rage state as a result of temporal lobe stimulation. It is exceedingly unlikely that an organized violent act requiring several sequential steps in its performance, such as obtaining a gun and using it, could represent a temporal lobe seizure.

Rarely, laughter may be the most striking feature of an automatism (*gelastic epilepsy*). A particular combination of gelastic seizures and precocious puberty has been traced to a hamartoma of the hypothalamus. Or the patient may walk repetitively in small circles (*volvular epilepsy*), run (*epilepsia procursiva*), or simply wander aimlessly, either as an ictal or postictal phenomenon (*poriomania*). These forms of seizure are actually more common with frontal lobe than with temporal lobe foci. Dystonic posturing of the arm and leg contralateral to the seizure focus is found to be a frequent accompaniment if sought—again, the origin is more often in the frontal than the temporal lobes, localizing particularly to the supplementary motor area. After the attack, the patient usually has no memory or only fragments of recall for what was said or done. Any type of complex partial seizures may proceed to other forms of secondary generalized seizures. The tendency to generalization holds true for all types of partial or focal epilepsy.

The patient with temporal lobe seizures may exhibit only one of the foregoing manifestations of seizure activity or various combinations of them. In a series of 414 patients studied by Lennox, 43 percent displayed some of the motor changes; 32 percent, automatic behavior; and 25 percent, alterations in psychic function. Because of the frequent concurrence of these symptom complexes, he referred to them as the *psychomotor triad*. Probably the clinical pattern varies with the precise locality of the lesion and the direction and extent of spread of the electrical discharge. Because of their focal origin and complex symptomatology, all these types of seizures are best subsumed under the heading of *complex partial seizures*. This term is preferable to *temporal lobe seizures*, since typical complex partial seizures sometimes arise from a focus in the medial-orbital part of the frontal lobe. Also, seizures originating in the parietal or occipital lobes may be manifested as complex partial seizures because of seizure spread into the temporal lobes. Often the brief ictal aura is not reflected in cortical epileptic activity and therefore may be missed by routine surface EEG recordings.

Complex partial seizures are not peculiar to any period of life, but they do show an increased incidence in adolescence and the adult years. In the series of Ounsted and coworkers, about one-third of such cases could be traced to the occurrence of severe febrile convulsions in early life (see further on). As a corollary, about 5 percent of all their patients with febrile seizures continued to have seizures during adolescence and adult life; in the latter group there were many in whom the seizures were of the temporal lobe type. Also, in Falconer's series in which a temporal lobectomy was performed for intractable epilepsy, there were many patients who had previously had this complicated type of febrile seizure. Neonatal convulsions, head trauma, and various other nonprogressive perinatal neurologic disorders are antecedents that place a child at risk of developing complex partial seizures (Rocca et al). Two-thirds of patients with complex partial seizures also have generalized tonic-clonic seizures or have had them at some earlier time, and it has been theorized that the generalized seizures may have led to secondary ischemic damage to the hippocampal portions of the temporal lobes. In the latter cases, carefully performed and quantitated MRI in the coronal plane may disclose a loss of volume in the hippocampi and adjacent gyri on one or both sides—i.e., *medial temporal sclerosis* (Fig. 16-2).

Complex partial seizures are notably variable in duration. Behavioral automatisms rarely last longer than a minute or two, although postictal confusion and amnesia may persist for a considerably longer time. Some complex partial seizures consist only of a momentary change in facial expression and a blank spell, resembling an absence. Almost always, however, the former are characterized by distinct ictal and postictal phases, whereas patients with absence attacks usually have an instantaneous return of full consciousness following the ictus.

Postictal behavior after partial complex seizures is often accompanied by widespread slowing in the EEG. With seizures of left-sided origin there is likely to be global and nonfluent aphasia. Prolonged disorientation for time and place suggests a right-sided source. Automatisms in the postictal period have no lateralizing connotation (Devinsky et al). However, postictal posturing and paresis of an arm (*Todd's paralysis*) or an aphasic difficulty are helpful in determining the side of the lesion (Cascino). Also, postictal nose wiping is carried out by the hand ipsilateral to the seizure focus in 97 percent of patients, according to Leutzmezer and colleagues, but we are in no position to confirm this.

Amnesic Seizures Rarely, brief, recurrent attacks of transient amnesia are the only manifestations of temporal lobe epilepsy, although it is unclear whether the amnesia in such patients represents an ictal or postictal phenomenon. These attacks of pure amnesia have been referred to as *transient epileptic amnesia*, or TEA (Palmini et al; Zeman et al). If the patient functions at a fairly high level during the attack, as may happen, there is some resemblance to transient global amnesia (page 379). However, the brevity and frequency of the TEA spells, their tendency to occur on awakening, the impaired performance on complex cognitive tasks, and, of course, a history of epilepsy and associated seizure discharges in the EEG help to make the distinction.

Behavioral and Psychiatric Disorders Some comments are in order concerning the issues of *personality*, *behavioral*, and *psychiatric disorders* in patients with complex partial seizures. Data as to prevalence of these disorders are limited and have been derived mainly from studies of selected groups of patients attending university hospitals and other specialty clinics that tend to treat the most difficult and complicated cases. In one such study (Victoroff), about one-third of the patients had a history of major depressive illness, and an equal number had symptoms of anxiety disorder; psychotic symptoms were found in 10 percent. Similar figures, also from a university-based epilepsy center, have been reported by Blumer et al. It must be emphasized that these remarkable rates of psychiatric morbidity do not reflect the prevalence in the entire population of epileptics.

The postictal state in patients with temporal lobe epilepsy sometimes takes the form of a protracted *paranoid-delusional* or *amnesic psychosis* lasting for days or weeks. The EEG during this period may show no seizure discharge, though this does not exclude repeated or sustained seizure activity in the amygdala and other deep temporal lobe structures. This disorder, virtually indistinguishable from schizophrenia in form (but not in temporal evolution), may also present in the interictal period. An excess of psy-

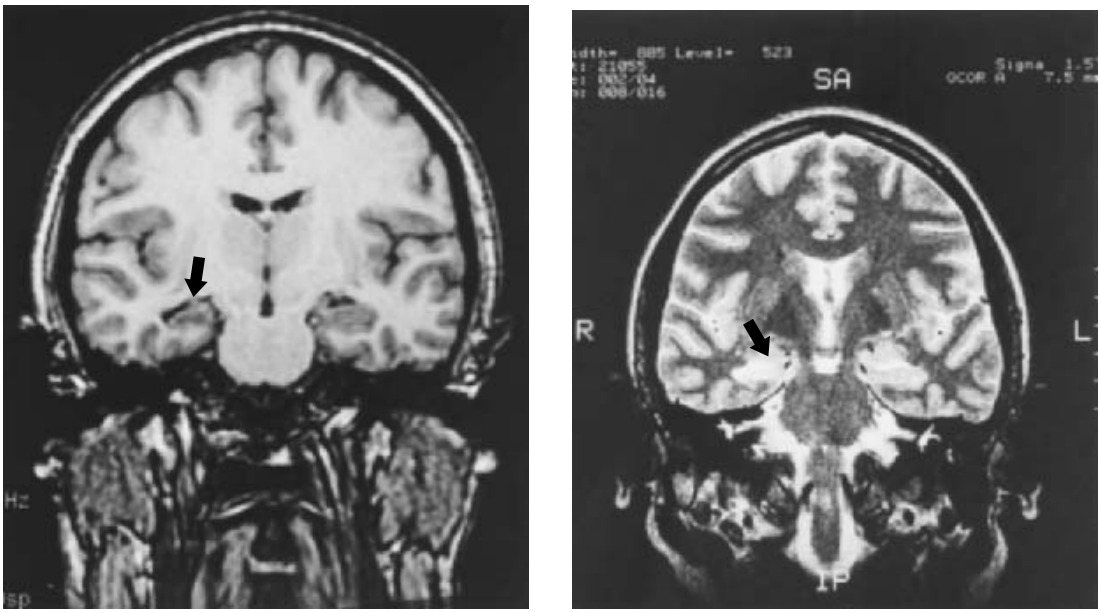

Figure 16-2. Medial temporal sclerosis. *A*. Thin-slice volumetric MRI in the coronal plane, showing shrinkage of the right hippocampus (shown by arrow) and secondary enlargement of the temporal horn of the lateral ventricle. *B*. T2-weighted image showing signal change in the hippocampi (shown by arrow). (Courtesy of Dr. Peter Williamson.)

chosis has been reported only in studies emanating from specialized centers; epidemiologic studies provide only limited evidence of an association with psychosis in the overall population of epileptics (see Trimble and Schmitz and the review by Trimble for a critical discussion of this subject). Again, the frequency of this association with temporal lobe epilepsy is uncertain.

Epileptic Personality Disorder It has long been observed that some patients with temporal lobe seizures may exhibit a number of abnormalities of behavior and personality during the interictal period. Often they are slow and rigid in their thinking, verbose, circumstantial and tedious in conversation, inclined to mysticism, and preoccupied with rather naive religious and philosophical ideas. Also, they are often subject to outbursts of bad temper and aggressiveness. Obsessionalism, humorless sobriety, emotionality (mood swings, sadness and anger), and a tendency to paranoia are other frequently described traits. Diminished sexual interest and potency in men and menstrual problems in women, not readily attributable to anticonvulsant drugs, are common among patients with complex partial seizures of temporal lobe origin. Geschwind proposed that a triad of behavioral abnormalities—hyposexuality, hypergraphia, and hyperreligiosity—constitute a characteristic syndrome in such patients.

Bear and Fedio have suggested that certain of these traits (obsessionalism, elation, sadness, and emotionality) are more common with *right* temporal lesions and that anger, paranoia, and cosmologic or religious conceptualizing are more characteristic of *left* temporal lesions. However, Rodin and Schmaltz, who administered the Bear-Fedio inventory to patients with both primary generalized and temporal lobe epilepsy, found no features that would distinguish patients with right-sided temporal foci from those with left-sided ones. Moreoever, they found no behavioral changes that would distinguish patients with temporal lobe epilepsy from other groups of epileptics. The problem of personality disturbances in epilepsy remains to be clarified (see review by Trimble).

SPECIAL EPILEPTIC SYNDROMES

There remain to be considered several epileptic syndromes and other seizure states that cannot be readily classified with the usual types of generalized or partial seizures. These special types are described below.

Benign Childhood Epilepsy with Centrotemporal Spikes (Rolandic Epilepsy, Sylvian Epilepsy) and Epilepsy with Occipital Spikes

This type of focal motor epilepsy is unique among the partial epilepsies of childhood in that it tends to be a self-limited disorder, transmitted in families as an autosomal dominant trait. The convulsive disorder begins between 5 and 9 years of age and usually announces itself by a nocturnal tonic-clonic seizure with focal onset. Thereafter, the seizures take the form of clonic contractions of one side of the face, less often of one arm or leg, and the interictal EEG shows high-voltage spikes in the contralateral lower rolandic or centrotemporal area. The seizures are readily controlled by a single anticonvulsant drug and gradually disappear during adolescence. The relation of this syndrome to acquired aphasia with convulsive disorder in children, described by Landau and Kleffner, is unsettled.

A similar type of epilepsy, usually benign in the sense that there is no intellectual deterioration and a cessation of seizures in adolescence, has been associated with spike activity over the oc-

cipital lobes, as identified by Panayiotopoulos. As described in the review by Taylor and colleagues, visual hallucinations, while not invariable, are the most common clinical feature; sensations of movements of the eyes, tinnitus, or vertigo are also reported in cases of occipital epilepsy. These authors point out symptomatic causes of the syndrome, such as cortical heterotopias. In both of these types of childhood epilepsy, the observation that spikes are greatly accentuated by sleep is a useful diagnostic aid.

Infantile Spasms (West Syndrome)

This is the term applied to a particular form of epilepsy of infancy and early childhood. West, in the mid-nineteenth century, described the condition in his son in exquisite detail. This seizure disorder, which in most cases appears during the first year of life, is characterized by recurrent, single or brief episodes of gross flexion movements of the trunk and limbs and, less frequently, by extension movements (hence the alternative terms *infantile spasms* or *salaam* or *jackknife seizures*). Most but not all patients with this disorder show severe EEG abnormalities, consisting of continuous multifocal spikes and slow waves of large amplitude. However, this pattern, referred to originally by Gibbs and Gibbs as *hypsarrhythmia* ("mountainous" dysrhythmia), is not specific for infantile spasms, being frequently associated with other developmental or acquired abnormalities of the brain. As the child matures, the seizures diminish; they usually disappear by the fourth to fifth year. If MRI and computed tomography (CT) scans are more or less normal, the usual pathologic findings according to Jellinger are cortical dysgeneses. Both the seizures and the EEG abnormalities may respond dramatically to treatment with adrenocorticotropic hormone (ACTH), corticosteroids, or the benzodiazepine drugs, of which clonazepam is probably the most widely used. However, most patients, even those who were apparently normal when the seizures appeared, are left mentally impaired. Infantile spasms may also be part of the *Lennox-Gastaut syndrome*, a seizure disorder of early childhood of grave prognosis (see page 274).

Febrile Seizures

The well-known *febrile seizure*, peculiar to infants and children between 6 months and 5 years of age (peak incidence 9 to 20 months) and with a strong tendency to be inherited, is generally regarded as a benign condition. Usually it takes the form of a single, generalized motor seizure occurring as the temperature rises or reaches its peak. Seldom does the seizure last longer than a few minutes; by the time an EEG can be obtained, there is usually no abnormality. Recovery is complete. Except for a presumed genetic relationship with benign epilepsy of childhood (Luders et al), which in itself is transient in nature, these patients' risk of developing epilepsy in later life is only slightly greater than that of the general population. In some families, such as those studied by Nabbout and colleagues, febrile seizures alone, without generalized epilepsy, have been associated with a particular gene defect by linkage analysis. Presumably, when the gene product is identified, some insight into the nature of defects that lower the seizure threshold will be forthcoming.

This benign type of febrile seizure should not be confused with a second and more serious type of illness in which an acute encephalitic or encephalopathic state presents during a febrile illness with focal or prolonged seizures, generalized or focal EEG abnormalities, and repeated episodes of febrile convulsions with the same or different illnesses (*complicated febrile seizures*). These seizures may recur not only with infections but also at other times. When patients with both types are lumped together under the rubric of *febrile convulsions*, it is not surprising that a high percentage are complicated by atypical petit mal, atonic, and astatic spells followed by tonic seizures, mental retardation, and partial complex epilepsy. Falconer, who studied psychomotor seizures in adults, noted retrospectively a high incidence of "febrile seizures" during the infancy and childhood in his cohort of surgical subjects. The present authors believe that he was referring to complicated febrile seizures, i.e., fever and convulsions with structural brain disease, which should be kept separate from the common benign febrile seizures. In a later study of 67 patients with proven medial temporal lobe epilepsy (French et al), 70 percent had a history of complicated febrile seizures during the first 5 years of life, although many did not develop temporal lobe epilepsy until their teens. Bacterial meningitis was another important risk factor; head and birth trauma were less common factors. All of the patients had complex partial seizures and half of them, in addition, had secondarily generalized tonic-clonic seizures.

Epidemiologic studies have substantiated this clinical point of view. Annegers and colleagues observed a cohort of 687 children for an average of 18 years after their initial febrile convulsion. Overall, these children had a fivefold excess of unprovoked seizures in later life. Among the children with simple febrile convulsions, the risk was only 2.4 percent. By contrast, children with what Annegers et al called complex febrile convulsions (focal, prolonged, or repeated episodes of febrile seizures) had a greatly increased risk—8, 17, or 49 percent, depending on the association of one, two, or three of the complicating features.

