

World Federation of Neurology

Seminars in  
Clinical Neurology

# Epilepsy: Global Issues for the Practicing Neurologist

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EPILEPSY: GLOBAL ISSUES FOR  
THE PRACTICING NEUROLOGIST



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## Epilepsy: Global Issues for the Practicing Neurologist

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# Preface

Epilepsy is one of the most common serious primary brain disorders, affecting 40 million people worldwide. According to the World Health Organization (WHO), epilepsy accounts for 1% of the Global Burden of Disease, equivalent to lung cancer in men and to breast cancer in women. It is not surprising, therefore, that 10 to 20 textbooks on epilepsy are published annually. These texts contain the very latest information on the diagnosis and treatment of various aspects of epilepsy; however, approximately 80% of people with epilepsy in the world live in developing countries, where modern diagnostic and treatment approaches do not exist. Upwards of 90% of people with epilepsy in these areas receive no treatment at all. It is surprising, therefore, that no textbook on epilepsy addresses the issues faced by neurologists who must deliver care with limited resources, often in a setting of tropical diseases and malnutrition that characterizes practice in developing countries. This text is specifically designed for this purpose.

The World Federation of Neurology has recognized the unmet need of neurologists who must practice medicine without many of the advantages that are often taken for granted in the industrialized world, and has undertaken the task of creating a series of textbooks on neurologic subspecialty topics, in an effort to address issues important for neurologists in developing countries, but which are not covered in standard textbooks. This is the first in the series specifically intended to achieve this goal. At this point, the book is a work in progress, because the authors' experience is limited to only a few areas of the extensive developing regions of the world, and undoubtedly, many important problems remain to be identified and addressed. Consequently, we will appreciate feedback from our colleagues who use this text to help us make it more comprehensive in future editions.

Although I, as chief editor, practice at the University of California in Los Angeles, with all the advantages available to neurologists in the industrialized world, my familiarity with the problems of people with epilepsy in developing countries has increased since 1993, when I served first as treasurer, then president, of the International League against Epilepsy (ILAE), and most recently as co-chair of the joint ILAE/International Bureau for Epilepsy (IBE)/WHO Global Campaign against Epilepsy. My personal lack of hands-on experience is complemented by the coauthors of this book, all of whom are neurologists practicing in developing countries. Gretchen Birbeck is a neurologist in a general medical clinic in rural Zambia, and she has written a handbook on epilepsy for healthcare workers in similar environments. Amadou Gallo Diop is a member of the neurology department at a medical college in Dakar, Senegal, and has been instrumental in organizing epilepsy programs for the WHO and the ILAE in Sub-Saharan Africa. Satish Jain heads an epilepsy center in New Delhi, India, and has been active in programs of the Southeast Asian region of the WHO. André Palmieri is the scientific director of an epilepsy center at a university hospital in Porto Alegre, Brazil, and was chair of the ILAE Commission on Latin American Affairs.

The authors are grateful to Martin Brodie from Glasgow, Scotland, an expert on the clinical pharmacology of antiepileptic drugs, who chaired the ILAE Commission on European Affairs

and is currently a vice president of that organization; Olivier Dulac, a pediatric epileptologist in Paris, France, who has worked in various developing countries; J.A.W. Sander of London, who has organized epidemiologic studies throughout the developing world, and is currently treasurer of the ILAE, and C.T. Tan, a general neurologist in Kuala Lumpur, Malaysia, who chairs the ILAE Commission on Asian and Oceanian Affairs, for their review and critical comments on the manuscript.

Jerome Engel, Jr., MD, PhD  
Los Angeles, California  
September 2004

# Editor's Preface

The mission of the World Federation of Neurology (WFN, wfneurology.org) is to develop international programs for the improvement of neurologic health, with an emphasis on developing countries. A major strategic aim is to develop and promote affordable and effective continuing neurologic education for neurologists and related health care providers. With this continuing education series, the WFN launches a new effort in this direction. The *WFN Seminars in Neurology* uses an instructional format that has proven to be successful in controlled trials of educational techniques. Modeled after the American Academy of Neurology's highly successful *Continuum*, we use proven pedagogical techniques to enhance the effectiveness of the course. These include case-oriented information, key points, multiple choice questions, annotated references, and abundant use of graphic material.

In addition, the course content has a special goal and direction. We live in an economic environment in which even the wealthiest nations have to restrict health care in one form or another. Especially hard pressed are countries where, of necessity, neurologic care is often reduced to the barest essentials or less. There is general agreement that much of this problem is a result of increasing technology. With this in mind, we have asked the faculty to present the instructional material and patient care guidelines with minimal use of expensive technology. Technology of unproven usefulness has not been recommended. However, at the same time, advice on patient care is given without compromising a goal of achieving the very best available care for the patient with neurologic disease. On occasion, details of certain investigative techniques are pulled out of the main text and presented separately for those interested. This approach should be of particular benefit to health care systems that are attempting to provide the best in neurologic care but with limited resources.

These courses are provided to participants by a distribution process unusual for continuing education material. The WFN membership consists of 86 individual national neurologic societies. Societies that have expressed an interest in the program and agree to meet certain specific reporting requirements are provided a limited number of courses without charge. Funding for the program is provided by unrestricted educational grants. Preference is given to neurologic societies with limited resources. Each society receiving material agrees to convene a discussion group of participants at a convenient location within a few months of receiving the material. This discussion group becomes an important component of the learning experience and has proved to be highly successful.

Our second course addresses the important area of epilepsy management. The Chair of this course, Professor Jerome Engel, Jr. a recognized international authority, has selected an outstanding faculty of experts. We very much welcome your comments and advice for future courses.

Theodore L. Munsat, M.D.  
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## WHAT IS EPILEPSY?

The nervous system has a limited repertoire of responses to insult; it can underact, causing negative signs and symptoms such as paralysis and blindness, or it can overact, causing positive signs and symptoms such as pain, hallucinations, and epileptic seizures. This, of course, is an oversimplification, because most neurologic disorders produce complex signs and symptoms with both negative and positive features; for instance, paresis is often accompanied by spasticity, and epileptic seizures often are followed by postictal functional impairment of some sort. Epileptic seizures represent the most common positive signs and symptoms of brain disturbance, and an individual with a life expectancy of age 70 has a one-in-ten chance of experiencing at least one epileptic seizure.

All epileptic seizures, however, are not epilepsy, which is defined as a condition associated with *recurrent* epileptic seizures. In the industrialized world, only about one-third of individuals who have a single seizure will go on to have one or more additional seizures and warrant a diagnosis of epilepsy. Furthermore, epilepsy, consisting of recurrent seizures, is not always a fixed condition, because many patients undergo spontaneous remission of their epileptic disorder. Thus, the prevalence of active epilepsy worldwide is only about 5 to 10 per 1,000 (see Chapter 3). Nevertheless, epilepsy is one of the most common primary brain disorders; it appears to be more prevalent in developing countries, where the risk of predisposing factors such as poor perinatal care, head trauma, and intracranial infection, including parasitic infestations, is often greater than in industrialized countries (Chapter 9), and most patients in these countries receive poor treatment, or none at

all. Indeed, it has been estimated that 80% of the global health burden of epilepsy is borne by the developing world, where more than 80% of people with epilepsy are not receiving treatment, or are often not even identified. This disparity between the number of people with active epilepsy and the number being adequately treated is referred to as the “treatment gap.” The information in this text is designed to help narrow the treatment gap.

### DEFINITIONS

The term *epilepsy*, or more correctly, *the epilepsies*, refers to a group of chronic neurologic conditions characterized by recurrent epileptic seizures. The diagnosis of an epileptic disorder implies that the neurologic dysfunction responsible for generating *epileptic seizures* continues to exist, even when seizures are not occurring. It is important to recognize, therefore, that epileptic seizures provoked in an otherwise normal brain, which do not recur after the provocative insult is removed, do not warrant a diagnosis of epilepsy. Such a diagnosis is only warranted when an enduring epileptogenic brain abnormality is diagnosed, or suspected, which has the potential to continue to generate epileptic seizures.

*Epileptic seizures* are the clinical manifestations (signs and symptoms) of excessive and/or hypersynchronous, usually self-limited, abnormal activity of neurons in the brain. Although it was once believed that epileptic seizures reflect disturbances involving only the cerebral cortex, it has recently become clear that subcortical structures are often also involved, and some epileptic seizures may be primarily generated at a subcortical level. Thus, the distinction between epileptic seizures and some subcortical positive symp-

### KEYPOINTS

- Eighty percent of the global health burden of epilepsy is borne by the developing world.
- Epileptic seizures provoked in an otherwise normal brain, which will not recur after the provocative insult is removed, does not warrant a diagnosis of epilepsy.

## KEYPOINTS

- When diagnosis is in doubt, it is better to make no diagnosis at all and wait until the condition has clearly declared itself before pronouncing a definitive verdict of an epileptic disorder.

toms, such as certain myoclonic phenomena, is not well-defined. The behavioral features of epileptic seizures reflect the functions of the brain areas involved, and may take the form of impaired higher mental function or altered consciousness, involuntary movements or cessation of movement, sensory or psychic experiences, or autonomic disturbances, and often evolve with a combination of these signs and symptoms. Specific epileptic seizure types are electroclinically defined, i.e., by their behavioral and electroencephalogram (EEG) features.

*Ictal event* refers to the epileptic seizure, whereas *postictal* refers to dysfunction occurring after the seizure is over, and *interictal* refers to the period between seizures, when ictal and postictal disturbances no longer exist. Although an aura is a simple partial seizure, and therefore an ictal event, some patients experience poorly defined prodromal symptoms that occur minutes or hours prior to epileptic seizure onset, which are not ictal events, and therefore can be considered pre-ictal phenomena.

*Epileptogenesis* refers to the development of an epileptic disorder, although the term is occasionally used also to refer to the initiation of epileptic seizures.

*Epileptic focus* is defined electrophysiologically as the brain area that appears to generate the most prominent interictal epileptiform EEG discharges. From this EEG perspective, epileptic conditions may be due to a single focus, bilateral independent foci, multiple foci, or there may be diffuse unilateral or generalized epileptiform abnormalities with no focal features. It is important to understand, however, that the actual epileptogenic abnormality is rarely limited to a discrete focal area of the brain, even in a patient who has a single, well-defined EEG epileptic focus. The area of brain necessary and sufficient for generating habitual epileptic seizures in patients with focal epilepsy is more correctly referred to as the *epileptogenic region*. The epileptogenic region is a theoretical concept, and its exact boundaries can only be implied from a variety of diagnostic information, including ictal behavior, interictal and ictal EEG, and neuroimaging.

*Epileptic encephalopathy* is a term applied to conditions, usually seen in infants and

children, in which the epileptogenic process itself is responsible for progressive interictal cerebral dysfunction. In this case, the patient loses previously acquired abilities. Exceptionally, the consequent motor, sensory, or cognitive disturbances are the only expression of the epileptic disorder.

*Control* and *cure* are terms that are poorly defined with respect to epileptic seizures. Epileptic seizures can be considered well-controlled when their frequency and/or severity is reduced by treatment to some acceptable level for some period of time, but no specific criteria have been established. Individuals with epilepsy are often referred to as *seizure free* when they no longer have disabling epileptic seizures, even though simple partial sensory seizures (auras) may persist. Epidemiologically, an individual is considered to have *active epilepsy* until seizure free and off medications for 5 years, so presumably after this point, it is appropriate to consider the individual *cured*. Complete elimination of the underlying epileptic disturbance is most common in those epileptic conditions that undergo spontaneous remission, and following surgical resection of the epileptogenic region. In most cases, pronouncement of a complete cure can only be made retrospectively.

## DIFFERENTIAL DIAGNOSIS OF EPILEPSY

Many intermittent and paroxysmal signs and symptoms can be mistaken for epilepsy, and differential diagnosis can be difficult, particularly in countries with limited resources where EEG, including inpatient video/EEG monitoring and sophisticated neuroimaging, are not available. Unfortunately, countries with limited resources, where it is difficult to rule out a diagnosis of epilepsy, often are culturally predisposed to damaging misconceptions that enhance the disability associated with a diagnosis of epilepsy (Chapter 8). Consequently, when diagnosis is in doubt, even in the industrialized world, but particularly in developing countries, it is better to make no diagnosis at all and wait until the condition has clearly declared itself before pronouncing a definitive verdict of an epileptic disorder. In this respect, it is of utmost importance to understand what is not epilepsy. In addition to nonepileptic events that

mimic epilepsy, discussed in Chapter 2, this includes single seizures, discussed in Chapter 5, and provoked seizures, which may be recurrent, but no longer occur when the underlying cause is removed (Figure 1.1).

Although an epileptic seizure is always an abnormal event, it can be a natural response of the normal brain to noxious insult and does not necessarily imply a persistent underlying epileptogenic abnormality. It is possible to provoke a seizure in anyone, but the susceptibility or threshold for the induction of such provoked ictal events varies considerably from one individual to another. For instance, someone with a low threshold to provoked seizures may have a single generalized tonic-clonic convulsion as a result of several nights of sleep deprivation, alcohol withdrawal, or use of a convulsant drug such as cocaine, and this should not be considered

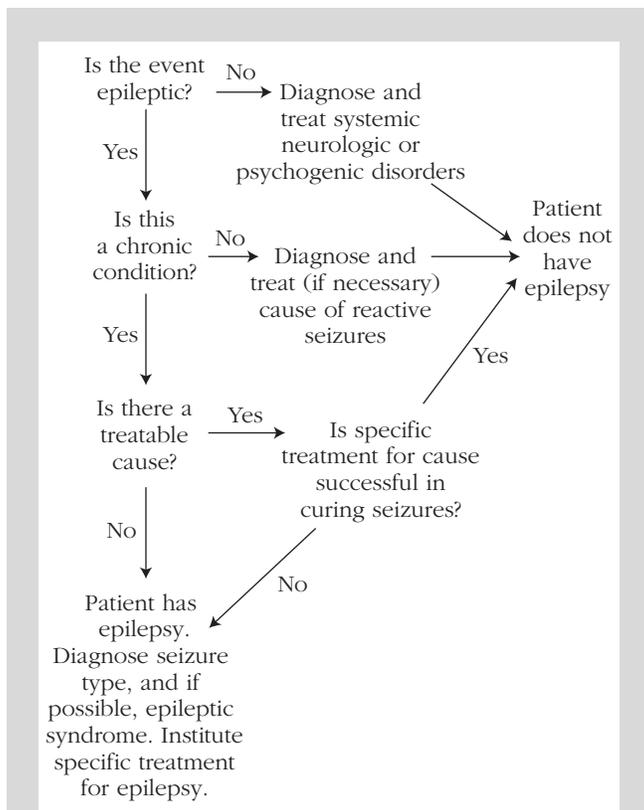
epilepsy, although it is an indication that the specific provocation should be avoided if possible. Seizures provoked by fever in infants and young children (Chapter 5) constitute the most common provoked ictal events that do not require a diagnosis of epilepsy. In some cases, single or recurrent seizures result from treatable causes such as intracranial infections, mass lesions, or other intracranial pathologies, which can be completely cured or removed. In these patients, if seizures do not continue after this treatment, a diagnosis of epilepsy is not warranted.

**CAUSES OF EPILEPSY**

Treatment approaches usually depend on the type of epilepsy (Chapter 2) and the etiology (Chapters 5, 6, and 7). The causes of epilepsy are most often multifactorial, and it is useful to consider three general factors (Figure 1.2). The first factor is the susceptibility of individual brains to generate seizures in response to epileptogenic perturbations. Whether an individual has a high or low susceptibility, or threshold, for seizures to occur is largely dependent on genetic factors, although structural damage to the brain can also alter threshold. Furthermore, threshold is not a static condition, but changes over time, so that most people have a lower threshold during drowsiness and slow-wave sleep than during wakefulness and REM sleep, and many women have lower thresholds before menses, and sometimes during ovulation. Virtually all antiepileptic drugs work by raising the threshold. The second factor is the specific epileptogenic abnormality, which could be an acquired lesion of the brain or a genetic disturbance (Chapter 3). Potentially epileptogenic disturbances are more likely to produce epilepsy in individuals with a low threshold than in individuals with a high threshold. Specific epileptogenic disturbances may require specific treatment that can eliminate seizures,

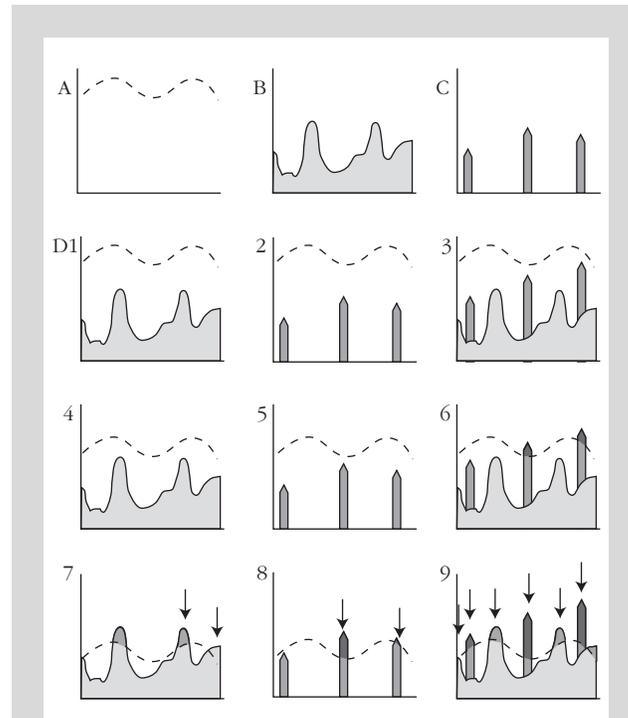
**KEYPOINTS**

- In some cases, single or recurrent seizures result from treatable causes such as intracranial infections, mass lesions, or other intracranial pathologies, which can be completely cured or removed. In these patients, if seizures do not continue after this treatment, a diagnosis of epilepsy is not warranted.



**FIGURE 1.1** Steps in evaluation of paroxysmal events.

From Engel J Jr. *Seizures and Epilepsy*. Philadelphia: F. A. Davis, 1989, with permission.



**FIGURE 1.2** Schematic diagram illustrating interactions of the fluctuating threshold for seizures determined by *nonspecific predisposing factors* (A); independent fluctuations of a *specific epileptogenic disturbance* (B); and *intermittent precipitating factors* (C). With a high threshold, epileptogenic disturbances and precipitating factors alone (D1, D2) and combined (D3) fail to generate seizures. With an intermediate threshold, epileptogenic disturbances and precipitating factors alone (D4, D5) fail to generate seizures, but seizures (arrows) occur when these factors are combined (D6). With a low threshold, epileptogenic disturbances and precipitating factors alone (D7, D8) are each capable of generating seizures, and combined (D9), generate even more seizures, perhaps constituting intractable epilepsy or status epilepticus.

From Engel J Jr. *Seizures and Epilepsy*. Philadelphia: F. A. Davis, 1989, with permission.

and if they are localized, they can often be surgically removed. The third factor consists of precipitating events that cause seizures to occur at a given point in time (Chapter 3). These may be seizures without epilepsy, for instance in children with febrile seizures or an individual who has an isolated seizure due to alcohol withdrawal or sleep deprivation, or these may be recurrent seizures in patients with epilepsy. Examples of the lat-

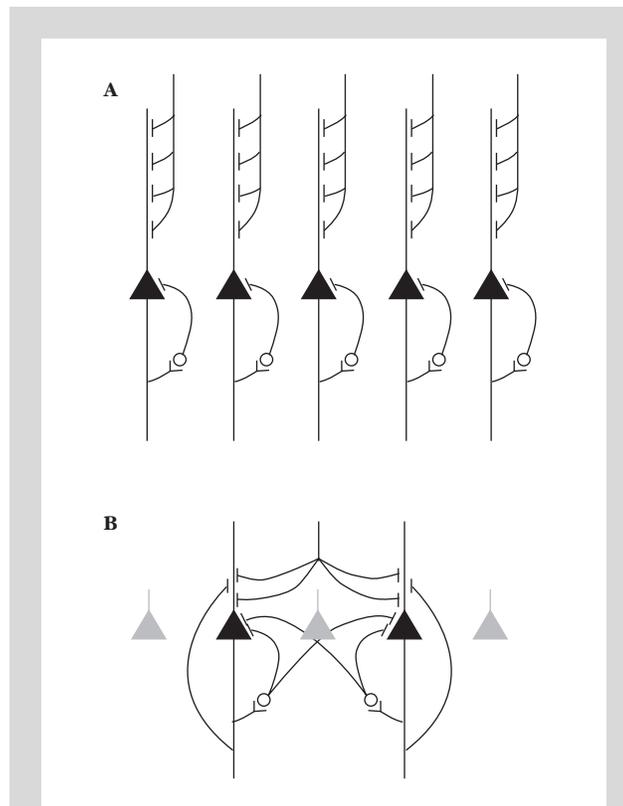
ter are most obvious in patients with reflex epilepsies who have seizures precipitated by specific sensory and cognitive experiences, but precipitating factors like sleep deprivation or menses may also be identified in patients with other types of epilepsy. The avoidance of precipitating factors when possible, and added protection when not possible, can be an important part of treatment.

Epileptic disorders are considered to be *idiopathic* or *primary* when they are just epilepsy and not the result of some other brain abnormality, *epilepsy sui generis*. Idiopathic epilepsies are usually benign, age-related, genetic disorders unassociated with lesions in the brain or other neurologic disturbances, and they often remit spontaneously. Epileptic disorders are considered to be *symptomatic* or *secondary* when they result from lesions or other disturbances of the brain that may produce other signs and symptoms besides epilepsy. These abnormalities may be acquired, or the result of a genetic disease such as tuberous sclerosis or phenylketonuria. Thus, genetic and acquired disturbances interact in a variety of ways that can result in epileptic seizures or epilepsies. With respect to inheritable factors in epilepsy, these may nonspecifically affect threshold, or they may be specific genetic disturbances that cause idiopathic epileptic syndromes or diseases associated with brain lesions resulting in symptomatic epileptic disorders. Diagnostic strategies are

aimed at determining the type of seizures and epilepsy in each patient and, if possible, identifying a treatable underlying cause (Chapter 4). Epileptic disorders that are probably symptomatic, but do not have an identified cause, are sometimes called *cryptogenic*. Further discussion of the classification of seizures and epilepsy can be found in Chapter 2, and specific causes of epilep-

sy, including genetic causes, are presented in Chapter 3.

Discussion of the fundamental mechanisms of epilepsy are beyond the scope of this text, but it is important to recognize that there are many different types of epilepsy, and they do not all share a common pathophysiologic basis. Enhanced inhibition and disturbed function of certain low-threshold calcium channels in the thalamus cause the abnormal hypersynchronization underlying generalized spike-and-wave discharges associated with absence seizures, and antiabsence drugs work by blocking these calcium currents. On the other hand, generalized tonic-clonic seizures may result from enhanced excitation in brainstem and neocortical structures, and these are successfully treated by drugs that block sodium and calcium channel-mediated excitation, suppress glutamatergic excitatory activity, and enhance gamma aminobutyric acid (GABA)-ergic inhibitory activity. The most common form of epilepsy in adolescents and adults, at least in the industrialized world, is mesial temporal lobe epilepsy (MTLE). This condition is undoubtedly underdiagnosed in the developing world because of limited neuroimaging. MTLE is usually associated with hippocampal sclerosis, which appears to be epileptogenic as a result of enhanced excitation and inhibition, resulting in hypersynchronization. It is likely that a genetic predisposition and early cerebral insult combine to cause the characteristic pattern of cell loss and gliosis in the hippocampus. Such early insults, for example prolonged febrile seizures, are common in developing countries. The synaptic reorganization of surviving neurons is believed to increase susceptibility for abnormal hypersynchronization, which then leads to



**FIGURE 1.3** Reciprocal innervation of a hypothetical neuronal system is shown schematically (A). This is the typical synaptic organization of neocortex and hippocampus.

Excitatory afferent input terminates on the dendrites of principal neurons (filled triangles). Axon collaterals from these principal neurons terminate on inhibitory interneurons (empty circles), which in turn make hyperpolarizing synapses on the soma of the same, and adjacent (not shown), principal neurons. With cell loss, a number of synaptic reorganizations are likely to occur, as shown schematically (B). Fewer afferent input fibers sprout to innervate more principal neurons, predisposing to hypersynchronization. Because the dendrites of principal neurons are shorter, these excitatory influences are closer to the axon hillock and more likely to induce neuronal firing. Neuronal excitability is further increased by the establishment of monosynaptic excitatory recurrent circuits. Some inhibitory interneurons also sprout new terminals to produce more powerful, and/or more extensive, recurrent inhibitory influences, further enhancing the potential for hypersynchronization.

From Engel J Jr. Functional explorations of the human epileptic brain and their therapeutic implications. *Electroenceph Clin Neurophysiol* 1990;76:296-316, with permission.

**KEYPOINTS**

- The most common form of epilepsy, at least in the industrialized world, is mesial temporal lobe epilepsy (MTLE). This condition is undoubtedly underdiagnosed in the developing world because of limited neuroimaging.

**KEYPOINTS**

- The Global Campaign against Epilepsy, a joint program of the WHO, ILAE, and IBE, was launched in 1997 to “bring epilepsy out of the shadows,” in order to address discrimination against those with epilepsy and to narrow the treatment gap in developing regions of the world.

the manifestation of epileptic seizures (Figure 1.3). Understanding these epileptogenic mechanisms has helped to design new antiepileptic drugs, and it is hoped that further insights will eventually lead to novel therapeutic approaches; however, a detailed understanding of the pathophysiology of epilepsy is only peripherally relevant to issues dealt with in this text on the diagnosis and treatment of epileptic seizures and epilepsies in developing countries.

### **ADDRESSING THE BURDEN OF EPILEPSY IN THE DEVELOPING WORLD**

Studies by the World Health Organization (WHO) have determined that epilepsy accounts for approximately 1% of the global burden of disease. Among primary disorders of the brain, epilepsy is one of the four most important causes of economic and personal loss, the other three being affective disorders, dementias, and alcohol abuse. Many industrialized countries have recognized this fact and are improving the diagnosis and treatment of epilepsy by setting aside additional funding for research, the creation of specialized epilepsy centers, and training of epilepsy specialists. This effort is greatly aided by recent advances in diagnostic technology, particularly neuroimaging, improved treatment approaches, which include the introduction of seven new antiepileptic drugs in the past decade (Chapter 6), and rapidly expanding use of alternative treatments, particularly surgery (Chapter 7). The International League against Epilepsy (ILAE), the international organization of medical professionals working in the field of epilepsy, has increased the number of its national chapters from 40 to over 90 in the past eight years, and increased attendance at its international congresses from 2,000 to over 5,000, indicating a tremendous redirection of personnel and resources within the medical community toward the problems of those with epilepsy. The International Bureau for Epilepsy (IBE), the international lay organization concerned with the myriad social problems that tragically add to the disabilities encountered by individuals with epilepsy, has experienced a similar increase in chapter membership and activities. Most of these developments, however, have had lit-

tle impact in developing countries, where the majority of individuals with epilepsy live.

More information about the ILAE and IBE, and about their chapters, can be found on their websites [www.ilae-epilepsy.org](http://www.ilae-epilepsy.org) and [www.ibe-epilepsy.org](http://www.ibe-epilepsy.org). The objectives of this text would be greatly enhanced by the establishment of ILAE and IBE chapters in those developing countries that do not already have them. These websites also contain information about the procedures for beginning new ILAE and IBE chapters. This is addressed in more detail in Chapter 9.

The Global Campaign against Epilepsy, a joint program of the WHO, ILAE, and IBE, was launched in 1997 to “bring epilepsy out of the shadows,” in order to address discrimination against those with epilepsy and to narrow the treatment gap in developing regions of the world. The objectives of the Global Campaign against Epilepsy are stated in Table 1.1. Not only have a majority of the ILAE and IBE national chapters taken up aspects of the Global Campaign in their own countries, but Regional Declarations, which identify problems and propose solutions for ministries of health and other health care organizations, have been created for Europe,

**TABLE 1.1** Objectives of the ILAE/IBE/WHO Global Campaign against Epilepsy: Bringing Epilepsy Out of the Shadows

- To increase public and professional awareness of epilepsy as a universal, treatable brain disorder;
- To raise epilepsy to a new plane of acceptability in the public domain;
- To promote public and professional education about epilepsy;
- To identify the needs of people with epilepsy on a national and regional basis; and
- To encourage governments and departments of health to address the needs of people with epilepsy, including awareness, education, diagnosis, treatment, care, services, and prevention.

sub-Saharan Africa, Latin America, Asia and Oceania, and North America, and one more is planned in the near future for the eastern Mediterranean region (Middle East and North Africa). Demonstration projects designed to identify people with epilepsy and bring them to treatment centers are now ongoing in China and Senegal, and are planned for Argentina and Zimbabwe.

In 1999, the WHO raised the Global Campaign against Epilepsy to cabinet level, making it one of its highest priority projects. Every regional office of WHO has pledged to commit personnel and resources to this campaign. Further information on the Global Campaign against Epilepsy can be obtained from its website [www.who.int/mental\\_health/management/global\\_epilepsy\\_campaign/en/](http://www.who.int/mental_health/management/global_epilepsy_campaign/en/), or by writing to: PO Box 21, 2100 AA Heemstede, The Netherlands.

### OBJECTIVES

This textbook is intended for neurologists working in developing countries. It assumes sophisticated training in neurology and access to standard textbooks (although current journals may not always be available); therefore, it is not a comprehensive review of epileptology. Rather than present material readily available in many excellent volumes (some of which are cited in the references to this chapter), this text is designed to address those aspects of epileptology relevant to neurologists practicing under conditions common in the developing world which may not be adequately covered in available published material.

The difficulties encountered in developing regions of the world derive from a poverty of resources and trained personnel, as well as an often inadequate and inefficient administrative and political infrastructure, usually compounded by tropical conditions. Risk factors for epilepsy in developing regions differ from those usually discussed in textbooks written for North American and European consumption, as a consequence of public health deficiencies, such as poor or absent prenatal care and failure to control infectious diseases; and of a relatively high incidence of head trauma from traffic accidents, endemic social violence, and enduring political conflicts. This not only means

that neurologists should look for different underlying causes of epilepsy in their patients than they would in the industrialized world, but that there is much that can be done to prevent epilepsy in these populations. In addition, medical care in the developing world may be severely compromised by several other factors. Large distances between clinical facilities and poor transportation limit patient access to care; a low level of education not only complicates the instruction of individual patients and their families about diagnosis and treatment, but also presents obstacles to improving knowledge, attitudes, and perceptions about epilepsy in the general population. Some prevalent cultural influences lead patients and their families to seek alternative health care, foster concepts that stigmatize people with epilepsy and increase the morbidity and mortality resulting from their seizures, and promote customs, such as consanguineous marriage, which contribute to a higher incidence of epilepsy.

The ratio of trained neurologists to people with epilepsy is extremely low in developing nations compared with that in the industrialized world. Consequently, neurologists in these situations are likely to be more effective, for most patients, as educators than primary caregivers. As such, health administrators in developing regions should consider the benefits of allowing neurologists to focus their professional activities on improving the capability of general practitioners, nurses, and other health workers to provide adequate care for people with epilepsy, leaving the neurologists to see only the most difficult patients themselves. Invariably, the paucity of well-trained neurologists, and in many cases the virtual absence of epileptologists in developing countries, is exacerbated by the “brain drain” when neurologists who seek further specialized training abroad do not return to their home country. However, the practice of neurology, and particularly of epileptology, in the developing world can be intellectually challenging, and tremendous opportunities for creative and important research exist. The U.S. National Institutes of Health, for instance, has shown increasing interest in supporting international collaborations for

### KEYPOINTS

- This text is designed to address those aspects of epileptology relevant to neurologists practicing under conditions common in the developing world which may not be adequately covered in available published material.
- Neurologists in these situations are likely to be more effective, for most patients, as educators than primary caregivers. As such, health administrators in developing regions should consider the benefits of allowing neurologists to focus their professional activities on improving the capability of general practitioners, nurses, and other health workers to provide adequate care for people with epilepsy

**KEYPOINTS**

- The emerging countries of the world do not have a monopoly on the financial, political, and cultural problems that contribute to inadequate health care for people with epilepsy. Most industrialized countries also have pockets of underprivilege where similar conditions prevail.

capacity-building research in low and middle income countries. The WHO has given epilepsy the highest priority for research support, and it is hoped that more neurologists interested in improving care for people with epilepsy in the developing world will remain in, or return to, their home countries to pursue these research activities.

