Epilepsy is the term given to a group of functional brain disorders, which present in the form of repetitive seizures. A first, or solitary, seizure should be clearly distinguished from epilepsy. Epilepsy is caused by abnormal excessive discharges of neurons in the brain. Epileptic seizures are nonspecific responses of the brain to all kinds of insults. Epilepsy, therefore, may have a multitude of causes.

There are several relatively new options for physicians to explore in the areas of epilepsy diagnosis and treatment. As the first-line of defence, family physicians must keep up-to-date in this area of diagnosis and treatment.

By Neelan Pillay, MB, ChB, FCP(SA), MRCD(UK), FRCPC
Seizures may commence at any age, from birth onward. Both the prevalence and incidence of epilepsy are dramatically higher among elderly patients, as compared to younger ones. Disorders that must be differentiated from epilepsy include migraine, syncope, transient ischemic attacks and nonepileptic seizures (psychogenic seizures). Once it is determined that the ictal event was epileptic, the next diagnostic step is to search for an underlying cause. In the majority of patients with epilepsy, diagnosis can be made with a detailed neurologic history and examination, an EEG and a CT scan and/or MRI scan. Seizures are a symptom of an underlying disorder, which may be genetic, traumatic, metabolic, infectious, malignant or associated with drug intoxication or withdrawal. Diagnostic advances in EEG include routine EEG, EEG-video monitoring and invasive EEG.

The understanding and treatment of epilepsy has been enormously improved by the development and use of brain imaging techniques, which provide information about the structure and function of the brain. The principal forms of structural imaging are: CT, MRI, single photon emission CT (SPECT), angiography, positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional MRI (fMRI) and subtraction ictal SPECT coregistered to MRI.

Treatment with antiepileptic medication is warranted when a diagnosis of epilepsy is made.

Clinical Manifestations

History and examination are the first steps in diagnosis in order to determine if the ictal event is epileptic. Disorders that must be differentiated from epilepsy include migraine, syncope, transient ischemic attacks (TIAs) and nonepileptic seizure (psychogenic seizures). Once it is determined that the ictal event was epileptic, the next diagnostic step is to search for an underlying cause.

Diagnostic evaluation is then aimed at determining what type(s) of seizures are occurring, whether the disorder might be considered primary or secondary, and whether the clinical features constitute a recognized epileptic syndrome. The clinical manifestations are extremely variable and depend on the cortical areas involved.

The International Classification of Epileptic Seizures divides the clinical manifestations into the following:

- Partial seizures, which begin in a part of one hemisphere of the brain; and
- Generalized seizures, which begin in both hemispheres of the brain simultaneously (Table 1).
into a syndrome, according to the classification set out by the International League Against Epilepsy. Classification is important in providing treatment and giving the patient a prediction as to the course and prognosis of his/her epilepsy. Many epileptic syndromes are recognized based on characteristic seizure types and other clinical features, including family history and associated neurologic disturbances (Table 2). Diagnosis of a specific syndrome has implications for the prognosis, as well as the treatment. Primary epileptic syndromes tend to be age-related and benign, often remitting in adolescence or early adulthood.

Symptomatic epilepsies
These are mostly localization-related and secondary to tumors, focal cortical dysplasia or past brain injuries.

Cryptogenic epilepsies
These are presumed to be symptomatic, but have an unknown etiology. Most localization-related epilepsies without an underlying lesion, or in which a lesion cannot be shown, are cryptogenic.