Reflex Epilepsy

For a long time it has been known that seizures could be evoked in certain epileptic individuals by a discrete physiologic or psychologic stimulus. The term *reflex epilepsy* is reserved for this small subgroup. Forster has classified these seizures in accordance with their evocative stimuli into five types: (1) *visual*—flickering light, visual patterns, and specific colors (especially red), leading to rapid blinking or eye closure; (2) *auditory*—sudden unexpected noise (startle), specific sounds, musical themes, and voices; (3) *somatosensory*—either a brisk unexpected tap or sudden movement after sitting or lying still, or a prolonged tactile or thermal stimulus to a certain part of the body; (4) *writing* or *reading* of words or numbers; and (5) *eating*.

Visually induced seizures are by far the most common type of reflex epilepsy. The seizures are generalized and are most often triggered by the photic stimulation of television or an EEG examination or by the photic or pattern stimulation of video games. In other types of reflex epilepsy, the evoked seizure may be focal (beginning often in the part of the body that was stimulated) or generalized and may take the form of one or a series of myoclonic jerks or of an absence or tonic-clonic seizure. Seizures induced by reading, voices, or eating are most often of the complex partial type; seizures induced by music are usually myoclonic. A few such instances of reflex epilepsy have been due to focal cerebral disease, particularly occipital lesions.

Clonazepam, valproate, carbamazepine, and phenytoin are all effective in controlling individual instances of reflex epilepsy. Some patients learn to avert the seizure by undertaking a mental task, e.g., thinking about some distracting subject, counting, etc.,

or by initiating some type of physical activity. Forster has demonstrated that in certain types of reflex epilepsy, the repeated presentation of the noxious stimulus may eventually render the stimulus innocuous. This technique requires a great deal of time and assiduous reinforcement, which limits its therapeutic value.

Epilepsia Partialis Continua

This is another special type of focal motor epilepsy characterized by persistent rhythmic clonic movements of one muscle group—usually of the face, arm, or leg—which are repeated at fairly regular intervals every few seconds and continue for hours, days, weeks, or months without spreading to other parts of the body. Thus epilepsia partialis continua is, in effect, a highly restricted and very persistent focal motor status epilepticus. The distal muscles of the leg and arm, especially the flexors of the hand and fingers, are affected more frequently than the proximal ones. In the face, the recurrent contractions involve either the corner of the mouth or one or both eyelids. Occasionally, isolated muscles of the neck or trunk are affected on one side. The clonic spasms may be accentuated by active or passive movement of the involved muscles and may be reduced in severity but not abolished during sleep.

First described by Kozhevnikov in patients with Russian spring-summer encephalitis, these partial seizures may be induced by a variety of acute or chronic cerebral lesions. In some cases the underlying disease is not apparent (this applies to about half of our cases), and the clonic movements may be mistaken for some type of slow tremor or extrapyramidal movement disorder. Most patients with epilepsia partialis continua show focal EEG abnormalities, either repetitive slow-wave abnormalities or sharp waves or spikes over the central areas of the contralateral hemisphere. In some cases, the spike activity can be related precisely in location and time to the clonic movements (Thomas et al). In the series of cases collected by Obeso and colleagues, there were various combinations of epilepsia partialis continua and cutaneous reflex myoclonus (cortical mycolonus occurring only in response to a variety of afferent stimuli); these investigators view epilepsia partialis continua as part of a spectrum of motor disorders that also includes stimulus-sensitive myoclonus, focal motor seizures, and grand mal seizures.

As would be expected, a wide range of causative lesions has been implicated—developmental anomalies, encephalitis, demyelinative diseases, brain tumors, and degenerative diseases; but in many instances, as mentioned, the underlying cause is not found even after extensive investigation. Epilepsia partialis continua has been particularly common in patients with Rasmussen encephalitis (page 289). As a rule, this type of seizure activity responds poorly or not at all to anticonvulsant medications, but there is little alternative other than to try several drugs in combination. Surgical extirpation or circumscription of the discharging cortex is a last resort.

Whether cortical mechanisms or subcortical ones are responsible for epilepsia partialis continua is an unresolved question. The electrophysiologic evidence adduced by Thomas and colleagues favors a cortical origin. The pathologic evidence is less definite. In each of eight cases in which the brain was examined postmortem, they found some degree of involvement of the motor cortex or adjacent cortical area contralateral to the affected limbs. However, all but one of these patients also had some involvement of deeper structures on the same side as the cortical lesion, on the opposite side, or on both sides.

Hysterical Seizures

These episodes, referred to as "psychogenic" seizures, are nonepileptic in nature—i.e., they are not caused by an abnormal neuronal discharge. They are mentioned here because they are quite common and frequently mistaken for epileptic seizures and treated with anticonvulsant drugs, to which they are characteristically unresponsive. Such seizures are most often a symptom of hysteria in the female (*Briquet disease*) or of compensation neurosis and malingering in males and females, in which case the terms *sham seizures* and *pseudoseizures* are appropriate. Of course, patients with true epileptic seizures sometimes exhibit hysterical seizures as well, and distinguishing the two may be difficult. Usually, however, the motor display in the course of a nonepileptic seizure is sufficient to identify it as such: completely asynchronous thrashing of the limbs and repeated side-to-side movements of the head; striking out at a person who is trying to restrain the patient; hand-biting, kicking, trembling, and quivering; pelvic thrusting and opisthotonic arching postures; and screaming or talking during the ictus. In general, pseudoseizures tend to occur in the presence of other people, to be precipitated by emotional factors, and to be prolonged for many minutes or hours; with few exceptions, tongue-biting, incontinence, hurtful falls, or postictal confusion are lacking. No single one of these features is determinative, however.

Prolonged *fugue states* in our practice usually have proved to be manifestations of hysteria or a psychopathy even in a known epileptic. The serum creatine kinase and prolactin levels are normal after hysterical seizures; this may be helpful in distinguishing them from genuine convulsions. Where doubt remains, a recording of the ictal or postictal EEG or the combined video and EEG recording of an attack will settle the issue. This subject is discussed further in Chap. 56.

THE NATURE OF THE DISCHARGING LESION

Physiologically, the epileptic seizure has been defined as a sudden alteration of central nervous system (CNS) function resulting from a paroxysmal high-frequency or synchronous low-frequency, high-voltage electrical discharge. This discharge arises from an assemblage of excitable neurons in any part of the cerebral cortex and possibly in secondarily involved subcortical structures as well. Of course, there need not be a visible lesion. In the proper circumstances, a seizure discharge can be initiated in an entirely normal cerebral cortex, as when the cortex is activated by ingestion or injection of drugs, by withdrawal from alcohol or other sedative drugs, or by repeated stimulation with subconvulsive electrical pulses ("kindling phenomenon").

Viewed from a larger physiologic perspective, seizures require three conditions: (1) a population of pathologically excitable neurons; (2) an increase in excitatory glutaminergic activity through recurrent connections in order to spread the discharge; and (3) a reduction in the activity of the normally inhibitory GABA-nergic projections. The last of these has been challenged, but it is supported by considerable data and serves as a reasonable model, as noted below. Understanding of the initial discharges and their spread has been greatly advanced by the identification of several rare forms of familial epilepsy that are the direct result of mutations in sodium, potassium, acetylcholine receptor, or GABA channels on neurons. These are discussed further under "Genetics of Epilepsy."

Just why the neurons in or near a focal cortical lesion discharge abnormally is not fully understood. Some of the electrical properties of a cortical epileptogenic focus suggest that its neurons have been deafferented. Such neurons are known to be hyperexcitable, and they may remain so chronically, in a state of partial depolarization, able to fire irregularly at rates as high as 700 to 1000 per second. The cytoplasmic membranes of such cells appear to have an increased ionic permeability, which renders them susceptible to activation by hyperthermia, hypoxia, hypoglycemia, hypocalcemia, and hyponatremia as well as by repeated sensory (e.g., photic) stimulation and during certain phases of sleep (where *hypersynchrony* of neurons is known to occur).

As an example, epileptic foci induced in the animal cortex by the application of penicillin are characterized by spontaneous interictal discharges, during which the neurons of the discharging focus exhibit large, presumably Ca-mediated paroxysmal depolarizing shifts (PDSs), followed by prolonged after-hyperpolarizations (AHPs). The latter also are due in part to Ca-dependent K currents but are better explained by enhanced synaptic inhibition. The PDSs occur synchronously in the penicillin focus and summate to produce surface-recorded interictal EEG spikes; the AHPs correspond to the slow wave of the EEG spike-and-wave complex (Engel). The neurons surrounding the epileptogenic focus are hyperpolarized from the beginning and are inhibitory and release gamma aminobutyric acid. Seizure spread probably depends on any factor or agent that activates neurons in the focus or inhibits those surrounding it. The precise mechanisms that govern the transition from a circumscribed interictal discharge to a widespread seizure state are not understood.

Biochemical studies of neurons from a seizure focus have not greatly clarified the problem. Levels of extracellular K are found to be elevated in glial scars near epileptic foci, and a defect in voltage-sensitive Ca channels has also been postulated. Epileptic foci are known to be sensitive to acetylcholine and to be slower in binding and removing it than is normal cerebral cortex. A deficiency of the inhibitory neurotransmitter GABA, increased glycine, decreased taurine, and either decreased or increased glutamic acid have been variously reported in excised human epileptogenic tissue, but whether these changes are the cause or result of seizure activity has not been determined. The interpretation of reported abnormalities of GABA, biogenic amines, and acetylcholine in the cerebrospinal fluid (CSF) of epileptic patients poses similar difficulties.

Concurrent EEG recordings from an epileptogenic cortical focus and subcortical, thalamic, and brainstem centers in the animal model have enabled investigators to construct a sequence of electrical and clinical events that characterize an evolving focal seizure. Firing of the involved neurons in the cortical focus is reflected in the EEG as a series of periodic spike discharges, which increase progressively in amplitude and frequency. Once the intensity of the seizure discharge exceeds a certain point, it overcomes the inhibitory influence of surrounding neurons and spreads to neighboring cortical regions via short corticocortical synaptic connections. If the abnormal discharge remains confined to the cortical focus and the immediate surrounding cortex, there are probably no clinical symptoms or signs of seizure, and the EEG abnormality that persists during the interseizure period reflects this restricted type of abnormal cortical activity. A provocative new finding, based on sophisticated mathematical analysis of EEG tracings, demonstrates subtle electrographic changes up to several minutes before the ictal discharge (see LeVan Quyen et al). This suggests that seizures are triggered either by a change in central thalamic rhythm generators or a subtle change in the electrical activity in the region of a focal lesion. The clinical utility of this finding has not been determined. Even more provocative are the findings of Litt and colleagues; using complex techniques in a small number of patients, they have detected prolonged bursts of seizure-like activity days before the onset of temporal lobe seizures. Their unconventional proposal is that these events cause a cascade of electrophysiologic changes that very gradually culminate in a seizure.

If unchecked, cortical excitation spreads to the adjacent cortex and to the contralateral cortex via interhemispheric pathways and also to anatomically and functionally related pathways in subcortical nuclei (particularly the basal ganglionic, thalamic, and brainstem reticular nuclei). It is at this time that the clinical manifestations of the seizure begin, the initial signs and symptoms depending on the portion of the brain from which the seizure originates. The excitatory activity from the subcortical nuclei is fed back to the original focus and to the other parts of the forebrain, a mechanism that serves to amplify their excitatory activity and to give rise to the characteristic high-voltage polyspike discharge in the EEG. There is propagation downward to spinal neurons as well, via corticospinal and reticulospinal pathways, yielding a generalized tonic-clonic convulsion.

The spread of excitation to the subcortical, thalamic, and brainstem centers is thought to correspond to the tonic phase of the seizure and loss of consciousness as well as to the signs of autonomic nervous system overactivity (salivation, mydriasis, tachycardia, increase in blood pressure). Vital functions may be arrested, but usually for only a few seconds. In rare instances, however, death may occur owing to a sustained cessation of respiration, a derangement of cardiac action, or some unknown cause. The development of unconsciousness and the generalized tonic contraction of muscles is reflected in the EEG by a diffuse high-voltage discharge pattern appearing simultaneously over the entire cortex.

Soon after the spread of excitation, a diencephalocortical inhibition begins and intermittently interrupts the seizure discharge, changing it from the persistent discharge of the tonic phase to the intermittent bursts of the clonic phase. Electrically, a transition occurs from a continuous polyspike to a spike-and-wave pattern. The intermittent clonic bursts become less and less frequent and finally cease altogether, leaving in their wake an "exhaustion" (paralysis) of the neurons of the epileptogenic focus and a regional increase in permeability of the blood-brain barrier. An overshoot of these inhibitory mechanisms is thought to be the basis of *Todd's postepileptic paralysis* (and of postictal stupor, sensory loss, aphasia, hemianopia, headache, and diffuse slow waves in the EEG, as described earlier) and regional edema in T2-weighted MR images. Plum and associates have observed a two- to threefold increase in glucose utilization during seizure discharges and suggested that the paralysis that follows might be due to neuronal depletion of glucose and increase in lactic acid. However, inhibition of epileptogenic neurons may occur in the absence of neuronal exhaustion. The exact roles played by each of these factors in postictal paralysis of function are not settled.

Bilaterally synchronous three-per-second high-voltage spike-and-wave discharges and seizures resembling absence attacks have been produced in animals by a number of experimental procedures. The spike-and-wave complex, which represents brief excitation followed by slow-wave inhibition, is the type of EEG pattern that

characterizes the clonic (inhibitory) phase of the focal motor or grand mal seizure. By contrast, this strong element of inhibition is present diffusely throughout an "absence" attack, a feature that perhaps accounts for the failure of excitation to spread to lower brainstem and spinal structures (tonic-clonic movements do not occur). However, the absence seizure can also at times activate the mechanism for rhythmic myoclonus, probably at an upper brainstem level.

Current physiologic data indicate that the characteristic EEG patterns of both generalized forms of epilepsy (i.e., tonic or tonic-clonic and absence) are generated in the neocortex and are enhanced by the synchronizing influences of subcortical structures. In both instances, the generalization of the clinical and electrical manifestations depends upon activation of a deep, centrally located physiologic mechanism, which, for reasons outlined in Chap. 17, includes the midbrain reticular formation and its diencephalic extension, the intralaminar and nonspecific thalamic projection systems (originally referred to by Penfield as the "centrencephalon"). There is no evidence, however, that seizure activity originates in these deep activating structures; therefore the term *centrencephalic epilepsy* has been replaced by *corticoreticular epilepsy*.

Complex partial seizures are almost always of temporal lobe origin, arising in foci in the medial temporal lobe, amygdaloid nuclei, and hippocampus. Only rarely do they originate in the convexity of the temporal lobe and propagate to the amygdaloid nuclei, hippocampus, and posteroinferior parts of the frontal lobe. Electrical stimulation in these areas reproduces feelings of depersonalization, emotionality, and automatic behavior, the characteristic features of psychomotor epilepsy. The automatic behavior appears to be a direct effect of the temporal lobe discharge in some instances and a postexcitatory or inhibitory effect in others. Loss of memory for the events of the episode may be due to the paralytic effect of the discharge on neurons of the hippocampus.

Of theoretical importance is the observation that a seizure focus, if active for a time, may sometimes establish, via commissural connections, a persistent secondary focus in the corresponding cortical area of the opposite hemisphere (*mirror focus*). The nature of this phenomenon is obscure; it may be similar to the "kindling" phenomenon mentioned earlier in animals, where a repeated nonconvulsive electrical stimulation of normal cortex induces a permanent epileptic focus. No morphologic change is visible in the mirror focus, at least by light microscopy. The mirror focus may be a source of confusion in trying to identify the side of the primary lesion by EEG, but there is little evidence that it can produce chronic seizures in humans. Similarly, there are no firm data supporting a role for kindling in the diagnosis and management of patients with epilepsy (Goldensohn).