It is necessary to recognize that conditions differ markedly from one developing country to another. For some large countries like India, China, and Brazil, there are sufficient resources and trained personnel to create medical centers of excellence equal to those in North America and Europe, but access to these centers is limited. Consequently, some people with epilepsy receive a high standard of medical care, while many others do not. Solving the financial and logistical problems that prevent the organization of adequate health care provision to all people with epilepsy in these countries is obviously quite different from those in countries, such as the majority in sub-Saharan Africa, which have little or no modern medical facilities or neurologists. Furthermore, obstacles to the adequate diagnosis and treatment of people with epilepsy in rural settings of developing countries are quite different from those in urban settings, and countries differ in the degree to which urban and rural problems contribute to the health care burden. Of course, the emerging countries of the world do not have a monopoly on the financial, political, and cultural problems that contribute to inadequate health care for people with epilepsy addressed in this volume. Most industrialized countries also have pockets of underprivilege where similar conditions prevail, as exemplified in the United States by certain ghetto neighborhoods in the large cities, some remote rural areas, and a few uniquely isolated ethnic and cultural groups, such as the Indian reservations and urban communities of recent immigrants from the developing world. It is likely, therefore, that efforts to resolve the problems that limit epilepsy prevention and health care delivery in developing countries will also contribute importantly to the resolution of similar problems in the industrialized world. More infor-

mation about resources in every country can be obtained from the WHO Atlas, WHO Geneva HQ, 2002, and about epilepsy in Africa from WHO AFRO, 2004.

Although this text is divided into 10 chapters that deal with the traditional topics covered by other epilepsy textbooks, each chapter is specifically organized to recognize the unique problems posed by epilepsy in the developing world, to emphasize approaches to diagnosis and treatment that are most applicable in areas with limited resources, and to assist in promoting the acceptance of people with epilepsy by defining and correcting the misinformation responsible for discrimination, mistreatment, and inappropriate restrictions that contribute greatly to their disability in many developing countries of the world.

**CONCLUSIONS**

Epileptic seizures represent the most common positive signs and symptoms of brain disturbance, and epilepsy is one of the most common primary brain disorders. The great majority of people with epilepsy live in the developing world, and most of them receive no treatment at all. Although much has been written documenting tremendous advances in the diagnosis and treatment of epilepsy in recent years, standard textbooks do not address the needs of neurologists who must care for patients with epilepsy in areas with limited resources where modern approaches are not available and in circumstances, such as tropical conditions, where different health problems exist. This text, designed to provide information of use to neurologists in developing countries that is not available in standard textbooks, begins with an introductory overview of definitions, basic concepts of differential diagnosis, a brief discussion of causes, and a description of the ILAE/IBE/WHO Global Campaign against Epilepsy designed predominantly to address the burden of epilepsy in the developing world. Subsequent chapters are concerned with differential diagnosis and classification, epidemiology and etiology, diagnostic approaches, treatment approaches, antiepileptic drugs, alternative therapy, psychosocial issues, and public health.

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# DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION OF SEIZURES AND EPILEPSY

There are many nonepileptic conditions that can produce an abrupt loss or alteration of consciousness, generalized convulsive movements, sudden falls to the ground, or even localized abnormal movements, sensations, or autonomic symptoms. Whenever a clinician encounters a patient with any of these manifestations, however, the first possibility that should come to his or her mind is that of an epileptic seizure. The need for a correct diagnosis of the type of spell cannot be overemphasized: Nonepileptic seizures may be life-threatening, affected patients with nonepileptic seizures need specific types of treatment, and the use of antiepileptic drugs (AEDs) may even worsen the condition. Furthermore, particularly in developing countries, an unwarranted diagnosis of epilepsy enhances disability as a result of the stigma and social limitations associated with this disorder, as well as an often burdensome cost of unnecessary AEDs. Conversely, the diagnosis of epilepsy can be missed if there is not a high degree of suspicion, particularly in infants and young children with epileptic encephalopathies, where the major symptoms are progressive neurologic or mental deterioration.

In this era of high technology applied to medicine in general, and particularly to neurology, it is reassuring that the diagnostic armamentarium needed for the differential diagnosis between epileptic and nonepileptic spells is usually simple. Most of the conditions mimicking epileptic seizures can be suspected on clinical grounds. Electroencephalograms (EEGs), electrocardiograms (ECGs), and imaging studies may be occasionally required, but the correct diagnosis is usually reached by history and examination. The key issue is to always keep in mind the

possibility of alternative diagnoses in patients who at first glance appear to have epileptic seizures.

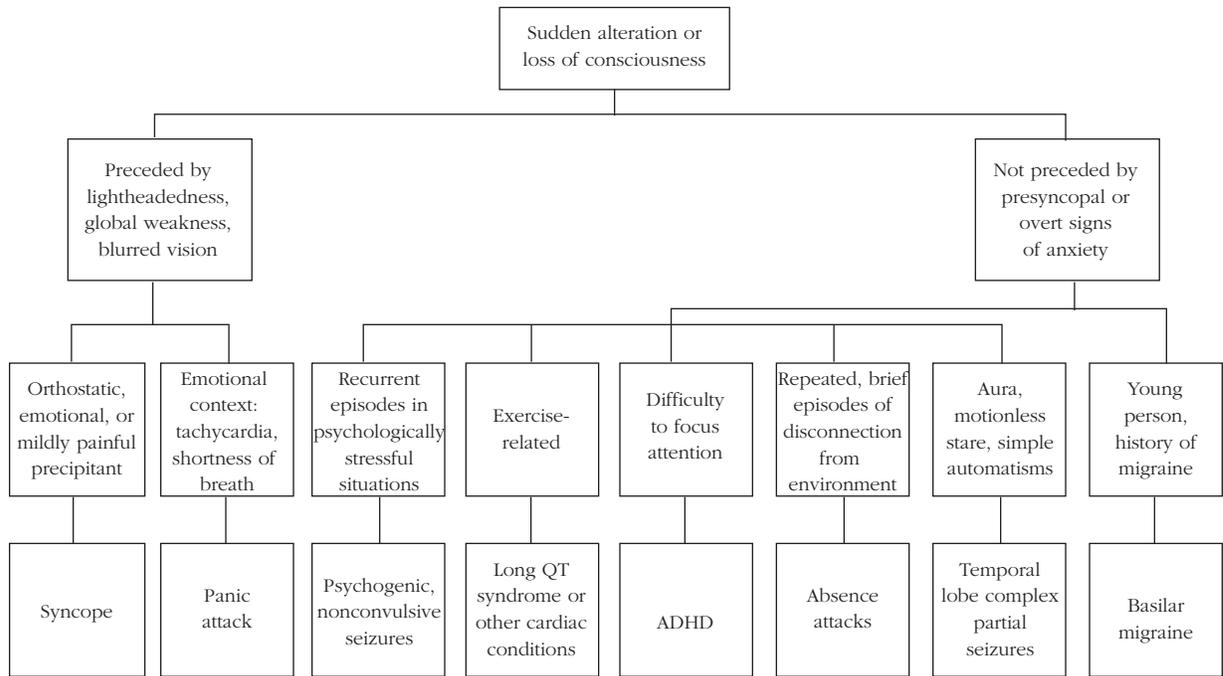
Once the diagnosis of epileptic seizures is established, therapeutic management, prognosis, and counseling are dependent upon the identification of the underlying cause, the exact type of seizure, and epilepsy syndrome (where possible). In developing countries, this implies a thorough knowledge of the presentation of epilepsies related to infectious processes, trauma, congenital disturbances, and other disorders commonly encountered in these environments. A flow chart for the differential diagnosis of epileptic seizures is shown in Figures 2.1 through 2.4.

## A CLINICAL APPROACH TO CONDITIONS OFTEN MISDIAGNOSED AS EPILEPSY

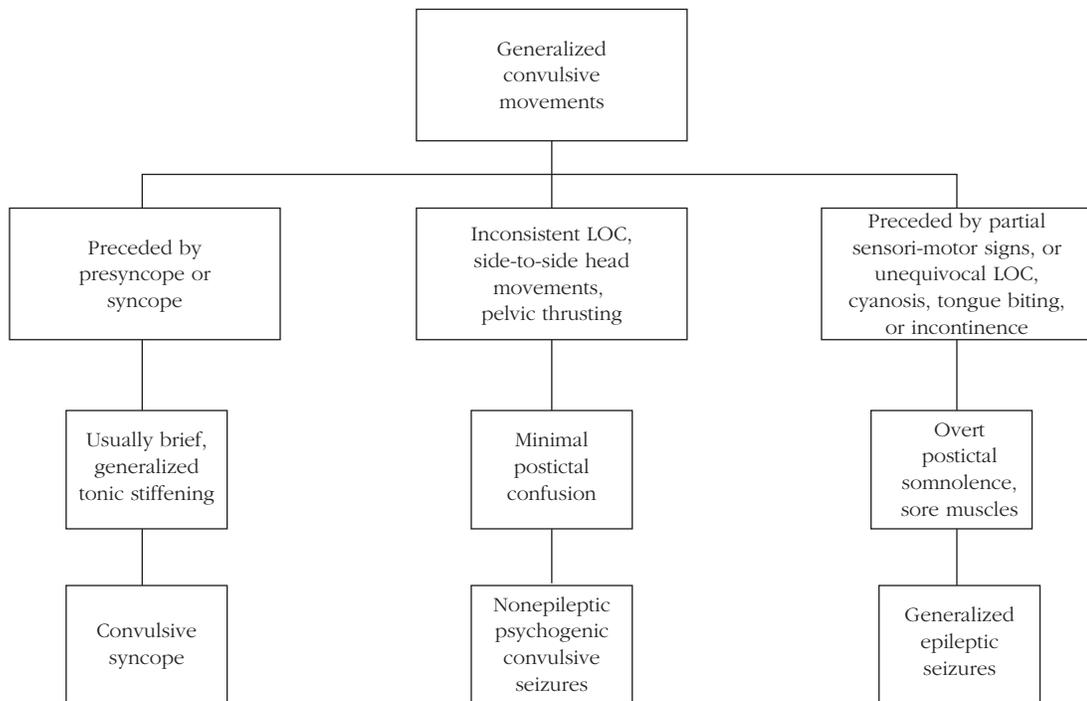
An extensive list of conditions that can be misinterpreted as epilepsy is shown in Table 2.1. Because an unwarranted diagnosis of epilepsy can have dire consequences, considerable space is devoted in this text to differential diagnosis, particularly emphasizing clinical points that help to distinguish epileptic seizures from other paroxysmal events when availability of sophisticated diagnostic technology is limited or absent. Most patients with nonepileptic spells who are evaluated in developing countries have the same conditions commonly seen in developed regions. However, a few conditions may be peculiar to developing countries. This section emphasizes differential diagnoses between epilepsy and other common paroxysmal disorders, based on clinical features. More complete descriptions of the other conditions are available in standard textbooks and will be dealt with only briefly here.

## KEYPOINTS

- Particularly in developing countries, an unwarranted diagnosis of epilepsy enhances disability as a result of the stigma and social limitations associated with this disorder, as well as an often burdensome cost of unnecessary AEDs.
- Most of the conditions mimicking epileptic seizures can be suspected on clinical grounds.



**FIGURE 2.1** Differential diagnosis of sudden alteration of consciousness.

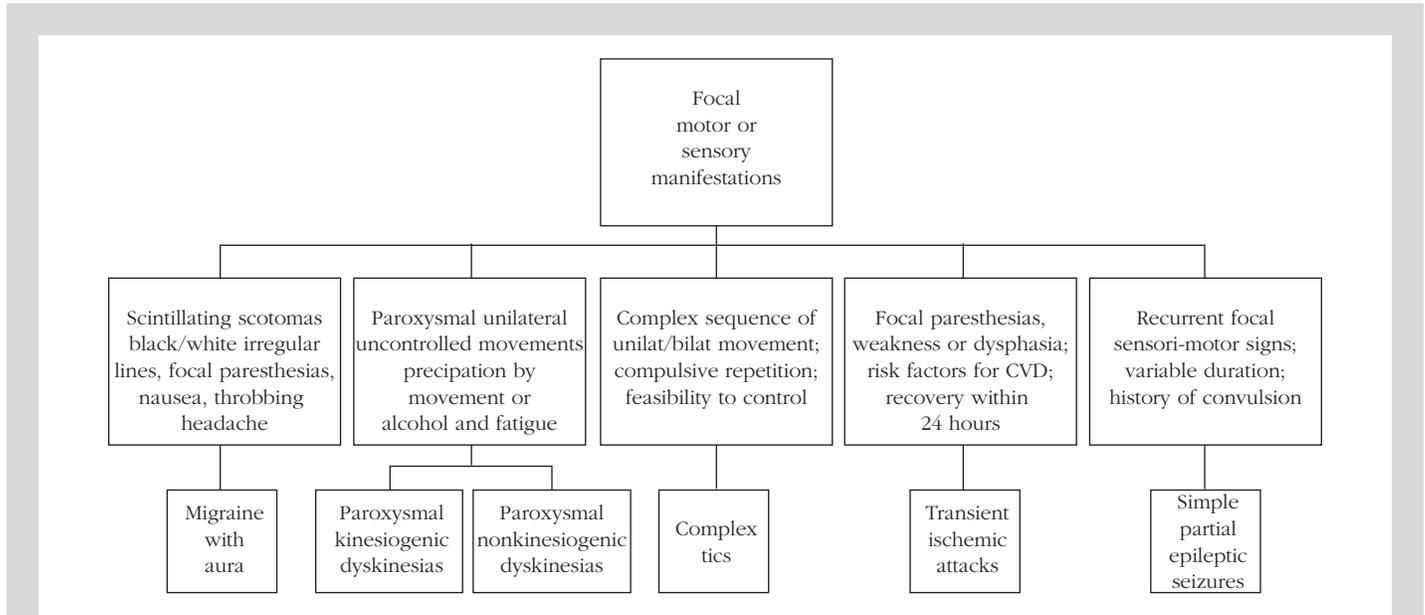


**FIGURE 2.2** Differential diagnosis of generalized convulsive movements.

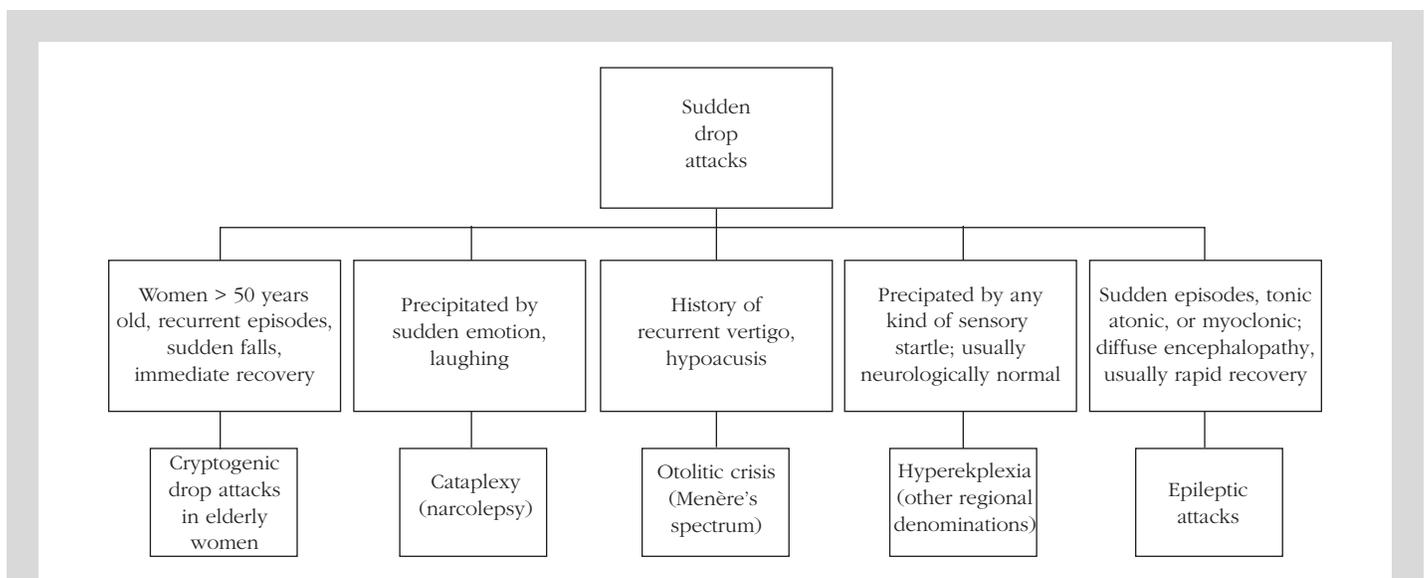
**Common Conditions Often Misdiagnosed as Epilepsy**

The paroxysmal events most frequently misdiagnosed as epileptic seizures are reviewed below, and summarized in Table 2.1 and in the algorithms shown in Figures 2.1 through

2.4. Neurologists in developing countries are often under pressure to examine too many patients in a short period of time. Thus, a practical clinical approach to patients presenting with spells will narrow diagnostic possibilities and optimize the use of more



**FIGURE 2.3** Differential diagnosis of paroxysmal focal signs and symptoms.



**FIGURE 2.4** Differential diagnosis of drop attacks.

**TABLE 2.1** Disorders Associated with Nonepileptic Paroxysmal Signs and Symptoms That Can Be Mistaken for Epilepsy**Systemic Disturbances**

- Syncope
  - Vasovagal
  - Cardiogenic
  - Orthostatic hypotension (associated with Shy-Drager, familial dysautonomia, hypovolemia, Parkinson's disease, diabetes, porphyria, amyloidosis, vasoactive drugs)
- Breath-holding spells
- Hyperventilation
- Toxic and metabolic disturbances
  - Alcoholic blackouts
  - Delirium tremens
  - Porphyria
  - Hypoglycemia
  - Pheochromocytoma
  - Asterixis with hepatic and renal failure
  - Tetanus
  - Rabies
  - Psychomimetic drugs
  - Tonic spasm with camphor and strychnine
  - Jitteriness in newborns

**Neurologic Disturbances**

- Cerebrovascular disorders
  - Transient ischemic attacks
  - Vertebral basilar insufficiency
  - Moya moya disease
  - Migraine
  - Transient global amnesia
- Sleep disorders
  - Narcolepsy (cataplexy, sleep paralysis, hypnogogic or hypnopompic hallucinations)
  - Neutral-state syndrome (micro-sleeps)
  - *Encephalitis lethargica*
  - Kleine-Levin syndrome
  - Pickwickian syndrome
  - Parasomnias
    - > Incubus
    - > Pavor nocturnus
    - > Somnambulism
    - > Sleep talking
    - > Bruxism
    - > Jactatio capitis nocturna (head banging)

- > Adult parasomnias (nocturnal wandering and night terrors)

## • Motor disorders

- Myoclonus
- Dystonia
- Chorea
- Athetosis
- Hemiballismus
- Tremors
- Paroxysmal dyskinesias
  - > Familial paroxysmal kinesigenic choreoathetosis
  - > Familial paroxysmal dystonic choreoathetosis
  - > Acquired paroxysmal dyskinesias
  - > Nocturnal paroxysmal dystonias
- Startle disease (hyperekplexia)
- Gilles de la Tourette syndrome
- Alternating hemiplegia in childhood
- Hemifacial spasms
- Cerebellar fits

## • Sensory disorders

- Paroxysmal vertigo
- Trigeminal neuralgia
- Peduncular hallucinosis

## • Neonatal disorders

- Some neonatal seizures
- Intraventricular hemorrhage

**Psychiatric disorders**

- Nonepileptic psychogenic seizures
- Episodic dyscontrol
- Dissociative states (dissociative hysterical neuroses)
  - Psychogenic fugue
  - Multiple personality disorder
  - Psychogenic amnesia
  - Depersonalization disorder
- Daydreaming (vs. absence seizures)
- Obsessive-compulsive behavior
- Panic attacks
- Schizophrenia (hallucinations)

advanced resources when needed to establish treatment strategies.

Many of the conditions to be reviewed below may be more prevalent in developing countries. Although specific data on the regional prevalence of these conditions may not be available, the profile of risk factors associated with them predicts a higher prevalence in poorer countries. Tropical diseases affecting the heart and insufficient control of other cardiovascular disorders, as well as the high occurrence of alcoholism, unemployment, depression, political instability, and domestic and social violence, are examples of risk factors associated with nonepileptic seizures.

### **Syncope**

Syncopal attacks are most often misdiagnosed as epileptic seizures when patients not only lose consciousness, but have tonic stiffening of the extremities (convulsive syncope). Vasovagal syncope often occurs in families and, interestingly, family members can also have migraine, benign rolandic epilepsy, or benign rolandic spikes. Vasovagal syncope occurs in physiologic situations in which either venous return is

reduced, or there is a sudden increase in parasympathetic (vagal) tone. Generally, a sensation of dizziness, weakness, and 'cold' progresses to a faint on rising from a bed or a chair. Alternatively, the person may be standing for a long time (as in a concert or church service), and then reach the point when baroreceptor reflex mechanisms fail, and syncope ensues. Sudden stressful situations, such as the sight of blood or bad news, can trigger a parasympathetic response and syncope. Often, the bradycardia and the progressively diminished brain perfusion is signaled by symptoms of impending loss of consciousness (presyncope): sounds in the environment become distant, legs weaken, and vision becomes blurred. When reported, these presyncopal symptoms are very helpful in making the correct diagnosis, because they tend to be stereotyped and differ from the most common forms of epileptic auras.

Primary cardiac disorders associated with syncope usually have a poor prognosis, and thus should be promptly identified and treated. The two main mechanisms leading to cardiogenic cerebral hypoperfusion and syncope are cardiac arrhythmias and pump fail-

## **CASE STUDY**

**Presentation:** A 16-year-old student loved to surf on weekends. He was referred after a third episode of loss of consciousness in the period of 1 year, which occurred while he was taking 1,200 mg/day of carbamazepine, because an interictal EEG showed rare right-sided centro-parietal spikes. His mother had a history of recurrent fainting during adolescence, in situations such as drawing blood or standing up for long periods of time. The first of his episodes occurred while standing at a bus stop on a summer afternoon. He felt weak, dizzy, and the next thing he remembers was being on the ground with people around him. Two months later, when a door squeezed his fingers, he cried, became pale, and fainted. The third episode occurred in a restaurant. He had had a large meal, and upon rising from his chair, he felt weak, dizzy, became pale, and fainted. This time, he had a few tonic convulsive movements, but quickly recovered. There was no past history of typical epileptic seizures.

**Evaluation:** Physical, cardiovascular, and neurologic examinations were normal. He had already been examined with a CT scan, which was normal. A 'tilt' test showed abnormal cardiovascular compensation of orthostatism, and was considered positive. A similar result was seen in his mother's examination, and thus a diagnosis of predisposition to vasovagal syncope was made.

**Treatment and outcome:** The patient has been on amitriptyline 50 mg/day at bedtime, with no recurrence of symptoms for more than a year. Carbamazepine was discontinued. The nature of the boy's diagnosis was fully discussed with the family, including the low risks of a syncopal episode while surfing.

**Comment:** Vasovagal syncope is a disorder with a familial predisposition. Genetic factors explain why several members of a family can present with the same syncopal symptoms as well as others with migraine, perirolandic spikes, and serotonergic abnormalities, such as anxiety and depression. A key aspect is a good cardiovascular evaluation to exclude disorders that may lead to serious consequences (such as the long QT syndrome). A common misconception is that the tonic stiffening that may occur represents an 'epileptic seizure.' In the context of the rolandic spikes, this led to the inappropriate prescription of an antiepileptic drug to this patient. These syncopal fits have a mechanism purely dependent on energetic failure of brainstem nuclei and do not represent epileptic phenomena. Thus, the use of AEDs is not indicated.

ure. The type of arrhythmia is dependent on the underlying cardiac disorder. Patients can have syncope due to the long QT syndrome and conduction defects dependent on previous ischemic events or chamber dilatation due to protracted hypertension and cardiac failure. The latter is likely to be common, even in young people in developing countries, because the primary and secondary prevention of cardiovascular conditions is often suboptimal. In addition, some disorders of the heart are much more frequent in developing countries, such as cardiomyopathy, which may result from rheumatic heart disease or Chagas' disease.

#### ***Nonepileptic Psychogenic Seizures***

It may be difficult to reliably differentiate a nonepileptic psychogenic from an epileptic seizure, although some aspects do help in the differential diagnosis. Nonepileptic psychogenic seizures usually present as recurrent generalized motor seizures. Non-nocturnal generalized motor seizures are rarely the only seizure type of a given patient and are almost never refractory to AEDs. A history of only recurrent daytime motor convulsions that do not respond to AEDs should raise the suspicion of psychogenic seizures. Unlike generalized tonic-clonic seizures, general-

ized nonepileptic psychogenic attacks can last for more than 15 minutes, but with rapid postictal recovery. Back and forth pelvic thrusts and side-to-side head movements are common in nonepileptic psychogenic seizures and inconsistent with epileptic seizures. Nonepileptic psychogenic seizures that mimic complex partial seizures are more difficult to diagnose. Keep in mind that even in industrialized countries, only rare selected cases need to be referred for video-EEG telemetry. These often are patients who have both epileptic seizures and nonepileptic psychogenic seizures.

#### ***Breath-holding Spells (BHSs)***

The most typical scenario of BHSs involves an infant or a child up to age 6 who starts crying following a minor injury or frustration, and then stops breathing. Clinical history is usually all that is needed to make the diagnosis. The first episode is frightening to parents, because the prolonged crying episode is followed by cyanosis, limpness, and loss of consciousness. Less frequently, a pallid form of BHS may occur. Both forms can present with tonic or clonic movements toward the end of the episode, due to transient brain hypoxia. BHSs are due to a combination of recurrent Valsalva maneuvers

### **CASE STUDY**

**Presentation:** A 34-year-old married man, with no children, had been unemployed for the last 3 years. He usually carried a stack of emergency room admission reports, "to show how much I've been suffering lately" (sic). He was an adopted and abused child, and had only seven years of formal education. He started to work during adolescence, but never stayed on a job for longer than a year or two. His wife provided the household with their basic needs. After losing one more job, about 3.5 years before presentation, the patient began with generalized convulsions. They could occur any time, but most commonly when there was some "tension in the air." His wife described what appeared to be generalized tonic clonic seizures, except that the episodes were very prolonged, lasting sometimes more than 20 minutes. He would be systematically taken to an emergency room, where he received IV diazepam and/or phenytoin and promptly recovered without postictal symptoms. The seizures did not have partial components. He was tried on many AED combinations, but none brought any significant seizure alleviation.

**Evaluation:** General and physical exams were normal. Over 20 interictal EEGs, a CT scan, and a MRI were all normal.

**Treatment and outcome:** After several visits to the clinic, AEDs were slowly discontinued. He is currently engaged in psychologic and psychiatric treatment, and receives fluoxetine and low dosages of haloperidol. The frequency of his emergency room visits has been decreasing slowly.

**Comment:** The diagnosis of nonepileptic psychogenic seizures may be difficult. Understanding the patient's background and current psychosocial context is crucial in the overall appraisal of the situation, but when the level of suspicion is high, it is important to pay attention to details of the seizures themselves. The long duration of what appeared to be generalized convulsive seizures, the prompt recovery of consciousness after the attacks, and the fact that the episodes were never milder or shorter despite the use of AED in adequate dosages, all suggest that nonepileptic seizures should be considered. The diagnosis is even more likely in the absence of EEG or structural imaging abnormalities.

and excessive parasympathetic (vagal) activation, resulting from forceful crying. There may be some genetic contribution, and EEG abnormalities, unrelated to the BHS, may at times be present. BHSs should not be confused with anoxia in young infants caused by tonic seizures. Benzodiazepines in this situation can precipitate respiratory arrest.

### **Panic Attacks**

A growing sensation of anxiety, fear of something vague, tachycardia, and effortful breathing that occurs during panic attacks may lead to loss of consciousness. In these episodes, some patients may have a parasympathetic syncope and others may hyperventilate and faint. Irrespective of the final mechanism, panic attacks are always associated with an initial sensation of anxiety. As with most neuropsychiatric conditions, panic attacks result from an interaction of genetic predisposition with environmental determinants of anxiety states.

### **Hyperventilation Syndrome**

Loss of consciousness associated with this entity is similar to that occurring during panic attacks. However, prolonged hyperventilation may be subtle and represent an unimpressive, often unnoticed, manifestation of anxiety. The final common pathway, nonetheless, may be the same, featuring growing alkalosis, hypocarbia, and cerebral hypoperfusion. In addition, the associated,

acute hypocalcemia often leads to dystonic contractions of the fingers, hands, wrist, and face, which may be confused with motor seizures. Because the manifestations of anxiety are less intense, hyperventilation syndrome may be more difficult to differentiate from epilepsy on clinical grounds alone. Nevertheless, a heightened level of suspicion usually allows the clinical diagnosis, which is helped by a history of flexion of both wrists.

### **Basilar Migraine**

The usual sequence of events in patients with basilar migraine leading to nonepileptic seizures is lightheadedness or vertigo followed by loss of consciousness and a throbbing headache upon recovery. Paroxysmal nystagmus with vertigo in young children is a variant of this disorder. A history of recurrent headaches is almost always present. While unconscious, the patient may stiffen his or her extremities, a picture that resembles the nonepileptic tonic seizures discussed above in regard to vasovagal syncope. The final common mechanism for both is transient brainstem metabolic or ischemic insult. Differentiating basilar migraine from epilepsy is not always simple, and the main features are depicted in Figure 2.1. Migraine auras can usually be distinguished from epileptic auras because the former progress much more slowly. One must keep in mind that EEG abnormalities can occur with migraine.

## **CASE STUDY**

**Presentation:** A 40-year-old woman witnessed, while hidden somewhere in her house, the murder of her husband, four children, a sister and parents-in-law by a group of rebels in a troubled region of a developing country. Three to four months later, she presented with “jumping,” feelings of sudden death, and panic attacks. Every loud noise (door, voices, etc.) provoked these symptoms. She also began hearing bizarre voices.

**Evaluation:** On clinical evaluation, she stands up suddenly, hands on her head, and calls for help. This scenario could be repeated briefly very often during a day. EEG was normal.

**Treatment:** Anxiolytics and antidepressant drugs alone were insufficient to improve her status. She found more relief from a series of baths with different vegetable materials, inhalation, amulets, and special mystical celebrations accompanied with religious songs and dances. The themes of these evocations are generally dedicated to the patient’s family and ancestors. Sacrifices of a sheep and a chicken were also made “to satisfy evil powers and calm the devils.”

**Outcome:** She became free of psychogenic seizures, but continued to have persistent delirium with the same initial themes during less severe panic attacks.

**Comment:** The conjunction of modern and traditional medicines provided the only solution to improve her mental and physical health. This beneficial association of both approaches is reported for many regions of the developing world. Knowledge of the cultural background of people with epilepsy or psychogenic seizures is necessary to optimize effective management.

**CASE STUDY**

**Presentation:** A 14-year-old girl began to have episodes of throbbing headaches and vomiting at age 11. At a 2- to 3-month interval, she would also feel dizzy and lose consciousness for several minutes, complaining of a throbbing headache upon recovery. Just before presentation, she had had a similar but more prolonged episode, in which the loss of consciousness was accompanied by tonic stiffening of the extremities. Recovery was also accompanied by headaches. Her mother had a long history of headaches followed by vomiting, and her younger sister had benign rolandic epilepsy and was taking a low dose of oxcarbazepine.