Idiopathic epilepsies
The cause of this type of epilepsy is unknown. Patients with idiopathic epilepsies possess normal

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Table 1

<table>
<thead>
<tr>
<th>Partial seizures</th>
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<tbody>
<tr>
<td>• Simple partial seizures</td>
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<tr>
<td>• Complex partial seizures</td>
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<tr>
<td>• Partial seizures becoming secondarily generalized seizures</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Generalized seizures</th>
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<tbody>
<tr>
<td>• Absence seizures</td>
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<tr>
<td>• Myoclonic seizures</td>
</tr>
<tr>
<td>• Clonic seizures</td>
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<tr>
<td>• Tonic seizures</td>
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<tr>
<td>• Tonic-clonic seizures</td>
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<td>• Atonic seizures</td>
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<table>
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<tr>
<th>Unclassified epileptic seizures</th>
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Table 2

<table>
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<tr>
<th>Classification of Epilepsies and Epileptic Syndromes</th>
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<tbody>
<tr>
<td><strong>Epilepsies related to localization (focal, local, partial)</strong></td>
</tr>
<tr>
<td>• Idiopathic (with age-related onset)</td>
</tr>
<tr>
<td>• Symptomatic</td>
</tr>
<tr>
<td>• Cryptogenic (presumed to be symptomatic, but of unknown cause).</td>
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<tr>
<td><strong>Generalized epilepsies</strong></td>
</tr>
<tr>
<td>• Idiopathic</td>
</tr>
<tr>
<td>• Cryptogenic or symptomatic</td>
</tr>
<tr>
<td><strong>Epilepsies and epileptic syndromes of undetermined type (focal or generalized)</strong></td>
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<td><strong>Special situation-related epileptic syndromes</strong></td>
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intellectual skills, while their examinations are normal and a genetic origin is implied. Most of the idiopathic epilepsies are generalized.

**Diagnostic Tools**

In the majority of patients with epilepsy, diagnosis can be made with the aid of a detailed neurologic history and examination, an electroencephalogram (EEG) and a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) scan. In certain patients, however, diagnosis requires recording the seizures during inpatient video-EEG monitoring.

Patients who usually require this sophisticated diagnostic procedure are those in whom the clinical diagnosis is obscure, or in those who require precise seizure localization in order to pursue epilepsy surgery.

**Determination of Etiology**

The final step in the diagnosis is to determine the etiology of the epilepsy. Seizures are a symptom of an underlying disorder, which may be genetic, traumatic, metabolic, infectious, malignant and associated with drug intoxication or withdrawal.

**Diagnostic Advances in EEG**

**Routine EEG**

Despite tremendous recent advances in neuroimaging, the EEG retains an important role in the diagnosis of epilepsy because seizures are a disorder of electrical function rather than of structure (Figure 1). Routine EEG may be useful in supporting a clinical diagnosis of epilepsy by showing epileptiform discharges (*e.g.*, spikes or sharp waves), as it is highly specific. Fewer than 50% of routine EEGs are abnormal in patients who are known to have epilepsy. While this yield increases with repeated EEGs, many patients with epilepsy continue to have normal EEGs.

**EEG-video monitoring**

Prolonged EEG-video monitoring is critical in providing information about electrographic seizures and seizure semiology. A definitive diagnosis of epilepsy can be made if a seizure occurs during an EEG recording, and electrographic ictal discharges can be correlated with habitual clinical signs and/or symptoms.

The prolonged nature of the recording allows a more thorough analysis of the EEG, thereby increasing the likelihood of capturing epileptiform discharges. This analysis also is aided by the use of automated spike detection. More importantly, video monitoring allows recording of the actual events for which medical attention is sought (*e.g.*, partial epilepsy arising from temporal lobe or where non-epileptic psychiatric consultation would be necessary).
Invasive EEG
This type of EEG is necessary when surgery is being considered and a regular (scalp) EEG evaluation fails to identify the zone of seizure onset with sufficient confidence. It also may be considered when the zone of seizure onset must be defined with high precision in relation to nearby cortex. Various techniques, each having advantages and limitations, are available, including subdural, epidural, foramen ovale and intracerebral (depth) electrodes.8

Neuroimaging in Epilepsy
The understanding and treatment of epilepsy has been enormously improved by the development and use of brain-imaging techniques, which provide information about the structure and function of the brain. The principal forms of structural imaging are:

Computed tomography
The number of lesions detected by CT is low; CT sensitivity is about 30% in epilepsy. MRI has largely superceded CT, but is more expensive and access to equipment is still limited. CT is often the first-line investigation and may be useful in acute situations to identify the nature of a stroke, or distinguish between a tumor and an abscess.