Severe seizures may be accompanied by a systemic lactic acidosis with a fall in arterial pH, reduction in arterial oxygen saturation, and rise in P_{CO_2}. These effects are secondary to the respiratory arrest and excessive muscular activity. If prolonged, they may cause hypoxic-ischemic damage to remote areas in the cerebrum, basal ganglia, and cerebellum. In paralyzed and artificially ventilated subjects receiving electroconvulsive therapy, these changes are less marked and the oxygen tension in cerebral venous blood may actually rise. Heart rate, blood pressure, and particularly CSF pressure rise briskly during the seizure. According to Plum and colleagues, the rise in blood pressure evoked by the seizure usually causes a sufficient increase in cerebral blood flow to meet the increased metabolic needs of the brain.

The Electroencephalogram in Epilepsy

(See also Chap. 2.)

The EEG provides confirmation of Hughlings Jackson's concept of epilepsy—that it represents a recurrent, sudden, excessive discharge of cortical neurons. The EEG is undoubtedly the most sensitive, indeed indispensable, tool for the diagnosis of epilepsy; but like other ancillary tests, it must be used in conjunction with clinical data. In patients with idiopathic generalized seizures and in a high proportion of their relatives, interictal spike-and-wave abnormalities without any clinical seizure activity are common, especially if the EEG is repeated several times. Contrariwise, a proportion of epileptic patients have a perfectly normal interictal EEG; occasionally, using standard methods of scalp recording, the EEG may even be normal during a simple or complex partial seizure. Furthermore, a small number of healthy persons (approximately 2 to 3 percent) show paroxysmal EEG abnormalities; some of them have a family history of epilepsy (particularly of absence seizures) and may themselves later develop seizures.

EEG abnormalities that characterize a spreading epileptogenic focus and generalization of seizure activity, both the grand mal and absence types, have been described in the preceding section and are illustrated in Chap. 2. At first there was thought to be a characteristic EEG picture for seizures, but further studies have not confirmed this, many patterns being possible. One consistent observation, however, has been that the region of earliest spike activity corresponds best to the epileptogenic focus. This rule guides epilepsy surgery. The postseizure or postictal state following generalized seizures also has its EEG correlate, taking the form of random generalized slow waves. Following partial or focal seizures, the EEG shows focal slowing. With clinical recovery, the EEG returns to normal or to the preseizure state. A single EEG tracing obtained during the interictal state is abnormal to some degree in 30 to 50 percent of epileptic patients; this figure rises to 60 to 70 percent if patients are subjected to three or more studies utilizing standard activating measures (hyperventilation, photic stimulation, and sleep; see Chap. 2). With structural lesions, focal slow and sharp activity, which is not clearly epileptiform, may be the only clue to a seizure focus.

A higher yield of abnormalities and a more precise definition of seizure types can be obtained by the use of several special EEG procedures. Overnight EEG recording is particularly helpful because focal abnormalities, particularly in the temporal lobes, may become prominent in stage II sleep. Sphenoidal leads have been used to detect inferomedial temporal seizure activity, but they are uncomfortable and probably add little more information than can be obtained by the placement of additional subtemporal scalp electrodes. In our experience, nasopharyngeal electrode recordings are too contaminated by artifact to be clinically useful. Activating procedures such as hyperventilation, photic stroboscopic stimulation, and sleep increase the yield of EEG recordings, as detailed in Chap. 2.

Beyond dependably identifying artifacts in the EEG recording, one of the main challenges for the electroencephalographer is to differentiate between normal patterns that simulate seizures and true epileptic discharges. These paroxysmal but ostensibly normal patterns appear mostly during sleep, each with a highly characteristic morphology. These include small sharp spikes, "14 and 6" polyspike activity, lambda and posterior occipital mu rhythm, and occipital sharp transients. These are pictured in most standard textbooks on the subject of EEG.

Several methods of *long-term EEG monitoring* are now in common use and are of particular value in the investigation of patients with surgically removable epileptogenic foci. The most common of these makes use of telemetry systems, in which the patient is attached to the EEG machine by cable or radio transmitter without unduly limiting his freedom of movement. The telemetry system is joined to an audiovisual recording system, making it possible to record seizure phenomena (even at night, under dim infrared light) and to synchronize them with the EEG abnormalities. An alternative is the use of a small cassette recorder that is attached to a miniature EEG machine worn by the patient at home and at work. The patient is instructed to push a button if he experiences an "event," which can later be correlated with EEG activity. The role of intensive neurodiagnostic monitoring in the investigation and treatment of seizures, which is also a necessary part of the evaluation for epilepsy surgery, is described in detail in the monographs of Engel and of Niedermeyer.

The EEG changes in epilepsy are discussed further in Chap. 2.

Other Laboratory Abnormalities Associated with Seizures

MRI is the most important diagnostic tool for the detection of structural abnormalities underlying epilepsy. Medial temporal sclerosis, glial scars, porencephaly, heterotopias, and other disorders of neuronal migration can be clearly visualized. After a seizure, particularly one with a focal component, MRI sometimes discloses subtle focal cortical swelling and signal change in the FLAIR sequence, or, if a contrast agent is administered, an ill-defined cortical blush may be visible on CT or MRI. There is a rough relationship between the duration of seizure activity and the intensity and size of these cortical changes. Likewise, angiography performed soon after a seizure may show a focal area of enhanced flow. This phenomenon was often a source of confusion when radionuclide scans were routinely performed for the evaluation of new seizures—focal increased uptake being mistaken for a tumor or stroke. All of these imaging abnormalities are thought to reflect transient disruption of the blood-brain barrier, and they rarely persist for more than a day or two. Less well understood is the finding on MRI of increased T2 signal (probably due to hypoxia) in the hippocampi after a prolonged seizure or status epilepticus.

The CSF occasionally contains a small number of white blood cells (rarely up to 50/mm^3, but more often in the range of 10/mm^3) in about 15 percent of patients after a seizure. A slight increase in protein is also possible. Like the imaging abnormalities these findings may lead to spurious conclusions about the presence of an intracranial infection, particularly if polymorphonuclear leukocytes predominate. Nonetheless, a significant pleocytosis after a seizure should always be construed as a sign of inflammatory or infectious disease.

Systemic acidosis is a common result of convulsive seizures, and it is not unusual for the serum pH to reach levels near or below 7 if taken immediately after a convulsion. Of more practical value is the fact that almost all generalized convulsions produce a rise in serum creatine kinase activity that persists for hours, a finding that could be used to greater advantage in emergency departments to assist in distinguishing seizures from fainting. Of course, extensive muscle injury from a fall or prolonged compression during a period of unconsciousness can produce the same abnormality.

Concentrations of serum prolactin, like those of other hypothalamic hormones, rise for 10 to 20 min after all types of generalized seizures, including complex partial seizures, but not in absence or myoclonic types. An elevation may help differentiate a hysterical seizure from a genuine one; however, serum prolactin may also be slightly elevated after a syncopal episode. Detection is facilitated by collecting capillary blood from the finger on filter paper for analysis (Fisher et al). There is also a postictal rise in ACTH and serum cortisol, but these changes have a longer latency and briefer duration. If changes in these hormonal levels are used as diagnostic tests, one must have information about normal baseline levels, diurnal variations, and the effects of concurrent medications. Changes in body temperature, which are said to sometimes precede a seizure, may reflect hypothalamic changes but are far less consistent and difficult to use in clinical work.

Pathology of Epilepsy

In most autopsied cases of primary generalized epilepsy of the grand mal and absence types, the CNS has been said to be grossly and microscopically normal. However, it is unlikely that the brains in these cases were examined completely—at least there is not a single case that has been subjected to whole-brain serial sectioning in a search for disorders of neural migration and old scars. Not surprisingly, there are also no visible lesions in the seizure states complicating drug intoxication and withdrawal, transient hyper- and hyponatremia, and hyper- and hypoglycemia, which presumably represent derangements at the cellular level.

In contrast, most of the so-called secondary epilepsies have definable lesions. These include zones of neuronal loss and gliosis (scars) or other signs of tissue loss such as a porencephaly, heterotopia, dysgenetic cortex, hamartoma, vascular malformation, and tumor. The frequency of these lesions is not fully known. Certainly the focal epilepsies are associated with the highest incidence of structural abnormalities, although in certain cases no morphologic change is visible. In several series of cases of temporal lobe excisions, such as that of Falconer, a specific pattern of neuronal loss with gliosis (sclerosis) in the hippocampal and amygdaloid region was found in the majority, and this abnormality is being increasingly recognized with MRI, as noted below. Vascular malformations, hamartomas, and low-grade astrocytomas were less frequent; in a small number, no abnormalities could be found.

The widespread use of CT and MRI represents an important surrogate approach to the pathologic study of epilepsy. More than 25 years ago, Gastaut and Gastaut reported that in primary grand mal and absence epilepsies, CT abnormalities were found in approximately 10 percent of cases, whereas in the Lennox-Gastaut syndrome, the West syndrome, and partial complex epilepsies it was found in 52, 77, and 63 percent, respectively. Atrophy, calcification, and malformations were the most frequent changes. MRI and particularly the FLAIR images have proved to be a particularly sensitive means of detecting epileptogenic lesions of the medial-basal portion of the temporal lobes (mesial temporal sclerosis; Fig. 16-2). Repeatedly, patients are observed in whom MRI disclosed a cortical or subcortical developmental malformation such as a cortical heterotopia or another surgically treatable lesion of the temporal lobe, even after CT scanning had failed to do so. More subtle epileptogenic foci may be demonstrated by positron emission tomography (PET) or by interictal single-photon emission computed tomography (SPECT). Ictal SPECT, which shows hyperperfusion of the seizure focus, is a more demanding but also more sensitive and specific procedure.

With reference to the focal epilepsies, it has not been possible to determine which component of the lesion is responsible for the seizures. Gliosis, fibrosis, vascularization, and meningocerebral cicatrix have all been incriminated, but they are found in nonepileptic foci as well. The Scheibels' Golgi studies of neurons from epileptic foci in the temporal lobe showed distortions of dendrites, loss of dendritic spines, and disorientation of neurons near the scars, but these findings have dubious status since they were not usually compared with similar nonepileptic lesions. Moreover, changes such as these have proved to be nonspecific and artifactual. Once a gliotic focus of whatever cause, bordered by groups of discharging neurons, becomes epileptogenic, it may remain so throughout the patient's lifetime. Nevertheless, with the passage of years, seizures tend to diminish or cease in as many as half of childhood and adult traumatic epilepsies.

The most common histologic finding in the brains of epileptics is a bilateral loss of neurons in the CA1 segment (Sommer sector) of the pyramidal cell layer of the hippocampus, extending into contiguous regions of both the pyramidal layer and the underlying dentate gyrus. It is still undecided whether this neuronal loss is primary or secondary and, if the latter, whether it was incurred at birth or happened later as the consequence of recurrent seizures. The cessation of seizures in many patients following surgical resection of the medial temporal lobe favors the first interpretation (page 298). Attesting to the uncertainty of cause or effect regarding hippocampal damage are case reports and surgical series too numerous to list that favor one view or the other. It can be stated, however, that seizures, even in adulthood, are capable of inducing hippocampal shrinkage. This does not preclude a causative role for medial temporal sclerosis (see editorial by Sutula and Pitkänen).

Role of Heredity

Most primary epilepsies are thought to have a genetic basis and, as in many other idiopathic diseases such as diabetes and atherosclerosis, the mode of inheritance is complex, i.e., polygenic. That a genetic factor is operative in primary generalized tonic-clonic seizures is suggested by the finding of a familial incidence in 5 to 10 percent of such patients and, in particular families, the inheritance of a generalized seizure disorder through specific chromosomal regions (Berkovic). The importance of genetic factors in the primary (idiopathic) epilepsies is also underscored by evidence from twin studies; in six major series, the overall concordance rate was 60 percent for monozygotic twins and 13 percent for dizygotic pairs.

In only a few of the idiopathic seizure disorders is a simple (mendelian) pattern of inheritance recognized. These include a subgroup of benign neonatal familial convulsions inherited as an autosomal dominant trait (Leppert) and a similar disorder of infantile onset and a benign myoclonic epilepsy of childhood (autosomal recessive).

Particularly informative are a special group of epileptic disorders in which monogenic genetic defects have been found to be related to ion channels or neurotransmitter receptors (Table 16-3). These were mentioned earlier in the discussion of the physiology of seizures and, despite their rarity, they suggest that idiopathic epilepsy may be due to a disruption in the function of these channels. Functional studies suggest that the consequences of almost all of these mutations are to enhance overall neuronal excitability. Examples include nocturnal frontal lobe epilepsy, which may present as a partial seizure (in which the offending mutations are in subunits of the nicotinic acetylcholine receptor subunit); generalized epilepsy with febrile seizures (subunits of a neuronal sodium channel); benign familial neonatal convulsions (two different potassium channels); and forms of juvenile myoclonic epilepsy and childhood absence epilepsy (subunits of the brain $GABA_A$ receptor). These are summarized in Table 16-3 and their number will almost certainly expand in the next few years. As with numerous other genetic neurologic disorders, a single mutation may produce different seizure types, and a single type may be the result of one of several different mutations. This is particularly true in a group that has been termed *generalized epilepsy with febrile seizures plus*. This denotes various combinations of uncomplicated febrile seizures, febrile seizures persisting beyond childhood, generalized, absence, myoclonic, atonic, and temporal lobe seizures. Several of the mutations mentioned above, two in sodium channels and one in a GABA receptor subunit, produce this constellation, the manifestations of any one of these mutations varying between members of a single family. Also notable is the low penetrance of some monogenic epileptic disorders, particularly the autosomal dominant one associated with nocturnal frontal seizures.

Another group of epilepsies with mendelian inheritance has been ascribed to genetic defects that do not implicate ion channels. Most of these are primarily myoclonic disorders in which the epilepsy is symptomatic. Thus, two forms of progressive myoclonic epilepsy, Unverricht-Lundborg disease and Lafora body disease, are the result respectively of mutations in genes encoding cystatin B and a protein, tyrosine phosphatase. Other forms of myoclonic epilepsy are presumably related to primary defects that cause different forms of ceroid lipofuscinosis (see Chap. 37). To these inherited forms of epilepsy may be added diseases such as tuberous sclerosis, which have a strong proclivity to cause seizures.

A more complex genetic element is also identified in several other classic childhood seizure disorders—absence epilepsy with three-per-second spike-and-wave discharges and benign epilepsy of childhood with centrotemporal spikes—both of which are transmitted as autosomal dominant traits with incomplete penetrance or perhaps in a more complicated manner. In the partial, or focal, epilepsies (which is the form that seizures take in two-thirds of adults and almost half of the children with epilepsy), the role of heredity is not nearly so clear. Yet in numerous studies there has been a greater-than-expected incidence of seizures, EEG abnormalities, or both among first-degree relatives. Among the familial cortical epilepsies, both a temporal and frontal lobe type are inherited in a polygenic fashion or in an autosomal dominant pattern. Undoubtedly also inherited is the tendency to develop simple febrile convulsions, though the mode of inheritance is uncertain.

The genetics of the epileptic disorders has been reviewed in detail by Steinlein, Delgado-Escueta and colleagues, Hirose and associates, Malafosse and Moulard, and Anderson and Hauser, whose articles are recommended.