**Evaluation:** General and neurologic examinations were unremarkable. Several EEGs showed infrequent bilateral rolandic and occipital interictal spikes, but were otherwise normal. Imaging exams were not deemed necessary.

**Treatment and outcome:** She took amitriptyline for 8 months. Although a few mild headache attacks occurred, she did not have any new episodes of loss of consciousness. After full discussion of the situation, the patient and her parents decided to stop the medication.

**Comment:** This girl probably had basilar migraine, in which episodes of dizziness and loss of consciousness in children or adolescents are followed by throbbing headaches. Tonic stiffening of the extremities can occur during the period of loss of consciousness. Many of these patients have some inconspicuous EEG abnormalities and also a family history of migraine or benign rolandic epilepsy. The nonepileptic nature of the episodes should be made clear.

***Transient Ischemic Attacks (TIAs)***

Focal paresthesias, weakness, or dysphasia, which appear suddenly and disappear after a few seconds or minutes may be partial seizures, but can also be due to TIAs. Differential diagnosis can rely solely on the clinical features and is not difficult in most cases. Despite apparent similarities and some clinical and epidemiologic intersections, the two conditions differ in terms of age of occurrence, type of motor manifestations, clinical evolution, and duration of the episodes. Although TIAs and strokes are more likely to occur in young people in developing countries than elsewhere, TIAs usually affect older people with risk factors for cerebrovascular disorders. TIA-related neurologic deficits usually evolve over a few minutes, the motor manifestations are almost always negative (e.g., paresis), and although the episodes may be short-lasting, they usually last several minutes. Focal seizures, on the other hand, occur in all age ranges; often produce clonic, tonic, or dystonic movements; reach a maximum in a few seconds; and seldom last more than a minute or two. Only rarely is EEG or neuroimaging necessary, and both are often normal in either condition.

***Paroxysmal Movement Disorders***

Paroxysmal dyskinesias with variable duration and precipitating factors can be confused with epilepsy because choreic, dyston-

ic, athetotic, or mixed movements can be brief and recurrent, thus more suggestive of epileptic phenomena. Sudden movement or exercise usually precipitates the kinesio-genic and exercise-induced dyskinesias, respectively, while other types may appear during sleep, or are related to fatigue, tension, or alcohol use (the paroxysmal, non-kinesiogenic dyskinesias). Consciousness is retained during the episodes, and except for the sleep-related form, the other types of paroxysmal dyskinesias tend to disappear during sleep.

Hyperekplexia is another form of paroxysmal movement abnormality in which sudden stimulus leads to massive myoclonus. The patient may fall to the ground, in what resembles an epileptic drop attack. In the newborn, hyperekplexia produces jerks and tonic attacks that can last for several minutes. This can be life-threatening but is stopped by neck flexion, a maneuver that can be taught to parents. Low doses of clonazepam usually control the tonic attacks. Hyperekplexia is a genetically determined hyperexcitability of cortical sensori-motor loops. This condition and similar disorders have many different names in different countries: “jumping Frenchman of Maine” in Canada, “latah” in Malaysia, “jauns” in Burma, “bahtsche” in Thailand, “mali mali” in The Philippines, “ainu imu” in Japan, “ikota” in Siberia, and “panic” among the Lapps of northern Scandinavia. The EEG is

usually normal, and unexpected startle is the *sine qua non* to the occurrence of the massive myoclonus. Hyperekplexia is not associated with other neurologic deficits, as opposed to startle-induced epilepsy, which usually occurs in children with diffuse brain damage.

Alternating hemiplegia in infants is often claimed to be related to migraine, although it has a more severe course. The diagnosis is made clinically. The first attacks in early infancy consist of episodic dystonia of the trunk and limbs that can be mistaken for tonic seizures. Later, the child exhibits episodes of unilateral paralysis alternating from one side to the other, often mistaken for postictal paralysis. Alternating hemiplegia, however, can coexist with epileptic disorders, including pharmacoresistant epilepsies.

Tremulousness or jitteriness is a benign nonepileptic condition of newborns. It can be distinguished from epileptic seizures by the characteristic rapid rhythmic movement, and by its abolition with passive flexion or restraint of affected limbs.

### **Myoclonus**

Myoclonus may or may not be an epileptic manifestation. Epilepsy is less likely when this condition occurs in the setting of another underlying medical condition. Nonepileptic myoclonus is usually one of several signs and symptoms of neurologic disorders involving hyperexcitability of motor systems, including cortical and subcortical dementias and diffuse cortical dysfunction associated with metabolic disorders. Likewise, epileptic myoclonus usually is not an isolated phenomenon, and the occurrence of other seizure types allows a definitive diagnosis of epilepsy. Subcortical (spinal) myoclonus can be clinically diagnosed on the basis of the recognition of the associated spinal cord disorder. Myoclonus-opsoclonus in infants and young children is recognized by sudden, often unilateral eye movements, and can be the presenting symptom of neuroblastoma. Focal and multifocal myoclonus is often seen in comatose patients after hypoxic insults, and the question of epileptic seizures can arise. Whereas epileptic seizures typically involve muscles well represented in the homunculus of the

motor cortex (e.g., face and fingers), nonepileptic focal and multifocal myoclonus usually involves muscles that do not have large cortical representation, such as truncal muscles.

### **Parasomnias**

Parasomnias include a host of abnormal motor and behavioral manifestations occurring during sleep. Some of these may mimic epileptic seizures, such as sleep terrors, somnambulism, or REM-related agitated behavior. The difficulties in formatting a differential diagnosis are compounded by the fact that partial seizures in many epileptic syndromes can occur predominantly during sleep. Furthermore, witnesses often miss the initial elements of the episode. Clinical features that suggest epileptic seizures include the occurrence of oroalimentary or gestural automatisms, focal motor phenomena, tongue biting, urinary incontinence, and occasional attacks during wakefulness. In the absence of any of these features, a parasomnia is likely. When sleep EEG studies or monitoring are not available, a therapeutic trial with a medication for treating the most likely entity should be performed. Such a trial usually allows a clinical diagnosis.

### **Attention Deficit-Hyperactivity Disorder (ADHD)**

The inattention and vacant look seen in any child, particularly in children with ADHD, can be misinterpreted as absence seizures. However, absence seizures are almost always characterized by brief episodes of disconnection with sudden onset and termination, usually occurring many times a day. In contrast, the distractibility associated with ADHD depends on whether the child is motivated by ongoing activities. Hyperventilation should precipitate an absence attack and make the diagnosis obvious.

### **Abnormal EEGs in Nonepileptic Children and Adolescents**

There is a strong, but by no means absolute, correlation between the occurrence of ictal EEG epileptiform discharges and the predisposition for epileptic seizures. Therefore, the EEG may be useful in the workup of patients presenting with paroxys-

**KEYPOINTS**

- Unless the EEG is performed correctly and interpreted by someone formally trained in EEG, it can do more harm than good.
- There is significant variability in the rate of maturation of EEG rhythms during wakefulness and sleep. Clinically relevant information obtained from EEG or brain mapping in the absence of bona fide epileptiform discharges or unequivocally localized slow wave activity is negligible.
- Headaches, agitated behavior, school difficulties, dizziness, and sleep disorders do not usually warrant EEG investigations.

mal clinical events that potentially represent epileptic seizures. Availability, interpretation, and clinical necessity of the EEG are important considerations, particularly in developing countries, where both expertise and technological resources are often scanty and unevenly distributed. Unless the EEG is performed correctly and interpreted by someone formally trained in EEG, it can do more harm than good.

The concept of brain dysrhythmia was inherited from developed countries, which championed the idea that deviations from normal distribution, symmetry, or synchrony of EEG rhythms had some clinical relevance. Nonspecific EEG disturbances provided an explanation for myriad somatic behavioral or cognitive symptoms, leading to several decades of inappropriate prescriptions of AEDs to treat the abnormal EEG rhythms. Unfortunately, as concepts of EEG interpretation have become more conservative, colorful computerized brain mapping of EEG rhythms have appeared. The latter has inaugurated the idea that if background EEG rhythms deviated from statistical normalcy,

then something was wrong, perhaps explaining the symptoms for which the brain mapping was ordered. This circular reasoning has been very difficult to eliminate in developing countries where such tests are available. It cannot be overemphasized that there is significant variability in the rate of maturation of EEG rhythms during wakefulness and sleep, and that clinically relevant information obtained from EEG or brain mapping in the absence of bona fide epileptiform discharges or unequivocally localized slow wave activity is negligible.

Paradoxically, in developing countries, where EEG may be relatively difficult to obtain, the test is often inappropriately ordered. Because the EEG is a relatively easy test to perform and sometimes is the only ancillary neurodiagnostic method available, it is not uncommon to see EEG referrals for a large variety of conditions where epileptic seizures might be incorrectly invoked to explain the signs and symptoms. For example, headaches, agitated behavior, school difficulties, dizziness, and sleep disorders do not usually warrant EEG investigations.

**CASE STUDY**

**Presentation:** A 10-year-old girl failed the third grade at elementary school. Her parents were often summoned by school teachers and psychologists, who claimed the girl was not interested in school activities. She was easily distracted, her writing was very slow, and she often did not finish her work. One year before referral, she had psychologic and neurologic evaluations. A primary learning disorder was ruled out, and there was nothing significantly wrong from a psychologic standpoint. Neurologic evaluation at that time disclosed left-sided centrotemporal spikes on the EEG, and for the last 9 months she was prescribed oxcarbazepine, 600 mg a day. However, she was not clinically improving.

**Evaluation:** Physical and neurologic examinations were normal. A review of the teacher's report made clear that the girl fulfilled criteria for ADHD. Another EEG confirmed bilateral centrotemporal spikes, increasing markedly in frequency during sleep.

**Treatment and outcome:** The parents were told that although children with epileptiform EEG spikes have an increased risk of seizures, this finding does not constitute an indication to use an AED. In addition, they were told that the EEG abnormalities had nothing to do with the ADHD, and that oxcarbazepine was not a treatment for those symptoms. She was put on methylphenidate in increasing dosages, up to 0.8 mg/kg/day, and has had remarkable improvement in her school performance.

**Comment:** The management of this patient shows that the EEG should be interpreted in the context of the clinical picture. The epileptogenic significance of benign perirolandic spikes in a child without clinical seizures is minimal. Avoid treating the EEG instead of the patient's clinical problem. Either the attentional problems of this girl were ignored, or the electrical abnormalities were interpreted as possibly interfering with cognitive function. The latter was clearly *not* the case.

In addition to nonepileptiform, usually negligible EEG findings, individuals without epilepsy may exhibit true interictal epileptiform EEG discharges. These are particularly likely to occur in the nonepileptic relatives of patients with familial epileptic disorders. If a correct differentiation between epilepsy and conditions mimicking epilepsy is to be made, then the physician must realize that patients without epilepsy can have epileptiform EEG discharges. This is particularly true in children with centrottemporal and occipital EEG spikes. In one study of people referred to an EEG laboratory for various reasons, including known or suspected epilepsy, only about 40% of those with centrottemporal EEG spikes and about 75% of those with frontal spikes had a history of epileptic seizures. Similarly, only about 75% of children with irregular 4 to 6 Hz generalized spike and wave complexes had a history of epileptic seizures. Conversely, people with epilepsy can have a normal EEG.

### Conditions Peculiar to Some Areas of the Developing World that May Be Misdiagnosed as Epileptic Spells

#### *Parasitic Disorders*

These usually present with diarrhea, malaise, vomiting, and abdominal distension. In addition,

some children may have extreme weakness and even loss of consciousness, simply as another constitutional symptom. However, some parasitic disorders are so endemic in poorer regions of the globe, that the first clinical diagnosis of malnourished children or adolescents who faint or develop motor or behavior disturbances is a parasitic disorder. Actually, this is the usual diagnosis of influential nonmedical personnel in these areas. Thus, in many instances, these children are treated through traditional medicine or even by primary care doctors who prescribe standard medication for parasitoses. The problem here is that true seizures often pass undiagnosed, at least until after several recurrences, when alternative diagnoses may be entertained.

#### *Neurocysticercosis*

Nonepileptic spells with loss of consciousness can occur due to acute intracranial hypertension associated with intraventricular cysts. The much more common scenario, however, is misdiagnosis of epilepsy as a result of different types of nonepileptic paroxysmal spells in patients in whom computed tomography (CT) shows single or multiple residual calcified cysts. In endemic regions for neurocysticercosis, particularly

#### KEYPOINTS

- The physician must realize that patients without epilepsy can have epileptiform EEG discharges.

#### CASE STUDY

**Presentation:** This 22-year-old woman with a history of recurrent throbbing headaches presented for evaluation because of recent episodes of loss of consciousness preceded by vertigo, diplopia, and paresthesias in both arms. After a similar episode 2 months earlier, she was prescribed carbamazepine, 800 mg/day. Neither episode was accompanied by motor manifestations or incontinence. Postictal symptoms lasted between 10 and 30 minutes. Previous medical history was otherwise unremarkable, but family history was positive for migraine and epilepsy.

**Evaluation:** General medical and neurologic examinations were normal, as were routine laboratory exams. Serum immunologic assays for cysticercosis were positive for IgG and negative for IgM. An EEG during wakefulness and sleep showed irregular background activity and a few sharp waves during wakefulness over the right temporo-occipital regions. A contrast-enhanced CT scan showed three small calcified nodules (about .5 centimeter in diameter), in the right frontal, right anterior temporal, and left parietal lobes.

**Treatment:** Carbamazepine was slowly discontinued, and verapamil (a calcium channel blocker) was started, at a single dose of 120 mg/day in the evening.

**Outcome:** A few instances of mild throbbing headache recurred in the ensuing year, but the patient did not report any other episode of loss of consciousness.

**Comment:** This patient most likely had basilar migraine, but an episode of loss of consciousness was misinterpreted as an epileptic seizure because of a mildly abnormal EEG and the presence of calcified lesions on CT scan. The latter are most likely related to a previous exposure to cysticercosis (as suggested by the serum immunologic findings) and do not represent active disease. Although calcified cysts may give rise to epileptic seizures, the possibility of alternative diagnoses for paroxysmal phenomena must be entertained in endemic regions.

**KEYPOINTS**

- In endemic regions for neurocysticercosis, particularly where CT is more easily available, it is a common mistake to assume that paroxysmal symptoms are epilepsy, when calcifications are found on CT.

where CT is more easily available, it is a common mistake to assume that paroxysmal symptoms are epilepsy, when calcifications are found on CT. This is certainly incorrect in many instances, and the indication for a CT scan in these regions should take into account the most likely diagnosis on a clinical basis. In this regard, such indication is similar to that previously discussed for the role of EEG.

***Stomach Congestion***

In some developing countries, episodes of loss of consciousness are often attributed to digestive tract abnormalities. Some epileptic seizures by chance occur after meals, which supports the traditional hypothesis that diversion of blood to the digestive tract leads to loss of consciousness. Similar to the discussion on parasitic disorders, these beliefs can delay diagnosis of true epileptic seizures. On the other hand, infants with epileptic spasms can have spasms during feeding, which causes them to cry, a situation that can be mistaken for colic.

**Distinguishing Isolated Epileptic Seizures from Epilepsy**

Epilepsy is a disorder of recurrent seizures, so a single event, even if it is unequivocally epileptic, does not make a diagnosis of epilepsy. Even recurrent epileptic seizures, if they are clearly provoked, for example as a result of alcohol withdrawal or use of proconvulsant agents, do not warrant a diagnosis of epilepsy. Treatment in these situations is not AEDs, but avoidance of the provocative insult where possible. More detailed discussions of the differential diagnosis between isolated epileptic seizures and epilepsy are presented in Chapters 1 and 4. Whether epileptic seizures are isolated or recurrent, however, the next step in providing care is to determine whether there is an underlying treatable cause. If epileptic seizures are due, for example, to an intracranial infection or a brain tumor, once this underlying cause is treated and epileptic seizures stop, a diagnosis of epilepsy is not warranted. Only if a treatable underlying cause is not identified; is identified, treated, and epileptic seizures persist; or is not treated at all, is it appropriate to make a diagnosis of epilepsy.

**CLASSIFICATION OF SEIZURES AND EPILEPSIES****Classification of Epileptic Seizures**

The current International League against Epilepsy (ILAE) classification recognizes many types of epileptic seizures (Table 2.2). These are divided into generalized seizures, meaning that they appear to begin simultaneously on both sides of the brain, and partial or focal, meaning that they appear to begin in a part of one hemisphere. Partial seizures are further divided into simple, if consciousness is preserved, and complex, if consciousness is impaired.

There are at least two important reasons why epileptic seizures should be correctly classified. The first is that the selection of AEDs is still heavily based on seizure type. The second is that the correct identification of the epilepsy syndrome depends on the correct classification of the seizure type(s) in a given patient. The identification of a syndrome is key to establishing the prognosis of epileptic conditions and to selecting specific pharmacologic and surgical approaches to treatment.

***Most Common Seizure Types***

The most common and important types of epileptic seizures are described here, followed by a discussion on potential pitfalls in this semiological diagnosis.

*Simple partial seizures without motor features* involve sensory, autonomic, and psychic symptoms. The latter can consist of complicated multimodality sensory phenomena, emotional experiences, alterations in memory such as *déjà vu* and *jamais vu*, and psychiatric phenomena, such as depersonalization, forced thinking, and delusions. Unlike many psychiatric symptoms, however, psychic epileptic events are stereotyped and relatively brief, interictal behavior is normal, and patients are aware that their experiences are unreal. These simple partial seizures can occur in isolation or progress to complex partial or generalized tonic-clonic seizures, in which case they are called *auras*. Autonomic or experiential phenomena suggest temporal lobe involvement, whereas somatosensory and elementary visual auras point to ictal generation in the

**TABLE 2.2** International Classification of Epileptic Seizures

- I. Partial (focal, local) seizures**
- A. Simple partial seizures
1. With motor signs
  2. With somatosensory or special sensory symptoms
  3. With autonomic symptoms or signs
  4. With psychic symptoms
- B. Complex partial seizures
1. Simple partial onset followed by impairment of consciousness
  2. With impairment of consciousness at onset
- C. Partial seizures evolving to secondarily generalized seizures
1. Simple partial seizures evolving to generalized seizures
  2. Complex partial seizures evolving to generalized seizures
  3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures
- II. Generalized seizures (convulsive or nonconvulsive)**
- A. Absence seizures
1. Typical absences
  2. Atypical absences
- B. Myoclonic seizures
- C. Clonic seizures
- D. Tonic seizures
- E. Tonic-clonic seizures
- F. Atonic seizures (astatic seizures)

**III. Unclassified epileptic seizures**

From: Commission on Classification and Terminology of the International League Against Epilepsy, 1981. Used with permission.

unmotivated fear, or olfactory and gustatory hallucinations may be attributed to the direct action or influence of spirits or other entities related to the religious folklore of different cultures. Such misattributions are certainly overrepresented in less educated communities of developing countries.

*Simple partial motor seizures* initially involve body parts well represented in the cortical motor strip homunculus, such as the hand or face, on one side of the body. As the seizure progresses, ictal involvement of a whole hemibody can occur. Both the type of initial motor phenomena and the characteristics of the propagated motor activity provide valuable information as to the cerebral localization of seizure origin and spread. Partial motor seizures can be conceptualized along two main axes: 1) type: whether the initial and sequential focal motor phenomena are clonic, tonic, dystonic, myoclonic, or atonic; and 2) topography of initial and secondary involvement of body parts. Paroxysmal motor movements involving truncal and other muscles not well represented in the cortical motor strip are usually myoclonic and not epilepsy.

*Complex partial seizures (CPSs)* originate in or involve limbic structures, usually mesial temporal, and often are preceded by simple partial seizures with autonomic or psychic symptoms. The most common of these are a sensation of epigastric rising and emotional experiences such as fear. Partial seizures are designated as complex when consciousness is impaired, although impairment of consciousness is not always easy to document. Typically, seizures begin with an arrest of movement and stare, during which patients may not be responsive to the environment. Commonly, there are oroalimentary automatisms such as chewing and lip-smacking, followed by more complex behavioral automatisms that may be influenced by the environment. For example, simple automatisms may involve gestures of upper or lower extremities or dystonic posturing, whereas more complicated automatisms may involve running or walking, or patients may continue repetitive activities such as washing dishes, or exhibit bizarre behaviors. By definition, complex partial seizures are associated with amnesia for the

posterior quadrant. Frontal lobe seizures, on the other hand, are often ushered in by feelings of lightheadedness, 'conscious confusion,' or other cephalic sensations. Interestingly, the experiential or psychic temporal lobe auras may be misinterpreted as unnatural phenomena. Thus, déjà vu and memory flashback experiences, sudden

## KEYPOINTS

- Ironically, patients in developing areas whose seizure disorders begin with GCSE have the best chance to benefit from medical treatment because the emergency leads them directly to a health center.

ictal event, and patients usually experience postictal confusion for several minutes.

*Typical absence seizures* are brief (10 seconds or less) episodes of unresponsiveness to the environment; these seizures both appear and disappear suddenly, without warning or postictal confusion. Patients usually display a blank, motionless stare for a few seconds, and episodes characteristically recur several times a day. Typical absences can often be precipitated by asking the child to hyperventilate during the examination. There can be subtle yet significant motor accompaniments such as eyelid myoclonia, perioral myoclonia, upper limb myoclonia, and even simple reactive automatisms. Perioral and upper limb jerks are more likely to be pharmacoresistant, and the latter is associated with a higher risk of mental delay.

*Atypical absence seizures* are distinct from typical absence episodes because they often last longer, can be associated with marked tonic or atonic motor components, and are usually followed by postictal confusion. Their precise onset and offset are difficult to determine. Whereas typical absence seizures occur in the benign idiopathic generalized epilepsies unassociated with other neurologic disturbances, atypical absences result from generalized brain damage and usually occur in patients who also have or develop mental retardation, additional neurologic impairment, and other types of epileptic seizures. These seizures are all usually pharmacoresistant.

*Generalized tonic clonic seizures* are the hallmark of the diffuse involvement of cortical and subcortical structures by ictal epileptic activity. They can be primarily generalized, starting directly as a generalized tonic and then clonic seizure, or secondarily generalized, evolving from any type of partial seizure, which then propagates through cortical and subcortical circuits and leads to the same final common pathway of a generalized tonic-clonic seizure. The intense, excessive, neuronal, and muscular activity usually leads to protracted postictal somnolence, confusion, and sore muscles. Patients can bite their tongues during the seizure and be incontinent of urine and feces. Generalized motor seizures can also be purely tonic, purely clonic, or clonic-tonic-clonic.

*Drop attacks* are seizures leading to sudden falls to the ground. These can be generalized atonic, myoclonic, myoclonic-atonic, or brief tonic attacks. At times, there is prompt recovery of consciousness after the fall, which, however, does not diminish the risk of injury. Some partial seizures can also lead to drop attacks, usually through very fast access to interhemispheric propagation pathways, such as the corpus callosum.

*Epileptic spasms* occur mainly in infancy, but occasionally later in life. The axial contraction, in flexion or tension, with upward deviation of the eyes, lasts longer than a myoclonic jerk (about 1 second) and usually recurs in clusters in 10-second intervals. The jerk is often followed by a cry, leading to misdiagnosis of colic.

### Status Epilepticus

*Status epilepticus (SE)* is characterized by seizures that do not spontaneously stop. Formally, SE is defined as recurrent epileptic seizures without full recovery of consciousness between seizures or continuous clinical and/or electrical seizure activity lasting more than 30 minutes. Consciousness may or may not be fully impaired, depending on the type of SE. SE is classified into generalized convulsive SE (GCSE), absence SE, complex partial SE, and simple partial SE (also called *epilepsia partialis continua*). GCSE is the most common type and is a medical emergency. If untreated, these events are associated with irreversible neuronal damage and death from both altered cerebral metabolism and secondary injury due to lactic acidosis, hypoxia, hypercarbia, hyperthermia, and direct brain insult. Causes of SE include poor AED compliance (especially in countries where drug distribution is unreliable), sudden and recent change or withdrawal of AEDs, acute illnesses such as meningoencephalitis, stroke, head injury, metabolic disorders, and alcohol or substance abuse. Rarely, GCSE may be the first manifestation of epilepsy. Ironically, patients in developing areas whose seizure disorders begin with GCSE have the best chance to benefit from medical treatment because the emergency leads them directly to a health center. Outcome depends on the age of the patient, underlying conditions, and duration of SE

before treatment is initiated. If GCSE is left untreated or is inadequately treated, the clinically evident GTCS can fade into subtle convulsive motor activity, usually mild myoclonus, making the diagnosis very difficult. Subtle convulsive SE can be diagnosed with the help of EEG monitoring, but a high level of suspicion may identify the subtle manifestations and circumvent the need for EEG monitoring. Treatment must be urgently instituted to prevent further damage.

Absence SE and complex partial SE are often referred to as nonconvulsive SE, and symptoms can overlap. Whereas the most striking features of both types of status consist of confusional states with occasional myoclonic jerks and automatisms, absence status is more often continuous and seen most commonly in children, whereas complex partial status typically is associated with fluctuating consciousness, often has more pronounced automatisms, and occurs more commonly in older children and adults. Absence status, particularly in children with symptomatic generalized epilepsy, can have very subtle myoclonic and cognitive features and continue for days to weeks without severe postictal symptoms. Prolonged complex partial status, however, is followed by severe memory impairment, and occasionally other focal neurologic deficits that may be enduring or permanent. Aggressive therapeutic intervention is justified to terminate complex partial status, but absence status in children should also be considered an emergency.

Simple partial SE, or *epilepsia partialis continua* (EPC), is a rare epileptic manifestation with a narrow etiological differential diagnosis. Most often, EPC presents as continuous or frequently recurring clonic or myoclonic jerks involving parts of a limb up to a whole hemibody, lasting from several hours to many days. EPC indicates the presence of an acute focal insult or of a structural lesion, which can be diffuse. Most commonly, the latter represents a tumor, cortical dysplasia, Rasmussen's encephalitis, or, in infants and small children, an inborn error of metabolism.

### **Common Causes for Misdiagnosis of Seizure Type**

Data leading to seizure diagnosis are usually obtained indirectly and based on the

accounts of the patient and reliable witnesses. Even in developed countries, only a small minority of patients with definite or suspected epilepsy have their seizures videotaped and correlated with the EEG, to be analyzed by a neurologist. Thus, the physician must encourage a detailed description, while making every effort to translate the patient's or witness' expressions into known and relevant semiological hallmarks of seizure types. People in developing countries often have misconceptions about the nature of an epileptic attack and tend to focus their observations on the generalized convulsive part of the seizure. Tonic-clonic generalized convulsive movements, with tongue biting and incontinence are frightening, and often eclipse the fact that the episode was heralded by a few jerks in one hand or in the corner of the mouth. Similarly, periods of unresponsiveness and oroalimentary automatisms, either as recurrent isolated episodes or preceding generalized seizures are often not voluntarily reported and require some direct questioning by the neurologist. Two difficult differential diagnoses are discussed next.

### ***Absences versus complex partial seizures.***

Typical absence attacks as part of idiopathic generalized epilepsy syndromes (see next section) are usually fully responsive to medical treatment with specific AEDs (particularly valproic acid and ethosuximide), thus constituting a fairly "benign" seizure pattern. In contrast, the environmental disconnection (often referred to by patients and relatives as "absences") observed in complex partial seizures are actually localization-related phenomena, thus more prone to be controlled by drugs like carbamazepine and phenytoin. Indeed, these latter medications may even worsen absence seizures. Therefore, correct diagnosis of the seizure type in this context has an immediate impact on treatment efficacy. Typical absences are usually very brief (less than 10 seconds), not preceded by auras, and not followed by postictal confusion. Simple automatisms can be present. Complex partial seizures dominated by environmental disconnection are often preceded by typical temporal lobe-type auras, tend to last at least 20 to 40 seconds, are often

### **KEYPOINTS**

- People in developing countries often have misconceptions about the nature of an epileptic attack and tend to focus their observations on the generalized convulsive part of the seizure. Tonic-clonic generalized convulsive movements, with tongue biting and incontinence are frightening, and often eclipse the fact that the episode was heralded by a few jerks in one hand or in the corner of the mouth. Similarly, periods of unresponsiveness and oroalimentary automatisms, either as recurrent isolated episodes or preceding generalized seizures are often not voluntarily reported and require some direct questioning by the neurologist.

accompanied or followed by oroalimentary or gestural automatisms, and are followed by postictal confusion. The differentiation between these seizure types is usually possible by clinical history, and only rarely are EEG or video-EEG needed.

**Primarily versus secondarily generalized seizures.** Partial ictal phenomena preceding secondary generalization may be missed when subtle, occurring during sleep, or when almost immediately followed by generalized convulsive movements. Indeed, the latter are such impressive phenomena that they dominate the episode and their reporting by patients and relatives. Missing a partial onset can lead to incorrect seizure and syndrome classification (see next section), and negatively impact medical management and progno-

sis. Antiepileptic drugs that are effective for primarily generalized seizures (particularly when part of idiopathic generalized epilepsies; see next section) can be less prone to fully control partial seizures with rapid secondary generalization. Careful history taking with explicit questioning of the patient and witnesses is often sufficient to distinguish between these conditions, although EEGs may occasionally be necessary.

### Classification of Epilepsy Syndromes

Similar to the approach to any other neurologic disorder, it is important for the clinician to arrive at a syndromic, topographic, and etiologic diagnosis in each patient with epilepsy. There are many different epileptic syndromes, which are distinguished on the basis of 1) type or types of epileptic

## CASE STUDY

**Presentation:** For more than a year, a couple living in a poor country had been facing a significant socioeconomic dilemma related to the costs of treatment of their 11-year-old son, who had recurrent episodes of disconnection from the environment. The episodes began 2 years earlier, and after sequential trials of phenobarbital, phenytoin, and carbamazepine, the boy was given newer and more costly antiepileptic drugs. These medications have also fallen short of controlling the attacks, but the boy was maintained on oxcarbazepine 1,500 mg/day. Since the beginning of his problem, school performance and behavior have worsened. Despite the impact of the costs on the household budget, the parents have complied with all physicians' prescriptions.

Seizures were initially noted at school and described as episodes lasting about 10 seconds, characterized by sudden arrest of activity, staring, and drooling. There was questionable confusion for a few seconds afterwards, although the boy could easily resume his activities. Two to four of these episodes occurred every day. About 1 year after the onset of seizures, he had a single nocturnal generalized tonic-clonic seizure. Previous medical history was remarkable for three brief febrile convulsions between ages 1 and 3 years, and there was also a positive family history for febrile convulsions and epilepsy.

**Evaluation:** General medical and neurologic examinations were normal. Two EEGs during wakefulness and sleep showed normal background activity and sharp waves over the centrottemporal regions, which increased markedly during sleep. Photic stimulation was not available at the EEG lab, and the boy did not cooperate with voluntary hyperventilation. A CT scan was normal, and the parents were informed that an MRI was needed—despite the fact that they would need to pay for the exam. The latter was also normal.

**Treatment:** Oxcarbazepine was slowly discontinued, and ethosuximide begun, up to a dosage of 750 mg/day.

**Outcome:** Seizures were completely controlled, although interictal centrottemporal sharp waves persisted on the EEG.

**Comment:** This boy had a form of idiopathic generalized epilepsy, most likely juvenile absence epilepsy. A combination of facts led to misdiagnosis of both the epileptic seizures and the epileptic syndrome, and therefore, to inadequate seizure control and increased costs of evaluation and treatment. A core aspect was the misinterpretation of absence seizures as complex partial seizures. The history of febrile convulsions and the focal epileptiform activity on EEG probably added to the diagnostic confusion. However, both a personal and family history of febrile convulsions and centrottemporal (rolandic) sharp waves are also observed in patients with idiopathic generalized epilepsy syndromes. Furthermore, generalized spike and wave complexes on the EEG may be missed in juvenile absence epilepsy, especially if photic stimulation is not available (a common situation in EEG labs in developing countries) and voluntary hyperventilation is not adequately performed. The very favorable response to ethosuximide—an inexpensive AED specific for absence and myoclonic seizures—supports the hypothesis of an idiopathic generalized epilepsy syndrome.