Magnetic resonance imaging
Contrary to CT, there is no radiation exposure and, therefore, MRI can be used in pregnancy (not within the first three months). The overall sensitivity is slightly over 80%. Successful surgical outcome is about 90% if MRI shows mesial temporal sclerosis (Figure 2).

Angiography
Its use is limited in epilepsy, except in vascular lesions and to perform the sodium amytal test to determine language lateralization in selected patients for epilepsy surgery. MR and CT angiography has replaced many of the procedures requiring conventional cerebral angiograms.
Single photon emission CT
SPECT uses a radioactive isotope emitting a single photon to measure blood flow and produce a tomographic image of the brain. During a seizure, SPECT can reveal an area of increased blood flow in the brain. It may be useful in a few candidates for surgery in whom other tests have not produced sufficiently accurate localization and for whom invasive recordings are not performed. Unlike PET, it is cheaper and available in most centers.

Positron emission tomography
PET also can measure brain metabolism and uses radioactive tracers, but a cyclotron is needed to produce the tracers. Apart from glucose and oxygen metabolism, it can measure cerebral blood flow (CBF). PET is more sensitive in infants with partial seizures. The major advantage is that it is an interictal procedure and, therefore, can be done on an outpatient basis.

Magnetic resonance spectroscopy
MRS provides chemical information of metabolites. Proton MRS can quantify neuronal loss (Figure 3). N-acetyl acetate (NAA) is present in mature neurons and is the surrogate measure for neuronal dysfunction or loss. MRS is more sensitive than MRI, and can measure gamma-aminobutyric acid (GABA) receptor function in vivo. NAA levels are reduced in temporal

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### Table 3

Choosing An Antiepileptic Drug For Seizure Type

<table>
<thead>
<tr>
<th></th>
<th>Partial Seizures</th>
<th>Generalized Seizures</th>
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<tr>
<td></td>
<td>Simple or Complex</td>
<td>Tonic-clonic</td>
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<tr>
<td>ACTH</td>
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<td>Carbamazepine</td>
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<td>Clobazam</td>
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<td>Ethosuximide</td>
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<td>Gabapentin</td>
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<td>Lamotrigine</td>
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<td>Phenobarbital</td>
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<td>Phenytoin</td>
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<td>Tiagabine</td>
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<td>Topiramate</td>
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<td>Valproate</td>
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<td>Vigabatrin</td>
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ACTH = adrenocorticotropic hormone
lesions. It is currently used for research purposes, but there is potential for clinical use in the future.

Functional MRI
fMRI is used to identify regions of the brain that are active during a task. The most important clinical application is in the pre-surgical evaluation of patients with epilepsy. It is mainly used in pre-surgical brain mapping, spike-triggered seizure localization and potential replacement of the invasive sodium amytal test (Wada’s test) for language lateralization. It is currently a research tool, but is expected to be used in the clinical setting in the future.

Subtraction ictal SPECT co-registered to MRI
In this test, two or more images obtained using different techniques are aligned, thereby optimizing image interpretation. The only requirements are access to digital image data sets and a computer workstation with image processing and co-registration software. In some cases with normal SPECT, SISCOM may be abnormal.

Management
Many new drugs for the treatment of epilepsy have become available in the past eight years. Treatment with antiepileptic medication is warranted when a diagnosis of epilepsy is made. Single seizures, therefore, usually are not treated unless there is sufficient evidence that an epileptic condition exists. Treatment begins with a single drug, and the dose is increased until seizures stop or adverse side effects occur. If the drug is unsuccessful, a second is added and the first is then tapered and discontinued, with monotherapy the preferred goal.