CLINICAL APPROACH TO THE EPILEPSIES

The physician faced with a patient who seeks advice about an episodic disorder of nervous function must determine, first, whether the episode in question is indeed a seizure; if so, she must determine its pattern and other characteristics; and, finally, she must undertake a search for its cause. In the diagnosis of epilepsy, history is the key; in most adult cases the physical examination is relatively unrevealing. The examination in infants and children is of greater

Table 16-3
Monogenic epileptic disorders

	GENE	PROTEIN INVOLVED
Channelopathies		
Sodium channels		
Familial generalized seizures with febrile seizures "plus"; see text	SCN1A,B, ($GABA_A$)	Sodium channel subunits, less often, GABA receptor
Benign familial neonatal convulsions	SCN2A	Sodium channel subunits
Potassium channels		
Benign infantile epilepsy	KCNQ2,3	Potassium channel subunits
Episodic ataxia type 1 with partial epilepsy	KCNA1	
Ligand-gated channels		
Autosomal dominant nocturnal frontal seizures	CHRNA 2,4	Nicotinic acetylcholine receptor subunits
Familial generalized and febrile seizures	GABRG2	$GABA_A$ receptor subunit
Juvenile myoclonic epilepsy	GABRA1 (CACNB4)	$GABA_A$ receptor subunit, less often, calcium channel subunit
Calcium channels		
Episodic ataxia type 2 with spike-wave seizures	CACNA1A	Calcium channel subunit
Malformations of cortical development		
Holoprosencephaly, generalized epilepsy	SHH, PTCH, ZIC2, SIX3, TGIF	Sonic hedgehog, SHH receptor, transcription factors
Schizencephaly, generalized epilepsy	EMX2	Homeodomain protein
Tuberous sclerosis, generalized epilepsy	TSC1, 2	Hamartin, tuberin
Lissencephaly, generalized epilepsy	LIS1	Platelet-activating factor acid hydrolase
Double cortex syndrome, generalized epilepsy	DCX	Doublecortin
Heterotopia, generalized epilepsy	FLN1	Filamin1
Fukuyama muscular dystrophy, lissencephaly, generalized epilepsy	FCMD	Fukutin
Walker-Warburg syndrome, generalized epilepsy	POMT1	*O*-mannosyl transferase
Muscle-eye-brain disease, generalized epilepsy	MEB	Lycosyltransferase, PMGnT1
Angelman syndrome: myoclonic, tonic-clonic, atonic seizures	UBE3A	Ubiquitin-protein ligase
Progressive myoclonic epilepsies (PME)		
Unverricht-Lundborg disease with PME	EPM1	Cystatin B
Lafora body disease with PME	EPM2A	Laforin, protein tyrosine phosphatase
Myoclonic epilepsy with ragged red fibers	tRNAlys	Mitochondrial lysine tRNA
Dentatorubro-pallidoluysian atrophy with PME	DRPLA	Atrophin-1
Gaucher disease	PSAP	β-glucocerebrosidase
Sialidosis type I	NEU1	Sialidase
Ceroid lipofuscinosis (CLN) and PME	CLN	CLN2, CLN3, CLN5, CLN6 also cause generalized, atonic and atypical absence seizures
Mixed seizure types		
Lipoid proteinosis and temporal lobe epilepsy	ECM1	Extracellular matrix protein 1
Temporal lobe epilepsy	LGI1	Leucine-rich glioma inactivated protein
CLN8; progressive non-myoclonic epilepsy with retardation	CLN8	Membrane protein in endoplasmic reticulum

value, since the finding of dysmorphic and cutaneous abnormalities allow the diagnosis of a large number of cerebral diseases that give rise to epilepsy.

Several laboratory studies should routinely be included in the initial diagnostic workup—complete blood count (CBC), blood chemistries, liver and thyroid function tests, EEG, and, most importantly, an imaging study of the brain, preferably MRI. CT scanning may be the only feasible study in an emergency or for very young children. Some patients may later need protracted video/EEG monitoring, either in the hospital or with portable equipment at home. Other forms of testing—e.g., cardiac stress tests, Holter monitors, tilt-table testing, long-term patient-activated cardiac monitors, and sleep studies—are sometimes indicated in order to exclude some of the nonepileptic disorders listed below.

The conditions most likely to simulate a seizure are syncope and transient ischemic attacks, but also to be considered are migraine, unexplained falls (drop attacks), sleepwalking and rapid-eye-movement (REM) sleep behavior disorder, panic attacks, hy-

poglycemia, cataplexy, paroxysmal ataxia and choreoathetosis, recurrent transient global amnesia, and hysterical pseudoseizures. Often, in emergency departments, it is difficult to differentiate the postictal effects of an unwitnessed seizure from mild confusion following cerebral concussion or from a brief loss of consciousness produced by a subarachnoid hemorrhage.

The clinical differences between a seizure and a *syncopal attack* are considered in Chap. 18. Here it is emphasized that no single criterion stands inviolate. The authors have erred in mistaking akinetic seizures for simple faints and vasovagal and cardiac faints for seizures. If blood is tested after the episode in question, elevation in creatine kinase (persistent for hours) and prolactin (for up to 10 min) may be helpful in the diagnosis of a convulsive seizure. Postictal confusion, incontinence, and a bitten tongue clearly bespeak seizure rather than syncope. Absence attacks may be difficult to identify because of their brevity. Helpful maneuvers are to have the patient hyperventilate in order to evoke an attack or to observe the patient counting aloud for 5 min. Those with frequent absence attacks will pause or skip one or two numbers.

The diagnosis of *complex partial seizures* is the most difficult. These attacks are so variable and so often induce disturbances of behavior and psychic function—rather than obvious interruptions of consciousness—that they may be mistaken for temper tantrums, hysteria, sociopathic behavior, or acute psychosis. The careful questioning of witnesses of an attack is essential. Verbalizations that cannot be remembered, walking aimlessly, or inappropriate actions and social behavior are characteristic. As stated above, we have placed emphasis on amnesia for the events of at least part of the seizure as a crucial criterion for the diagnosis of temporal lobe epilepsy. In all obscure forms of epilepsy, prolonged EEG and video monitoring may prove diagnostic. A mild complex partial seizure, consisting of a brief loss of consciousness and lip-smacking, may be mistaken for an absence unless it is kept in mind that the former (but not the latter) is commonly followed by a period of confusion and dysphasia when the language areas are involved.

Epilepsy complicated by states of constitutional mental dullness and confusion poses special problems in diagnosis. Most epileptic patients seen in a general hospital or in office practice show no evidence of mental retardation, regardless of the type of seizure. Undoubtedly, seizures are more common in the mentally retarded, but recurrent seizures in themselves seldom cause intellectual deterioration (Ellenberg et al); when this does happen, one should suspect an underlying degenerative or hereditary metabolic disease. An exception to this statement is the patient with frequent and uncontrolled subclinical seizures (nonconvulsive status) who is drugged or in a postseizure psychotic state. Hospital admission and a systematic study of the seizure state and drug levels are necessary in the analysis of this problem.

Migraine should not be mistaken for a seizure, for reasons discussed on page 153. One feature of the focal neurologic disorder of classic migraine is particularly helpful—namely, the pace of the sequence of cerebral malfunction over a period of minutes rather than seconds, as in partial epilepsy. Even this criterion may fail occasionally, especially if both migraine and partial seizures are joined, e.g., as expressions of a vascular malformation of the brain.

Useful in the identification of a *transient ischemic attack* (TIA) and its separation from partial epilepsy are the patient's age, evidence of disease of the heart or carotid arteries, and the lack of disorder of consciousness or amnesia. Again, if the ischemic attack is marked by an evolution of symptoms, they tend to develop more slowly than those of a seizure, and by their nature TIAs tend to produce a focal loss of function without convulsions. However, a "limb-shaking" TIA and convulsive phenomena at the outset of basilar artery occlusion may be nearly impossible to distinguish from epilepsy.

Drop attacks (falling to the ground without loss of consciousness) remain an enigma (page 329). In most cases, we have failed to substantiate their association with circulatory disturbances of the vertebrobasilar system and seldom have we observed them to be an expression of atonic or myoclonic epilepsy, but such an occurrence has been reported with the Lennox-Gastaut syndrome. In some instances they represent simple unexpected falls, especially in stout older women who are sedentary. The degenerative disease progressive supranuclear palsy may also present itself in this way (Chap. 39).

Regarding the distinction of narcolepsy, paroxysmal ataxia or choreoathetosis, transient global amnesia, hysterical fugues, panic attacks, and REM sleep behavior disorder from seizures, it is sufficient to be aware of the diagnostic criteria for each of these conditions.

The Probable Causes of Seizure(s) at Different Age Periods

(Table 16-4 and Fig. 16-3)

Having concluded that the neurologic disturbance under consideration is one of seizure, the next issue is to identify the type of seizure; indeed, this determines in most cases the nature of treatment. Since there are so many seizure types, especially in childhood and adolescence, each one tending to predominate in a certain age period, a clinical advantage accrues to considering seizure problems from just this point of view, i.e., the problem of epilepsy as it presents in each period of life, along with the neurologic and EEG findings, as well as the response to drugs, etiology, and prognosis.

Figure 16-3 displays the frequency of each seizure type and the main causes of seizures in each age group. These data are assembled from various sources and are approximate, but they highlight several points of clinical importance. First, implicit is the fact that the age of the patient greatly affects the incidence of certain seizure types; e.g., absence and myoclonic seizures are relatively more common in children and adolescents. Furthermore, the underlying causation varies greatly by age as discussed further on.

Neonatal Seizures The neonatologist is often confronted by an infant that begins to convulse in the first days of postnatal life. In most instances, the seizures are fragmentary—an abrupt movement or posturing of a limb, stiffening of the body, rolling up of the eyes, a pause in respirations, lip-smacking, chewing, or bicycling movements of the legs. Even the experienced observer may have difficulty at times in distinguishing seizure activity from the normal movements of the neonate. If manifest seizures are frequent, the diagnosis is less difficult. The seizures correlate with focal or multifocal cortical discharges; however, as is the case with most EEG changes in neonates, these are poorly formed and less distinct than seizure discharges in later life. Presumably the immaturity of the cerebrum prevents the development of a fully organized seizure pattern. The EEG is nonetheless helpful in diagnosis. Periods of EEG suppression may alternate with sharp or slow waves, or there may be discontinuous theta activity. Unfortunately, electrical seizure activity may be unattended by

Table 16-4
Causes of recurrent seizures in different age groups (see also Fig. 16-3)

AGE OF ONSET	PROBABLE CAUSE[a]
Neonatal	Congenital maldevelopment, birth injury, anoxia, metabolic disorders (hypocalcemia, hypoglycemia, vitamin B_6 deficiency, biotinidase deficiency, phenylketonuria, and others)
Infancy (1–6 months)	As above; infantile spasms; West syndrome
Early childhood (6 months–3 years)	Infantile spasms, febrile convulsions, birth injury and anoxia, infections, trauma, metabolic disorders, cortical dysgenesis, accidental drug poisoning
Childhood (3–10 years)	Perinatal anoxia, injury at birth or later, infections, thrombosis of cerebral arteries or veins, metabolic disorders, cortical malformations, Lennox-Gastaut syndrome, "idiopathic," probably inherited, epilepsy (Rolandic epilepsy)
Adolescence (10–18 years)	Idiopathic epilepsy, including genetically transmitted types, juvenile myoclonic epilepsy, trauma, drugs
Early adulthood (18–25 years)	Idiopathic epilepsy, trauma, neoplasm, withdrawal from alcohol or other sedative drugs
Middle age (35–60 years)	Trauma, neoplasm, vascular disease, alcohol or other drug withdrawal
Late life (over 60 years)	Vascular disease (usually postinfarction), tumor, abscess, degenerative disease, trauma

[a] Meningitis or encephalitis and their complications may be a cause of seizures at any age. This is true also of severe metabolic disturbances. In tropical and subtropical countries, parasitic infection of the CNS is a common cause.

clinical manifestations. An early onset of myoclonic jerks, either fragmentary or massive, with an EEG pattern of alternating suppression and complex bursts of activity is particularly ominous according to Aicardi. Another extremely malignant form of neonatal seizure evolving later into infantile spasms and Lennox-Gastaut syndrome and leaving in its wake severe brain damage was described by Ohtahara. Most of the reported patients were left mentally retarded (Brett).

Neonatal seizures occurring within 24 to 48 h of a difficult birth are usually indicative of severe cerebral damage, usually anoxic, either antenatal or parturitional. Such infants often succumb, and about half of the survivors are seriously handicapped. *Seizures having their onset several days or weeks after birth* are more often an expression of acquired or hereditary metabolic disease. In this latter group, hypoglycemia is the most frequent cause; another, hypocalcemia with tetany, has become infrequent. A hereditary form of pyridoxine deficiency is a rare cause, sometimes also inducing seizures in utero and characteristically responding promptly to massive doses (100 mg) of vitamin B_6 given intravenously. Biotinidase deficiency is another rare but correctable cause. Nonketotic hyperglycemia, maple syrup urine disease, as well as other metabolic disorders may lead to seizures in the first week or two of life and are expressive of a more diffuse encephalopathy.

Benign forms of neonatal seizures have also been identified. Plouin has described a form of benign neonatal clonic convulsions beginning on days 2 and 3, up to day 7, in which there were no specific EEG changes. The seizures then remit. The inheritance is autosomal dominant. There are other nonfamilial cases with onset on days 4 to 6, wherein the partial seizures may even increase to status epilepticus; the EEG consists of discontinuous theta activity. In both these groups, the outlook for normal development is good and seizures seldom recur later in life. There are also benign forms of polymyoclonus without seizures or EEG abnormality in this age period. Some occur only with slow-wave sleep or feeding. They disappear after a few months and require no treatment. A form of benign nocturnal myoclonus in the neonate has also been documented. When therapy is necessary, phenobarbital has been preferred.

Infantile Seizures (Occurring in the First Months, Up to 2 Years) Neonatal seizures may continue into the infantile period, or seizures may begin in an infant who seemed to be normal up to the time of the first convulsive attack. The most characteristic pattern at this age is the massive sudden myoclonic jerk of head and arms leading to flexion or, less often, to extension of the body (*infantile spasms*, salaam spasms). This form, known as the West syndrome as described earlier, is the most threatening of all infantile seizures. We have observed the same seizure type in infants with tuberous sclerosis (diagnosed in infancy by dermal white spots), phenylketonuria, or Sturge-Weber angiomatosis, but most often it is associated with other diseases beginning in this age period. West syndrome is probably a metabolic encephalopathy of unknown type or, in some cases, a cortical dysgenesis (Jellinger) and is identified by an EEG picture of large bilateral slow waves and multifocal spikes (*hypsarrhythmia*). Again, there is a benign form of infantile myoclonic epilepsy in which repetitive myoclonic jerking occurs in otherwise normal infants whose EEGs show only spike waves in early sleep.

However, when the myoclonus begins in infancy with fever and unilateral or bilateral clonic seizures or with partial seizures followed by focal neurologic abnormalities, there is a likelihood of developmental delay. The latter types are sometimes referred to as *complicated febrile seizures*, but, as indicated above, they must be distinguished from the benign familial febrile seizure syndrome. Infantile spasms cease by the fifth year and are replaced by partial and generalized grand mal seizures. They do not respond well to the usual anticonvulsant medications.