**CASE STUDY**

**Presentation:** This 62-year-old noninsulin-dependent diabetic man experienced generalized tonic-clonic seizures exclusively during sleep 3 years before presentation. His wife did not report focal components, describing instead generalized body stiffening preceded by a loud scream from the very onset of the attacks. Despite treatment with 2,250 mg/day of valproic acid, seizures recurred every month. There were no other vascular risk factors. Family history was positive for stroke, but negative for epilepsy.

**Evaluation:** General medical and neurologic examinations showed only reduced pinprick and tactile sensation in both feet. Fasting glucose, creatinine, and LDL cholesterol levels were mildly elevated, but other laboratory tests were normal. Two EEGs during wakefulness and sleep were normal. Neuroimaging exams were not available in the patient's region.

**Treatment:** Phenytoin was started and titrated up to 350 mg/day. Valproic acid was slowly discontinued.

**Outcome:** Seizures have not recurred for 2 years.

**Comment:** In the context of generalized seizures occurring only during sleep, normal EEGs, and unavailable neuroimaging facilities, the diagnosis of the type of epileptic seizure and syndrome may be difficult. The clinical key to the present case was that "de novo" idiopathic generalized epilepsy with tonic-clonic seizures is not common at this patient's age. Thus, in the event of inadequate seizure control with an antiepileptic medication best suited to control primarily generalized seizures, the possibility of secondarily generalized seizures without obvious focal features should be considered. With no additional cost, this hypothesis can be tested by introducing or substituting an AED with a greater specificity for partial onset seizures.

seizures; 2) age of seizure onset; 3) etiology; 4) degree of associated neurologic and intellectual deficits; 5) clinical evolution of the epilepsy and any underlying condition; 6) pattern of EEG abnormality; and 7) abnormalities on imaging exams. Identifying an epileptic syndrome implies a particular therapeutic approach and prognosis; however, many patients have epileptic conditions that do not fit into a recognized syndromatic category.

The currently accepted ILAE classification of epilepsies and epilepsy syndromes (Table 2.3) divides these conditions into generalized and localization-related. The former are due to diffuse bilateral disturbances, whereas the latter are due to abnormalities related to a part of one hemisphere. In addition, syndromes are divided into *idiopathic*, which are benign, age-related genetic disturbances manifesting only as epilepsy; *symptomatic*, which are secondary to lesions of the brain, either acquired or genetic; and *cryptogenic*, meaning probably symptomatic, but the etiology is unknown. The prognosis of symptomatic epilepsies depends on the prognosis of the underlying substrate.

## Most Common Epilepsy Syndromes

### *Symptomatic Partial Epilepsies*

Recurrent partial seizures associated with a localized lesion are the defining features of symptomatic partial epilepsies. Although definitive studies have not been done, the most common symptomatic partial epilepsies found in developing countries are most likely to be mesial temporal lobe epilepsy with hippocampal sclerosis, and neocortical epilepsies due to neurocysticercosis, other infectious disorders, trauma, and malformations of cortical development (MCD). The identification of the lesion often relies on neuroimaging, but clinical history and neurologic examination can suffice to raise a high level of suspicion of this group of entities. At times, this scenario is associated with normal neuroimaging, leading to a diagnosis of 'cryptogenic' partial epilepsy—symptomatic epilepsy for which the cause is beyond the resolution of available neuroimaging.

***Mesial temporal lobe epilepsy.*** About two-thirds of all symptomatic partial epilepsy syndromes involve the temporal lobes, particularly their anteromesial structures,

**TABLE 2.3** International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders

<p><b>1. Localization-related (focal, local, partial)</b></p> <p>1.1 Idiopathic (primary)</p> <ul style="list-style-type: none"> <li>• Benign childhood epilepsy with centrotemporal spikes</li> <li>• Childhood epilepsy with occipital paroxysms</li> <li>• Primary reading epilepsy</li> </ul> <p>1.2 Symptomatic (secondary)</p> <ul style="list-style-type: none"> <li>• Temporal lobe epilepsies</li> <li>• Frontal lobe epilepsies</li> <li>• Parietal lobe epilepsies</li> <li>• Occipital lobe epilepsies</li> <li>• Chronic progressive epilepsy partialis continua of childhood syndromes characterized by seizures with specific modes of precipitation</li> </ul> <p>1.3 Cryptogenic, defined by:</p> <ul style="list-style-type: none"> <li>• Seizure type</li> <li>• Clinical features</li> <li>• Etiology</li> <li>• Anatomical localization</li> </ul> <p><b>2. Generalized</b></p> <p>2.1 Idiopathic (primary)</p> <ul style="list-style-type: none"> <li>• Benign neonatal familial convulsions</li> <li>• Benign neonatal convulsions</li> <li>• Benign myoclonic epilepsy in infancy</li> <li>• Childhood absence epilepsy (pyknolepsy)</li> <li>• Juvenile absence epilepsy</li> <li>• Juvenile myoclonic epilepsy (impulsive petit mal)</li> <li>• Epilepsies with generalized tonic-clonic seizures on awakening</li> <li>• Other generalized idiopathic epilepsies</li> <li>• Epilepsies with seizures precipitated by specific modes of activation</li> </ul> <p>2.2 Cryptogenic or symptomatic</p> <ul style="list-style-type: none"> <li>• West syndrome (infantile spasms, Blitz-Nick-Salaam Krämpfe)</li> <li>• Lennox-Gastaut syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Epilepsy with myoclonic-astatic seizures</li> <li>• Epilepsy with myoclonic absences</li> </ul> <p>2.3 Symptomatic (secondary)</p> <p>2.3.1 Nonspecific etiology</p> <ul style="list-style-type: none"> <li>• Early myoclonic encephalopathy</li> <li>• Early infantile epileptic encephalopathy with suppression bursts</li> <li>• Other symptomatic generalized epilepsies</li> </ul> <p>2.3.2 Specific syndromes</p> <ul style="list-style-type: none"> <li>• Epileptic seizures may complicate many disease states.</li> </ul> <p><b>3. Undetermined epilepsies</b></p> <p>3.1 With both generalized and focal seizures</p> <ul style="list-style-type: none"> <li>• Neonatal seizures</li> <li>• Severe myoclonic epilepsy in infancy</li> <li>• Epilepsy with continuous spike-waves during slow wave sleep</li> <li>• Acquired epileptic aphasia (Landau-Kleffner syndrome)</li> <li>• Other undetermined epilepsies</li> </ul> <p>3.2 Without unequivocal generalized or focal features</p> <p><b>4. Special syndromes</b></p> <p>4.1 Situation-related seizures (Gelegenheitsanfälle)</p> <ul style="list-style-type: none"> <li>• Febrile convulsions</li> <li>• Isolated seizures or isolated status epilepticus</li> <li>• Seizures occurring only when there is an acute or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia</li> </ul>
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From: Commission on Classification and Terminology of the International League Against Epilepsy, 1989. Used with permission.

which have a low epileptogenic threshold when confronted with a wide variety of insults. The most common associated pathology is hippocampal sclerosis. Although MRI is needed to identify the sclerotic hippocampus, the syndrome of mesial temporal lobe epilepsy associated with hippocampal sclerosis may be suspected when typical temporal auras and complex partial seizures are associated with an initial precipitating insult during early childhood, usually a febrile seizure.

**Partial epilepsies due to neurocysticercosis.** Cysticercosis is an endemic parasitic disorder in many developing countries, where neurocysticercosis is a common cause of epileptic seizures. Seizures may occur as a manifestation of the acute cerebral infection or as a sequelae of the calcified cysts. In the former scenario, other signs and symptoms usually are present, suggestive either of increased intracranial pressure (e.g., headache, malaise, nausea, and vomiting) or of localized cortical dysfunction, in the form of sensorimotor or cognitive deficits. The attacks are usually partial, with occasional secondary generalization. Epilepsy associat-

ed with calcified cysts is usually an isolated entity after resolution of the acute infection. Interestingly, seizure semiology may or may not be functionally related to the site of single or multiple calcifications, and electroclinical features of mesial temporal lobe epilepsy often are the presenting picture, irrespective of the location of the calcifications. CT scanning and EEGs in an endemic region are usually sufficient for diagnosis and treatment. If CT is unavailable in endemic areas, cutaneous and muscle symptoms plus serology may suffice to make the diagnosis.

**Disappearing CT lesions.** This syndrome appears to be unique to India. The CT/MRI scans usually show a small, subcortical contrast enhancing, hyperdense ring or disc lesion surrounded by a variable area showing edema. Most of the CT/MRI lesions disappear completely or show a near complete resolution within a few weeks without any specific treatment except AEDs. The so-called “disappearing CT lesions” or “single, small enhancing lesions (SSELs)” are now accepted to be a common feature in a large number of patients with epilepsy from India, where such cases constitute about 10% of all

## CASE STUDY

**Presentation:** A 15-year-old boy presented with a history of jerking of the right upper limb followed by a secondarily generalized tonic-clonic seizure lasting for a few minutes. He noticed weakness of the right upper limb after the seizure, and the weakness improved over the next 2 hours. The next day, he had another seizure similar to the previous one, but without any postictal limb weakness. He had no previous history of seizures and none of his family members were affected with seizures.

**Evaluation:** His neurologic examination was normal. The CT scan of the head showed evidence of a single small ring-enhancing lesion in the left posterior frontal cortical region with surrounding edema. The EEG was reported to be normal.

**Treatment and Outcome:** He was treated with phenytoin (250 mg per day) and subsequently remained seizure free. A repeat contrast-enhanced CT scan of the head after 6 months of the first scan showed complete resolution of the lesion and was interpreted as normal. He was continued on phenytoin for the next year and the drug was then gradually stopped. He continues to be seizure free when last seen about 4 years after the first seizure.

**Comment:** This is an example of a benign symptomatic epilepsy syndrome peculiar to the Indian subcontinent. This syndrome accounts for about 10% of all epilepsy cases in large Indian centers and most patients are usually young and have a few simple partial seizures with or without secondarily generalized seizures. Some of them may have evanescent postictal focal neurologic deficits. The syndrome is so benign that seizures among most of these patients remain under control irrespective of the AED used. The exact duration of AED therapy has not been defined, but most physicians would treat such patients with AEDs for about 1 to 2 years.

**KEYPOINTS**

- If there is one group of epileptic disorders that may be considered as potentially preventable through improved education and professional commitment, it is that related to perinatal hypoxic-ischemic encephalopathy.

epilepsy patients presenting at various centers. These patients are usually young and have a few simple partial seizures with or without secondarily generalized seizures. Some of them may have postictal focal neurologic deficits that disappear in a few days. The etiology of the SSELS is presumed to be diverse, but some have been proved to be of cysticercal origin.

***Partial epilepsies due to malformations of cortical development (MCD).*** A combination of genetic and environmental factors can lead to MCDs, which often present with epilepsy accompanied or not by variable degrees of mental retardation and other signs of neurologic dysfunction. The exact nature of the associated epileptic picture depends on the type and extent of the malformation. Early prenatal care is critical for the prevention of some types of these disorders. MCD often leads to severe partial symptomatic epilepsies refractory to medical treatment. In developing countries, MCD should be suspected as the epilepsy etiology when there is no history of perinatal or postnatal distress, and a CT scan rules out neurocysticercosis. Early onset of partial seizures or spasms is the usual presentation.

***Symptomatic Generalized Epilepsies***

These relatively intractable epileptic disorders result from diffuse brain damage of moderate to severe intensity and are usually associated with developmental delay, cognitive dysfunction, and behavioral abnormalities. Severe early infantile myoclonus or infantile spasms is often the mode of onset. Seizures are polymorphic and include generalized tonic, tonic-clonic, atonic, myoclonic, and atypical absence spells. The most common underlying etiology of symptomatic generalized epilepsies in developing countries is hypoxic-ischemic encephalopathy.

***Hypoxic-ischemic encephalopathy.*** Hypoxic-ischemic encephalopathy due to perinatal distress is a frequent cause of epilepsy in developing regions. A shortage of doctors, poorly trained midwives, and unexplained delays in making decisions about the most adequate form and timing of delivery are all too common. If there is one group of epilep-

tic disorders that may be considered as potentially preventable through improved education and professional commitment, it is that related to perinatal hypoxic-ischemic encephalopathy. The extent of the ultimate brain insult will determine the type and severity of the epileptic disorder and associated cognitive and motor dysfunction, but a combination of partial and severe generalized seizures coupled with abnormal psychomotor development is the gloomy outcome for a significant percentage of these children.

***Idiopathic Generalized Epilepsies***

As a group, the idiopathic generalized epilepsies deserve special emphasis, because their correct identification usually leads to effective medical treatment, thus decreasing the burden of epilepsy for patients and relatives. Several discrete age-related syndromes have been identified, but some unifying features should be considered: patients are developmentally and neurologically normal; seizures consist of either primarily generalized tonic-clonic attacks, typical absences, bilateral myoclonus, or a combination of these; a positive family history of epilepsy or febrile convulsions is often present; EEGs have at least reasonably well organized background activity and generalized spike and wave or polyspike and wave discharges at 3 Hz or faster; and seizures are usually fully responsive to medication. Seizures commonly remit spontaneously when onset is before puberty, but lifelong treatment is usually necessary for the juvenile onset forms.

***Idiopathic Partial Epilepsies***

These benign conditions typically begin in childhood, remit spontaneously in adolescence, and seizures can be so mild and infrequent that no treatment is required. The most common syndrome is benign childhood epilepsy with centrotemporal spikes. Most children with this disorder are developmentally normal and neurologically intact and have fairly stereotypical focal sensorimotor seizures of the face, which may be accompanied by head turning or motor involvement of the ipsilateral hemibody. The EEG reveals unilateral or bilateral centrotem-

poral spikes with a characteristic transverse dipole. This is one of the few epilepsy syndromes for which anticipation of remission by adolescence truly applies. The combination of typical ictal semiology and EEG in a normal child allows the correct diagnosis. A variant is associated with occipital spikes, vomiting, and asymmetrical tonic activity lasting up to 2 hours.

### Plans for a New Classification Scheme for Seizures and Epilepsies

A major criticism of the ILAE classification of epileptic seizures, which was intended to be purely phenomenological because of lack of information on pathophysiologic and anatomic substrates in 1981, when it was adapted, has been the need for a priori assumptions about etiology and detailed EEG data before a diagnosis could be made. This makes the classification difficult to apply in developing countries, where EEG recordings and other diagnostic tests are not easily obtained. This problem negatively impacted epidemiologic studies in developing regions of the world, as well as in clinical practice. Consequently, the ILAE has now proposed two approaches to the classification of epileptic seizures. The first of these consists of a purely semiological description of the ictal signs and symptoms, which requires no a priori assumptions and no laboratory information. This purely phenomenological descriptive approach, therefore, would be easy to apply everywhere in the world, regardless of available diagnostic resources. The second approach would treat epileptic seizures as diagnostic entities, similar to epileptic syndromes. Seizure types are currently considered based on modern concepts regarding specific pathophysiologic and anatomic substrates. Diagnosis of a specific seizure type, therefore, will have etiologic, therapeutic, and prognostic implications. A diagnosis of seizure type, or types, in an individual patient can supplement the syndromic diagnosis and, in the not uncommon situation where a syndromic diagnosis cannot be made, further diagnostic evaluation and treatment can be determined by the diagnoses of seizure types.

The list of accepted epileptic syndromes is also being updated based on the latest infor-

mation, which now includes extensive genetic studies. Despite great conceptual advances in our understanding of the fundamental mechanisms of the epilepsies since the current ILAE Classification of the Epilepsies was adopted in 1989, many, if not most, patients presenting with one or more epileptic seizures have a constellation of signs and symptoms that still do not fit neatly into an accepted syndromic diagnosis. This is particularly true in areas with limited resources, where modern diagnostic facilities are not readily available. For these patients, phenomenological description of ictal semiology and diagnosis of a seizure type will be important for guiding management.

The ILAE has also proposed a diagnostic scheme consisting of five axes, which can be used to fully characterize the epileptic condition in each individual patient (Table 2.4). The first four axes, ictal phenomenology, seizure type, syndrome, and etiology, are arranged in order of increasing diagnostic complexity, and details may not be available to definitively assign a diagnosis for the latter axes, particularly in developing countries; however, assumptions can be made based on diagnoses assigned in the earlier axes to plan management. The optional fifth axis, impairment, is based on a proposed WHO classification of impairment in neurologic disorders and can be useful for advising patients and others regarding functional prognosis, including compensation for disability.

The ILAE is now debating how to organize and categorize the lists of epileptic seizures and epileptic syndromes into useful classifications. Any new classifications of epileptic seizures and epilepsies cannot stray too far from the current classifications, because the tremendous advantages gained from the universal application of certain basic taxonomic concepts should not be lost. Some changes in terminology, however, have already been proposed (Table 2.5). These classifications will be designed to take into account the fact that they will be used in diverse ways, each with its own inherent taxological requirements. Some will demand simplicity, e.g., for teaching, use by primary care physicians, and in developing countries where detailed diagnostic evaluations are not possible. Others will require unique special-

**TABLE 2.4** Proposed Diagnostic Scheme for People with Epileptic Seizures, and with Epilepsy

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that utilizes standardized terminology and that is sufficiently flexible to take into account the following practical and dynamic aspects of epilepsy diagnosis:

1. Some patients cannot be given a recognized syndromic diagnosis.
2. Seizure types and syndromes change as new information is obtained.
3. Complete and detailed descriptions of ictal phenomenology are not always necessary.
4. Multiple classification schemes can, and should, be designed for specific purposes (e.g., communication and teaching; therapeutic trials; epidemiologic investigations; selection of surgical candidates; basic research; genetic characterizations).

This diagnostic scheme is divided into five parts, or axes, organized to facilitate a logical clinical approach to the development of hypotheses necessary to determine the diagnostic studies and therapeutic strategies to be undertaken in individual patients:

**Axis 1:** Ictal phenomenology—from the Glossary of Descriptive Ictal Terminology, can be used to describe ictal events with any degree of detail needed.

**Axis 2:** Seizure type—from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.

**Axis 3:** Syndrome—from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.

**Axis 4:** Etiology—from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.

**Axis 5:** Impairment—this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the WHO ICD.

From Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001;42:796–803 with permission.

ized details, e.g., for various types of epidemiologic purposes, experimental drug trials, epilepsy surgery, and basic research. For these reasons, a flexible group of classifications is envisioned, perhaps in a modular format, which can be reorganized for specific purposes and easily changed as experience with application dictates and as new information becomes available. Participation in this process by epileptologists working in developing countries is as important as participation by epileptologists working in fields of epidemiology, clinical pharmacology, epilepsy surgery, and basic research. Similarly, experience gained from the extensive use of any new classifications in developing countries will be as important as experience from use in other areas for deciding on subsequent revisions and refinements.

## CONCLUSIONS

A differential diagnosis between epilepsy and other conditions is of primary importance in the care of individuals presenting with suspected events. An unwarranted diagnosis of epilepsy is to be avoided in any case, but is of particular concern in developing countries, where patients who receive this diagnosis may be victims of stigma and social exclusion, and where the cost of AEDs can cause extreme financial hardship. Accurate differential diagnosis can be achieved in most cases on clinical grounds but requires familiarity not only with the typical presentation of epileptic seizures and epilepsy syndromes, but with a variety of conditions such as breath-holding spells, panic attacks, hyperventilation syndrome, basilar migraine, psychogenic seizures, syncope, transient ischemic attacks, movement disorders, myoclonus, parasomnias, and attention deficit-hyperactivity disorder, which are commonly mistaken for epilepsy.

Furthermore, it is important to recognize that paroxysmal events in association with evidence of conditions common in developing countries, such as neurocysticercosis, do not mean that the events are epileptic, or if they are, that they are in fact due to the most obvious disease process. A single epileptic seizure also is not epilepsy; it may be a provoked or acute symptomatic event that does not indicate the presence of a chronic epilep-

**TABLE 2.5** Definitions of Key Terms

- Epileptic Seizure Type:** An ictal event believed to represent a unique pathophysiologic mechanism and anatomic substrate. This is a diagnostic entity with etiologic, therapeutic, and prognostic implications. (New concept)
- Epilepsy Syndrome:** A complex of signs and symptoms that define a unique epilepsy condition with different etiologies. This must involve more than just the seizure type; thus, frontal lobe seizures per se, for instance, do not constitute a syndrome. (Changed concept)
- Epilepsy Disease:** A pathologic condition with a single specific, well-defined etiology. Thus, progressive myoclonus epilepsy is a syndrome, but Unverricht-Lundborg is a disease. (New concept)
- Epileptic encephalopathy:** A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. (New concept)
- Benign epilepsy syndrome:** A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae. (Clarified concept)
- Reflex epilepsy syndrome:** A syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that are also associated with spontaneous seizures, are listed as seizure types. Isolated reflex seizures can also occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures. (Changed concept)
- Focal seizures and syndromes:** Replaces the terms partial seizures and localization-related syndromes. (Changed terms)
- Simple and complex partial epileptic seizures:** These terms are no longer recommended, nor will they be replaced. Ictal impairment of consciousness will be described when appropriate for individual seizures, but will not be used to classify specific seizure types. (New concept)
- Idiopathic epilepsy syndromes:** A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurologic signs or symptoms. These are presumed to be genetic and are usually age-dependent. (Unchanged term)
- Symptomatic epilepsy syndrome:** A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain. (Unchanged term)
- Probably symptomatic epilepsy syndrome:** Synonymous with, but preferred to, the term cryptogenic, used to define syndromes that are believed to be symptomatic, but no etiology has been identified. (New term)

From Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001;42:796–803, with permission.

togenic disturbance. A diagnosis of epilepsy requires the presence of an enduring brain abnormality capable of generating recurrent spontaneous seizures. Understanding the classification of epileptic seizures, and of epilepsy syndromes, is essential to making a

correct diagnosis that in turn will determine whether additional diagnostic evaluation is necessary to search for an underlying treatable cause, as well as to infer specific treatment and provide prognostic information.

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## EPIDEMIOLOGY AND ETIOLOGY

The epidemiology of epilepsy in the developing world is poorly documented and the prevalence and etiology of epileptic disorders in these areas often differ from those in published textbooks, which report information largely derived from studies in the industrialized and developed world. Poverty, illiteracy, poor sanitation, and poor access to health care are probably directly or indirectly responsible for the large burden of epilepsy found in developing countries.

Birth injuries and parasitic diseases are common and account for a considerable proportion of epilepsy in developing countries. Tropical conditions, societal violence, accidents, war, and consanguinity may also contribute to the burden of epilepsy in these regions. A disproportionately young population also results in differential causes for epilepsy relative to developed countries. The neurologists and other physicians practicing in the developing world need to be aware that a substantial proportion of the epilepsy they encounter results from treatable or preventable causes.

### EPIDEMIOLOGY

Epilepsy contributes substantially to the burden of noncommunicable diseases in the developing world. For example, recent work in South Africa indicates that epilepsy accounts for ~16% of all noncommunicable disorders. Within India, epilepsy costs consume ~0.5% of the gross national product. Despite these indicators of the importance of epilepsy in such environments, epidemiologic data from the developing world are limited. Available population-based data from developed countries cannot be extrapolated to developing nations because of problems associated with diagnosis, ignorance regarding the

disorder, sociocultural milieu, and different causative factors.

### Incidence

Undoubtedly, to fully understand the epidemiology of epilepsy, one should have information regarding the incidence of epilepsy—meaning new cases of the disease occurring in the population over some specified time period. Unfortunately, the stigma of the disorder and lack of readily available medical resources result in delayed presentation for care. An accurate assessment of *new* cases of epilepsy remains extremely difficult to obtain in the developing world, so estimates from cross-sectional data are often utilized for this purpose.

Data from the United States indicates an epilepsy incidence of 40/100,000 person-years, whereas incidence reports from the developing world seem somewhat higher. For example, the incidence is 49.3/100,000 in rural southern India, 122–190/100,000 in Ecuador, and 64/100,000 in Ethiopia. Incident cases occur most often in the very young and the very old. The incidence in the United States is 82/100,000 person-years among children under 1 year and 77/100,000 person-years in people over 60 years of age. Males appear to have a slightly higher incidence of epilepsy than females. This gender differential probably results from a disproportionately high rate of traumatic brain injuries in males relative to females.

Cumulative incidence (CI) refers to the likelihood of having developed epilepsy by some specified age and, therefore, CI increases throughout the life span. Data on the CI of epilepsy are even more difficult to obtain than incidence data, and no CI data for epilepsy in the developing world are available. In developed countries, the CI is

### KEYPOINTS

- The neurologists and other physicians practicing in the developing world need to be aware that a substantial proportion of the epilepsy they encounter results from treatable or preventable causes.
- Available population-based data from developed countries cannot be extrapolated to developing nations.

**KEYPOINTS**

- In many regions of the developing world, the prevalence of epilepsy appears to be significantly higher than the prevalence of 5 to 7/1,000 seen in developed countries.

estimated to be 1% at 15 years of age, increasing to 3% at 74 years and 4.4% at 85 years. Note that the CI of epilepsy is significantly less than the CI of *any* seizure, which is 10% by 85 years of age.

**Prevalence**

Epilepsy prevalence is substantially easier to assess than incidence. As per the World Health Organization, epilepsy is considered “active” among those people with epilepsy who have experienced at least one seizure and/or have been on antiepileptic drugs (AEDs) for seizures in the preceding 2 years. However, most epidemiologic studies define someone with “active” epilepsy as anyone with a history of epilepsy who has experienced a seizure and/or been on AEDs for seizures in the past 5 years.

In many regions of the developing world, the prevalence of epilepsy appears to be significantly higher than the prevalence of 5 to 7/1,000 seen in developed countries (Table 3.1). A review of more than 100 epidemiologic studies indicates an unequal distribution of epilepsy with a higher prevalence in developing countries. The great variability in this table, however, also reflects differences in methodology.

The prevalence of epilepsy varies widely within regions of developing countries, and not all developing regions report rates above those seen in the developed world. This high variance is seen even when cases are evaluated by the same methods and the same researchers, suggesting that environmental exposures or other local factors contribute substantially to the burden of disease in these

areas. If epilepsy in some developing regions is associated with substantially increased mortality, then prevalence rates may underestimate the disorder’s impact on the population. Some studies have reported regions of high incidence, but not high prevalence, suggesting either high remission or high mortality rates.

Epilepsy subtypes also differ between developed and developing regions. Comparative studies have found rates of focal epilepsies (epilepsies due to an epileptogenic region in a part of one hemisphere) to be substantially higher in developing countries. Focal epilepsies comprise only 62% of seizure disorders in France compared to 80% in India, 77% in Nigeria, and 74% in Sri Lanka. Insults related to tropical location and economic disadvantage, which result in focal brain injury, could potentially explain higher rates of epilepsy and therefore a predominance of focal epilepsies in low-income, tropical countries.

**TABLE 3.1** Results of Some Published Door-to-Door Surveys of Prevalence Rates in a Variety of Developing Countries

Location	Pub Date	Population	# of Cases	Prev Ratio (/1,000)
Urban Nigeria	1987	18,654	101	5.0 *
Rural Kashmir	1988	63,645	157	2.5
Bombay	1988	14,010	50	3.7 *
Rural Ethiopia	1990	60,820	316	10.0 *
Ecuador	1992	72,121	575	8.0
Rural Tanzania	1992	18,183	185	12.6 *
Rural Guanajuato	1992	7,187	179	20.8
Urban Tunisia	1993	35,370	141	3.5 *
Pakistan	1994	24,130	241	9.9 *
Turkey	1997	11,497	81	6.7 *
Rural Bolivia	1999	9,955	112	14.0 *
Kerala, India	2000	238,102	1,175	4.7 *
Riyadh, Saudi Arabia	2001	23,700	155	6.5
Urban Brazil	2002	982	20	5.1
China	2003	55,616	257	4.6

Contributed by Allen Hauser, MD, Columbia University (note that citations for individual studies cannot be included here, but can be obtained from Dr. Hauser.)

\* age-adjusted

When reviewing epidemiologic data from developing countries, one should recognize that most study limitations lead to an underestimation of seizure disorders. People are reluctant to admit to suffering from a stigmatizing condition, especially if few medical services are available to them once the disorder is recognized. Absence and focal seizures that fail to generalize will likely be underrecognized. Decreased epilepsy-associated stigma, improved health care services, and increased research infrastructure are needed to optimally evaluate epilepsy epidemiology and etiology in developing countries.

### Natural History

Spontaneous remissions do occur even in untreated people with epilepsy, and concerns that “seizures beget seizures” have not been substantiated in longitudinal, population-based studies in developed countries. Neither the duration of epilepsy nor the number of seizures appears to reliably reflect the response a patient will have to AEDs, but symptomatic seizures associated with an underlying brain lesion are much less likely to spontaneously remit. Some epileptic syndromes have a good prognosis and are likely to remit. These include neonatal epilepsy, childhood absence epilepsy, and benign rolandic epilepsy. Juvenile myoclonic epilepsy and mesial temporal lobe epilepsy are less likely to spontaneously remit.

### Morbidity and Mortality

Epilepsy substantially increases mortality risk, particularly in environments that generally lack medical resources, including basic anti-convulsants, and have health care providers poorly trained to diagnose and treat neurologic disorders. The extreme social stigma associated with seizures in some cultures is particularly detrimental. Untreated individuals who have frequent seizures and live where open fires are used for cooking and heating often experience severe burns. Patients with epilepsy in some regions often exhibit scars from significant burns or fractures that occurred during seizure activity. In hospital-based observations in sub-Saharan Africa, such scars are evident in ~30% of patients. Where water is collected from rivers or streams and fishing provides a significant

source of food, drowning among people with epilepsy is also common.

Many commonly held beliefs contribute to the morbidity and mortality of epilepsy. For example, where epilepsy is thought to be contagious, bystanders and perhaps even family members may be reluctant to assist someone during a seizure. Under such circumstances, people with epilepsy can drown while onlookers do nothing. People who have fallen into a fire may suffer full-thickness burns rather than the superficial wound that would have occurred if someone had simply pulled them from the fire. Substantial seizure-related injury can potentially be averted with public health education to discourage such beliefs.

In the United States, even among people with severe epilepsy, only 20% of deaths are directly attributable to the seizure disorder, and the standardized mortality ratio (risk of death among people with epilepsy/risk of death in the general population) is 2:3. Unfortunately, within developing countries, the morbidity and mortality of epilepsy appear to be substantially greater. Death and injury occur primarily due to status epilepticus (especially in the setting of abrupt medication withdrawal), burns, and drowning. Standardized mortality ratios for people with epilepsy in developing regions, meaning the ratio of the number of deaths observed among people with epilepsy relative to the number of deaths expected in the general population, are not available. However, one 30-year follow-up study in Tanzania found a 67% mortality rate among people with epilepsy, and most deaths were seizure-related.

### Socioeconomic Impact

The magnitude of the negative socioeconomic impact of epilepsy varies depending on the environment. Within many developed countries, laws make it illegal to discriminate in employment against people with disabilities, assisting in protecting the rights of people with epilepsy. Unfortunately, few developing countries have laws offering such protection. In fact, some countries may even have legislation that contributes to discrimination against people with epilepsy. Data from Africa, Asia,

### KEYPOINTS

- Epilepsy substantially increases mortality risk.
- Many commonly held beliefs contribute to the morbidity and mortality of epilepsy.