The choice of antiepileptic drug depends primarily on the seizure type and the diagnosis of a specific syndrome, if possible (Table 3). All of these drugs provide added seizure control. They also are being used more often in situations other than epilepsy treatment, such as pain management and treatment of psychiatric disorders, chronic pain and migraine. All antiepilepsy drugs are central nervous system depressants and are associated with sedation, dizziness, ataxia, cognitive and visual disturbances, and gastrointestinal symptoms.

Routine laboratory studies, including a complete blood count and liver function tests, should be performed prior to instituting antiepileptic medications. These tests can be repeated, along with serum drug levels, as medication is being increased. Once a steady-state level has been achieved, routine testing is no longer necessary unless adverse side effects appear or seizures recur. Serum drug levels are useful when the following are present:
- Problems with drug absorption or metabolism;
• Toxic side effects or breakthrough seizures occur while more than one drug is being used; and
• Noncompliance is suspected.

**Choice of drugs and comparative efficacy**

Although most neurologists still choose carbamazepine or phenytoin as first-line drugs for patients with partial-onset seizures, and valproate for patients with generalized-onset seizures, the favorable side effect profiles of some of the newer agents raise questions about whether this is the best practice. Drugs with low risks of cognitive or cerebellar toxicity, such as gabapentin or lamotrigine, may be preferred in elderly patients. Relatively potent drugs, such as topiramate, may be consumed earlier rather than later for patients with known refractory syndromes. Those with milder epilepsies may be tried first on drugs with relatively benign side-effect profiles.

Choosing drugs for women of childbearing age is a special problem. Women and their physicians must choose between the older drugs, with a definite but relatively low teratogenic risk, and the newer drugs with possibly low, but unknown, risks.

**Ketogenic diet**

The ketogenic diet was first advocated in 1921 after it was noted that ketosis and acidosis induced by a high-fat, low-carbohydrate diet had anticonvulsant effects similar to those of starvation. The diet was rarely used once drugs became available to treat epilepsy, however, there has been a recent resurgence of interest in this treatment modality. A recently introduced popular modification to the diet is the medium-chain triglyceride variant. The diet is indicated for use primarily in young children with intractable symptomatic generalized epilepsy. Overall, 30% to 50% of children respond favorably to this treatment option. There are some potential concerns regarding its effects on growth in children and on serum cholesterol levels in adults.

**Vagus nerve stimulation**

Vagus nerve stimulation (VNS) is an entirely new treatment modality that has been extensive-
ly studied. The mechanism of action is unclear, but it is likely mediated by the widespread afferent connections of the vagal nerve. Efficacy is comparable to adjunctive AEDs.

Furthermore, efficacy may increase over time. VNS has no significant neurocognitive or systemic toxicity. The only common side effect is hoarseness of the voice or a mild cough upon stimulation.

Epilepsy surgery
A total of 30% of epileptic patients’ seizures cannot be controlled satisfactorily with AEDs. Many of these patients can be seizure-free by surgical intervention. Epilepsy surgery is now well-documented and provides effective treatment for some patients with intractable epilepsy.9

It is estimated that the number of surgeries performed is well below the number of possible surgeries, despite the fact that surgery is now a well-accepted modality for the treatment of medically intractable epilepsy.10

Medical intractability is a relative concept rather than an absolute one. The number of AEDs that should be tried before a patient is deemed medically intractable is a matter of judgment. It is now well documented, however, that when the first drug fails an adequate trial, the chances that another drug will succeed are less than 20%. If a second trial fails, the chances of future success with a medication are less than 10%.11

Surgery should not be a treatment of last resort that is considered only after exhaustive and futile trials of every available AED. In practice, a typical medical trial may include two to four major drugs, with some used as monotherapy and at maximal tolerated dosages. When considering surgical options as a treatment for epilepsy, a patient’s seizures must be frequent enough or severe enough to interfere significantly with quality of life (Table 4). Recent advances in imaging have significantly reduced the need for invasive EEG.

In general, postoperative seizure control is most successful in patients with temporal lobe epilepsy and has a greater than 90% rate of excellent outcome when MRI and EEG data are concordant.12

References