Seizures Presenting in Early Childhood (Onset during the First 5 to 6 Years) At this age, the first burst of seizures may take the form of status epilepticus and, if not successfully controlled, may end fatally. Or the convulsive state may present around the age of 4 years as a focal myoclonus with or without astatic seizures, atypical absence, or generalized tonic-clonic seizures. The EEG, repeated if initially normal, is most helpful in diagnosis; it reveals a paroxysmal 2- to 2.5-per-second spike-and-wave pattern on a background of predominant 4- to 7-Hz slow waves. Many of these cases qualify as the Lennox-Gastaut syndrome, are difficult to treat, and are likely to be associated with developmental retardation (see page 274). The MRI may be helpful in identifying a birth injury or cortical dysgenesis.

In contrast, the more typical absence, with its regularly recur

ring three-per-second spike-and-wave EEG abnormality, also begins in this age period (rarely before 4 years) and carries a good prognosis. This seizure disorder responds well to medications, as indicated further on. Its features are fully described on page 274.

A number of partial epilepsies may appear for the first time during this age period and carry a good prognosis, i.e., the neurologic and intellectual capacities remain relatively unimpaired and seizures may cease in adolescence. These disorders begin between 3 and 13 years of age, and there is often a familial predisposition. Most are marked by distinctive focal spike activity that is greatly accentuated by sleep (see above, in reference to benign childhood epilepsy with centrotemporal or occipital spikes). In one form, unilateral tonic or clonic contractions of the face and limbs recur repeatedly with or without paresthesias; anarthria follows the seizure. There are central and temporal spikes in the EEG interictally. According to Gastaut, the focus may involve an occipital lobe with EEG spiking on eye closure. An acquired aphasia was noted by Landau and Kleffner to mark the beginning of an illness in which there are partial or generalized motor seizures and multifocal spike or spike-and-wave discharges in the EEG. Tumor and arteriovenous malformation are rare causes in this age group.

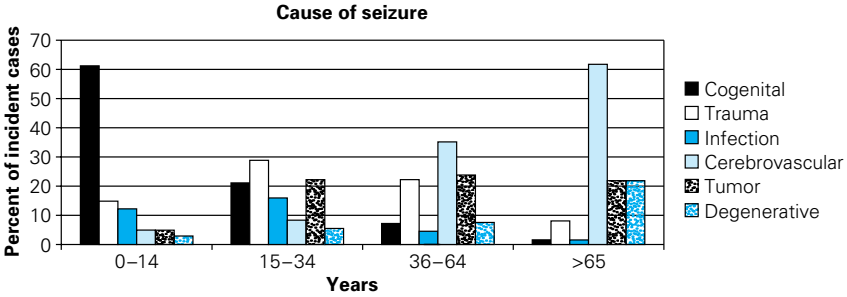

Figure 16-3. Distribution of the main causes of seizures at different ages. Evident is the prevalence of congenital causes in childhood and the emergence of cerebrovascular disease in older patients. (Adapted from several sources including Hauser and Annegers and the texts of Engel and of Pedley.)

Rasmussen Encephalitis In other rare cases, a lesion, usually identified by biopsy, takes the form of a chronic focal encephalitis. In 1958, Rasmussen described three children in each of whom the clinical problem consisted of intractable focal epilepsy in association with a progressive hemiparesis. The cerebral cortex disclosed a mild meningeal infiltration of inflammatory cells and an encephalitic process marked by neuronal destruction, gliosis, neuronophagia, some degree of tissue necrosis, and perivascular cuffing. Many additional cases were soon uncovered, and by 1991, in a publication devoted to this subject (edited by Andermann), Rasmussen was able to summarize the natural history of 48 personally observed patients.

The expanded view of the syndrome has added several interesting features. All the patients were children aged 3 to 15 years, more girls than boys. Half of them had epilepsia partialis continua. The progression of the disease led to hemiplegia or other deficits and brain atrophy in most cases. The CSF has shown pleocytosis and sometimes oligoclonal bands. Focal cortical and subcortical lesions have been well visualized by MRI and are bilateral in some cases. The neuropathology of five fully autopsied cases revealed extensive destruction of the cortex and white matter with intense gliosis but with lingering inflammatory reactions. The finding of antibodies to glutamate receptors in a proportion of patients has raised interest in an immune causation (see review by Antel and Rasmussen). An autoimmune hypothesis has been supported by the findings of Twyman and colleagues that these antibodies cause seizures in rabbits and lead to the release of the neurotoxin kainate in cell cultures. However, Wiendl's group and others have found these antibodies in many types of focal epilepsy and question their specificity for the Rasmussen type of encephalitis.

The unrelenting course of the disease has defied medical therapy. In some patients the process has eventually burned out, but in those with continuous focal epilepsy the seizures continued despite all antiepileptic drugs. The use of full doses of corticosteroids, if started within the first year of the disease, proved beneficial in 5 of the 8 patients treated by Chinchilla and colleagues. Repeated plasma exchanges and immune globulin have been tried, but the results are difficult to interpret. When the disease is extensive and unilateral, neurosurgeons have in the past resorted to partial hemispherectomy. The authors have cared for a number of such patients with the same discouraging results.

Seizures in Later Childhood and Adolescence These represent the most common epileptic problem in general practice. Here, we face two different issues: one relates to the nature and management of the first seizure in an otherwise normal young person and the other to the management of a patient who has had one or more seizures at some time in the past. With respect to the first, a search for a cause by CT, MRI, CSF examination, and EEG rarely discloses a tumor or a vascular malformation and the epilepsy is then classed as idiopathic. The type of seizure that first brings the child or adolescent to medical attention is most likely to be a generalized tonic-clonic convulsion and often marks the beginning of a juvenile myoclonic epilepsy, as described on page 275. In the second type of case, in which there had been some type of seizure at an earlier period, one should suspect a developmental disorder, parturitional hypoxic-ischemic encephalopathy (birth injury), or one of the hereditary metabolic diseases.

Several groups of patients fall between these two distinct types. Development may have been slightly delayed, but reportedly no seizures had occurred earlier in life. Closer investigation may disclose absence seizures, not always recognized as such by parents or teachers, and a typical absence EEG, which points more directly to a genetic factor and to a more favorable prognosis.

When the seizures are an expression of a long-standing epileptic focus or foci that had been associated with mental backwardness, scholastic failure, and inadequacy of social adjustment, the diagnostic and therapeutic problem becomes much more difficult and demanding. Poor observations by the family, muddled thinking, and bizarre ideation on the part of the patient as well as poor compliance with therapy may pose problems as difficult as the seizures themselves. Some patients of this latter group will eventually fall into the category of epilepsy with complex partial seizures. In adulthood, the seizures may continue to interfere with work, marriage, and family relationships. In the interictal periods, the patients may exhibit bursts of bad temper, and they commonly have wide mood swings of sadness and anger or elation. As indicated earlier, paranoid ideation or a frank hallucinatory-delusional

psychosis sometimes appears and lasts for weeks after a single seizure, without any specific EEG changes.

In the large group with *intractable seizures in early life*, many of which are indiscriminately called febrile seizures, nearly half end up in the group identified as temporal lobe epilepsies. Huttenlocher and Hapke, in a follow-up study of 145 infants and children with intractable epilepsy, found that the majority had borderline or subnormal intelligence. This group stands in contrast to the group of otherwise normal adolescents with a first seizure whose scholastic progress and social and emotional adjustment are little if at all affected.

Juvenile myoclonic epilepsy also has its onset during this age period. As described earlier, it is identified by intermittent myoclonic jerks when the patient is tired or after the ingestion of alcohol. Seizures are usually grand mal but are infrequent. The EEG shows a characteristic polyspike pattern, and treatment with certain anticonvulsants is very successful at suppressing the seizures and myoclonus (see page 295).

Finally, a first generalized seizure may bring to attention an adolescent who is abusing alcohol or another drug. Usually it is difficult from the clinical information alone to determine the type and quantity of the drug(s) and the setting in which the seizure occurred—whether in relation to overdose or withdrawal. While steps must be taken to exclude an infection of the nervous system, vascular occlusion, or trauma, the more important issue is generally not the seizure but the addiction and its control.

Regarding treatment, opinion is divided on whether treatment is required for the older child or adolescent who comes to medical attention because of a first seizure. When a large number of such cases have been left untreated, such as in the series reported by Hesdorfer and colleagues, the risk of another seizure over 10 years was 13 percent unless the first episode was status epilepticus, in which case the risk was 41 percent. Age, sex, and the circumstances of the seizure (withdrawal from drugs or alcohol, myoclonic episodes, family history, etc.) all figured into the risk.

Seizures with Onset in Adult Life and Secondary to Medical Disease Several primary diseases of the brain often announce themselves by an acute convulsive state, particularly *primary and metastatic brain tumors*; these are discussed further on in the section on seizures of late adult life. Here we focus on generalized medical disorders as causes of single and repeated seizures.

Withdrawal Seizures The possibility of abstinence seizures in patients who had chronically abused alcohol, barbiturates, or benzodiazepine sedative drugs must always be considered when seizures occur for the first time in adult life (or even in adolescence). Suspicion of this mechanism is raised by the stigmata of alcohol abuse or a history of prolonged nervousness and depression requiring sedation. Also, sleep disturbance, tremulousness, disorientation, illusions, and hallucinations are often associated with the convulsive phase of the illness. Seizures in this setting may occur singly, but more often in a brief flurry, the entire convulsive period lasting for several hours and rarely for a day or longer, during which time the patient may be unduly sensitive to photic stimulation. Alcohol and other drug-related seizures are discussed in more detail on pages 1008 and 1022.

Infections An outburst of seizures is also a prominent feature of all varieties of *bacterial meningitis*, more so in children than in adults. Fever, headache, and stiff neck usually provide the clues to diagnosis, and lumbar puncture yields the salient data. Myoclonic jerking and seizures appear early in acute *herpes simplex encephalitis* and other forms of viral, treponemal, and parasitic encephalitis, including those derived from HIV infection, both directly and indirectly; with toxoplasmosis and brain lymphoma; and in subacute sclerosing panencephalitis. In tropical countries, cysticercosis and tuberculous granulomas of the brain are very common causes of epilepsy. Seizure(s) without fever or stiff neck may be the initial manifestation of syphilitic meningitis, a fact worth noting with the increasing incidence of this process in AIDS patients.

Endogenous Metabolic Encephalopathies *Uremia* is a condition with a strong convulsive tendency. Of interest is the relation of seizures to the development of anuric renal failure, generally from acute tubular necrosis but occasionally due to glomerular disease. Total anuria may be tolerated for several days without the appearance of neurologic signs, and then there is an abrupt onset of twitching, trembling, myoclonic jerks, and generalized motor seizures. Tetany may be added. The motor display, one of the most dramatic in medicine, lasts several days until the patient sinks into terminal coma or recovers, depending on the outcome of the renal disease and its treatment by dialysis. When this twitch-convulsive syndrome accompanies lupus erythematosus, seizures of undetermined cause, or generalized neoplasia, one should suspect it has its basis in renal failure.

Other *acute metabolic illnesses and electrolytic disorders* complicated by generalized and multifocal motor seizures are hyponatremia and its opposite, a hypernatremic hyperosmolar state, thyrotoxic storm, porphyria, hypoglycemia, hyperglycemia, hypomagnesemia, and hypocalcemia. In all these cases *rapidly evolving electrolyte abnormalities are more likely to cause seizures than those occurring gradually*. For this reason it is not possible to assign absolute levels of electrolyte, BUN, or glucose concentrations above or below which seizures are likely to occur. Lead (in children) and mercury (in children and adults) are the most frequent of the metallic poisons that cause convulsions.

In most cases of seizures due to metabolic and withdrawal states, treatment with anticonvulsants is usually not necessary as long as the underlying disturbance is rectified. Indeed, anticonvulsants are often ineffective if the metabolic disorder persists.

Generalized seizures, with or without twitching, may occur in the advanced stages of many other illnesses, such as *hypertensive encephalopathy*, sepsis—especially gram-negative septicemia with shock—hepatic stupor, and intractable congestive heart failure. Usually, seizures in these circumstances can be traced to an associated metabolic abnormality and are revealed by appropriate studies of the blood.

Medications as a Cause of Seizures A large number of medications can cause seizures, usually when toxic blood levels are attained. The antibiotic imipenem and excessive doses of other penicillin congeners will on occasion cause seizures, particularly if renal failure leads to drug accumulation. Cefapime, a fourth-generation cephalosporin, widely used for the treatment of gram-negative sepsis, can result in status epilepticus, especially if given in excessive dosage (Dixit et al). The tricyclic antidepressants, bupropion (Wellbutrin), and lithium may cause seizures, particularly in the presence of a structural brain lesion. Lidocaine and aminophylline are known to induce a single convulsion if administered too quickly or in excessive doses. The use of the analgesic tramadol has also been associated with seizures. Curiously, the anesthetic propofol, which is discussed further on as a potent anticonvulsant in the treatment of status epilepticus, has caused seizure and marked myoclonic phenomena in some patients. These may occur during induction or emergence from anesthesia or as a delayed problem (Walder et al).

The list of medications that at one time or another have been

associated with a convulsion is long, and if no other explanation for a single seizure is evident, the physician is advised to look up in standard references the side effects of the drugs being given to the patient. In a few of our otherwise healthy adult patients, extreme *sleep deprivation* coupled with ingestion of large doses of antibiotics or adrenergic medications or other remedies that are used indiscriminately for the symptomatic relief of colds has been the only plausible explanation after extensive search for the cause of a single or doublet seizure.

Global Arrest of Circulation and Cerebrovascular Diseases Cardiac arrest, suffocation or respiratory failure, carbon monoxide poisoning, or other causes of *hypoxic encephalopathy* tend to induce diffuse myoclonic jerking and generalized seizures as cardiac function is resumed. The myoclonic-convulsive phase of this condition may last only a few hours or days, in association with coma, stupor, and confusion; or it may persist indefinitely as an intention myoclonus-convulsive state (Lance-Adams syndrome).

Convulsive seizures are uncommon in the acute or evolving phases of an arterial stroke. The ischemic convulsive phenomena of a "limb-shaking TIA" and a burst of generalized clonic motor activity during basilar artery occlusion have been mentioned earlier but are uncommon. Only exceptionally will acute embolic infarction of the brain cause a focal fit at its onset. With these infrequent exceptions, a new seizure should not be attributed to an acute arterial occlusion in the cerebrum. More relevant is the fact that embolic infarcts involving the cortex later, after an interval of months or longer, become epileptogenic in almost 10 percent of cases. Thrombotic infarcts are almost never convulsive at their onset.

In contrast, *cortical venous thrombosis* with underlying ischemia and infarction is highly epileptogenic. The same is true for hypertensive encephalopathy and thrombotic thrombocytopenic purpura (TTP), which has a strong tendency to cause nonconvulsive status epilepticus. The rupture of a saccular aneurysm is sometimes marked by one or two generalized convulsions. Subcortical cerebral hemorrhages, spontaneous or traumatic, occasionally become sources of recurrent focal seizures.

Seizures with Acute Head Injury It is not uncommon for severe concussion to be followed by one or more brief convulsions (see Chap. 35). The appearance is similar in most cases to the clonic twitching and brief tonic phase that accompanies a faint. From time to time, a prolonged clonic convulsion occurs. The nature of this event, whether originating in the reticular formation as a component of concussion or from some disruption of cortical activity, is not clear. Almost invariably in our experience, the EEG recorded hours or a day later is normal, and imaging procedures are likewise normal or show a small contusion. There is little to guide one in treatment of these patients; we tend to give a course of anticonvulsant medications lasting several months. Another EEG is taken before discontinuing the medications.

Seizures during Pregnancy Here one contends with two types of problem: one, the woman with epilepsy who becomes pregnant; the other, the woman who has her first seizure during pregnancy. In respect to the first group, about half of the epileptic women who become pregnant have no change in seizure frequency or severity; in about 25 percent, the frequency increases; and in an equal number, it lessens. In a large cohort of such women, there was a slight increase in the number of stillbirths and a doubling in the expected incidence of mental retardation and nonfebrile seizures in their offspring.