**KEYPOINTS**

- In malaria-endemic regions, malarial fevers are the most common cause of fever-related seizures, although some argue that seizures occurring in this setting are symptoms of primary central nervous system involvement rather than a febrile seizure.

and Latin America indicate that people with epilepsy have less access to education, employment, and marriage than their unaffected counterparts. Some countries even list epilepsy as lawful grounds for divorce.

**Febrile Seizures**

Febrile seizures (FSs) are seizures that occur in association with fever in children between 6 months and 5 years of age. Most often, FSs occur during the second year of life. To diagnose FS, the fever should not be due to any intracranial infection, including meningitis or encephalitis. In malaria-endemic regions, malarial fevers are the most common cause of fever-related seizures, although some argue that seizures occurring in this setting are symptoms of primary central nervous system (CNS) involvement rather than a FS. FSs have been classified as “simple” or “complex.” Complex FSs include seizures with focal onset, a single FS lasting for more than 15 minutes, or recurrent FS within 24 hours. Important risk factors predicting recurrence of FS are: a) young age of onset, b) evidence of developmental delay, c) family history of FS among first-degree relatives, and d) low grade fever for a short duration before the febrile seizure occurred.

Data from developed countries indicate that FSs occur in about 3% to 4% of all children. Most FSs are benign events, as only about 5% of all children with FS develop epilepsy. The risk of epilepsy is estimated to be 2.4% following a simple FS compared to 8% to 15% after a complex FS. Risk factors associated with the development of epilepsy after FS include: a) evidence of developmental delay and, b) family history of epilepsy. Fever-associated seizures may be more common in developing countries, especially in regions with endemic *P. falciparum* malaria. Furthermore, in developed countries complex FS represent only ~15% of FSs whereas reports from developing regions indicate that complex FS comprise >50% of febrile seizures and that multiple complex features are common. High rates of complex FS in developing countries may be due to a selection bias, with only significantly ill children presenting for care. Alternatively, such complex FSs may be due to the underlying fever-

inducing illness (i.e., malaria) or may be the manifestation of previous CNS insults.

**RISK FACTORS FOR SEIZURES AND EPILEPSY**

Risk factors for epilepsy vary depending on the age of the individual. Children, and particularly infants, appear to have a lower seizure threshold than adults (including the FS phenomena exclusively seen in children), but may be more resistant than adults to the development of recurrent, unprovoked seizures. For example, children are more likely to have a seizure after head injury, but are less likely than adults to develop epilepsy after head injury. Epilepsy in adults occurs most often in the elderly and reflects the higher incidence of CNS injury in this population due to stroke, dementia, and other neurodegenerative processes. The location of CNS injuries also impacts the risk of recurrent seizures, with the temporal and frontal regions appearing to be most epileptogenic and the occipital and subcortical regions less so. Recognizing that in at least 30% of people with epilepsy, no underlying cause can be identified even with state-of-the-art imaging and technology, several clear risk factors do exist. Table 3.2 indicates the common causes of epilepsy in sub-Saharan Africa.

It is important to remember that the risk factors for seizures may not always be the same as the risk factors for epilepsy. Unprovoked seizures can either be secondary to a known enduring disturbance of the brain or due to unknown causes. On the other hand, provoked seizure(s) are those that occur in the setting of an acute transient insult to the brain. Usually such acute symptomatic seizures occur as isolated events, but the insult can also be associated with permanent brain injury and lead to the development of epilepsy later. For example, acute head injury or stroke can produce acute symptomatic seizures and/or chronic seizure disorders.

**Acquired Risk Factors*****Infections and Infestations***

In Latin America and parts of Asia, neurocysticercosis is the commonest cause of epilepsy. Studies in the 1960s in Africa, found

**TABLE 3.2** Reported Causes of Seizures and Epilepsy Regarding the Age of Onset in Sub-Saharan Africa

**0 to 4 months:** Neonatal asphyxia; perinatal trauma; infections; cerebral malformation; subdural hematoma; hypoglycemia; hypocalcemia; inborn errors of metabolism.

**4 months to 2 years:** Sequelae of previous causes; infections; vascular causes; inborn errors of metabolism.

**2 to 10 years:** Sequelae of previous causes; idiopathic generalized epilepsy; infections; post-traumatic epilepsy; intoxication; inborn errors of metabolism; primary tumors.

**10 to 20 years:** Sequelae of previous causes; idiopathic generalized epilepsy; post-traumatic epilepsy; intoxication including alcohol and other drugs; infections; inborn errors of metabolism, malformations, neurodegenerative disorders.

**20 to 40 years:** Sequelae of previous causes; trauma; brain tumors; alcohol; infections; vascular diseases, tumors and abscesses, neurodegenerative disorders.

**40 to 60 years:** Tumors; Alcohol; head trauma; infections; vascular causes; metabolic disorders.

**>60 years:** Vascular causes and metabolic disorders primary and secondary tumors; neurodegenerative disorders; infections.

From "Epilepsy in Africa: Bridging the Gap", Report, WHO/AFRO, 2004

neurocysticercosis evident in only 10% of epilepsy cases. More recent work suggests greater prevalence, but high rates of asymptomatic cerebral cysticerci, high rates of positive serologies for *T. solium* in the general population, and the lack of brain imaging facilities make interpretation of these findings difficult. Seizures secondary to CNS tuberculosis are also common in many developing countries. Today, many cases of CNS tuberculosis are associated with HIV infection. Nearly 50% of patients with TB meningitis experience seizures sometime during the course of their illness, and a high incidence of focal seizures has been reported.

Tropical infectious diseases thought to contribute substantially to the epilepsy burden in developing countries include malaria, neurocysticercosis, and onchocerciasis. In regions with endemic *P. falciparum*, high rates of complex fever-associated seizures have been reported in children with malarial fevers. If these seizures are indicative of malaria-induced CNS injury, such events might predispose to later epilepsy. Additional factors such as poor perinatal management and delivery, as well as bacterial and viral CNS infections, undoubtedly play a role. The relationship between HIV/AIDS and chronic seizure disorders in developing countries has not been well described. HIV-related CNS infections, such as toxoplasmosis, can certainly cause seizures, but without aggressive treatment of the underlying infection, few of these patients will survive. Children with HIV encephalopathy, who often present with developmental delay, are at increased risk of seizure disorders. Relapsing Nipah virus is a cause of recurrent seizures in Malaysia and other areas of southeast Asia.

#### **Head Trauma, Stroke, and Degenerative Brain Disorders**

High rates of head trauma in developing countries occur through a wide variety of mechanisms. Poor enforcement of motor vehicle safety, including roads frequented by overcrowded vehicles without seat belts, brakes, and/or headlights is particularly problematic. Riding motor bikes without a helmet is a common cause of brain injury. Societal violence and war contribute substantially to traumatic brain injury in developing regions. Prolonged unconsciousness after head trauma, post-traumatic amnesia for more than 30 minutes, intracranial bleeding, penetration of the brain by a missile, and depressed skull fractures are complications associated with a greater likelihood of developing epilepsy after head injury. The risk for epilepsy is greatest in the first few years after the trauma, but can persist for at least 15 years, depending on the nature of the injury.

The incidence and prevalence of stroke and degenerative brain disorders were thought to be lower among developing coun-

tries, mainly due to the relatively younger age of the population. However, an increase in the average life span in some developing countries, coupled with “Westernized diets” and increased tobacco use, have resulted in an increase in cerebrovascular accidents and dementia in these areas.

Seizures have been reported to occur in ~8% of patients with acute stroke. Among acute stroke survivors with occlusive cerebrovascular disease, up to 20% develop epilepsy, most of them within the first 2 years following stroke, although the risk for post-stroke epilepsy remains for a much longer period. Patients with cortical infarcts are at a greater risk. As in post-traumatic epilepsy, early post-stroke seizures (in the first week following stroke) are associated with an increased risk for epilepsy compared to stroke patients who do not have seizures at the time of the infarct.

Roughly 15% of patients with Alzheimer’s disease (AD) experience unprovoked seizures in the course of their illness. In industrialized countries, AD accounts for almost 15% of all newly diagnosed cases of epilepsy in the elderly (after the age of 65). There is an urgent need to have reliable data on the occurrence of epilepsy after head injury, stroke, and degenerative brain disorders among populations living in developing countries. Such information would assist with public health interventions to prevent epilepsy and health services planning.

#### **Toxic Exposures**

Toxic exposures specific to developing regions may predispose to sporadic seizures. Organophosphate poisoning, a common event among children in rural regions, frequently presents with *status epilepticus*. Pesticides are often used and stored inappropriately, and public education could potentially avert many of these events. Traditional medicines, such as an African medicine containing a combination of cow urine and nicotine, may also precipitate seizures. Whether such toxic exposures predispose to later epilepsy is unknown.

#### **Hereditary Risk Factors**

Genetic factors also contribute to the causation of epilepsy, but the extent to which her-

itable traits contribute varies according to the types of epilepsy. Hereditary epilepsies with simple Mendelian inheritance are not common, but gene mutations for some of these syndromes have been identified and have contributed to our understanding of the mechanisms involved in the genesis of seizures. Epilepsies and other episodic disorders, such as benign familial neonatal convulsions and generalized epilepsy with febrile seizures plus (GEFS+), result from mutations in ion channels and are referred to as channelopathies. However, most of the common idiopathic epilepsy syndromes are suspected to reflect complex inheritance, either secondary to the added effect of multiple mutant genes (“polygenic”) or examples of “multifactorial inheritance” (disorders resulting from an interaction of an inherited predisposition with an environmental insult). Hereditary factors could play a different role in the causation of epilepsy in some developing countries due to the practice of consanguineous marriage, especially among first cousins.

#### **Hereditary Epilepsies with Complex Inheritance**

The most common forms of idiopathic generalized epilepsies are childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures on awakening. These four syndromes account for 30% of all epilepsies in the developed world and are the most common genetic epilepsies. Many clinical features of these epilepsies overlap, but significant differences among the syndromes are the age of seizure onset and prognosis for complete remission. An important distinguishing feature is that most of these syndromes present with at least two types of seizures, but the temporal order in which different seizure types manifest in different patients is not fixed.

Hereditary focal epilepsies with complex inheritance also occur, the most common of which is benign childhood epilepsy with centrotemporal spikes. There are idiopathic focal childhood seizures from occipital and other locations as well. Most respond well to medications, or may be so benign as not to require any medications, and remit spontaneously in adolescence.

For a variety of reasons, these epilepsy syndromes are often not recognized by physicians practicing in developing countries. The importance of a syndromic approach among patients with epilepsy lies not in arriving at a correct diagnosis per se, but in using this diagnosis to counsel the family regarding prognosis, select the most appropriate drug treatment, and determine the duration of treatment warranted.

#### ***Other Rare Epilepsies Associated with Simple Mendelian Inheritance***

Several other less common epilepsies result from simple Mendelian inheritance, such as the progressive myoclonus epilepsies. However, these disorders are exceedingly rare and generally require diagnostic technologies not available in developing world settings. Mitochondrial disorders include myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). The overlapping features of mitochondrial disorders include seizures, dementia, progressive external ophthalmoplegia, sensory neural hearing loss, cardiac abnormalities, and elevated levels of lactate and pyruvate.

Phakomatoses include a group of developmental disorders characterized by a variety of skin lesions evident in childhood and therefore potentially identifiable clinically. These disorders are often followed later in life by the development of tumors in other organs, including the CNS. Tuberous sclerosis (TS) and neurofibromatosis 1 are two relatively common autosomal dominant phakomatoses. TS patients present with the classical triad of seizures, mental subnormality, and skin lesions (hypopigmented macules, adenoma sebaceum, shagreen patches, and subungual fibromas). TS-associated tumors may undergo malignant transformation. TS commonly presents with infantile spasms and the subsequent development of generalized tonic-clonic seizures, myoclonic jerks, and even partial seizures.

Despite the theoretical possibility of inheriting epilepsy, the overall risk of inheriting epilepsy from a parent is close to zero for most types of epilepsy and very small for others. However, the common occurrence of

consanguinity in developing countries can contribute to an increased incidence of certain hereditary epilepsies; therefore, this practice should be avoided. While it is well known that epilepsy itself and the antiepileptic drugs used during pregnancy do result in complications among a very small number of children born to women with epilepsy, there is no justification for barring marriage or childbearing.

#### **CONCLUSIONS**

Modifiable risk factors for seizures and epilepsy need to be identified to facilitate the prevention of seizures and epilepsy in the population. Potentially preventable cases of epilepsy substantially add to the societal burden of this chronic disorder. Simple measures such as improved antenatal care, adequate sanitation, and basic road safety could prevent many cases of brain injury. People residing in developing countries are at greater risk of experiencing CNS insults, for example through perinatal injuries, CNS infections (including cerebral malaria and neurocysticercosis), or head trauma relative to people in developed countries. This suggests that people presenting with a single seizure in developing countries are at higher risk of harboring an underlying CNS injury and may therefore have a higher risk of developing epilepsy than the “single seizure” patient from the developed world. No systematic evaluation of this has been completed. Public health measures instituted to decrease brain insults and injury would ultimately result in decreased epilepsy and a better prognosis for all those affected by sporadic seizures. Although hereditary factors contribute to the risk of epilepsy and consanguinity increases this risk, the overall risk from hereditary factors is small and people with epilepsy should not be advised against childbearing, though consanguinity should be discouraged.

#### **KEYPOINTS**

- While it is well known that epilepsy itself and the antiepileptic drugs used during pregnancy do result in complications among a very small number of children born to women with epilepsy, there is no justification for barring marriage or childbearing.
- Although hereditary factors contribute to the risk of epilepsy and consanguinity increases this risk, the overall risk from hereditary factors is small and people with epilepsy should not be advised against childbearing, though consanguinity should be discouraged.

**CITATIONS AND RECOMMENDED READING**

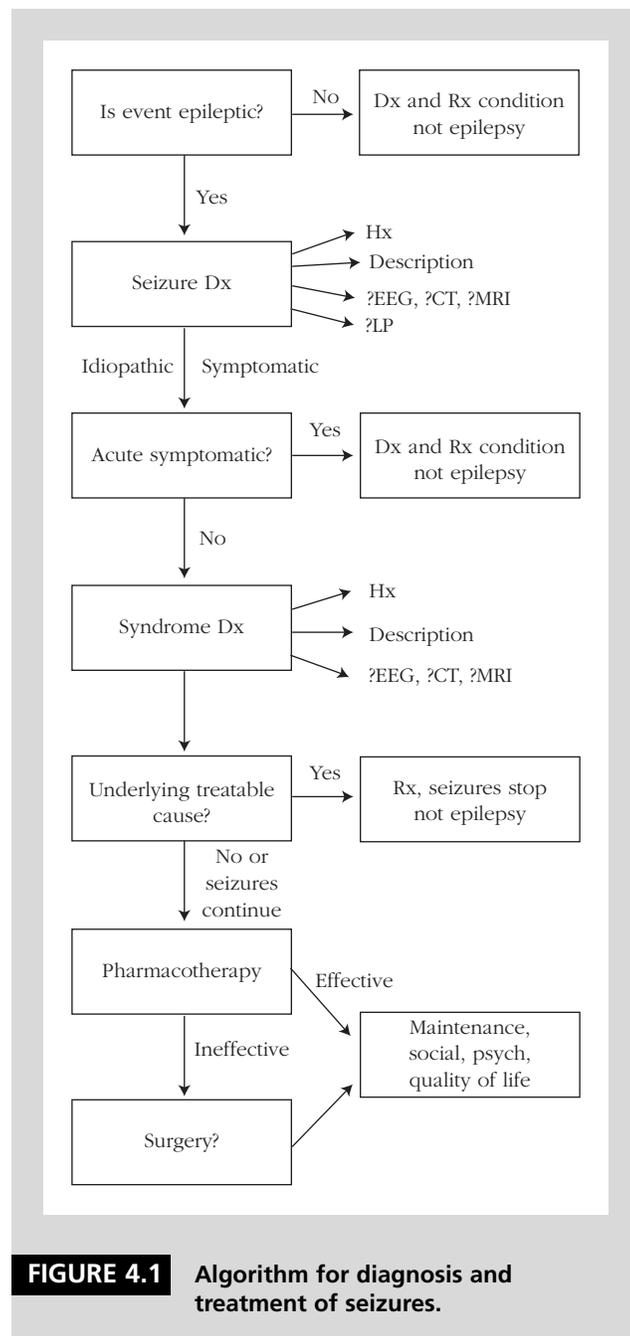
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# DIAGNOSTIC APPROACHES

Limited diagnostic resources in developing countries demand a cost-effective approach to evaluating patients with spells. Such an approach is heavily dependent on the clinical skills of the neurologist. Data obtained through history and physical examination, complemented by epidemiologic knowledge, should direct the diagnostic workup. Three questions are paramount when approaching a patient with a spell. The first is whether it is an acute episode occurring for the first time in the patient's life, or if it is a recurrence of a given type of spell for which help already may have been sought. The second concerns the nature of the episode: Are the events truly epileptic? If the epileptic nature of the spells is established, then the seizure type(s) should be classified. Finally, the syndromic diagnosis and the etiology of the brain disorder leading to seizures should be established. An algorithm for evaluation of patients with events that might be epileptic seizures is shown in Figure 4.1.

### First Seizure, Single Seizure, and Recurrent Spells: The Boundaries of the Definition of Epilepsy

The physician faced with a patient experiencing a single seizure must first determine whether this is a presenting symptom of a life-threatening disorder that should be promptly identified and treated, or the presenting symptom of a benign idiopathic form of epilepsy, which does not necessarily require extensive



**FIGURE 4.1** Algorithm for diagnosis and treatment of seizures.

**KEYPOINTS**

- The occurrence of a febrile seizure before the age of 12 months requires that the child be referred to a hospital for lumbar puncture to rule out meningitis.

neurodiagnostic evaluation, or a provoked event that is unlikely to recur. The approach to a patient with a new onset acute seizure is completely different from the approach to a patient who has been having seizures for some time, particularly because a seizure in the latter is less likely to reflect some potentially life-threatening substrate (see also Chapter 1).

A history and examination consistent with drug or alcohol abuse, decompensation of a metabolic disorder, intracranial infection, increased intracranial pressure, or stroke requires extensive further evaluation to rule out an underlying cause that requires immediate attention. The patient's relatives should be asked about any underlying metabolic or cardiovascular diseases, such as diabetes or arterial hypertension, and also for the occurrence of fever, headache, somnolence, vomiting, acute behavioral changes, and acute motor deficits in the hours or days surrounding the episode. This should be complemented by a thorough physical and neurologic examination, including elucidation of high blood pressure, the presence of meningeal signs, papilledema, and focal neurologic deficits. Focal features of the ictal event also increase the likelihood that this is a symptomatic, rather than idiopathic or provoked, condition. In most circumstances, ancillary laboratory tests will be needed, including at least a complete blood count, electrolytes, and serum glucose, as well as a computed tomography (CT) scan (or an MRI if available). In selected circumstances, a lumbar puncture to rule out meningitis or encephalitis and blood levels of illicit drugs or alcohol will be needed.

**Adults**

A history of a generalized tonic-clonic convulsion following sleep deprivation, alcohol or sedative drug withdrawal, or other well-known precipitating factors in an otherwise healthy person with a normal history, physical, or neurologic examination, and routine laboratory findings suggests a provoked event which is not likely to recur as long as precipitating stimuli are avoided. An electroencephalogram (EEG) and CT (or MRI) scan are still indicated to look for some predisposing abnormality, but where resources

are limited, these tests are less necessary when clear precipitating factors are present. An EEG performed within 24 to 48 hours of the seizure can show nonspecific diffuse abnormalities, which are expected postictal changes and do not rule out a diagnosis of a provoked seizure. To avoid unnecessary further evaluation and antiepileptic drugs, it is better to wait a week before performing the EEG.

***Febrile Seizures in Infants and Children***

In infants and children, fever is a precipitating factor, but identification of intracranial infection is difficult. Focal seizures are the most characteristic feature of herpes encephalitis in infancy and childhood. Lumbar puncture and CT scan may be normal. It is urgent to treat before status epilepticus leads to brain damage. The occurrence of a febrile seizure before the age of 12 months requires that the child be referred to a hospital for lumbar puncture to rule out meningitis. A third cause of seizures with fever, particularly in developing countries, is malaria (see Chapter 5). A febrile seizure in infants with or without any identifiable underlying condition, which is focal and prolonged, can cause hippocampal atrophy and later mesial temporal lobe epilepsy. In the middle of the first year of life, the same seizure type can be the expression of Dravet syndrome, and the occurrence of recurrent bilateral independent seizures suggests this diagnosis. In the context of severe dehydration, whether febrile or nonfebrile, dural sinus thrombosis could occur, and the diagnosis relies on CT scan or the discovery of hemorrhagic cerebrospinal fluid on lumbar puncture.

***Nonfebrile Seizures in Infants and Children***

In neonates and infants, nonfebrile seizures can be due to hypoglycemia or hypocalcemia. In the latter case at the age of 2 to 3 months, other signs of rickets contribute to the diagnosis. It may seem paradoxical to see rickets in tropical countries, but infants are usually kept in the shadow of the house to prevent the risks related to excess of sun. Acute trauma is another common cause. Macrocephaly is rarely present when trau-

matic encephalopathy produces seizures. Fundoscopic examination showing hemorrhage is useful. Only lumbar puncture and CT scan permit the diagnosis. Ischemic encephalopathy begins several hours after birth. Seizures are usually tonic and repeated for several hours in a comatose neonate. Very early onset of convulsions during the first hours of life would suggest pyridoxine or pyridoxal phosphate dependency, even if there is evidence of prenatal distress (premature birth or dysmaturity). Seizures are polymorphic, unilateral, and generalized, including tonic, clonic, myoclonic, and spasms. The child is usually agitated and crying strongly. Repeat focal seizures involving a given part of the body indicate either ischemia, in which case the seizures will cease after a few hours, or a malformation, including hemimegacephaly. In this disorder, asymmetrical spasms would soon add to the pattern.

Between 2 and 4 months of age, status epilepticus without evidence of a triggering factor can result from the same disturbance that causes sudden infant death syndrome (near miss), the apnea often being overlooked because it occurred during sleep.

In infants and children, exogenous intoxication with chemical or pharmaceutical compounds can produce severe convulsion. Reflex epileptic seizures are rare in infants. One example is hot water epilepsy in which before the age of 5 years in previously normal children, a bath in hot water triggers arrest of activity, hypotonia, pallor, or cyanosis, then evidence of loss of consciousness. No seizures occur without this triggering factor.

A single seizure in children can also be the first manifestation of a benign age-related idiopathic epilepsy, which often can be diagnosed by a detailed description of the ictal event by a reliable observer. A history of similar seizure types in other family members is helpful, but very rarely present. Often, the patient presents because of a single generalized tonic-clonic seizure, but prior absences or myoclonic jerks, which help to make a specific diagnosis, have not been recognized as epileptic events and can only be elicited by careful questioning. Diagnosis of an age-related idiopathic

epilepsy syndrome is further supported by absence of a history of risk factors for epilepsy, a normal physical and neurologic exam, and unremarkable laboratory findings. In these cases, further expensive diagnostic evaluation is not necessary. Where EEG is available, a characteristic pattern of interictal spikes on a normal background often helps to make a diagnosis of a specific idiopathic syndrome.

It is common in developing countries for generalized tonic-clonic seizures to be the only ictal event of particular concern to individuals and their families. Consequently, a patient presenting with a single generalized tonic-clonic seizure does not necessarily have an acute condition. A careful history may reveal simple or complex partial seizures occurring for many years prior to the seizure that precipitated the clinic visit, or nocturnal seizures may have been missed but can be elicited by asking if the patient awakens occasionally with severe muscle soreness, a bitten tongue, or a wet bed. When there is such a history of prior unrecognized seizures, this is a chronic condition, a diagnosis of epilepsy is appropriate, and treatment is necessary. Depending on the seizure types, history, physical, and neurologic examination, further diagnostic evaluation is indicated, as discussed subsequently.

#### **Epileptic versus Nonepileptic Seizures**

Misdiagnosis of other entities as epilepsy leads to social stigma, a failure to recognize and treat the true underlying pathology, and the unwarranted risk and expense of antiepileptic drugs. Because epilepsy is a chronic condition requiring continuous treatment for a substantial time, misdiagnosis can result in unnecessary long-term pharmacologic treatment. Paradoxically, in underdeveloped communities where neurologic care is substandard relative to developed regions, the misdiagnosis of epilepsy is frequent and the patient may be at a lesser risk of iatrogenic harm when managed by “traditional healers.” Of course, neither situation is acceptable, and the remainder of this chapter will discuss ways to improve neurologic care through an appropriate diagnosis of epilepsy. Refer to Chapter 2 for a detailed discussion of the differential diagnosis of

#### **KEYPOINTS**

- It is common in developing countries for generalized tonic-clonic seizures to be the only ictal event of particular concern to individuals and their families. Consequently, a patient presenting with a single generalized tonic-clonic seizure does not necessarily have an acute condition. Partial seizures may have occurred but were not recognized as such.

**KEYPOINTS**

- The possibility that epileptic seizures may be secondary to some acute or subacute, yet treatable, cerebral insult must be kept in mind by physicians practicing in developing countries.
- Seizures that do not have generalized tonic-clonic components are often not recognized as epileptic.
- Open and interactive discussion during the consultation is also important as a teaching tool for both the patient and relatives. It is essential that the patient and family members have a simplified understanding of the specific behaviors that the doctor considers to be a seizure, for purposes of clinical follow-up.

epilepsy and nonepileptic entities, particularly those that are common in developing countries.

**Seizures versus Epilepsy**

As described in Chapter 1, not all *seizures* indicate the presence of *epilepsy*. “Epilepsy” is the chronic persistence of a brain dysfunction, which leads to recurrent epileptic seizures. Some individuals may have a single epileptic seizure, while others may have a few recurrent seizures during life, always related to a specific transient provoking factor. These people do not have epilepsy. Examples include generalized seizures in susceptible individuals under conditions of alcohol withdrawal or prolonged sleep deprivation, or excessive use of illegal stimulant drugs such as cocaine or amphetamines. Still others may harbor specific lesions, such as cortical tumors or parasitic cysts, which may clinically present with a few seizures, but whose tendency to further episodes is eliminated by resection or medical treatment of the lesion.

**Underlying Treatable Causes**

The possibility that epileptic seizures may be secondary to some acute or subacute, yet treatable, cerebral insult must be kept in mind by physicians practicing in developing countries (see also Chapter 3). In these regions, the prevalence of symptomatic seizures and epilepsies is higher than that found in developed countries. Thus, an underlying treatable cause for new onset seizures should be sought and the condition managed as early as possible, reducing the risk of permanent injury and epilepsy.

In developing countries, febrile illnesses such as malaria and pneumonia are associated with febrile convulsions and should be diagnosed and treated early. Mass lesions associated with tuberculosis or neurocysticercosis should always be considered as a possible etiology of new onset seizures both in adults and children in regions where these conditions occur frequently. Indeed, cysticercosis remains a major public health problem in many Latin American, Asian, and African regions. Other potentially preventable etiologies with a major representation in developing countries include head injuries,

infections, and perinatal trauma. Finally, congenital CNS abnormalities, tumors, vascular lesions, and metabolic disorders are responsible for variable proportions of symptomatic seizures. While the etiologic diagnosis of the epilepsies may be more difficult in developing countries, due to limited investigative resources, many can be diagnosed on the basis of simple clinical and epidemiologic knowledge, complemented by nonsophisticated serologic studies.

**Seizure Types/Epilepsy Syndromes**

One of the major difficulties in the optimal treatment of epileptic seizures and epilepsy syndromes in developing countries is that the classification framework proposed by ILAE (see Chapter 2) is often not taken into consideration by medical personnel. This leads to underdiagnosis of potentially treatable conditions and to undesirable therapeutic short cuts, such as the use of similar antiepileptic drug regimens, in similar dosages, irrespective of the seizure type or the underlying disorder giving rise to the seizures. Adequate seizure and syndrome diagnosis can simplify the diagnostic workup, provide prognostic information, and direct treatment decisions.

**HISTORY-TAKING AND THE DIAGNOSIS OF EPILEPTIC EVENTS**

To understand the nature of a potentially epileptogenic event and to have an approximate idea of the seizure type, one must understand the circumstances surrounding a seizure. Seizures that do not have generalized tonic-clonic components are often not recognized as epileptic. Thus, it is important for the physician to know the semiologic evolution of the most common seizure types and to actively interact with the patient and witnesses during history-taking. Specific, direct questioning of key semiologic features is often the only possible way to elicit a reliable history. The diagnosis of epilepsy and determination of seizure type should be made on the basis of history and examination with technological studies used to support diagnosis, particularly when the results of such studies will influence management decisions. Open and interactive discussion during the consultation is also important as

a teaching tool for both the patient and relatives. It is essential that the patient and family members have a simplified understanding of the specific behaviors that the doctor considers to be a seizure, for purposes of clinical follow-up.

## About the Seizure

### *The Circumstances*

An epileptic seizure can occur anywhere, anytime. A description of the circumstances should first determine whether the seizure is a new acute event, or whether it is a typical seizure for someone with long-standing epilepsy. If it is a single event, it is paramount to identify and then treat acute symptomatic seizures that reflect a potentially life-threatening underlying condition. It is also necessary to distinguish between provoked seizures that are not likely to recur, and those that might indicate the initial symptom of a chronic epileptic disorder. The physician should collect data on seizure evolution and also on the usual circumstances surrounding seizure occurrence. This also allows the application of measures to prevent both the attacks and their potential harmful consequences. The physician should elucidate precipitating events such as menses, sleep deprivation, alcohol intake, emotional changes,

delay in taking medication, or excessive physical exercise. Furthermore, because seizures occurring only during sleep are associated with smaller risks than those occurring when the patient is awake, the relation to sleep-wake cycle is an important piece of information. Finally, the possibility of seizures occurring in situations where the patient may be particularly at risk should be anticipated to prevent tragic events such as burns or drowning.

### *Questioning the Patient*

Peri-ictal information obtained from the patient is frequently incomplete or equivocal. However, any symptoms preceding seizure onset for minutes to hours should be noted, including tiredness, sleepiness, dizziness, malaise, headache, or nervousness. When consistent, symptoms such as these can reflect preictal prodromal states and can warn the patient that a seizure is approaching. Even though this information is often volunteered, its potential meaning may not be realized and should be emphasized. It is important to differentiate these prodromal symptoms from the aura. It is helpful to explain from the start the several possible “phases” in the evolution of a seizure, and then guide the patient through that.

## KEYPOINTS

- Recurrent, unexplained injuries, particularly burns, should raise the suspicion of seizures. If a history of seizure is not offered voluntarily, a direct question about seizures, using local (not medical) terminology, should be addressed to the patient and care providers. This question must be asked in a private setting. In open wards with other patients and families nearby, the discussion should take place outside of the ward.

## CASE STUDY

**Presentation:** A 6-year-old female was seen on the Burn Unit for a brief, generalized seizure. She had been admitted 4 days prior with full-thickness burns over >30% of her body, primarily on her upper trunk. Initially, the consultant suspected this was an acute, symptomatic seizure related to metabolic derangements associated with such a severe injury.

The child was surprisingly awake, alert, and oriented. Her neurologic examination was unremarkable.

Review of the medical record indicated multiple admissions and visits for injuries including facial lacerations from a fall, a clavicle fracture, and an earlier burn to her right foot. The family had been unable to adequately explain the circumstances of these injuries and child abuse was suspected.

On direct questioning, the grandmother admitted reluctantly that the child had had “fits” almost weekly for the past 3 years. The injuries were all seizure-related. The family clearly felt ashamed about the child’s condition and were fearful that they would be ostracized if it was known that someone in the family suffered from epilepsy. They were surprised when informed that medications might stop or at least decrease the number of seizures experienced.

**Treatment/Outcome:** Oral phenobarbital was initiated and no further seizures occurred. Unfortunately, the child’s wounds became infected and failed to respond to available treatments. She died of sepsis 2 weeks later.