Issues regarding a coagulopathy in the fetus exposed to phenobarbital and certain of the other drugs are well known to obstetricians and pediatric specialists and are treated with the oral administration of vitamin K 20 mg/day during the eighth month or 10 mg IV 4 h before birth and 1 mg IM to the neonate. The conventional anticonvulsants also seem to be safe for the baby during breast-feeding in that only small amounts are excreted in lactated milk. For example, carbamazepine in human milk is found to be 40 percent of the mother's serum concentration, and this results in a neonatal blood level that is below the conventionally detectable amount. Phenytoin is excreted at 15 percent of maternal serum concentration, and valproate, being highly protein-bound, is virtually absent in breast milk. No adverse effects have been attributed to these small amounts of drug.

The special issue of the teratogenicity of antiepileptic drugs is addressed further on.

Eclampsia (See also Chap. 34.) This syndrome appears during the last trimester of pregnancy and may announce itself by hypertension and convulsions; the latter are generalized and tend to occur in clusters. The standard practice is to induce labor or perform cesarean section and manage the seizures as one would manage those of hypertensive encephalopathy (of which this is one type). The administration of magnesium sulfate continues to be the favored treatment by obstetricians for the prevention of eclamptic seizures; two randomized trials have re-established its value in preventing seizures in pre-eclamptic women (Lucas et al) and in avoiding a second convulsion once one had occurred (Eclampsia Trial Collaborative Group). Magnesium sulfate, 10 g IM, followed by 5 g every 4 h, proved comparable to standard doses of phenytoin as prophylaxis for seizures. Our colleagues use a regimen of 4 g IV over 5 to 10 min followed by a maintenance dose of 5 g every 4 h IM or 1 to 2 g/h IV. Whether magnesium is as effective in the management of active convulsions of toxemia remains uncertain. In nontoxic gestational epilepsy, about 25 percent of patients are found to have some disease (neoplastic, vascular, or traumatic) that will persist.

Focal or Generalized Seizures in Late Adult Life

Hauser and Kurland have reported a marked increase in the incidence of seizures as the population ages—from 11.9 per 100,000 in the 40- to 60-year age group to 82 per 100,000 in those 60 years of age or older. A person in the latter age group who begins to have seizures of either partial or generalized type is always to be suspected of harboring a primary or secondary tumor or an infarct that had not declared itself clinically. This is a matter usually settled by the neurologic examination and by CT or MRI. Tumor, either primary or secondary, will be found to account for about half the cases of seizures occurring for the first time in late adult life. In our clinical material, almost 10 percent of patients with infarction involving the cerebral cortex later developed recurrent partial or generalized seizures, but most published series cite a lower proportion. According to Sung and Chu, previous infarcts are by far the most common lesions underlying status epilepticus in late adult life, but our experience has been that old trauma is as common. Cortical and subcortical encephalomalacia, the result of previous traumatic contusions, is a particularly important cause of seizures among alcoholics; the lesions are revealed by brain imaging and are typically located in the anterior frontal and temporal lobes. Brain abscess and other inflammatory and infectious illnesses are less common except in tropical regions. Seizures as a result of Alzheimer and other degenerative diseases do occur but are uncommon.

In the not infrequent cases of an adult with a first seizure that

Table 16-5
Common antiepileptic drugs

GENERIC NAME	TRADE NAME	USUAL DOSAGE		PRINCIPAL THERAPEUTIC INDICATIONS	SERUM HALF-LIFE, HOURS	EFFECTIVE BLOOD LEVEL,[a] μG/ML
		CHILDREN, MG/KG	ADULTS, MG/DAY			
Major anticonvulsants used as monotherapy						
Valproic acid	Depakote	30–60	1000–3000	Generalized tonic-clonic, partial, absence, myoclonic	6–15	50–100
Phenytoin	Dilantin	4–7	300–400	Generalized tonic-clonic, partial, absence, myoclonic	12–36	10–20
Carbamazepine	Tegretol	20–30	600–1200[b]	Generalized tonic-clonic, partial	14–25	4–12
Phenobarbital	Luminal	3–5 (8 for infants)	90–200	Generalized tonic-clonic, partial	40–120	15–40
Lamotrigine	Lamictal	0.5	3–500	Generalized	15–60	
Adjuvant and special use anticonvulsants						
Topiramate	Topamax		400	Generalized tonic-clonic, atypical absence, myoclonic, partial	20–30	
Vigabatrin			4000	Partial and secondary generalized, Lennox-Gastaut	20–40	
Tiagabine	Gabitril		30–60	Partial and secondary generalized,	7–9	
Gabapentin	Neurontin	30–60	900–1800[b]	Partial and secondary generalized,	5–7	
Primidone	Mysoline	10–25	750–1500[b]	Generalized tonic-clonic, partial	6–18	5–12
Ethosuximide	Zarontin	20–40	750–1500	Absence	20–60	50–100
Methsuximide	Celontin	10–20	500–1000	Absence	28–50	40–100
ACTH		40–60 Units daily		Infantile spasms		
Clonazepam	Klonopin	0.01–0.2	2–10	Absence, myoclonus	18–50	0.01–0.07
Anticonvulsants for status epilepticus *(initial loading or continuous infusion doses shown)*[c]—phenytoin and phenobarbital used in doses higher than shown above						
Diazepam	Valium	0.15–2	2–20	Status epilepticus		
Lorazepam	Ativan	0.03–0.22	2–20	Status epilepticus		
Midazolam	Versed		0.1–0.4 mg/kg/h	Status epilepticus		
Propofol	Diprivan	2.5–3.5	2–8 mg/kg/h	Status epilepticus		
Fosphenytoin	Cerebyx	30–50 mg	1000–1500	Status epilepticus		10–20

[a] Average trough values.
[b] May require slow dose escalation.
[c] Administered intravenously.

remains unexplained after thorough evaluation, it has been our practice to administer an anticonvulsant and to re-evaluate the situation in a matter of 6 to 12 months, with the goal of eventually discontinuing medication. Usually, a second MRI and EEG are performed to exclude focal abnormalities that were not appreciated during the initial evaluation, but often these studies are again unrevealing. This approach has been prompted by data such as those of Hauser and colleagues, who found that about one-third of patients with a single unprovoked seizure will have another seizure within 5 years; the risk is even greater if there is a history of seizures in a sibling, a complex febrile convulsion in childhood, or a spike-and-wave abnormality in the EEG. Moreover, the risk of recurrence is greatest in the first 24 months. In patients with two or three unexplained seizures, three-quarters have further seizures in the subsequent 4 years.

TREATMENT OF EPILEPSY

The treatment of epilepsy of all types can be divided into four parts: the use of antiepileptic drugs, the surgical excision of epileptic foci and other surgical measures, the removal of causative and precipitating factors, and the regulation of physical and mental activity.

The Use of Antiepileptic Drugs—General Principles

The use of antiepileptic drugs is the most important facet of treatment. In approximately 70 percent of all patients with epilepsy, the seizures are controlled completely or almost completely by the use of antiepileptic drugs; in an additional 20 to 25 percent, the attacks are significantly reduced in number and severity. The most commonly used drugs are listed in Table 16-5, along with their dosages, effective blood levels, and serum half-lives. Because of the long half-lives of phenytoin, phenobarbital, and ethosuximide, these drugs need be taken only once daily, preferably at bedtime. Valproate and carbamazepine have shorter half-lives, and their administration should be spaced during the day. It is also useful to be familiar with the serum protein-binding characteristics of antiepileptic drugs and the interactions among these drugs, and between antiepileptic and other drugs.

Certain drugs are somewhat more effective in one type of seizure than in another, and it is necessary to use the proper drugs in optimum dosages for different circumstances. Initially, only one drug should be used and the dosage increased until sustained therapeutic levels have been attained. If seizures are not controlled by

Table 16-6
Choices of antiepileptic drugs by type of adult seizure disorder

SEIZURE TYPE	INITIAL CHOICE	SECOND LINE
Tonic-clonic	Phenytoin, carbamazepine, valproate	Lamotrigine, oxcarbazepine
Myoclonic	Valproate	Lamotrigine
Partial	Carbamazepine, phenytoin	Valporate, lamotrigine, oxcarbazine
Absence	Valproate	Ethosuximide, lamotrigine
Unclassifiable	Valproate	Lamotrigine

SOURCE: Adapted by permission from Brodie MJ, Schachter SC. *Epilepsy*, 2nd ed. Oxford, England, Health Press, 2001.

the first drug, a different drug should be tried, but frequent shifting of drugs is not advisable; each should be given an adequate trial before another is substituted. A general approach to the choice of drug in certain common forms of epilepsy is given in Tables 16-6 for adults and 16-7 for children, but it must be noted that there are a number of drugs that may be appropriate in each circumstance. A guide to various combinations of drugs that are helpful in refractory cases is given in Table 16-8. In changing medication, the dosage of the new drug should be increased gradually to an optimum level while the dosage of the old drug is gradually decreased; the sudden withdrawal of a drug may lead to an increase in seizure frequency or status epilepticus, even though a new drug has been substituted. If seizures are still not controlled, a second drug can then be added. Seldom if ever are more than two drugs necessary; the physician should make an effort to succeed with one drug and with no more than two given in adequate dosage. Once an anticonvulsant or a combination of anticonvulsants is found to be effective, their use in most cases should be maintained for a period of years, or indefinitely if circumstances justify their long-term use.

Table 16-7
Choices of antiepileptic drugs in childhood seizure disorders

SEIZURE TYPE	INITIAL CHOICE	SECOND	THIRD
Tonic-clonic	Valproate, carbamazepine	Lamotrigine, oxcarbazine	Phenytoin
Myoclonic	Valproate	Lamotrigine	Phenobarbital, clobazam
Absence	Valproate	Lamotrigine, ethosuximide	Clobazam
Partial	Carbamazepine, phenytoin	Valproate, gabapentin, oxcarbazine	Lamotrigine, vigabatrin, topiramate
Infantle spasms	Vigabatrin, cortico-steroids	Valproate	Lamotrigine
Lennox-Gastaut	Valproate	Topiramate, lamotrigine	Felbamate

SOURCE: Adapted by permission from Brodie MJ, Schachter SC. *Epilepsy*, 2nd ed. Oxford, England, Health Press, 2001.

Table 16-8
Combination antiepileptic regimens for refractory seizures

COMBINATION	INDICATION
Valproate and lamotrigine or levetiracetam	Partial or generalized seizures
Valproate and ethosuximide	Generalized absence
Carbamazepine and valproate	Complex partial seizures
Vigabatrin and lamotrigine or tiagabine	Partial seizures
Topiramate and lamotrigine or levetiracetam	Numerous types

SOURCE: Adapted by permission from Brodie MJ, Schachter SC. *Epilepsy*, 2nd ed. Oxford, England, Health Press, 2001.

The therapeutic dose for any given patient must be determined, to some extent, by trial and error and by measurement of serum levels, as described below. Not uncommonly a drug is discarded as being ineffective, when a slight increase in dosage would have led to suppression of the attacks. It is, however, also an error to administer a drug to the point where the patient is so dull and stupefied that the toxic effects are more incapacitating than the seizures. It is highly doubtful that prolonged administration of anticonvulsant medication is a factor in the development of the mental deterioration that occurs in a small percentage of patients with convulsive seizures. In fact, improvement in mentation more often occurs following control of the seizures by the proper dosage of appropriate antiepileptic drugs.

The management of seizures with drugs is greatly facilitated by having patients chart their daily medication and the number, time, and circumstances of seizures. Some patients find it helpful to use a dispenser that is filled on Sunday, for example, with sufficient medication to last the week. This indicates to the patient whether a dose had been missed and whether the supply of medications is running low.

The proper use of anticonvulsant drugs is considerably enhanced by the measurement of their *serum levels*. The concentrations of almost all the commonly used drugs can be measured on a single specimen by immunoassay or by the older gas-liquid chromatography method. These measurements are helpful in regulating dosage, detecting irregular drug intake, identifying the toxic agent in patients taking more than one drug, and assuring patient compliance. Blood for serum levels is ideally drawn in the morning before breakfast and the first ingestion of anticonvulsants ("trough levels"), a practice that introduces consistency in the measurement of drug concentrations.

The effective serum levels for each of the commonly used anticonvulsant drugs are indicated in Table 16-5. The upper and lower levels of the "therapeutic range" are not to be regarded as immutable limits within which the serum values must fit. In some patients, seizures are controlled at serum levels below the therapeutic range; in others, the seizures continue despite serum values within this range. In the latter patients, seizures are sometimes controlled by raising levels above the therapeutic range but not to the point of producing clinical toxicity. In general, higher serum concentrations of drugs are necessary for the control of simple or complex partial seizures than for the control of tonic-clonic seizures alone. It is to be noted that the blood level is not a precise measure of the amount of drug entering the brain, because—in the case of the most widely used anticonvulsants—the larger proportion of

drug is bound to albumin and does not penetrate nervous tissue. Laboratory measurements of the serum concentration, however, detect only the protein-bound fraction. In patients who are malnourished or chronically ill or who have a constitutional reduction in proteins, this may lead to intoxication at low total serum levels. Certain anticonvulsants also have active metabolites that may produce toxicity but are not measured by methods ordinarily used to determine serum concentrations of antiepileptic drugs. This is particularly true for the epoxide of carbamazepine. The situation may be further complicated by interactions between one anticonvulsant and the metabolites of another, as, for example, the inhibition of epoxide hydrolase by valproic acid, leading to toxicity through the buildup of carbamazepine epoxide. In circumstances of unexplained toxicity in the face of conventionally obtained serum levels that are normal, it is therefore important to measure the levels of free drug and the concentration of active metabolites by chromatographic techniques. Drugs in common use for which tests of serum levels are not easily available include levetiracetam, lamotrigine, topiramate, tiagabine, gabapentin and others; this requires an empiric dosing schedule based on recommended amounts and dose escalations for each age group.

Finally, the pharmacokinetics of each drug plays a role in toxicity and the serum level that is achieved with each alteration in the dose. This is particularly true of phenytoin, which has nonlinear kinetics once serum concentrations reach 10 mg/mL, as the result of saturation of liver enzymatic capacity. For this reason, the typical increase in dose from 300 to 400 mg daily often results in a disproportionate elevation of the serum level and toxic side effects. These elevations are also accompanied by a prolongation of the serum half-life, which increases the time to reach a steady-state phenytoin concentration after dosage adjustments. Contrariwise, carbamazepine is known to induce its own metabolism, so that doses adequate to control seizures at the outset of therapy are no longer effective several weeks later.

Always to be considered in the use of an antiepileptic drug, as already mentioned, is its possible interactions with other drugs. Many such interactions have been demonstrated, but only a few are of clinical significance, requiring adjustment of drug dosages (Kutt). Important drugs in this respect are chloramphenicol, which causes the accumulation of phenytoin and phenobarbital, and erythromycin, which causes the accumulation of carbamazepine. Antacids reduce the blood phenytoin concentration, whereas cimetidine does the opposite. Salicylates may reduce the plasma levels of anticonvulsant drugs. Among anticonvulsant drugs, valproate often leads to accumulation of phenytoin and of phenobarbital by displacing them from serum proteins; equally important, warfarin levels are decreased by the addition of phenobarbital or carbamazepine and may be increased by phenytoin. Enzyme-inducing drugs such as phenytoin, carbamazepine, and barbiturates can greatly increase the chance of breakthrough menstrual bleeding in women taking oral contraceptives, and adjustments in the amount of estradiol must be made.

Hepatic failure can seriously affect antiepileptic anticonvulsant drug concentrations, since most of these drugs are metabolized in the liver. Serum levels must be checked frequently, and if there is hypoalbuminemia, it is advisable to obtain free drug levels for reasons just mentioned. Renal failure has only an indirect effect on the concentrations of the commonly used anticonvulsants, but some newer agents, such as vigabatrin and gabapentin, are excreted through the kidneys. The main renal effects have to do with alterations in protein binding that are induced by uremia. In end-stage renal failure, serum levels are not an accurate guide to therapy, and the goal should be to attain free phenytoin concentrations of 1 to 2 mg/mL. In addition, uremia causes the accumulation of phenytoin metabolites, which are measured with the parent drug by enzyme-multiplied immunoassay techniques. In patients who are being dialyzed, total blood levels of phenytoin tend to be low because of decreased protein binding; in this situation it is also necessary to track free (unbound) phenytoin levels. Because dialysis removes phenobarbital and ethosuximide, dosage of these drugs may have to be increased. Decreased phenytoin levels are also known to occur during viral illnesses, and supplementary doses are occasionally necessary.

Once an effective anticonvulsant regimen has been established, it must usually be continued for many years. Because of the long-term toxic effects of such a regimen, many neurologists choose not to institute anticonvulsant therapy after the occurrence of a single generalized seizure in an otherwise normal child or adult (normal EEG and MRI and no family history of seizures). Our more conservative approach of administering an anticonvulsant for 6 to 12 months and then re-evaluating the patient has already been mentioned.

Discontinuation of Anticonvulsants Withdrawal of anticonvulsant drugs may be undertaken in patients who have been free of seizures for a prolonged period. There are few firm rules to guide the physician in this decision. A safe plan, applicable to most forms of epilepsy, is to obtain an EEG whenever withdrawal of medication is contemplated. We have taken the approach that if the tracing is abnormal by way of showing paroxysmal activity, it is generally better to continue treatment. A prospective study by Callaghan and colleagues has shown that in patients who had been seizure-free during 2 years of treatment with a single drug, one-third relapsed after discontinuation of the drug, and this relapse rate was much the same in adults and children and whether the drug was reduced over a period of weeks or months. The relapse rate was lower in patients with absence and generalized-onset seizures than in those with complex partial seizures and secondary generalization. A recent study by Specchio and colleagues gave results similar to those of the large Medical Research Council Antiepileptic Drug Withdrawal Study—namely, that after 2 years on a single anticonvulsant during which no seizures had occurred, the rate of relapse was 40 percent 2 1/2 years later and 50 percent at 5 years after discontinuation; this compared to the seizure recurrence rate of 20 percent for patients remaining on medication. Other authors have suggested that a longer seizure-free period is associated with a lesser rate of relapse (see reviews of Todt and of Pedley and comments above, under "Focal or Generalized Seizures in Late Adult Life"). Patients with juvenile myoclonic epilepsy, even those with long seizure-free periods, should probably continue with medication lifelong, but there have been no thorough studies to our knowledge to support this dictum. The appropriate duration of treatment for post-infarction epilepsy has not been studied, and most neurologists continue to use one drug indefinitely. Interestingly, epilepsy caused by military brain wounds tends to wane in frequency or to disappear in 20 to 30 years, then no longer requiring treatment (Caveness).

The Use of Specific Drugs in Treatment of Seizures

General Comments *Phenytoin*, *carbamazepine*, and *valproate* are more or less equally effective in the treatment of both gener-

alized and partial seizures (see Table 16-5 for typical initial dosages). Valproate is probably less effective in the treatment of complex partial seizures. The first two of these drugs putatively act by blocking sodium channels, thus preventing abnormal neuronal firing and seizure spread.

Since carbamazepine has somewhat fewer side effects, it is preferred as the initial drug by many neurologists, but phenytoin and valproate have very similar therapeutic and side-effect profiles. Carbamazepine and valproate are probably preferable to phenytoin for epileptic children because they do not coarsen facial features and do not produce gum hypertrophy or breast enlargement. In many cases, phenytoin or carbamazepine alone will control the seizures. If not, the use of valproate (which facilitates GABA activity) alone or the combined use of phenytoin and carbamazepine produces better control. In others, the addition of valproate to carbamazepine may prove effective. Because of the high incidence of myoclonic epilepsy in adolescence, it has been our practice to use valproate as the first drug in this age group. Weight gain and menstrual irregularities (see below) during the period of initiation of valproate may also figure into the decision regarding the choice of initial drug for otherwise uncomplicated seizures in women.

Finally, it should be said that most of the commonly used antiepileptic drugs cause, to varying degrees, a decrease in bone density and an increased risk of fracture from osteoporosis in older patients, particularly in women. Several mechanisms are probably active, among them, induction of the cytochrome P450 system, which enzymatically degrades vitamin D. No specific recommendations have been offered to counteract this effect of bone loss. Calcium supplements or one of the bisphosphonates are advised if there is no contraindication.

Phenytoin Both oral and intravenous forms are available. Rash, fever, lymphadenopathy, eosinophilia and other blood dyscrasias, and polyarteritis are manifestations of an idiosyncratic *phenytoin hypersensitivity*; their occurrence calls for discontinuation of the medication. *Overdose with phenytoin* causes ataxia, diplopia, and stupor. The prolonged use of phenytoin often leads to hirsutism (mainly in young girls), hypertrophy of gums, and coarsening of facial features in children. Chronic phenytoin use over several decades may occasionally be associated with peripheral neuropathy and probably with a form of cerebellar degeneration (Lindvall and Nilsson); it is not clear if these are strictly dose-related effects or if there is an idiosyncratic reaction. An antifolate effect on blood and interference with vitamin K metabolism have also been reported, for which reason pregnant women taking phenytoin should be given vitamin K before delivery and the newborn infant should receive vitamin K as well to prevent bleeding. Phenytoin should not be used together with disulfiram (Antabuse), chloramphenicol, sulfamethizole, phenylbutazone, or cyclophosphamide, and the use of either phenobarbital or phenytoin is not advisable in patients receiving warfarin (Coumadin) because of the undesirable interactions already described. Choreoathetosis is a rare idiosyncratic side effect.

Carbamazepine This drug causes many of the same side effects as phenytoin, but to a slightly lesser degree. Leukopenia is common, and there have been rare instances of pancytopenia, hyponatremia, and diabetes insipidus as idiosyncratic reactions. It is essential, therefore, that a complete blood count be done before treatment is instituted and that the white cell count be checked regularly. A more recently introduced analogue of carbamazepine *oxcarbazepine* is said to have even fewer of these side effects than the parent drug, but its long-term therapeutic value still has to be established. Hyponatremia has been reported in 3 percent of patients taking the latter drug. Should drowsiness or increased seizure frequency occur, this complication should be suspected.

Valproate All preparations of this drug may be occasionally hepatotoxic, an adverse effect that is usually (but not invariably) limited to children 2 years of age and younger. The use of valproate with hepatic enzyme–inducing drugs increases the risk of liver toxicity. However, mild elevations of serum ammonia and mild impairments of liver function tests in an adult do not require discontinuation of the drug. An increasingly emphasized problem with valproate has been weight gain during the first months of therapy. In one study there was an average addition of 5.8 kg, and even more in those disposed to obesity. In addition, menstrual irregularities and polycystic ovarian syndrome may appear in young women taking the drug, perhaps as a consequence of the aforementioned weight gain.

An intravenous form of valproate is available. The maximum recommended rate of administration is 20 mg/min.

Phenobarbital Introduced as an antiepileptic drug in 1912, phenobarbital is still highly effective, but because of its toxic effects—drowsiness and mental dullness, nystagmus, and staggering—is seldom used as a first-line drug. The adverse effects of *primidone* are much the same. Both drugs may provoke behavioral problems in retarded children. It is still used to advantage as an adjunctive anticonvulsant and as primary therapy in infantile seizures.

Newer and Ancillary Antiepileptic Drugs *Lamotrigine* closely resembles phenytoin in its antiseizure activity and toxicity and is thought to have less risk of teratogenic effects, as mentioned below. It functions by selectively blocking the slow sodium channel, thereby preventing the release of the excitatory transmitters glutamate and aspartate. It is effective as a first-line and adjunctive drug for generalized and focal seizures and may be an alternative to valproate in young women because it does not provoke weight gain and ovarian problems. The main limitation to its use has been a serious rash in about 1 percent of patients, always requiring discontinuation of the drug, and lesser dermatologic eruptions in 12 percent. It should be pointed out that certain registries have reported far lower rates. The slow introduction of the medication may reduce the incidence of drug eruptions (see below). Rare cases of reversible chorea have been reported, especially with the concurrent use of phenytoin. Combined use with valproate greatly increases the serum level of lamotrigine.

Levetiracetam is a novel sodium channel blocker that has been useful in the treatment of partial seizures, mainly as an adjunctive drug. It is very well tolerated if initiated slowly but produces considerable sleepiness and dizziness otherwise and if used at high doses. There are no important interactions with other antiepileptic drugs.

Felbamate, a drug similar to meprobamate, has shown promise as an adjunctive form of treatment of generalized seizures, complex partial seizures, and Lennox-Gastaut syndrome, but its use has been greatly limited because of the rare occurrence of bone marrow suppression and liver failure.

Two other drugs, *gabapentin* and *vigabatrin*, were synthesized specifically to enhance the intrinsic inhibitory system of gamma-aminobutyric acid (GABA) in the brain. Gabapentin is chemically similar to GABA, but actually its anticonvulsant mechanism is not known. It is moderately effective in partial and secondary generalized seizures and has the advantage of not being metabolized by the liver. Vigabatrin and the related drugs *progabide* and *tiagabine* are inhibitors of GABA transaminase and are effective in the treatment of partial seizures and, to a lesser extent, primary generalized sei-

zures. Neither is bound to plasma protein, and they have the advantage of few toxic effects and no known adverse drug interactions.

Topiramate, another new antiepileptic agent, has much the same mode of action and degree of effectiveness as tiagabine. It may cause serious dermatologic side effects, especially if used with valproate, and appears to induce renal stones in 1.5 percent of patients. Angle-closure glaucoma has also been reported as a complication. A minor problem has been the development of hyperchloremic metabolic acidosis.

Ethosuximide (Zarontin) and valproate are equally effective for the treatment of absence seizures, the latter one being used mainly in children more than 4 years of age. It is good practice, in order to avoid excessive sleepiness, to begin with a single dose of 250 mg of ethosuximide per day and to increase it every week until the optimum therapeutic effect is achieved. *Methsuximide* (Celontin) is useful in individual cases where ethosuximide and valproate have failed. In patients with benign absence attacks that are associated with photosensitivity, myoclonus, and clonic-tonic-clonic seizures (including juvenile myoclonic epilepsy), valproate is the drug of choice. Valproate is particularly useful in children who have both absence and grand mal attacks, since the use of this drug alone often permits the control of both types of seizure. The concurrent use of valproate and clonazepam has been known to produce absence status.

Teratogenic Effects of Antiepileptic Medications Since it is essential to prevent convulsions in the pregnant epileptic woman, anticonvulsant medication should not be discontinued or arbitrarily reduced, particularly if there have been a number of convulsions in the recent past. The conventional drugs (phenytoin, carbamazepine, phenobarbital, valproate) are all appropriately tolerated in pregnancy. Plasma levels of most anticonvulsant drugs, both the free and protein-bound fractions, fall slightly in pregnancy and are cleared more rapidly from the blood. The main practical issue is the potential teratogenicity of many of the anticonvulsant drugs. The most common recorded teratogenic effects has been cleft lip and cleft palate, but infrequently a subtle facial dysmorphism ("fetal anticonvulsant syndrome"), similar to the fetal alcohol syndrome, has also been described. In general, the risk of major congenital defects is low; it increases to 4 to 5 percent in women taking anticonvulsant drugs during pregnancy, in comparison to 2 to 3 percent in the overall population of pregnant women. These statistics are essentially confirmed in the large study by Holmes and colleagues, conducted among several Boston hospitals. When all types of malformations were included, both major and minor, 20 percent of infants born to mothers who took anticonvulsants during pregnancy showed abnormalities compared to 9 percent of mothers who had not taken medications. However, similar to other large surveys, major malformations appeared in only 5 percent of infants exposed to anticonvulsants, in contrast to 2 percent in the nonexposed. These authors identified "midface hypoplasia" (shortened nose, philtrum, or inner canthal distance) and finger hypoplasia as characteristic of anticonvulsant exposure; these changes were found in 13 and 8 percent of exposed infants, respectively. The infants born of a group of women with epilepsy who had not taken anticonvulsants during pregnancy showed an overall rate of dysmorphic features comparable to that in control infants, but there was still a 2 to 3 percent rate of facial and finger hypoplasia. This risk is shared more or less equally by all the major anticonvulsants.

The risk of neural tube defects is also slightly increased by anticonvulsants, and greatest is for the use of valproate; it can be reduced by giving folate before pregnancy has begun, but some epilepsy experts prefer to avoid the use of valproate during pregnancy altogether. Also, these risks are greater in women taking more than one anticonvulsant, so that monotherapy is a desirable goal. Furthermore, the risk is disproportionately increased in families with a history of these defects. Some of the newer anticonvulsants should probably be used cautiously until greater experience has been obtained. For example, claims have been made of safety in this regard for lamotrigine and many specialists have changed from the more conventional drugs to this one in women who anticipate becoming pregnant.

If a woman with seizure disorder has been off epilepsy medications for a time before getting pregnant and seizes during the pregnancy, the best choice of medications is probably phenytoin. Exposure of the fetus late in gestation poses few teratogenic risks. The special case of eclamptic seizures is managed by infusion of magnesium.

It should also be mentioned that most anticonvulsants induce the activity of hepatic enzymes, and this may result in the failure of contraceptive pills due to the accelerated metabolism of steroids. Epileptic women of childbearing age should be advised that higher doses of the estradiol component are required.

Skin Eruptions from Antiepileptic Drugs As mentioned in the discussion above, these are the most common idiosyncratic reactions to the drugs used to treat epilepsy. The aromatic compounds (phenytoin, carbamazepine, phenobarbital, primidone, and lamotrigine) are the ones most often responsible. Furthermore, *there is a high degree of cross-reactivity within this group*, particularly between phenytoin, carbamazepine and phenobarbital, and possibly lamotrigine. The problem arises most often in the first month of use. The typical eruption is maculopapular, mainly on the trunk; it usually resolves within days of discontinuing the medication. More severe rashes may develop, sometimes taking the form of erythema multiforme and Stevens-Johnson syndrome, or even toxic epidermal necrolysis. A rare hypersensitivity syndrome is one of high fever, rash, lymphadenopathy, and pharyngitis. Eosinophilia and hepatitis (nephritis) may follow.

If any of these reactions require that one of the aromatic drugs be replaced, valproate, gabapentin, topiramate, or levetiracetam are reasonable substitutes, depending, of course, on the nature of the seizures.

Treatment of Seizures in the Neonate Treatment of the *special types of convulsions in the neonatal period* and in infancy and childhood is discussed by Fenichel and by Volpe. In general, phenobarbital is preferred for seizure control in infancy.

Probably the form of epilepsy that is most difficult to treat is the childhood *Lennox-Gastaut* syndrome. Some of these patients have as many as 50 or more seizures per day, and every combination of anticonvulsant medications may have no effect. Valproic acid (900 to 2400 mg/day) will reduce the frequency of spells in approximately half the cases. The newer drugs—lamotrigine, topiramate, vigabatrin—are each beneficial in about 25 percent of cases. Clonazepam also has had limited success.