**Comment:** Fear of stigma and lack of knowledge about epilepsy treatments may result in concealment of epilepsy and tragic, avoidable deaths undoubtedly occur. Recurrent, unexplained injuries, particularly burns, should raise the suspicion of seizures. If a history of seizure is not offered voluntarily, a direct question about seizures, using local (not medical) terminology, should be addressed to the patient and care providers. This question must be asked in a private setting. In open wards with other patients and families nearby, the discussion should take place outside of the ward.

**KEYPOINTS**

- The dread of a generalized tonic-clonic seizure is so culturally ingrained that minor ictal phenomena (for instance, the staring and automatisms of complex partial seizures) are often neglected or entirely missed.

In addition, one should attempt to identify any pattern of recurring, potentially seizure-provoking factors. The latter most often will include sleep deprivation, excessive tension (preoccupation), alcohol abuse or withdrawal, missed dosages of antiepileptic medications, and hormonal changes occurring in the catamenial period. Some of these factors are related to poverty or low levels of education and can be difficult to prevent.

The patient should be asked explicitly about the presence of an aura, and the most common types of auras should be described as examples. If unusual symptoms appear just before loss of contact with the environment or loss of consciousness, these symptoms should be characterized in detail. The possibility that such symptoms do represent auras is increased by their occasional occurrence as the sole “ictal” manifestation. Events following the aura may or may not be perceived by the patient. Loss of awareness is characteristic of complex partial seizures, which propagate predominantly through limbic/subcortical pathways. In partial motor seizures that secondarily generalize, on the other hand, the patient can often relate the sequence of body parts involved before loss of consciousness. Specific questioning on the clonic or tonic (sustained) nature of head turning or limb contractions can provide important clues to lateralization and localization of the cortical generators. Likewise, the occurrence of recurrent, brief episodes of loss of awareness or of early morning myoclonus are important clues to the presence of an idiopathic generalized epilepsy syndrome, even in the absence of tonic-clonic generalized seizures.

The functional impact of the seizures can be inferred from frequency and severity, as well as postictal dysfunction and symptoms such as headache, somnolence, malaise, depression, and lack of initiative. Even mild complex partial seizures can have a disabling effect for hours following the attack, attesting to the broad neurochemical changes that can be produced by a seizure.

***Physical Consequences***

Culturally, epilepsy is equated with generalized tonic-clonic seizures and their phys-

ical consequences. The spectacle of a generalized event associated with frothing, tongue biting, and urinary incontinence has a tremendous impact on bystanders and relatives. The idea that someone may be suddenly “seized” by such a horrendous attack contributes to the stigma of epilepsy. Patients and relatives can be offered some assurance that such generalized attacks are often the easiest to bring under control with adequate antiepileptic drug management, provided compliance is also adequate. Furthermore, it should be emphasized during history taking that most seizures do not reach the stage of secondary generalization, and thus, minor features should also be identified and reported. The dread of a generalized tonic-clonic seizure is so culturally ingrained that minor ictal phenomena (for instance, the staring and automatisms of complex partial seizures) are often neglected or entirely missed. Because complex partial seizures may also result in injuries, their identification is important, and specific questions regarding what happens before generalization supervenes should be posed.

Taken in isolation, loss of consciousness, frothing at the mouth, and urinary incontinence could be associated with other types of (nonepileptic) spells (see also Chapter 2). Prolonged vasovagal or cardiogenic syncope, for instance, can be associated with urination, and even with tonic stiffening and frothing at the mouth. However, the whole picture of sequential tonic and then clonic violent movements associated with tongue biting, frothing, and urination is very characteristic of a generalized epileptic seizure. As discussed in Chapter 8, relatives and colleagues should be instructed on ways to protect the patient against injuries during a seizure and when urgent medical assistance is required.

***Questions to Accompanying Persons***

Because the patient is at least partially unaware of his or her environment during the majority of seizures, reliable information on the circumstances and details of the attack need to be obtained from accompanying persons. The educational level and the possible biases of the informant should be

taken into account. Important data include clues to localization of the ictal generators (e.g., patient's mention of a sudden feeling, a partial motor onset, staring followed by orolimentary automatisms), as well as evidence that might help confirm the episode as epileptic (or raise the suspicion of a nonepileptic fit). In this regard, some features that could more likely pertain to syncope or psychogenic seizures should be specifically questioned (see Chapter 2).

Asking what kind of help has been provided to the patient during seizures, particularly during complex partial or generalized tonic-clonic attacks, also offers the opportunity to provide instructions on the most appropriate measures to be taken in future episodes. These include the description of measures to protect the patient against unnecessary injury, the correction of misconceptions regarding the safety of handling the patient's secretions (i.e., the fact that saliva and urine do not transmit epilepsy and that objects should not be forced into the mouth), and the need to avoid interference with the patient's movements which could cause combative behavior during the immediate postictal period. In addition, a description of any treatment applied at the time of a seizure should be elicited. Education about these points can then be provided.

Because seizures may be precipitated by excessive alcohol use or withdrawal, as well

as by consumption of central nervous system-active drugs, any information regarding such treatments is of value. A history of similar episodes in the past, in the same context, can give a clue to a harmful behavioral pattern that should be specifically modified through treatment.

### *Family Perceptions about the Seizures*

Different attitudes can be observed from the family of a patient with epilepsy. In a few isolated societies of the developing world, epilepsy is sometimes seen as a manifestation of supernatural powers, thus leading to a "positive" appraisal of the recurring seizures. However, in most instances, families of persons with epilepsy "overprotect" the patient, and directly or indirectly support a kind of marginalization from the mainstream of society. Close relatives at times are ashamed of a seizure occurring in public places and tend to isolate the patient from such environments. Globalization of the access to information is changing this picture to the benefit of the people with epilepsy. A more positive attitude of the family is now seen in some societies. Common prejudices, such as the belief that an epileptic woman should not get married, are declining in regions where social marketing has successfully provided epilepsy education to the public.

### KEYPOINTS

- Close relatives at times are ashamed of a seizure occurring in public places and tend to isolate the patient from such environments.

### CASE STUDY

**Presentation:** This woman is now 40 years old. She has suffered from generalized tonic-clonic seizures since the age of 9, and was not treated with modern antiepileptic drugs until she was 27. Since age 19, her seizures very often occurred while cooking meals over a wood fire in her family's kitchen. She experienced many falls into the fire with severe burns.

**Evaluation:** She did not see a physician until age 27 because in her African cultural context, a person falling into the fire during a fit is considered to be "an untreatable patient." Healers had convinced her family not to go to a health center, despite the opinion of one of her brothers, who later became an MD. He eventually succeeded in convincing their mother to "secretly" try a modern approach at the University hospital. On clinical examination, this lady presented with several burns in various parts of her forearms, trunk, back, and legs. Several EEGs were abnormal.

**Treatment:** The best results were obtained with a combination of phenobarbital, sodium valproate, and lorazepam. Her MD brother is supplying the drugs.

**Outcome:** This woman now has one to three seizures a month, rather than the 10-a-day she had prior to treatment. Her skin lesions are still apparent, and some have developed cheloid patterns, which continue to embarrass her.

**Comment:** This case illustrates a dramatic reality in some developing countries. In certain cultural contexts, it is believed that "when a person seizes and falls into a fire, that means that it is a resistant case and that there is nothing the traditional healer can do." This can lead to death or to severe injuries, as in this case. Only very progressive educational programs can reduce the incidence of such disabling consequences.

**About Remote History**

In addition to the elicitation of aspects that will bear on the etiology of the epilepsy and on precipitating or protective factors that increase or decrease the chances of seizure recurrence, the medical history must determine whether a given seizure was an acute, unexpected, event in a person without a history of recurrent seizures or simply another seizure in a patient with chronic epilepsy. This is of particular importance in areas where resources are limited, because the need for more costly evaluations is greater in those presenting with a single seizure that could indicate an acute life-threatening condition, than in those with known chronic epilepsy.

***The Medical Past of the Patient: Birth, Development, Immunization, and Medical Antecedents***

It is important to collect information on the patient's past medical history, including conditions of gestation (duration, intercurrent illnesses, and use of prescription, over-the-counter, or illicit drugs), delivery (including where and by whom, whether the baby cried immediately, and the need for resuscitation), and early postnatal period. In addition, age of acquisition of developmental milestones should be assessed. In developing countries, one of the most preventable etiologies of epilepsy and epileptic encephalopathies is poor prenatal and perinatal care. Mismanagement due to lack of facilities or personnel is vexingly frequent, and the circumstances of pregnancy and delivery should be specifically questioned. Furthermore, events such as episodes of high fever due to systemic infections or a past history of meningitis, cerebral malaria, febrile convulsions, head trauma, or other cerebral injury, should be sought.

***Frequency and Provoking Factors***

As mentioned in other parts of this volume, close attention should be paid to the possible relationship between seizure occurrence and seizure-provoking factors. Developing country environments increase the likelihood of several factors that can precipitate seizures. Foremost is suboptimal compli-

ance with the intake of antiepileptic drugs. Such noncompliance may be driven by cultural factors (such as the perception by relatives that the patient is taking too much medication, or that the medication will prove harmful in the future), by the inconsistent availability of antiepileptic medications in public pharmacies, and/or by inadequate personal resources to access these medications. The temporal relationship between seizure occurrence and missed medication, as well as with other known provoking factors (such as excessive alcohol intake and sleep deprivation) should always be considered.

***Illicit Drug Abuse and Other Habits***

Illicit use of central nervous system-active drugs is a universal phenomenon. Drug producing and poorly enforced drug-restricting regulations lead to major drug-related casualties in developing countries. Large-scale drug availability leads to high rates of drug use and abuse, which in turn may produce both seizures related to overdose and secondary brain lesions, causing subsequent epilepsy. Furthermore, persons who already have epilepsy may experience periods of seizure recurrence or increase in frequency when using illicit drugs. Alcohol use, abuse, and withdrawal can cause similar problems. History should clarify whether drug-related seizures in a given individual represent the overuse of a stimulant drug or the sudden withdrawal of a sedative drug in someone who is known to have epilepsy, or if the seizures are an acute reaction of a normal brain. In the latter case, a diagnosis of epilepsy is unwarranted, but in either situation, counseling should be instituted to prevent further seizures.

***Family History***

Genetic factors can play a significant role in the occurrence of epilepsy in a given individual. There are several levels of genetic predisposition to seizures, which range from the presence of sporadic seizures or epilepsy in other family members, to the presence of electro-clinically defined epilepsy syndromes with a proven or strongly suspected genetic etiology. Thus, the clinical history should include data on

the occurrence of seizures in other family members, ideally complemented by details on the types of seizures and specific diagnoses given for those affected. A sound genetic history concerning such details is very difficult in developing countries and data in patients' files are often insufficient. However, a detailed family history, including information on febrile convulsions, should be obtained. Although syndrome-specific details may not be available for affected family members, the simple fact that several members of a given family have experienced seizures may be of diagnostic and therapeutic value.

A thorough family history may be difficult to obtain. In many developing countries, family members may attempt to conceal from other relatives that a particular child or adolescent has or had seizures. Finally, the issue of consanguineous marriages should be considered. Such unions are frequent in some ethnic groups and may lead to epilepsy, usually as part of a more severe neurologic syndrome.

#### ***Previous Events That Might Have Been Seizures***

Once a firm suspicion of epilepsy or of a single epileptic seizure is raised, the occurrence of previous events that might have been seizures but were not recognized as such should be explored. This common situation within the context of developing countries has already been mentioned above, namely, the ignorance that partial seizures with minor manifestations are also manifestations of epilepsy. Thus, one has to ask the patient and relatives about previous recurrent episodes of staring, minor automatisms, periods of confusion following some type of strange behavior, focal motor seizures without secondary generalization, and tongue-biting or incontinence during sleep. In addition, the patients should be asked about recurrent visual, auditory, somatosensory, olfactory and gustatory sensations, as well as about psychic phenomena that could represent auras. Patients and relatives often miss these minor episodes, and not uncommonly, a diagnosis of epilepsy can be traced back to several years.

#### **Cultural Resistance to Providing an Accurate History, And Cultural Clues That Aid Diagnosis**

A family may attempt to hide people with epilepsy from society. Such efforts make it more difficult to obtain a reliable history about the actual nature of the seizures, the degree of control with medication, and the presence of epilepsy in other family members. Only education can overcome these attitudes. Campaigns such as the ILAE/IBE/WHO global campaign to bring epilepsy "Out of the Shadows" appropriately target this problem.

In some societies, scarifications of epileptic patients are used to designate aspects of their disorder. For example, scarifications in Togo, West Africa, are done at the frontal root of the hairline for subtle or simple cases. When seizures become severe, the scarifications are more visible on the forehead and the cheeks. In Zambia, tattoos or scarifications are also common on the region of the body where focal seizures begin, i.e., the hand with Jacksonian seizures.

#### **Physical Examination**

##### ***General Physical Examination***

A complete physical examination should be conducted during the evaluation of patients with possible epilepsy. The examination can give clues to the presence of heart or any other systemic disease that could be implicated either in the generation of acute seizures or in secondary brain injury leading to chronic epilepsy. A detailed discussion of these entities is beyond the scope of this text, and only a few entities will be highlighted. The general appearance of the patient can suggest a state of dehydration or show diffuse edema, suggesting the presence of electrolyte abnormalities. This is important in poorer regions of the globe, where malnutrition can lead to severe electrolyte imbalance. A history of diabetes mellitus should prompt a search for additional signs of dehydration that can accompany severe hyperglycemia. Arrhythmias, valvular disorders, or cardiac failure can all be sources of cardiac emboli that can lead to brain infarcts. Infarcts can occur without clinical deficits and may manifest only with

#### **KEYPOINTS**

- A thorough family history may be difficult to obtain. In many developing countries, family members may attempt to conceal from other relatives that a particular child or adolescent has or had seizures. Finally, the issue of consanguineous marriages should be considered. Such unions are frequent in some ethnic groups and may lead to epilepsy, usually as part of a more severe neurologic syndrome.
- The examination can give clues to the presence of heart or any other systemic disease that could be implicated either in the generation of acute seizures or in secondary brain injury leading to chronic epilepsy.

**KEYPOINTS**

- When a patient is suspected of having neurocysticercosis, one should carefully look for tiny subcutaneous nodules. A nodule can even be biopsied. Simple X-rays can be used to show the presence of calcified cysts.

seizures. Chagas' disease, which is endemic in many developing countries, is a common etiology of cardiac problems that can cause seizures. Patients with severe, chronic obstructive pulmonary disease can have periods of hypoxia or hypercapnia that can lower the seizure threshold. In addition, stigmata of chronic liver and kidney disease in the skin, extremities, or abdomen should raise suspicion of seizures in the context of liver or renal failure. Of course, an objective physical examination is much facilitated by a complete history.

***Examination under Special Conditions***

The patient's age can focus the physical examination. For instance, children presenting with seizures should have their body temperature checked and receive a thorough evaluation for infections, including examination for the presence of meningeal signs. In developing countries, particularly in regions with endemic parasitosis or malnutrition, physical signs related to chronic diarrhea, malnutrition, skin lesions, and other related abnormalities often provide a clue to the etiology of the seizures or epilepsy, without the need for costly laboratory tests. Similarly, the physical examination of elderly patients should focus on evidence of actual or impending organ failure, and on physical signs that can detect risk factors for specific diseases common in older people (e.g., hypertension, chronic obstructive pulmonary disease).

When a patient is suspected of having neurocysticercosis, one should carefully look for tiny subcutaneous nodules. If facilities are available, a nodule can even be biopsied to look for evidence of cysticercal granuloma. Occasionally, simple X-rays can be used to show the presence of calcified cysts, especially when the thigh regions are X-rayed. Rarely, muscle enlargement has also been documented secondary to cysticercal cysts in the affected muscles.

After head trauma, it is crucial to examine the patient for physical clues of acute intracranial hemorrhage or skull fractures that can lead to cerebrospinal fluid fistulae and predispose to infections. The presence of hemorrhage through the ears or bruises around the orbits suggests skull base frac-

ture, while lacerations around the temples should raise the suspicion of middle meningeal artery rupture, with a risk of extradural or subdural hematomas. Of course, the presence of pupillary abnormalities as well as the level of consciousness should be continuously checked.

***Examining the Patient after a Seizure***

When possible, a physical examination should be performed immediately after an attack, aimed at identifying signs of injury, cyanosis, cardiac rhythm abnormalities, acute motor deficits, and the level of consciousness. The presence of bruises, tongue or other oral lesions, as well as of prolonged stupor or obtundation suggests that the seizure was indeed epileptic and generalized. Vital signs and cardiac rhythm should be checked. Any focal motor or sensory deficits or aphasia should be noted, because these may represent acute postictal phenomena with significant localizing value (see below).

***Seizure Sequelae***

Seizure sequelae can represent either neurologic deficits provoked by acute neuronal exhaustion and other neurochemical changes depressing neuronal function, or injuries sustained during the actual or previous seizures. Scars may offer evidence of previous seizure-related injuries. The presence of scars probably indicates the need to improve seizure control. Scar identification offers an opportunity to educate the patient and his or her relatives about measures to avoid further similar injuries. For example, the patient should be instructed to stay away from open fires, at least until seizures are reliably controlled. Other preventive measures are dealt with in Chapter 8. Some patients may experience protracted postictal behavior abnormalities, including aggressiveness, irritability, or overt depression. The identification of these motor and cognitive abnormalities assists relatives in understanding the nature of these abnormalities, may decrease the tendency of family to blame the patient, and provides the physician with an opportunity to discuss the best way to manage seizures.

## NEUROLOGIC EXAMINATION

The neurologic examination is different depending on whether the patient presents with a single seizure or is known to have epilepsy with chronically recurrent seizures. In the former scenario, an active search should be made for the presence of meningeal signs, papilledema, and focal motor deficits that would indicate an acute brain insult that should be promptly diagnosed and treated. On the other hand, in patients known to have epilepsy, the physical examination will primarily be directed at signs of chronic brain lesions. The rational use of scarce investigative resources in developing countries requires prioritizing neuroimaging studies to those patients whose physical and neurologic examination present abnormalities suggestive of acute or progressive intracranial localized lesions. The presence of hemiparesis and hemiatrophy usually attests to remote hemispheric insult, usually during the pre- or perinatal period. In contrast, hemiparesis without hemiatrophy suggests a more recent lesion that should be fully evaluated. Several investigators have identified a mild “emotional” facial palsy, contralateral to the side of onset of temporal lobe seizures. The presence of clinically identifiable mental retardation is also a useful sign, suggesting either a diffuse encephalopathy or a unilateral (usually hemispheric) disease with severe secondary impact on overall brain function. Children and adolescents with mental retardation are at an increased risk for seizures. The cognitive status, an important part of the initial physical examination, should be assessed during each outpatient visit. A careful appraisal of the age of acquisition of psychomotor milestones, taken in conjunction with the rate of progress the patient is making at school or when in contact with peers, can give a fairly reliable idea of the presence and severity of mental retardation. Furthermore, skin lesions can give clues as to the underlying nature of an epileptic disease. Café-au-lait spots, hypochromic or hypomelanotic lesions, facial hemangiomas, and linear nevus sebaceum are all associated with intracranial lesions that give rise to epilepsy. Finally, fundoscopic examination can reveal lesions associated with diseases

that cause epilepsy. Such examination can disclose abnormalities suggestive either of a phacomatosis (e.g., neurofibromatosis, tuberous sclerosis), a storage disorder (e.g., sialidosis, with a marked cherry red spot in the fundi), a metabolic disease (e.g., the retinitis pigmentosa associated with mitochondrial diseases), or can show signs of intracranial hypertension, indicative of a mass lesion, that should be aggressively diagnosed and treated.

## COMPLEMENTARY DIAGNOSTIC PROCEDURES

### Electroencephalogram (EEG)

One problem with EEG studies in developing countries is that the quality of the recordings and of the interpretation is often substandard. In many regions, recordings are performed by poorly trained technicians, and interpretation is done in a hurry. Unfortunately, as in the industrialized world, EEG is too often overused as a way of increasing medical income without demanding much time and effort. In addition, the EEG is erroneously perceived by patients and relatives as a reliable measure of the evolution of the epileptic disorder, and this perception is encouraged by some physicians. Conversely, the EEG tends to be underused (or less available) for some purposes due to restrictions that have little to do with unquestionable medical need. These situations must be taken into account when discussing indications and cost-effectiveness of the EEG in developing countries.

### *EEG in the Diagnosis of Epilepsy*

An abnormal EEG is not essential for a diagnosis of epilepsy, and it should never substitute for careful history-taking. In most instances, the diagnosis of epilepsy is clinically not challenging, and EEG has a limited role for this purpose. On the other hand, there are situations in which the physician faces a difficult differential diagnosis between epilepsy and other disorders that may mimic epilepsy (see Chapter 2), and the EEG can, at times, be helpful to confirm that recurrent spells are most likely epileptic seizures. Nevertheless, EEG findings can be misleading in two ways: They can be

## KEYPOINTS

- The rational use of scarce investigative resources in developing countries requires prioritizing neuroimaging studies to those patients whose physical and neurologic examination present abnormalities suggestive of acute or progressive intracranial localized lesions.
- An abnormal EEG is not essential for a diagnosis of epilepsy, and it should never substitute for careful history-taking.
- A clear diagnostic hypothesis should be in the physician’s mind *before* the EEG is ordered, to avoid the simplistic and often mistaken approach of prescribing antiepileptic medications for people with epileptiform abnormalities on the EEG, without regard for the clinical picture.

**CASE STUDY**

**Presentation:** An 18-year-old woman suffers from headaches, which are often diffuse, but from time to time lateralized to either the right or the left side. The types of pain are variably tension or pulsatile. These symptoms are accompanied by a feeling of drowsiness, blurred vision, and chest pressure. The headaches usually are brief and transient. She has seen several doctors over 3 years, and was diagnosed as “epileptic” without evidence.

**Evaluation:** ECG and blood investigation were normal, except for a moderate anemia. EEG demonstrated nonspecific abnormalities with slow waves and some rapid rhythms. Since the first one, seven more EEGs have been performed: four on the demand of the patient; three from general practitioners. The results were approximately the same, leading to no change in treatment.

**Treatment:** Several types of analgesics and tranquilizers were prescribed. On the basis of the first EEG, a general practitioner prescribed lorazepam once a day.

**Outcome:** Every attempt to stop lorazepam was “unsuccessful” by EEG criteria, despite the fact that the patient was clinically fine with very few headaches.

**Comment:** This case demonstrates EEG abuse, leading to misdiagnosis and maintenance of a nonindicated treatment. It emphasizes the importance of treating the patient and not the EEG.

**KEYPOINTS**

- An understanding of the local epidemiology of epilepsy is of great help in streamlining any evaluation.

normal in a significant percentage of patients with epileptic seizures, or epileptiform discharges may be present in persons who do not have epilepsy. Therefore, a clear diagnostic hypothesis should be in the physician’s mind *before* the EEG is ordered, to avoid the simplistic and often mistaken approach of prescribing antiepileptic medications for people with epileptiform abnormalities on the EEG, without regard for the clinical picture.

#### ***EEG in the Diagnosis of Seizure Type and Syndrome***

In contrast to its limited role in the diagnosis of epilepsy, the EEG can be very important for a correct delineation of the seizure type and/or the epileptic syndrome. In some situations, EEG findings are the key to diagnosis of the type of seizure and have a significant impact on the choice of antiepileptic medication. Thus, interictal EEG patterns can determine whether episodes of loss of awareness or brief automatisms are due to complex partial seizures or to generalized absences. In addition, in patients presenting with generalized motor seizures, the finding of a focal region of electrical abnormality on the interictal EEG can help differentiate a partial epilepsy leading to secondarily generalized seizures from a generalized epilepsy syndrome. This is often difficult from clinical history alone, particularly in those patients who have a genetic or acquired tendency to fast

seizure generalization, and in those in whom these seizures occur during sleep.

The diagnosis of the specific epilepsy syndrome is, sometimes, dependent on the EEG findings. Cost-effective use of EEG requires an understanding of the importance of syndromic diagnosis to patient management. For instance, a diagnosis of juvenile myoclonic epilepsy or of temporal lobe epilepsy due to mesial temporal sclerosis leads to specific actions in terms of further evaluation and treatment, and the identification of the epileptiform and background abnormalities related to the symptomatic generalized epilepsies has significant prognostic impact. In contrast, subdividing specific subsyndromes according to absence seizures in idiopathic generalized epilepsies has much less practical value, and scarce resources for long-term EEG are better directed at other clinical situations.

#### **Laboratory Investigations**

##### ***What Is Useful and What Is Not***

In most cases, epilepsy is unassociated with laboratory abnormalities. Thus, the physician practicing in developing countries must understand those situations in which laboratory investigations are needed: 1) to diagnose specific diseases that may cause epilepsy or isolated epileptic seizures, 2) to detect abnormalities that require adjustments in antiepileptic treatment, 3) to monitor bio-

chemical and hematologic side effects of antiepileptic drugs, and, occasionally, 4) to monitor serum levels of antiepileptic medications.

There are a number of situations in developing countries where the etiology of symptomatic seizures or epilepsies will be diagnosed through laboratory tests. An understanding of the local epidemiology of epilepsy is of great help in streamlining any evaluation. Substandard prenatal care can pose a greater risk for congenital or neonatal hypothyroidism, syphilis, cytomegalovirus, and other infectious diseases, as well as metabolic derangements such as hypoglycemia, and hypocalcemia. Thus, children with seizures in the neonatal period should be at least evaluated for these more common disorders. Poor hygienic conditions at delivery increase the risk for acute bacterial infections, including sepsis or meningitis in the first days or months of life. Hence, seizures in a baby without obvious metabolic derangement should be evaluated with a complete blood cell count (CBC) and a lumbar puncture (LP). Irrespective of age, the possibility of infectious diseases endemic in specific areas should be kept in mind. These include cysticercosis, malaria, and others, which should be diagnosed through specific blood and cerebrospinal fluid (CSF) tests. The need for LP in children presenting with febrile convulsions is specifically discussed below. Cost-efficiency dictates that more sophisticated exams should be used only sparingly when such studies will diagnose rare diseases with a uniformly gloomy prognosis (e.g., the causes of progressive myoclonus epilepsies).

Hematologic and biochemical panels, when available, are indicated prior to the introduction of antiepileptic drugs for patients with known or suspected pre-existing systemic diseases or who start their epilepsy at an older age. Thus, patients with or at risk for hepatic or kidney diseases, abnormalities of the cardiac rhythm, and other systemic illnesses, which can be worsened by specific antiepileptic drugs or whose metabolic impact can interfere with the pharmacokinetics of the antiepileptic medications, should be evaluated before treatment is introduced.

The use of tests to monitor potential biochemical and hematologic side effects of antiepileptic drugs and to monitor serum drug levels requires balancing responsible practice based on clinical experience—with the risk of potential negligence. The majority of patients using antiepileptic drugs do not develop significant hematologic or biochemical abnormalities. Except in circumstances of a previous history of drug-induced abnormalities, very young or very old age, or comedication with other potentially harmful drugs, these “monitoring” tests should be used sparingly, no more often than once a year, unless clinical side effects occur. An example is a patient complaining of easy fatigability, who has ankle edema and uses carbamazepine; he/she should be checked for the presence of hyponatremia. Periodic clinical evaluation for adverse side effects is much more important than laboratory evaluations, and severe idiopathic side effects such as hepatotoxicity and blood dyscrasias usually appear clinically before they are detected by “routine” blood tests.

Routinely repeated, systematic monitoring of antiepileptic drug serum levels is expensive and unnecessary. With a few exceptions, discussed in Chapter 5, adjusting the therapeutic regimen on the basis of drug levels can do more harm than good. A common situation encountered in developing countries is the inappropriate addition of a second or a third antiepileptic drug when seizures persist despite “therapeutic” levels of a first drug, rather than increase of the first drug to effect or toxicity. Another common situation is the reduction of a well tolerated dosage of an antiepileptic drug that is controlling the seizures, because the serum level is above the “therapeutic” laboratory values. Dose adjustments of antiepileptic drugs should be made on the basis of clinical parameters of seizure control and side effects obtained by physical examination and consultation with the patient and relatives. If seizures are well controlled with minimal side effects, there is no need to modify the treatment, irrespective of the serum levels (which should not be even ordered in this situation). If a patient is having seizures and not complaining of side effects, the dosage should be slowly but

#### KEYPOINTS

- Poor hygienic conditions at delivery increase the risk for acute bacterial infections, including sepsis or meningitis in the first days or months of life. Hence, seizures in a baby without obvious metabolic derangement should be evaluated with a complete blood cell count and a lumbar puncture.
- Dose adjustments of antiepileptic drugs should be made on the basis of clinical parameters of seizure control and side effects obtained by physical examination and consultation with the patient and relatives.

**KEYPOINTS**

- In very young children, the risk of herniation is less than the risk of missing an intracranial infection, and LP should be performed when CT is not available.

steadily increased, irrespective of the actual serum levels. Adding a second drug because the level of the first is “within therapeutic range” risks worsening seizure control or provoking side effects, depending on whether the new drug is enzyme inducing or inhibiting (see Chapter 5).

***When to Do a Lumbar Puncture (LP)***

When to do an LP for a *febrile illness associated with a seizure* is of particular interest. LP should be performed without delay on a patient with a febrile illness and signs and symptoms of central nervous system involvement unrelated to the seizure, which raises the suspicion of meningitis or encephalitis, unless there is evidence of increased intracranial pressure and a risk of herniation. In contrast, when there are no signs of central nervous system involvement in a child who has a febrile illness due to some other (usually mild) infection, the occurrence of a seizure will most likely represent a typical febrile convulsion, and an LP is usually not necessary.

The indications for LP are less clear in children with prolonged febrile convulsions or febrile status epilepticus, in whom the probability of a central nervous system infection is higher than with single seizures. The safest approach, especially in children younger than a year in whom meningial signs and symptoms can be absent, would be to perform an LP. LPs can also be performed more often in patients who live in endemic areas for specific infectious diseases with a potential to cause meningitis or encephalitis. In developing countries, this would apply, for example, to people presenting with febrile seizures in areas endemic for malaria. Although the presence of a meningo-encephalitis due to these disorders will usually be signaled by other clinical signs and symptoms such as meningeal irritation, behavioral changes, or abnormal level of consciousness and physical illness, this is often not true in very young infants. Other studies, such as immunologic tests, are not usually performed, and examination of the cerebrospinal fluid will be needed later only for confirmation of the diagnosis, rather than acutely after the seizure. Brain abscesses and the edema surrounding cysts and other

lesions due to infectious disorders can be associated with fever, seizures, and focal signs of neurologic dysfunction. The possibility of meningitis or encephalitis accompanied by focal signs indicates a risk of cerebral herniation, and the decision when and if to perform an LP must be taken on an individual basis. A detailed fundoscopic examination often indicates the presence of increased intracranial pressure that would contraindicate a lumbar puncture, at least until imaging is available. Ideally, patients such as these should have at least a CT scan; however, in very young children, the risk of herniation is less than the risk of missing an intracranial infection, and LP should be performed when CT is not available.

**Neuroimaging**

Cost-effective indications for neuroimaging in epileptic patients living in developing countries depend on balancing several clinical and epidemiologic aspects. One is that a third of all epilepsies are idiopathic generalized syndromes, most likely with a genetic basis, and usually unassociated with structural abnormalities detectable in neuroimaging studies. These patients can be identified by a careful history, physical examination, and EEG. In addition, many chronic epilepsies are due to lesions whose nature can be anticipated by clinical history and neurologic examination. These occur in children, adolescents, and even adults who had well documented pre-, peri-, or postnatal insults, leading to epilepsy and hemiparesis or other focal neurologic deficits, accompanied or not by mental retardation. For these patients, an exact anatomical diagnosis is less relevant, unless seizures are refractory to antiepileptic drugs and surgery is contemplated (see Chapter 7). Conversely, every effort should be made to make an anatomical diagnosis in patients with focal seizures of recent onset, or in those whose seizures become medically refractory over the years.