In the treatment of infantile spasms, ACTH or adrenal corticosteroids have been effective, but vigabatrin is now found to be as effective, including in patients with underlying tuberous sclerosis (see Elterman et al).

Status Epilepticus

Recurrent generalized convulsions at a frequency that prevents regaining of consciousness in the interval between seizures (grand mal status) constitute the most serious therapeutic problem (an

overall mortality of 20 to 30 percent, according to Towne and colleagues, but probably lower in recent years). Most patients who die of epilepsy do so because of uncontrolled seizures of this type, complicated by the effects of the underlying illness or an injury sustained as a result of a seizure. Rising temperature, acidosis, hypotension, and renal failure from myoglobinuria is a sequence of life-threatening events that may be encountered in cases of status epilepticus. Prolonged convulsive status (for longer than 30 min) also carries a risk of serious neurologic sequelae ("epileptic encephalopathy"). The MRI during and for days after a bout of status epilepticus frequently shows signal abnormalities in the region of a focal seizure or in the hippocampi, most often reversible, but we have had several such patients who awakened and were left in a permanent amnesic state. The MRI changes are most evident in FLAIR sequences. With regard to acute medical complications, from time to time a case of neurogenic pulmonary edema is encountered during or just after the convulsions, and some patients may become extremely hypertensive, then making it difficult to distinguish the syndrome from hypertensive encephalopathy.

Treatment (Table 16-9) The many regimens that have been proposed for the treatment of status attest to the fact that no one of them is altogether satisfactory and none is clearly superior (Treiman et al). The present authors have had the most success with the following program: when the patient is first seen, an initial assessment of cardiorespiratory function is made and an oral airway established. A large-bore intravenous line is inserted; blood is drawn for glucose, blood urea nitrogen, electrolytes, and a metabolic and drug screen. A normal saline infusion is begun and a bolus of glucose is given (with thiamine if malnutrition and alcoholism are factors).

Table 16-9
Approach to the treatment of status epilepticus in adults (see text)

Initial assessment
Assure adequate ventilation, oxygenation, blood pressure
Intubate if necessary, based on low oxygen saturation and labored breathing
Insert intravenous line
Administer glucose and thiamine in appropriate cirumstances
Send toxic screen
Assess quickly for cranial and cervical injury if onset of seizures is unwitnessed
Immediate suppression of convulsions
Lorazepam or diazepam, 2 to 4 mg/min IV to a total dose of 10 to 15 mg with blood pressure monitoring when higher rates or doses are used
Initiation or reloading with anticonvulsants
Phenytoin 15–18 mg/kg IV at 25–50 mg/min in normal saline or fosphenytoin at 50 to 75 mg/min
General anesthetic doses of medication for persistent status epilepticus
Midazolam 0.2-mg/kg loading dose followed by infusion at 0.1 to 0.4 mg/kg/h or propofol 2 mg/kg/h
Further treatment if convulsions or electrographic seizures persist after several hours
May add valproate or phenobarbital 10 mg/min to total dose of 20 mg/kg as additional anticonvulsants intravenously, or carbamazepine or levetiracetam by nasogastric tube if there is gastric and bowel activity
Consider neuromuscular paralysis with EEG monitoring if convulsions persist
Pentobarbital 10 mg/kg/h
Inhalational anesthetics (isoflurane)

To rapidly suppress the seizures, diazepam is given intravenously at a rate of about 2 mg/min until the seizures stop or a total of 20 mg has been given. Or lorazepam, 0.1 mg/kg given by intravenous push at a rate not to exceed 2 mg/min, may be administered, being marginally more effective than diazepam because lorazepam putatively has a longer duration of action in the CNS (see Tables 16-2 and 16-9).

Immediately thereafter, a loading dose (15 to 18 mg/kg) of phenytoin is administered by vein at a rate of less than 50 mg/min. More rapid administration risks hypotension and heart block; it is therefore recommended that the blood pressure and electrocardiogram be monitored during the infusion. Phenytoin must be given through a freely running line with normal saline (it precipitates in other fluids) and should not be injected intramuscularly. A large study by Treiman and colleagues has demonstrated the superiority of using lorazepam instead of phenytoin as the first drug to control status, but this is not surprising considering the longer latency of action of phenytoin. Alldredge and colleagues have shown that diazepines can even be administered by paramedical workers with good effect in status epilepticus, terminating the seizures in about half of these patients. Nonetheless, a long-acting anticonvulsant such as phenytoin is given immediately after diazepam has controlled the initial seizures. An alternative is the water-soluble drug fosphenytoin, which is administered in the same doses as phenytoin but can be injected at twice the maximum rate. Moreover, it can be given intramuscularly in cases where venous access is difficult. However, the delay in hepatic conversion of fosphenytoin to active phenytoin makes the latency of clinical effect approximately the same for both drugs.

In an epileptic patient known to be taking anticonvulsants chronically but in whom the serum level of drug is unknown, it is probably best to administer the full recommended dose of phenytoin or fosphenytoin. If it can be established that the serum phenytoin is above 10 mg/mL, a lower loading dose is advisable. If seizures continue, an additional 5 mg/kg is indicated. If this fails to suppress the seizures and status has persisted for 20 to 30 min, an endotracheal tube should be inserted and O_2 administered.

Several approaches have been suggested to control status that persists after these efforts. The conventional and still dependable one is infusion of either thiopental, starting with 5 mg/kg, or phenobarbital, at a rate of 100 mg/min until the seizures stop or a total dose of 20 mg/kg is reached. In our experience, a long period of stupor must be anticipated after seizure control is obtained, but some epileptologists still prefer this as the initial treatment. Hypotension often limits the continued use of the barbiturates, but Parviainen and colleagues were able to manage this problem by fluid infusions, dopamine, and neosynephrine (we tend to depend on neosynephrine). Alternatively, at this stage, we have resorted to the approach of Kumar and Bleck, of giving high doses of midazolam (0.2 mg/kg loading dose followed by an infusion of 0.1 to 0.4 mg/kg/h as determined by clinical and EEG monitoring). If seizures continue, the dose can be raised as blood pressure permits. We have had occasion to use in excess of 20 mg/h because of a diminishing effect over days. This regimen of midazolam and phenytoin may be maintained for several days without major ill effect in previously healthy patients. Propofol given in a bolus of

2 mg/kg and then as an intravenous drip of 2 to 8 mg/kg/h is an effective alternative to midazolam, but after 24 h the drug behaves like a high dose of barbiturate and there may be difficulty due to hypotension.

If none of these measures controls the seizures, all medication except phenytoin should be discontinued and a more aggressive approach taken to subdue all brain electrical activity by the use of general anesthesia. The preferred medications for this purpose have been pentobarbital and propofol, which, despite their poor record as primary anticonvulsants, are easier to manage than the alternative inhalational anesthetic agents. An initial intravenous dose of 5 mg/kg pentobarbital or 2 mg/kg propofol is given slowly to induce an EEG burst-suppression pattern, which is then maintained by the administration of 0.5 to 2 mg/kg/h pentobarbital or up to 10 mg/kg/h of propofol. Every 12 to 24 h, the rate of infusion is slowed to determine whether the seizures have stopped. The experience of Lowenstein and colleagues, like our own, is that most instances of status epilepticus that cannot be controlled with the standard anticonvulsants and midazolam will respond to high doses of barbiturates or propofol, but that these infusions cause hypotension and cannot be carried out for long periods.

Should the seizures continue, either clinically or electrographically, despite all these medications, one is justified in the assumption that the convulsive tendency is so strong that it cannot be checked by reasonable quantities of anticonvulsants. A few patients in this predicament have survived and awakened, even at times with minimal neurologic damage. Isoflurane (Forane) has been used in these circumstances with good effect, as we have reported (Ropper et al), but the continuous administration of such inhalational agents is impractical in most critical care units. Halothane has been ineffective as an anticonvulsant, but ether, although impractical, has in the past been effective in some cases. In the end, in these patients with truly intractable status, one usually depends on phenytoin, 0.5 g, and phenobarbital, 0.4 g/day (smaller doses in infants and children, as shown in Tables 16-9), and on measures that safeguard the patient's vital functions. Valproate is available as an intravenous preparation, making it suitable for administration in status, but its potential role in this circumstance has not been extensively studied.

A word must be added concerning neuromuscular paralysis and continuous EEG monitoring in status epilepticus. With failure of aggressive anticonvulsant and anesthetic treatment, there may be a temptation to paralyze all muscular activity, an effect easily attained with drugs such as pancuronium, while neglecting the underlying seizures. The use of such neuromuscular blocking drugs without a concomitant attempt to suppress seizure activity is inadvisable. If such measures are undertaken, continuous or frequent intermittent EEG monitoring is essential; this may also be also helpful in the early stages of status epilepticus in that it guides the dosages of anticonvulsants required to suppress the seizures.

In the related but less serious condition of *acute repetitive seizures*, in which the patient awakens between fits, a diazepam gel, which is well absorbed if given rectally, is available and has been found useful in institutional and home care of epileptic patients, although it is quite expensive. A similar effect has been attained by the nasal or buccal (transmucosal) administration of midazolam, which is absorbed from these sites (5 mg/mL, 0.2 mg/kg nasally; 2 mL to 10 mg buccally). These approaches have found their main use in children with frequent seizures who live in supervised environments, where a nurse or parent is available to administer the medication.

Petit mal status should be managed by intravenous lorazepam, valproic acid, or both, followed by ethosuximide. Nonconvulsive status is treated along the lines of grand mal status, usually stopping short of using anesthetic agents.

Surgical Treatment of Epilepsy

The surgical excision of epileptic foci in simple and complex partial epilepsies that have not responded to intensive and prolonged medical therapy is being used with increasing effectiveness in a growing number of specialized epilepsy units. At these centers, it has been estimated that approximately 25 percent of all patients with epilepsy are candidates for surgical therapy and more than half of these may benefit from surgery. With increasing experience and standardized approaches, especially in patients with temporal lobe epilepsy, it has been suggested that many patients are waiting too long before the surgical option. A perspective that may promote surgery in even more patients is the observation that about 60 percent of patients with partial seizures will respond to a conventional anticonvulsant but that among the remainder, few will respond to the addition of a second or third drug.

To locate the discharging focus requires a careful analysis of clinical and EEG findings, often including those obtained by long-term video/EEG monitoring and, sometimes, intracranial EEG recording by means of intraparenchymal depth electrodes, subdural strip electrodes, and subdural grids. Recently, functional imaging and specialized EEG analysis have been introduced to supplement these methods.

The most favorable candidates for surgery are those with complex partial seizures and a unilateral temporal lobe focus, in whom rates of cure and significant improvement approach 90 percent in some series, but overall, are probably closer to 50 percent after 5 years. A randomized trial conducted by Wiebe and colleagues gave representative results after temporal lobectomy of 58 percent of 40 carefully studied patients remaining seizure-free after 1 year, in contrast to 8 percent on medication alone. Furthermore, as reported by Yoon and colleagues, among those patients who remain free of seizures for 1 year after surgery, over half are still free of seizures after 10 years and most of the remainder had one or fewer episodes per year. It should be emphasized that most patients undergoing surgery in all these studies still require some anticonvulsant medication. Excision of cortical tissue outside of the temporal lobe accomplishes complete seizure-free states in about 50 percent. Taking all seizure types together, only about 10 percent of patients obtain no improvement at all and less than 5 percent are worse.

Other surgical procedures of value in selected cases are section of the corpus callosum and hemispherectomy. The most encouraging results with callosotomy have been obtained in the control of intractable partial and secondarily generalized seizures, particularly when atonic drop attacks are the most disabling seizure type. Removal of the entire cortex of one hemisphere, in addition to the amygdala and hippocampus, has been of value in children and also in some adults with severe and extensive unilateral cerebral disease and intractable contralateral motor seizures and hemiplegia. Rasmussen encephalitis, Sturge-Weber disease, and large porencephalic cysts at times fall into this category. Surgical, focused radiation, or endovascular reduction of arteriovenous malformations may reduce the frequency of seizures, but the results in this regard are somewhat unpredictable (see Chap. 34).

Driving and Epilepsy Only a few states in the United States and most provinces of Canada mandate that physicians report patients

with seizures under their care to the state Motor Vehicle Bureau. Physicians should nonetheless counsel such a patient regarding the obvious danger to himself and others if a seizure should occur (the same holds for the risks of swimming unattended). What little data are available suggest that accidents caused directly by a seizure are rare and, in any case, 15 percent have been due to a first episode of seizure that could not have been anticipated. In some states where a driver's license has been suspended on the occurrence of a seizure, there is usually some provision for its reinstatement—such as a physician's declaration that the patient is under medical care and has been seizure-free for some period of time (usually 6 months or 1 to 2 years). The Epilepsy Foundation website can be consulted for updated information regarding restrictions on driving, and this serves as an excellent general resource for patients and their families (www.efa.org).

Regulation of Physical and Mental Activity

The most important factors in seizure breakthrough, next to the abandonment of medication, are loss of sleep and abuse of alcohol or other drugs. The need for moderation in the use of alcohol must be stressed, as well as the need to maintain regular hours of sleep. These seemingly anachronistic suggestions in an age of many available anticonvulsants are still valid.

A moderate amount of physical exercise is desirable. With proper safeguards, even potentially more dangerous sports, such as swimming, may be permitted. However, a person with incompletely controlled epilepsy should not be allowed to drive an automobile, operate unguarded machinery, climb ladders, or take tub baths behind locked doors; such a person should swim only in the company of a good swimmer and wear a life preserver when boating.

Psychosocial difficulties must be identified and addressed early. Simple advice and reassurance will frequently help to prevent or overcome the feelings of inferiority and self-consciousness of many epileptic patients. Patients and their families may benefit from more extensive counseling, and proper family attitudes should be cultivated. Oversolicitude and overprotection should be discouraged. It is important that the patient be allowed to live as normal a life as possible. Every effort should be made to keep children in school, and adults should be encouraged to work. Many communities have vocational rehabilitation centers and special social agencies for epileptics, and advantage should be taken of such facilities.

Other Therapeutic Measures

Ketogenic Diet Since the 1920s, interest in this form of seizure control has varied, being revived periodically in centers caring for many children with intractable epilepsy. Despite the absence of controlled studies showing its efficacy or a reasonable hypothesis for its mechanism, several trials in the first half of the twentieth century and again more recently have demonstrated a reduction in seizures in half of the patients, including handicapped children with severe and sometimes intractable fits. The regimen is initiated during hospitalization by starvation for a day or two in order to induce ketosis, followed by a diet in which 80 to 90 percent of the calories are derived from fat (Vining). The difficulties in making such a diet palatable leads to its abandonment by about one-third of children and their families. A summary of experience from the numerous trials of the ketogenic diet can be found in the review by Lefevre and Aronson. They concluded that, despite the lack of a controlled trial, the diet can be effective in refractory cases of epilepsy in childhood. It has also been commented that some benefit persists even after the diet has been stopped.

Vagal Nerve Stimulation This experimental technique has found favor in cases of intractable partial and secondarily generalizing seizures. A pacemaker-like device is implanted in the anterior chest wall and stimulating electrodes are connected to the vagus at the left carotid bifurcation. The procedure is well tolerated except for hoarseness in some cases. Several trials have demonstrated an average of one-quarter reduction in seizure frequency among patients who were resistant to all manner of anticonvulsant drugs (see Chadwick for a discussion of recent trials). The mechanism by which vagal stimulation produces its effects is unclear, and its role in the management of seizures is still being defined. Cerebellar stimulation has also been used in the control of seizures, with no clear evidence of success.

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