***Cranial X-ray***

Cranial X-ray is of limited value in the evaluation of epilepsy and should be performed only when CT is not available and there is a suspicion of a calcified lesion associated with the seizures, such as in areas endemic

for cysticercosis. Additionally, other conditions can be associated with intracranial calcifications, including Sturge-Weber disease, tuberous sclerosis, and celiac disease. Although diagnosis of these conditions is usually apparent from general examination, when there is doubt, X-ray can show typical patterns of calcified lesions that render these diagnoses more likely. Finally, the detection of skull fractures following epileptic drop attacks is another potential indication for cranial X-ray.

### CT Scanning

CT scanning detects much more intracranial abnormalities than a skull X-ray, but much less than MRI. CT scans can detect acute bleeding as the cause of acute onset seizures and also calcified lesions associated with infections or phacomatoses. In such situations, plain CT can be better than MRI, at least outside major academic centers. CT can

be used to rule out focal mass lesions in patients with fever, convulsions, and focal signs, reducing the risk of a LP. CT is important to evaluate patients in whom an MRI would be ideal, but is not available for any reason. These are patients with partial epilepsies of recent onset with no obvious etiology, who may harbor a potentially curable progressive lesion. CT scan is almost as useful as an MRI scan to document cysticercal cysts in the brain, although many times when CT scan is equivocal, an MRI scan can still show the presence of cysticercal cysts. Occasionally, when CT shows a single cyst, an MRI can show more than one lesion. MRI is a much better imaging technique for intraventricular cysts. MRI is a superior investigation as compared to CT scan, but is not necessary to diagnose cerebral cysticercosis. Finally, CT has been a great adjunct in the detection of central nervous system disorders related to HIV-AIDS. Toxoplasmosis,

### KEYPOINTS

- CT has been a great adjunct in the detection of central nervous system disorders related to HIV-AIDS. Toxoplasmosis, lymphomas, and other cerebral lesions related to opportunistic infections can cause seizures and are detected or strongly suspected on the basis of a CT scan. Thus, in developing countries, where AIDS is a major public health problem, CT is still useful in the evaluation of acute seizures, allowing prompt introduction of specific treatment related to an array of HIV/AIDS-related brain lesions

### CASE STUDY

**Presentation:** A 43-year-old woman was seen in the ER for repeated seizures occurring with fever, which started that morning. For 2 days, she had been suffering from headache, vomiting, and drowsiness. She had been having right partial motor then secondarily generalized seizures for two years. There was a history of blood transfusion prescribed for an operation 7 years ago. HIV2, HTLV-1, and syphilis seropositivity had been detected and confirmed 8 months before. She presented at that time with acute transitory meningitis, which resolved after 5 days of antibiotic therapy.

**Evaluation:** Three different EEGs showed diffuse slow waves and inconstant spikes. There were no MRIs in her country, and she could not afford a CT scan. A cranial X-ray showed small calcifications in the right hemisphere.

**Treatment:** She was treated with phenobarbital, then, when seizures continued, carbamazepine 400 mg twice a day. She was placed on a ward, because there was no room in the intensive care unit. She received diazepam IV, phenobarbital IM, and trimethoprim and sulfamethoxazole associated with antipyretic medications.

**Outcome:** Her situation worsened and she was transferred after 2 days to the intensive care unit and placed on oxygen because of aspiration. Due to her advanced clinical status, it was too late for her to benefit from the new drugs. She finally received a free CT scan, which demonstrated multiple associated hyperdense and heterogeneous lesions predominantly in the left hemisphere, strongly suggestive of toxoplasmosis. Her condition deteriorated with continued right partial secondarily generalized seizures, then status epilepticus, and she died before she could benefit from anti-toxoplasmosis therapy.

**Comment:** This case illustrates an increasing reality in many developing countries and poses the problem of neuro-AIDS and its associated epileptic seizures. What is due to HIV itself and what is due to opportunistic infections? Transient meningitis and progressive encephalopathy are often suspected and reported, but in many developing countries, a high incidence of secondary infectious diseases can colonize the brain and present as an epilepsy syndrome. The appropriate approach for this patient would have been to strongly suspect opportunistic infection by *Toxoplasma gondii* at an early stage, and to begin a therapeutic trial of pyrimethamine and sulfadiazine (or clindamycin if the patient is allergic to sulfadiazine). It was appropriate to avoid doing lumbar puncture without evidence that there was no brain mass, which only a CT scan could demonstrate. If obtained, the cerebrospinal fluid would have shown a mild to moderate pleocytosis and elevated protein content. Brain biopsy can also be diagnostic. With early use of CT scan to support the hypothesis of brain toxoplasmosis, early anti-toxoplasmosis treatment (and sustained lifelong prophylaxis with trimethoprim/sulfamethoxazole or clindamycin/ pyrimethamine), continued antiepileptic therapy, and government-subsidized antiretroviral drugs, the prognosis would have been much better because recurrence of such treatable opportunistic epileptogenic brain lesions can be prevented.

**KEYPOINTS**

- The majority of patients presenting with seizures to an outpatient clinic or doctor's office (as opposed to a hospital emergency department) do not have any major acute disorder and, even when this is suspected, knowledge of the epidemiology of the region where the physician is practicing is helpful in streamlining the clinical approach.

lymphomas, and other cerebral lesions related to opportunistic infections can cause seizures and are detected or strongly suspected on the basis of a CT scan. Thus, in developing countries, where AIDS is a major public health problem, CT is still useful in the evaluation of acute seizures, allowing prompt introduction of specific treatment related to an array of HIV/AIDS-related brain lesions.

**MRI**

MRI is the ideal neuroimaging modality to evaluate patients with epilepsy. From a cost-effective perspective, however, the role of MRI in this evaluation should be placed in the context of the previous discussion regarding the place of neuroimaging in epilepsy in general, the applications of CT scanning, and the difficulties in obtaining an MRI in developing countries.

MRI is very important in two situations. One is when a progressive lesion not detected by CT is suspected in patients with partial seizures of recent onset accompanied by focal neurologic deficits. The other concerns patients with refractory epilepsies in whom surgical treatment is contemplated. A significant number of nonprogressive epileptogenic lesions is detected by MRI and often missed by CT, the malformations of cortical development being the most notable example. In these patients, MRI is *irreplaceable* for identifying surgically treatable epilepsy syndromes and diseases, to help determine the epileptogenic zone, and to delineate the amount of tissue to be resected. The issue of surgical treatment of the epilepsies is dealt with in Chapter 7.

**Functional Imaging**

There is little or no indication for functional imaging studies in the evaluation of epilepsy outside tertiary centers involved in the workup of surgical candidates (see Chapter 7). Most instances in which single photon emission computed tomography (SPECT) is used to study patients with epilepsy outside the context of presurgical evaluation represent inadequate utilization of resources, which should be discouraged, even more so in developing countries.

**HOW TO PROCEED WHEN YOU DO NOT HAVE ACCESS TO COMPLEMENTARY TESTING**

History, physical, and neurologic examinations alone often suffice for a diagnosis of the seizure type and the most likely epilepsy syndrome, thus allowing a successful treatment in patients with epilepsy. The majority of patients presenting with seizures to an outpatient clinic or doctor's office (as opposed to a hospital emergency department) do not have any major acute disorder and, even when this is suspected, knowledge of the epidemiology of the region where the physician is practicing is helpful in streamlining the clinical approach. Thus, in endemic areas, patients should probably receive antiparasitic medication if they present acutely with seizures and complementary testing is not available. These clinical and empirical measures are important from a public health perspective, and also to single out those patients in whom all efforts should be undertaken to transfer to a larger center and perform complementary testing.

**CONCLUSIONS**

The diagnostic approach to the epilepsies is a good example of how much history-taking and clinical examination can still be of practical and pragmatic use in neurology. The approach, however, differs depending on whether the seizure is an acute single event or a chronic condition that has just come to the attention of the medical practitioner. A large number of diagnostic and therapeutic steps can be taken effectively on clinical grounds alone, and this has been the unifying theme of this chapter. Neurologists practicing in developing countries should excel in the clinical approach to persons with seizures and epilepsy, because this is the only way to rationalize the use of the scarce technological resources that should be reserved for patients posing specific diagnostic and treatment challenges.

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## PRACTICAL APPROACHES TO TREATMENT

The ultimate objective in the management of people with epilepsy, in all regions of the world, is treatment to prevent recurrence of attacks, reverse cognitive and motor impairment, and improve quality of life. Decisions regarding treatment include when to start and when to stop treatment, how to select the appropriate antiepileptic drugs (AEDs), and how to monitor efficacy and adverse events that require changes in therapy. In developing areas of the world, negative perceptions related to a diagnosis of epilepsy and to the chronic use of medication are more common than in the industrialized world, as are problems posed by reduced AED availability, the impact of AED cost, unreliable supplies of AEDs, and difficulties in complying with periodic outpatient visits. Consequently, in general, physicians in the developing world should have a higher threshold for initiating pharmacotherapy after a single unprovoked seizure, and a lower threshold for withdrawing pharmacotherapy after a given period of seizure freedom. These decisions are often complicated in developing countries by the limitation of diagnostic resources, such as neuroimaging and EEG, which makes it more difficult to determine whether events in question are epileptic seizures warranting treatment with AEDs. This chapter considers these issues in the management of patients with different types of epileptic disorders in the context of the various treatment options that may be available in countries with limited resources.

### WHEN AND HOW TO START TREATMENT

#### Differential Diagnosis, Risk of Seizure Recurrence, and Psychosocial Morbidity

Epilepsy, by definition, presents the threat of recurrent seizures, often in an unpredictable way. AED treatment helps decrease the risk

of such recurrences. However, because patients will often present after a single event, and not everyone with a single seizure goes on to experience further events, the decision on “when to start” AED treatment requires much consideration. In many poor regions of developing countries, ancillary technology that might directly or indirectly help establish the nature of dubious spells (e.g., EEG, imaging studies) will often not be available. Such resource-poor regions may also have limited health care resources with difficult drug accessibility and limited AED options (e.g., only phenobarbital). In these circumstances, when doubts remain on the nature of the first spell, treatment should be withheld until it becomes clear that the episodes are recurrent and their epileptic nature becomes clinically established. As discussed in Chapter 4, the latter is dependent on a detailed, dynamic history.

The need to balance the cost of antiepileptic medication and the potential stigmatizing effect of a diagnosis of epilepsy against the impact of one or more additional seizures must be addressed for each patient individually when making a therapeutic decision. Here, issues peculiar to developing countries come into play, such as the negative attitudes associated with a diagnosis of epilepsy on the one hand, and on the other, the prospect of losing a job should a seizure recur at work (and the difficulty of getting another one later), or the fact that children are usually rejected from nurseries and school if they have seizures. Also, people are often under professional or personal pressure to drive, and tend not to comply with doctors’ requests to not drive while the clinical situation gets clarified. Thus, the overall psychosocial environment of developing countries must be taken into

### KEYPOINTS

- Physicians in the developing world should have a higher threshold for initiating pharmacotherapy after a single unprovoked seizure, and a lower threshold for withdrawing pharmacotherapy after a given period of seizure freedom.
- The need to balance the cost of antiepileptic medication and the potential stigmatizing effect of a diagnosis of epilepsy against the impact of one or more additional seizures must be addressed for each patient individually when making a therapeutic decision.

**KEYPOINTS**

- Start treatment with a single, traditional (older) AED of proven efficacy for the seizure type/epilepsy syndrome in question. This monotherapy approach suits the economic limitations of developing countries, and is usually at least as effective as any other regimen, including the newer and more expensive drugs.
- Most people with epilepsy have seizures that are easy to treat, respond to relatively low doses of all appropriate AEDs, and can usually be managed by primary care physicians.

account in the decision on when to start treatment.

**How to Start Treatment**

Once it is decided that AED treatment should be started, cost-effectiveness is important and should guide drug choice. Ideally, an equation based on seizure type, need for prompt achievement of therapeutic levels, side effect profile, and drug availability should dictate the decision on what drug to use. Unfortunately, in developing countries, drug availability often takes precedence over the other factors (see Chapter 6).

A practical way to follow the general principles mentioned above, for most types of epilepsy, is to start treatment with a single, traditional (older) AED of proven efficacy for the seizure type/epilepsy syndrome in question. This monotherapy approach with a traditional AED suits the economic limitations of developing countries, and is usually at least as effective as any other regimen, including the newer and more expensive drugs. Furthermore, among the older AEDs, some like phenobarbital and phenytoin can be given with a loading dose when necessary, or at least with a full dose. This contrasts with most other drugs, including the new drugs, which usually require that therapy be initiated over a considerable time (“start low, go slow”). A loading dose, however, is rarely necessary for routine initiation of AED therapy, and is usually reserved for acute life-threatening situations such as generalized tonic-clonic status epilepticus.

Some specific epilepsy syndromes in children benefit from the newer drugs where they are available. Infantile spasms respond to vigabatrin, given orally, in over 60% of the cases. Tonic-clonic seizures starting between 2 and 5 years of age, and either repeated or combined with drop attacks, are most likely to result from myoclonic-astatic epilepsy, and require valproate combined with lamotrigine. The same applies for the occurrence of drop attacks with hyperkinesias occurring between 5 and 8 years of age that are likely to indicate Lennox-Gastaut syndrome.

**TRIAGE OF EPILEPTIC CONDITIONS**

Most people with epilepsy have seizures that are easy to treat, respond to relatively low

doses of all appropriate AEDs, and can usually be managed by primary care physicians. The majority of patients with these types of epilepsy will experience no disability if treatment is initiated appropriately, and for some, seizures will eventually remit and medication will no longer be necessary. In reality, ~40% of patients with epilepsy have epileptic seizures that are difficult to control, but for many of these, more intensive pharmacotherapy, or alternative treatments, particularly surgery, will result in seizure freedom. In developed countries, these patients usually require referral to a tertiary epilepsy center to accurately diagnose the epileptogenic abnormality and to initiate effective medical or surgical treatment. Truly refractory epilepsy requires supportive care, at times involving institutionalization where such facilities are available. For these patients, specialized pharmacotherapeutic, and in some cases surgical or other alternative treatments, as well as psychosocial services offered by a tertiary epilepsy center, can greatly reduce the disability associated with residual seizures and maximize quality of life. It is essential that primary care physicians and general neurologists distinguish between these three types of epileptic conditions and effect timely referrals when specialized expertise is necessary and available. Where these services are absent, family counseling to provide a safe environment, and the establishment of local support groups, can be extremely beneficial.

**Easy-to-Control Epilepsies**

About half the people with epilepsy manifest with only a few seizures that are easy to control with low to moderate dosages of traditional AEDs. They consist largely of inherited disorders, which are corroborated by a family history of single seizures or epilepsy. Patients with easy-to-control epilepsies usually present after a first or a few partial or generalized seizures, which may or may not have had convulsive movements. In developing countries, the number of available AEDs may be limited. It is not uncommon that public services provide only one, or at best two, AED(s), which, however, are usually effective in easy-to-control epilepsies. More costly AEDs are also available in many

developing countries, and it is not uncommon that physicians indirectly add an unnecessary significant financial burden to patients and families by prescribing high cost AEDs as first options, even in these mild cases. Education is the key to limiting such practicing and achieving rational AED prescription, particularly in patients with easy-to-treat epilepsy. Inexpensive drugs in monotherapy, often at low doses, will suffice for many patients.

### Hard-to-Control Epilepsies

Successful seizure control in patients with cryptogenic or symptomatic epilepsies is a continuous challenge, and can only be met through 1) adequate clinical diagnosis of the type of seizure and epilepsy syndrome; 2) practical use of the concepts of maximum tolerated AED dosages and serum levels; 3) reasonable anticipation of the level of dosage of the selected AED(s) that will most likely be needed to increase chances of seizure control; and 4) adequate knowledge of AED pharmacokinetics, including the putative favorable and unfavorable interactions with other AEDs.

A correct characterization of the seizure type(s) should take into account the fact that

many people in developing countries believe that epilepsy or an epileptic seizure is present only when there are convulsive, tonic-clonic generalized movements. Thus, people tend to limit their report to these types of seizures. This can be potentially misleading, stressing the need to specifically ask about focal features that might precede generalization. Historical or clinical evidence for a major brain insult, particularly focal motor signs or developmental delay, strongly suggests a symptomatic epilepsy syndrome and anticipates difficulties in achieving complete seizure control with AEDs. In hard-to-control epilepsies, familiarity with the pharmacokinetic properties of AEDs allows prescription of adequate dosages, which are often close to the maximum tolerated ranges, and rational polytherapy when more than one drug is necessary.

If new AEDs have a place in developing countries, it is for these hard-to-control epilepsies. Thus, before assuming medical refractoriness (see below), at least some patients should be tried on the new AEDs. This is contingent on drug availability and the epilepsy syndrome. In practice, new AEDs should be considered for those patients whose epilepsies are both refractory

### KEYPOINTS

- More costly AEDs are also available in many developing countries, and it is not uncommon that physicians indirectly add an unnecessary significant financial burden to patients and families by prescribing high cost AEDs as first options, even in these mild cases. Inexpensive drugs in monotherapy, often at low doses, will suffice for many patients.
- A correct characterization of the seizure type(s) should take into account the fact that many people in developing countries believe that epilepsy or an epileptic seizure is present only when there are convulsive, tonic-clonic generalized movements.
- If new AEDs have a place in developing countries, it is for hard-to-control epilepsies.

### CASE STUDY

**Presentation:** A 48-year-old man has had generalized tonic-clonic seizures since the age of 9, treated with phenobarbital. During the first 10 years, he received 100 mg of phenobarbital with five to seven fits per month. The dose was increased to 150 mg, then to 200 mg, leading to a reduction in seizure frequency to one or two per month. He progressively improved and became totally seizure free. The dose was gradually reduced to 150, 100, and 50 mg per day, then 25 mg every other day.

**Evaluation:** The first EEGs were abnormal, but the latest were normal. No drug level facility was available.

**Treatment and outcome:** The patient is still taking 25 mg of phenobarbital every other day. His weight is 65 Kg. He has been taking this dose for 3 years and is seizure free. His doctor, judging that this dose is very low, decided to stop the medication. The patient disagreed but respected this medical decision. Three weeks later, he came back to his doctor because he had a severe *generalized tonic-clonic* seizure for the first time in 7 years. The medication was restarted and he has done well since.

**Comment:** This situation is very often encountered in developing countries. Many patients receive low doses of AEDs, far below the doses used in the industrialized world, with a good outcome. When patients are taking very low doses of antiepileptic medications, it does not necessarily mean that they do not need them. This does not, however, countermand the overriding recommendation to discontinue medication when possible.

**KEYPOINTS**

- The percentage of the drug within the various body tissues is specific for each drug.

to traditional AEDs and not surgically remediable. Even with an adequate approach to drug selection and prescription, about a quarter to a third of all patients with epilepsy will fall short of complete seizure control.

Early identification of patients with seizures that are unresponsive to medical therapy, but that may be responsive to alternative treatments, can improve the efficacy of these interventions, particularly surgery. In many cases, neurologists can predict medical unresponsiveness after two or three appropriate drug trials have failed due to inefficacy, as opposed to intolerance. Of course, close questioning, tablet counting, and careful examination to verify adherence to the prescribed AED regimen is needed to assure the “refractory” seizures are not simply due to medical noncompliance. In the few developing countries where surgery is an option, it is then important to determine whether the patient has a surgically remediable epilepsy syndrome. This is usually the task of a tertiary epilepsy center. However, one cannot overemphasize the role of the community neurologist in identifying patients who may be helped by epilepsy surgery early enough to avoid irreversible adverse social and psychological consequences of disabling seizures.

**Refractory Epilepsies**

A subset of patients have truly refractory epilepsies, and their early identification is often possible. Of course, in most of the developing world, where surgery and other tertiary facilities are unavailable, many patients with hard-to-control epilepsies are, for practicable purposes, refractory. Nevertheless, in those developing countries where resources for surgical treatment exist but are scarce, it is important to identify truly refractory patients, because surgery is usually palliative at best and is not a cost-effective intervention. These patients typically have diffuse cortical dysfunction resulting from malformations, hypoxic-ischemic encephalopathies, or neonatal meningitis, and their epilepsy is usually associated with developmental delay, as well as with cognitive, motor, and behavioral dysfunction. Seizures are usually frequent and polymorphic, and characteristically include generalized tonic,

atonic, and tonic-clonic seizures, as well as atypical absences and myoclonic jerks. Several age-related medically refractory epilepsy syndromes are recognized, including the severe myoclonic epilepsies of infancy (Dravet’s syndrome), Ohtahara, West, and Lennox-Gastaut syndromes. Emphasis should be placed on the potential for prevention in many patients in whom insults result from substandard pre-, peri-, and post-natal care, affecting the management of pregnancy, labor, delivery, or the neonatal period. AED management of these complex cases is difficult and aims at the best possible balance between seizure control and side effects.

**BASIC PRINCIPLES AND PHARMACOKINETICS OF ANTIEPILEPTIC DRUGS****Absorption to Clearance, and the Concept of Half-Life**

The biological availability of AEDs is determined by a dynamic process, which begins through absorption, proceeds with distribution in the various body compartments, and concludes with the metabolic and excretory mechanisms related to their elimination. The temporal sequence of these processes within the context of chronic treatment is better conceptualized as a continuum, and absorption, distribution, and elimination actually coexist at different levels. For practical purposes, all these processes should be viewed as potential limiting factors to the achievement of the best possible therapeutic effect from a given AED, that is, the ratio between antiepileptic efficacy and side effects. Key variables related to individual AED pharmacokinetics are given in Chapter 6.

The rate of absorption determines the interval between the ingestion of the pill and the attainment of its peak serum levels (peak level). This, in turn, determines the onset of therapeutic action as well as the temporal pattern of occurrence of side effects. Once absorbed, the drug is distributed within the different body tissues. The percentage of the drug within the various body tissues is specific for each drug.

Finally, AEDs are metabolized and excreted. This step is responsible for the clearance

of the drug and its gradual elimination from the body. Most AEDs in current use are metabolized through the liver, and thus peculiarities of hepatic metabolism are pivotal to both dosage planning and to the anticipation of type and degree of interaction with other drugs (including other AEDs). This leads us to the concept of biological half-life, the time it takes for the serum concentration of a given drug to decrease by 50% after absorption and distribution have been completed. Thus, AEDs with faster metabolism will have shorter half-lives and will need to be administered more frequently. Half-life is very long in prematures, equal to the adult at term, then decreases dramatically until the second month of life. Therefore, dose per body weight should be double that of the adult in infants, and 1.5 times that of the adult in children.

#### **Enzyme Induction, Enzyme Inhibition, and the Pharmacokinetic Counterparts of AED Mono- versus Polytherapy**

Most, but not all drugs are detoxified in the liver. Hepatic metabolism occurs through a concerted action of enzymatic systems, which are influenced by a variety of factors, including hepatic dysfunction and the interference of a variety of drugs (including AEDs). The interaction among different AEDs at the level of hepatic enzymatic systems is the main reason why polytherapy (that is, combination of two or more drugs) often leads to an increased incidence of toxic side effects and may even interfere with the efficacy of one or all of the drugs being used. This is related to the fact that some drugs are enzyme inducers, while others are enzyme inhibitors, respectively accelerating or slowing down the metabolism of other drugs used concurrently, with a direct impact in the latter's half-life. Thus, polytherapy with enzyme inducers leads to reduced antiepileptic efficacy in comparison with that achieved with correctly applied monotherapy, while polytherapy with enzyme inhibitors can result in enhanced adverse dose-related toxicity. Polytherapy may be necessary, however, in difficult-to-control epilepsy. In these situations, potential metabolic interactions must be considered in the choice of drugs.

#### **Planning the Adequate Dosage for Each Patient**

The goal of AED dosages for individual patients is maintenance of serum levels that are adequate to prevent seizure recurrence, while at the same time below those causing undesirable side effects (the therapeutic range). Once a maintenance dose of an AED is instituted, steady-state serum levels are achieved within five half-lives of the drug, but actual levels fluctuate between doses (Figure 5.1). To avoid wide swings in peak (highest) and trough (lowest) levels, dosage interval should correspond to 50% of the half-life of the drug. This strategy also can protect the patient against a seizure when medication intake is occasionally delayed or missed.

#### **DEALING WITH ADVERSE EFFECTS**

Adverse effects are almost inevitable with high-dose AED use. The aim is to use amounts appropriate to each individual so that any side effects are deemed acceptable. Tolerance to adverse effects usually occurs and should be anticipated as an encouragement to patient compliance at treatment outset. Nevertheless, some degree of compromise is usually needed, its most obvious rationale being that adequate seizure control significantly reduces the limitations imposed by the epileptic condition and permits, as much as possible, a normal life.

The need to reach a satisfactory balance between beneficial and adverse effects of AED treatment should be discussed with the patient and his or her relatives, and the neurologist should always be willing to revise the AED regimen. Unfortunately, there can be a limitation to this process, which is even more marked in developing countries, where economic factors reduce the choice of AEDs available to most patients.

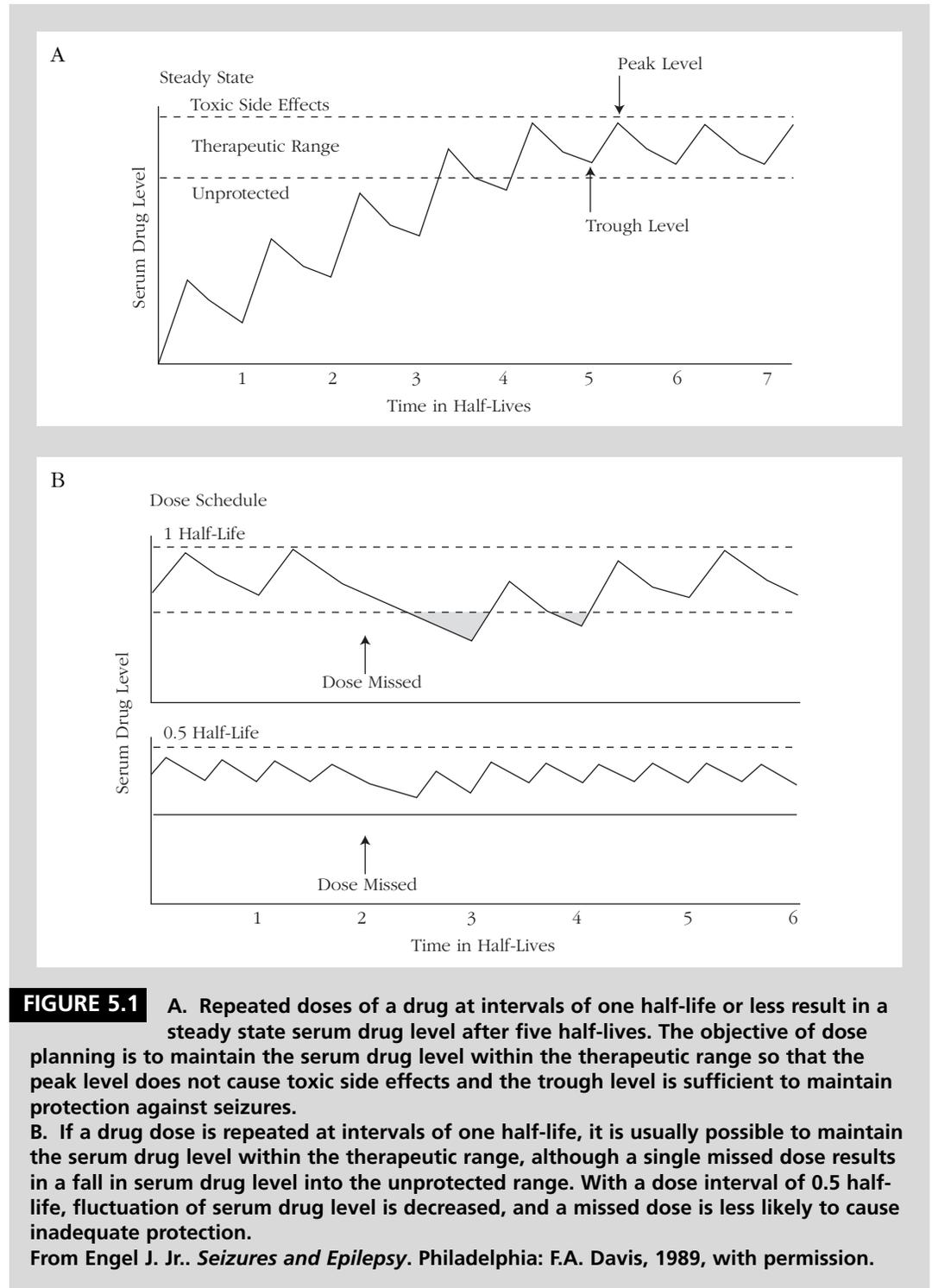
Clearly, there are situations in which compromise is appropriate, and others when it is not. For instance, the more difficult to control the seizures, the more reasonable it is to accept some degree of side effects, providing adequate control is a realistic goal. This is the typical scenario of the hard-to-control but (medically) controllable epilepsies. Conversely, epilepsy syndromes toward the two ends of the spectrum of controllability

#### **KEYPOINTS**

- Dose per body weight should be double that of the adult in infants, and 1.5 times that of the adult in children.
- To avoid wide swings in peak (highest) and trough (lowest) levels, dosage interval should correspond to 50% of the half-life of the drug. This strategy also can protect the patient against a seizure when medication intake is occasionally delayed or missed.

**KEYPOINTS**

- In these most severe conditions, suboptimal seizure control is often inevitable. Adjust the AED regimen to a more comfortable level, with lower dosages and/or fewer drugs, which may lead to a similar degree of seizure control as compared to more toxic regimens, but a better overall quality of life.



may not invite too much compromise. Thus, in most easy-to-control epilepsies, complete seizure control can be achieved with most AEDs, and more than minimal side effects should prompt consideration of an alterna-

tive drug. For entirely different reasons, compromise may be inadequate in the truly medically refractory epilepsies. In these most severe conditions, suboptimal seizure control is often inevitable, and morbidity

should not be increased by severe adverse effects. A more reasonable approach, therefore, is to adjust the AED regimen to a more comfortable level, with lower dosages and/or fewer drugs, which may lead to a similar degree of seizure control as compared to more toxic regimens, but a better overall quality of life.

The management of adverse effects begins by attempting to minimize or prevent their occurrence. The principle of “start low and go slow” should be usually applied, with the few exceptions related to the introduction of phenytoin and phenobarbital and the acuteness of the clinical situation. When dose-related adverse effects occur during the course of chronic treatment, a number of strategies can be used. First, the total daily dose can be further subdivided, circumventing the need for dose reduction. This is a useful strategy with drugs like carbamazepine, for which a QID regimen with smaller individual dosages can often eliminate dose-related side effects observed with BID or TID regimens. Second, dosage can be reduced when symptoms of toxicity are reported. This may or may not be safe, however. For instance, performed in isolation, this may be a dangerous move in patients with hard-to-control-but-controllable epilepsies, in whom adequate seizure control was achieved only when maximally tolerated dosages of a drug used in monotherapy were reached. Thus, should one consider dosage reduction, a second drug with low potential for interaction should be added as a measure of compensation. Third, in patients who are already receiving more than one AED, the potential for interaction should be checked and taken into consideration as an explanation for the dose-related adverse effects. In this context, reduction of the dosage of an enzyme inhibitor drug could accelerate the metabolism of the other AED, reducing the adverse effects. Finally, for medications for which a controlled-release formulation is available, its substitution may reduce side effects related to peak serum levels resulting from rapid drug absorption. This latter strategy, however, is of limited use in developing countries, because controlled-release preparations are more expensive and usually not made available through public health systems.

Whereas dose-related side effects can often be avoided by increasing the dose slowly, often dissipate after a week or two, and invariably reverse when medication is discontinued, idiosyncratic side effects are much more serious and can be life-threatening. Reactions such as Stevens-Johnson syndrome, aplastic anemia, and liver failure are fortunately rare, but can occur with most AEDs. Usually they cannot be predicted by laboratory studies, so the absence of the ability to carefully monitor blood chemistries and hematology does not present a particular handicap. Rather, patients must be warned about symptoms of these disorders, such as rashes, recurrent infections, bleeding, and jaundice, and advised to contact their physician immediately if these should occur. When appropriate emergency laboratory evaluations fail to rule out a serious adverse event, or if laboratory facilities are not available, the AED should be discontinued.

Long-term side effects of AEDs, such as neuropathies, connective tissue disorders, and cerebellar degeneration, can also occur, particularly with chronic use of phenytoin and phenobarbital. In most cases, these effects are not symptomatic, but phenytoin can produce gingival hyperplasia and cosmetic changes that are disturbing, and phenobarbital can produce Depuytren's contractures. In some people, valproate causes weight gain and alopecia, which can be a problem, particularly for young women.

#### **MONITORING ANTIEPILEPTIC DRUG SERUM LEVELS**

Facilities for monitoring serum levels are often not available in developing countries, but where they are, it is important that they not be overused. Even in the industrialized world, adjustments in AED regimens are primarily based on clinical grounds, irrespective of the serum levels. Dosage adjustments should always be made on an individual basis and dictated by the performance of a given AED regimen in terms of seizure control on the one hand and side effect profile on the other.

Serum levels above or below the published therapeutic range have little meaning, unless the patient is having seizures or complaining of toxic side effects. Published ther-

#### **KEYPOINTS**

- Idiosyncratic side effects are serious and can be life-threatening. Usually they cannot be predicted by laboratory studies. Patients must be warned about symptoms of these disorders.
- When appropriate emergency laboratory evaluations fail to rule out a serious adverse event, or if laboratory facilities are not available, the AED should be discontinued.
- Facilities for monitoring serum levels are often not available in developing countries, but where they are, it is important that they not be overused.

**KEYPOINTS**

- Most literature on AED serum levels has been generated in industrialized countries. Therefore, the appropriateness of extrapolating “adequate” or “inadequate” serum levels for genetically different individual patients or populations in developing countries can be challenged.

apeutic ranges for AEDs are population averages, and individual patients vary greatly in response to drugs. A common mistake is to precipitously change the AED regimen solely because of specific serum level determinations, disregarding both efficacy and side effects in the individual patient. It is inadequate to simply replace an AED (or add a second, a third, or a fourth AED) because seizures persist despite “adequate serum levels,” even when there are no side effects. A key concept here is that of the maximum tolerated dosage—irrespective of serum level determinations—that can be achieved in an individual patient by gradually increasing the dose until either seizure control or intolerable side effects ensue. Furthermore, most literature on AED serum levels has been generated in industrialized countries. Therefore, the appropriateness of extrapolating “adequate” or “inadequate” serum levels for genetically different individual patients or populations in developing countries can be challenged. Validation studies in these populations are needed.

There are some situations in which determination of serum levels is useful. These include the need: 1) to determine, for future reference in the event of clinical changes (seizure breakthrough or toxic side effects), the individual therapeutic range of a drug once an effective dose has been reached; 2) to rule out poor compliance as a possible cause for otherwise unexplainable seizure recurrence; 3) to decide whether seizure recurrence may be due to some pharmacokinetic peculiarity leading to low serum levels, including rapid drug clearance or drug interaction; 4) to determine which AED should be held responsible for unexpected, undesirable side effects when the patient is on polytherapy, and 5) to identify changes in levels due to physical factors such as weight change (especially in children), pregnancy, diseases that affect absorption, protein binding and elimination, and addition of medications that can cause pharmacokinetic interactions. Serum levels are particularly useful with larger doses of phenytoin because of its unique saturation kinetics.

When serum levels are difficult to obtain or not available, the questions posed by the situations just mentioned should be

approached through judicious environmental and pharmacologic manipulation. Compliance can be increased by asking someone to help in the administration of the pills for a certain period of time. If suboptimal levels are suspected, the dosage of the main AED should be progressively and carefully increased to the maximum tolerated dosages. This will rule out low serum levels as the reason for seizure recurrence, even without the actual determination of the latter. Finally, to solve the issue of side effects in the context of polytherapy, the dosage of the AED less likely to be the cause of side effects should be increased, with the subsequent reduction or discontinuation of the other drug(s).

**STOPPING TREATMENT****When to Consider**

Because a diagnosis of epilepsy and the chronic use of AEDs are attended by psychological, social, and physical disadvantages, the need to maintain patients on medication after a period of seizure freedom must be carefully reevaluated. This is even more so for patients in developing countries, for whom the psychosocial consequences of epilepsy have a greater impact and the cost and availability of AEDs are of significant concern.

Before analyzing the risks of seizure recurrence for individual patients upon discontinuation of AEDs, one should define the epilepsy syndrome and the amount of time the patient has been seizure free on medication. A good approach is to explain that when the time comes, the decision will be taken in conjunction with the patient and his or her family. The prerequisite for discussing the discontinuation of AED treatment is the attainment of a prolonged period of seizure freedom, particularly in the context of non-lesional epilepsies.

Several factors increase or decrease the chances of successful discontinuation of AEDs in a given patient (Table 5.1). In the industrialized world, almost half of patients with epilepsy will be able to discontinue medication; however, the number may be smaller in developing countries, where risk factors for symptomatic epilepsies are much

**TABLE 5.1** Risk Factors for Recurrence after Discontinuation of Antiepileptic Drugs in Patients Who Are Seizure Free for 1 To 4 Years\*†

**Factors most commonly found in the most relevant studies**

- Defined etiology (remote symptomatic epilepsies, abnormal imaging)
- First seizure after 10 years of age
- Partial seizures
- Mental retardation and other abnormalities in neurologic examination
- EEG spikes at time of tapering

**Factors found in single or smaller number of studies**

- Epilepsy onset after age 5
- Interval between seizures of less than 1 month at onset of illness
- Longer duration of active disease (took longer to control seizures)
- Start withdrawing AEDs after age 6
- Abnormal (epileptogenic) EEG during withdrawal
- Less than three years of remission
- Psychiatric diagnosis

\* Some factors apply to specific subpopulations, such as children/adolescents, adults, or only patients with cryptogenic epilepsies.

† Some factors were not confirmed in all studies.

more common than for idiopathic epilepsies. Patients whose seizures are most likely to remit over time are those in whom a genetic predisposition is the predominant or single pathogenetic mechanism, and the contribution of any major remote lesional component is minimal or nonexistent. Syndromic diagnosis provides the best predictor of the chances that a given patient will eventually discontinue medication.

An important issue for neurologists practicing in developing countries is that the decision to discontinue AEDs, as in the decision to begin AEDs, transcends the simple fact that seizures may recur. It must balance

what is at stake should a seizure return against the cost and possible side effects of AEDs, as well as the stigma of continuing to be viewed as epileptic. If the epileptic condition is already known to the employer, arrangements can be made to protect the patient against physical harm during at least a 2-year period of dosage reduction and eventual AED discontinuation. For instance, this might include asking a farmer or a plant manager to remove the patient from operating machines, or asking the manager of a bank to arrange for the patient to avoid direct public contact as a cashier. If the employer is not aware of the epileptic condition, the patient may either try to raise this issue at work or take the risks. For women, other relatives might be asked to assume potentially dangerous tasks such as cooking over an open fire or drawing water from open sources. In developing countries, the decision to take such risks usually is not left only to the patient, but involves other responsible relatives. Commonly, patients with low educational levels are unable to fully appreciate what is at stake should seizures recur. When patients work for themselves, in activities that are incompatible with recurrent seizures, such as taxi driving or other professional driving, AED discontinuation may not be practical.

Discontinuation of AEDs is less likely to result in seizure recurrence if it is carried out slowly, tapering dosages at 1- to 2- to 3-month intervals, in a process that may last a year. When the patient is on polytherapy, this process could last even longer, because only one drug should be discontinued at a time. The majority of seizure recurrences will take place during taper, but protective measures, such as not driving, should continue for 3 to 6 months after the drug is completely discontinued. Thus, in adolescents with apparently easy-to-control epilepsies, it is better to attempt AED discontinuation before the patient begins to drive, because it is always better to postpone than to suspend a driver's license.

In developing countries, many issues may be more important for patients and their caregivers than driving. In children, one common problem is that teachers very often don't want a child with epilepsy in their

**KEYPOINTS**

- An important issue for neurologists practicing in developing countries is that the decision to continue AEDs must balance what is at stake should a seizure return against the cost of AEDs, as well as the stigma of continuing to be viewed as epileptic.
- In adolescents with apparently easy-to-control epilepsies, it is better to attempt AED discontinuation before the patient begins to drive, because it is always better to postpone than to suspend a driver's license.
- In developing countries, many issues may be more important for patients and their caregivers than driving.

**KEYPOINTS**

- The best preventive measure against burns is not to be exposed to fire. This is not an easy undertaking for women in developing countries, who often have to cook for several children, with no further help.
- The family should be clearly informed that fingers or objects should not be introduced into the patient's mouth during the attack.
- Harm from water may be even more serious than that from fire, because persons with epilepsy may drown while bathing or swimming.

classroom even if the seizures are well controlled. Many students after finishing school join educational courses at places away from home and very often they live alone. The parents of children with epilepsy whose AEDs are being withdrawn have great anxiety in such situations. Marriage at or around the time of discontinuation of AEDs is another problem, especially for young women with epilepsy. The fear of seizure recurrence during the wedding ceremony (that very often may be long affairs requiring girls to be awake for two to three nights in countries on the Indian subcontinent) is another important aspect of the problem.

**DEALING WITH SEIZURES**

Most seizures occur at home, school, or the workplace. Learning how to approach and protect the person with epilepsy during a seizure is thus important for relatives, teachers, and colleagues who will confront this situation on repeated occasions. Only a small fraction of epileptic seizures are prolonged to a point where transference to an emergency room is warranted. Most episodes simply need an organized approach by the witnesses to prevent harm from fire, water, excessive bruises, and interference with respiration.

Patients whose seizures are not fully controlled should refrain from cooking, because all too often, burns from boiling water, oil, or by simply placing the hands on the stove occur during seizures. The best preventive measure against burns is not to be exposed to fire. This is not an easy undertaking for women in developing countries, who often have to cook for several children, with no further help. Occasionally, a patient may wander around in an automatic, semi-purposeful fashion and potentially approach a stove or a fireplace during a complex partial seizure. A high level of vigilance is required from relatives to prevent the confused patient from doing so, and ideally, patients with these seizure types should not be in environments where there is fire. In practical terms, this means that persons with epilepsy should not be in a kitchen while food is being cooked or in an area near a fireplace or bonfire.

Harm from water may be even more serious than that from fire, because persons

with epilepsy may drown while bathing or swimming. Epileptic patients should be strongly advised against bathing in bathtubs, and those with suboptimal seizure control should not go on boats alone. Advice on swimming is more difficult and should be construed on an individual basis. Patients must not swim alone, but swimming accompanied by vigilant relatives or friends under protected situations may be feasible as long as the accompanying individual is capable of pulling the person with epilepsy to safety if a seizure occurs.

Partial motor and generalized seizures can lead to bruises or fractures, and the patient's head and arms should be held or protected with a cushion to avoid repeated trauma against the floor or other surface. The potential for injuries should be anticipated and prevented. For instance, by relocating the patient's bed in relation to the wall, recurrent injuries due to clonic movements or dystonic posturing against the wall in sleep-related seizures can be prevented. In addition, objects that could harm the patient should be taken away. A more challenging situation is that posed by sudden drop attacks, which often accompany severe epilepsies and lead to injury. Some of the measures that could be helpful in these situations are difficult to implement in households of developing countries, such as constant supervision and modification of the type of floor to reduce the impact of injury. One helpful measure is the use of a protection helmet, although compliance with this is variable.

During generalized tonic-clonic seizures, there is a need to assure ventilation and prevent aspiration. Tight clothes should be loosened and glasses removed. The patient should be turned to his or her side and the head gently held. A supine position must be avoided so that saliva and mucus can run out of the mouth. Excess salivation may be wiped with a tissue. The family should be clearly informed that fingers or objects should not be introduced into the patient's mouth during the attack. Someone should stay with the patient until consciousness is regained.

Prolonged seizures, particularly when generalized, need to be stopped through

emergency medical intervention with IV drugs and other supporting measures. Thus, if a seizure does not stop in a matter of a few minutes, or if generalized tonic-clonic seizures recur without return of consciousness in-between, transfer to an emergency room should be organized, to prevent the harmful consequences of status epilepticus. Patients should also be taken to an emergency room if they have experienced their first seizure, they have injured themselves during the seizure, or they are pregnant. Otherwise, the loss of time and cost associated with an emergency room visit further adds to the disability associated with an epileptic seizure.

**SPECIAL ISSUES IN PHARMACOTHERAPY**

**When to Treat a Single Seizure or Infrequent Seizures**

Estimates of seizure recurrence after a first unprovoked seizure vary from 20% to 70% within the next two to five years, although most patients will have their second seizure within a year of the first. The lower recurrence figures apply to patients who have had a generalized (as opposed to focal) attack with no past history of febrile seizures, and who present with a normal neurologic development and examination, no family history of seizures, and normal EEG and brain imaging after the first seizure. The presence of one or more of these predisposing factors progressively increases the likelihood of recurrence. Thus, consideration of AED initiation is entertained after a single seizure only if one or more of the known predictors of subsequent seizures can be documented in a given individual (Table 5.2). It is useful for patients to understand that if AED therapy is instituted and they remain seizure free for several years, they face the choice of tapering or discontinuing the drug. Thus, unless the intention is to treat the patient for a lifetime, instituting treatment after a single unprovoked seizure to prevent recurrence of another does not resolve the problem, but merely postpones it. Coupled with the fact that patients in the developing world face significantly more difficulties

**TABLE 5.2 Risk Factors for Recurrence after a First Unprovoked Seizure\***

**Factors most commonly found in the most relevant studies**

- History of prior febrile convulsions
- Defined etiology (abnormal imaging, remote symptomatic etiology)
- Todd’s paresis
- Seizure during sleep
- Abnormal EEG

**Factors found in single or smaller number of studies**

- Family history of epilepsy

\* Some factors apply to specific subpopulations, such as children/adolescents, adults, or only patients with cryptogenic epilepsies.

related to cost and availability of AEDs, these considerations should strongly encourage a high threshold for initiating treatment after a single seizure in these countries.

One situation to be singled out is the risk of recurrence after a first seizure related to acute or transitional phases of neurocysticercosis. It has been shown that while active infection persists, the risk of seizure recurrence is high, and an AED should be maintained during this period. After resolution, usually in 6 months to a year, the risk of seizure recurrence is low, and discontinuation of the AED should be considered.

Some patients with chronic epilepsy have very infrequent seizures, a condition sometimes referred to as oligoepilepsy. When seizures occur many years apart, the risks posed by a subsequent ictal event may not warrant the cost, inconvenience, and possible adverse side effects of continuous AED treatment. Often in industrialized countries, patients and their physicians choose not to undergo treatment for seizures that occur many years apart, and there would seem to be even more justification for foregoing treatment in such patients in developing countries.

**KEYPOINTS**

- Coupled with the fact that patients in the developing world face significantly more difficulties related to cost and availability of AEDs, these considerations should strongly encourage a high threshold for initiating treatment after a single seizure in these countries.
- When seizures occur many years apart, the risks posed by a subsequent ictal event may not warrant the cost, inconvenience, and possible adverse side effects of continuous AED treatment.

### CASE STUDY

**Presentation:** The patient is a 35-year-old man in good health. At the age of 26, after a day spent swimming, playing football, and other physical activities under the sun, on the beach, he experienced a sudden massive generalized tonic-clonic seizure. There was no medical or surgical event in his early past and no complaints on this day. He had been successfully treated for malaria with new drugs 2 months ago. There is a history of *absence epilepsy* in a cousin.

**Evaluation:** He was transported by friends to the hospital 35 km away, in a state of drowsiness and generalized pain. Blood and urine examinations were performed, including *Plasmodium falciparum* parasitology, without any abnormality. The day after, an X-ray and EEG were performed and were normal. Because there was no contraindication, a lumbar puncture was performed and was also normal.

**Treatment:** IV glucose with 10 mg of diazepam was given the first night, but not repeated. He was given paracetamol for his generalized pain.

**Outcome:** Since this seizure, no other events have occurred. He is performing very well at work.

**Comment:** This case illustrates the need for a high threshold before instituting a long-term treatment for an uncertain condition. In such cases, it is important to carry out a full evaluation, to be sure that there is no underlying treatable disorder (e.g., infections, metabolic, hemorrhagic, traumatic). Even if modern diagnostic tests are not available, careful surveillance can lead to a good outcome. A symptomatic neuromalaria seizure could be considered, but is unlikely for someone of his age in an endemic area, even if he had experienced a recent episode of malaria 2 months ago. A history of *absence epilepsy* in a relative is also not sufficient to conclude that he has chronic epilepsy. Such people in developing countries could be better off treated by traditional healers than by the modern medical system, where an inexperienced MD might prescribe lifelong AED therapy for a single seizure that would never recur.

### CASE STUDY

**Presentation:** A 17-year-old man presented with a history of recent onset of recurrent seizures. He would have jerking of his right arm and leg, occasionally evolving into secondarily generalized seizures. The seizures occurred every few days. There was no family history of seizures or other risk factors for epilepsy.

**Evaluation:** The patient's examination was unremarkable. He had no subcutaneous nodules. A contrast enhanced CT scan of the brain revealed multiple, bilateral small rounded calcified lesions in the brain parenchyma without surrounding edema.

**Treatment and Outcome:** Seizures no longer occurred after he began taking phenytoin, 300 mg/day.

**Comment:** This patient's seizures could readily be ascribed to acute neurocysticercosis; however, the calcified lesions could also be an incidental finding, given their common occurrence in developing countries. Further imaging, such as MRI if available, is recommended to exclude other, more serious or treatable etiologies. The AEDs in acute cases of neurocysticercosis are prescribed to prevent seizure recurrence, and can be stopped after about 6 months if the patient remains seizure free, even if the CT lesions persist.

**CASE STUDY**

**Presentation:** A 34-year-old male accountant was brought for assessment after what was initially thought to be a single seizure. Although he had no memory for the event, eye-witness accounts reported a versive right head turn followed by generalized tonic-clonic activity and postictal confusion. Closer history-taking revealed that he had experienced complex febrile seizures as a child that also began with the head turning and had gone on to experience approximately one seizure every 2 years since then for at least the past 6 years. He had previously been treated with phenobarbital, but reported severe cognitive side effects that resulted in job losses. The only other reasonably available AED, carbamazepine, caused him to develop a severe rash.

**Evaluation:** His examination was unremarkable. EEG and CT were not available in his community. His general health had not changed in the past 5 years, and he denied any headaches or interim neurologic symptoms.

**Treatment/Outcome:** After some discussion, the patient opted to forego treatment, given the limited options available to him and the adverse effects these agents had previously caused. He did not own a vehicle or drive. He was counseled regarding the risks of open fires and bodies of water, exposure to heights, etc. Over the subsequent 8 years, he continued to be seen annually by the neurologist to assure no progressive problems developed. He continues to have a seizure approximately every 24 months, but with no significant sequelae, given the precautions he takes, and he has been able to remain gainfully employed.

**Comment:** Under the circumstances, this patient was best served by counseling and reassessments. Treatment might have prevented his rare seizures, but would almost certainly have had a more negative impact on his quality of life.

### Febrile Seizures and Fever-Related Seizures

Febrile seizures are common and illustrate the interactions between maturational and genetic vulnerability to seizures during the first years of life. Episodes occur between 6 months and 7 years of age, with a peak between ages 1 and 3. Differentiation from epilepsy and intracranial infection (see Chapter 4) is not always easy, and rests both on typical clinical features and clinical evolution. Febrile seizures occur in children with normal development, usually during a common viral illness, when the temperature is rising. Most episodes are single, generalized, and short-lasting, features that characterize *simple* febrile convulsions. Infrequently, they are focal, last more than 20 minutes, recur within 24 hours, or are followed by a postictal abnormality in the neurologic examination. The latter *complex* febrile convulsions are accompanied by a higher risk of epilepsy in the future. Seizures in the context of fever in children with previous brain damage or the association of febrile and nonfebrile seizures suggest the presence of epilepsy. A first episode without a clear cause must be thoroughly evaluated, particularly to rule out meningitis.

Parental counseling and indication of measures to actively treat the rising temper-

ature (paracetamol and tepid bath) is all that is needed in most circumstances to prevent recurrence of simple febrile seizures. However, in the event of recurrent episodes, or if the first episode is complex, additional prophylactic treatment might be considered. This may be effected either through rectal diazepam at the time of fever, or through chronic administration of phenobarbital or valproic acid until age 5. The risks and benefits of initiating prophylactic anticonvulsants for complex fever-associated seizures that occur in the setting of malaria remain unclear. When trying to determine whether to initiate treatment in this setting, one should consider the magnitude of the risk of a prolonged, untreated seizure recurring in the patient's environment, the likelihood of parental adherence to treatment, and the impact of any drug-related side effects.

Some considerations apply to the management of febrile seizures in developing countries. First, in regions where malaria is endemic, this infection should always be ruled out. Second, preventive measures for malaria and for other childhood infections, such as measles vaccination, should be enforced. Third, the indications for chronic prophylaxis are much wider for practical, epidemiologic, and psychosocial reasons. In practice, diazepam for rectal use is not avail-

**KEYPOINTS**

- The risks and benefits of initiating prophylactic anticonvulsants for complex fever-associated seizures that occur in the setting of malaria remain unclear. When trying to determine whether to initiate treatment in this setting, one should consider the magnitude of the risk of a prolonged, untreated seizure recurring in the patient's environment, the likelihood of parental adherence to treatment, and the impact of any drug-related side effects.

**CASE STUDY**

**Presentation:** A 4-year-old boy from a region with endemic *P. falciparum* malaria presented in status epilepticus with a fever of 40.2 degrees Celsius. The rains had recently commenced and a great deal of malaria was being seen at the hospital. He responded to 10 mg of IV diazepam initially and was also given rectal acetaminophen. He regained consciousness briefly, but seizures recurred 2 hours later.

**Evaluation:** A thick blood smear confirmed 4+ parasites and a lumbar puncture was entirely normal. A review of his medical records revealed that the child had experienced three previous episodes of status epilepticus—all occurring in the setting of acute malaria with high fevers during the rainy season. He had experienced other fever-associated seizures also, but his mother denied any history of seizures occurring without “body hotness,” and all seizures documented in the child’s medical record had occurred with fevers. His older brother had also experienced seizures with fever as a child.

**Treatment and Outcome:** He was given IV 50% dextrose at 1 ml/kg and a 15 mg/kg load of phenobarbital. IV quinine in 5% dextrose was initiated. He regained consciousness over the next 12 hours. His hospital course was otherwise unremarkable, and his examination on day 3 was remarkable only for decreased hearing attributed to the cinchonism secondary to quinine.

**Comments:** Does this child have epilepsy? Should he receive some prophylactic treatment to prevent further episodes of status? If yes, should he receive antimalarial agents for preventive therapy? Or anticonvulsants? And how long should these medications be continued?

This child likely suffered from recurrent provoked seizures related to repeated malaria infection, not epilepsy. In malaria-endemic regions, children may experience 3 to 5 infections annually from age 1 to 6. It is encouraging that his brother, who had similar events as a child, had not continued to experience these after age 7. One might consider treating this child with prophylactic chloroquine, but most of the malaria in the region in question was recognized to be resistant to chloroquine, and partial treatment could cause false negative test results. More effective agents for prophylaxis, such as mefloquin, were too expensive for the family to purchase.

After discussion with the mother, the child was discharged on phenobarbital, to be continued until the season when malaria risks decline. The mother was instructed to bring the child back for review when the rains started the following year, so the medication could be reinitiated for the 3 months of peak seasonal malaria. She was also provided with a treated bed net and acetaminophen to be used if the child developed fevers. She was told very explicitly that the medicine to treat the fever would *not* treat malaria and she must seek care for the child if fevers recurred.

**KEYPOINTS**

- Antiepileptic treatment for patients presenting with acute seizures due to neurocysticercosis should not be long-term.

able in many developing countries. Also, the occurrence of childhood infections is higher, increasing the risk of recurrence. Finally, febrile convulsions in nurseries or maternal schools may be a significant issue both for attending professionals and working mothers, with potentially harmful psychosocial impact.

**Neurocysticercosis**

Neurocysticercosis, the most common cause of seizures in many parts of the developing world, presents unique therapeutic challenges, not only for antiepileptic treatment, but for antiparasitic treatment. When larval

cysts located in the brain parenchyma or subarachnoid space degenerate, they release excretory products that are highly epileptogenic. Recurrent acute seizures usually resolve spontaneously within months, unless the formation of a surrounding granuloma serves as a chronic epileptogenic lesion. Consequently, antiepileptic treatment for patients presenting with acute seizures due to neurocysticercosis should not be long-term. Attempts to taper and discontinue medication after 3 or 4 months are usually successful and, in this case, indicate that a chronic epileptic condition does not exist. Where computed tomography (CT) or mag-

netic resonance imaging (MRI) are available, it can be used to assist antiepileptic treatment. Resolution of epileptogenicity is often accompanied by disappearance of the active cyst. Less than one-quarter of patients experience seizure recurrence on drug withdrawal when active cysts are no longer present on imaging. After the acute stage, dead cysts can appear on CT as small calcifications. Therefore, the finding of such calcifications on CT at the time of seizure onset suggests a chronic condition, and prognosis for drug withdrawal is poorer than when active cysts are seen. If seizures recur with drug withdrawal, chronic pharmacotherapy is necessary. When pharmacotherapy fails to control seizures, and an epilepsy surgery center is available, surgical excision of the epileptogenic granuloma is indicated.

A more controversial issue is whether and when to treat neurocysticercosis with antiparasitic medication. The argument against antiparasitic treatment is that acute cysts resolve without this intervention, while antiparasitic agents, such as albendazole, accelerate the release of toxic substances, increasing the risk for more severe seizures and increased intracranial pressure. Furthermore, this response could result in the formation of a more vigorous granulomatous reaction, which could be more likely to cause chronic epilepsy. Deaths associated with antiparasitic treatment are rare, however, especially in patients with low cyst burden and absence of increased intracranial pressure or hydrocephalus. A recent clinical trial (García et al., 2004) found that albendazole was well tolerated, and no deaths occurred in 60 patients treated. Although acute seizures were initially more frequent in the albendazole-treated patients, they were controlled by antiepileptic medication, and the later occurrence of generalized tonic-clonic seizures (but not partial seizures) in treated patients was less frequent than in patients given placebo. A larger, multicenter trial is necessary to better resolve the safety and efficacy of antiparasitic treatment before it can be recommended in this situation.

As noted in Chapter 2, diagnosis of cysticercosis is most appropriately made by MRI, CT, or X-ray, but where neither CT nor X-ray

are available, serology and evaluation of skin and muscle can be helpful. For the majority of patients with seizures due to neurocysticercosis, CT is not available, and other tests are either negative or not possible to perform. Therefore, the decision to treat with antiparasitic drugs may be moot, and relatively little is lost by opting not to introduce the risk and cost of another drug regimen. As also noted in Chapter 2, however, another important issue is that in endemic areas, calcified cerebral cysts on CT may be a fortuitous finding.

Furthermore, on the Indian subcontinent at least, single small enhancing lesions may not indicate cysticercosis and often disappear spontaneously (see Chapter 4). Consequently, the diagnosis of neurocysticercosis or findings of small calcifications in patients presenting with acute seizures does not necessarily mean that the seizures are due to this disturbance. Because viable (nondegenerating) cysts are commonly asymptomatic, antiparasitic administration in such patients with epilepsy due to another cause could unnecessarily create a second epileptogenic lesion that would complicate diagnosis and treatment. An argument for antiparasitic treatment of viable cysts is that these will eventually die, with a risk of consequent seizures, and that treatment can permit the seizures to appear under more controlled conditions. Recent studies do not address this issue, but most specialists recommend not treating viable asymptomatic cysts. Caution should be exercised in patients presenting with headaches or signs of increased intracranial pressure, where antiparasitic therapy can increase morbidity and mortality.

### Epilepsy in Pregnancy

The physiological changes that occur during pregnancy result in altered distribution and elimination of AEDs. This may interfere with seizure control, particularly in women who were already poorly controlled before conception. Increased plasma estrogens, water and sodium retention, vomiting, poor compliance with AEDs, anxiety, and sleep irregularities are some of the factors that may affect seizure frequency during pregnancy.

There are several aspects to consider when planning AED therapy during pregnancy. These include preconceptional coun-

### KEYPOINTS

- CT or MRI can be used to assist antiepileptic treatment. Resolution of epileptogenicity is often accompanied by disappearance of the active cyst.
- The finding of calcifications on CT at the time of seizure onset suggests a chronic condition, and prognosis for drug withdrawal is poorer than when active cysts are seen.
- The argument against antiparasitic treatment is that acute cysts resolve without this intervention, while antiparasitic agents, such as albendazole, accelerate the release of toxic substances, increasing the risk for more severe seizures and increased intracranial pressure.
- Where neither CT nor X-ray are available and other tests are either negative or not possible to perform, relatively little is lost by opting not to introduce the risk and cost of another drug regimen.
- The diagnosis of neurocysticercosis or findings of small calcifications in patients presenting with acute seizures does not necessarily mean that the seizures are due to this disturbance.
- Most specialists recommend not treating viable asymptomatic cysts.

## KEYPOINTS

- When evaluating a patient thought to have eclampsia, it is important to ask specific questions about a history of prior epileptic seizures, because a history of epilepsy may not have been disclosed to those delivering obstetrical care, especially among women recently wed who have not revealed their seizure disorder to their husband's family.
- Vitamin K<sub>1</sub> (10 mg/day by mouth) during the last few weeks of pregnancy reduces the chances of neonatal intracerebral hemorrhage when mothers are on enzyme-inducing AEDs.

selling, choice of drug, adjustment of the AED regimen throughout gestation, and delivery planning. When it is possible to adjust the AED regimen before conception, attempts should be made to ensure the best possible control with monotherapy at the minimum effective dosages, and folate supplementation should be started. In developing countries, limited access to public health systems may reduce the chances of pre-conceptional counseling, although public campaigns in this regard should be instituted. Although no AED is yet proven to be absolutely free of teratogenic effects, some of the newer drugs may have a relatively lower risk than commonly used older ones. If possible, valproic acid should be avoided because of an apparently greater risk of causing neural tube defects, especially in the presence of a positive family history of teratogenic drug effects.

The increase in the volume of distribution of most AEDs in the third trimester may lead to seizure recurrence due to reduced serum levels. The latter should be checked and dosage adjusted accordingly, particularly in patients who experienced difficulties in seizure control before conception and in those who already had seizures during pregnancy. Pregnancy also is associated with reduced serum protein and a resultant increase in the free fraction of protein-bound AEDs. This, in turn, causes increased renal clearance and lower total serum levels, but the amount of unbound drug available to the brain remains the same. If serum drug levels fall during pregnancy as a result of decreased protein binding, increasing the drug dosage may not be necessary and, indeed, may increase the risk of toxicity. Vitamin K<sub>1</sub> (10 mg/day by mouth) during the last few weeks of pregnancy reduces the chances of neonatal intracerebral hemorrhage when mothers are on enzyme-inducing AEDs. All these measures highlight the pivotal role of good quality prenatal care in the outcome of pregnancies of women with epilepsy, and no specific management guidelines substitute for that. Neurologists from developing countries should work in concert with gynecologists and policy-makers to improve the quality of prenatal care for pregnant women with epilepsy.

There is a two- to threefold increase in the incidence of major malformations and minor anomalies among babies born to mothers with epilepsy. The use of AEDs during pregnancy plays a major role in the increased risk of abnormalities like cleft lip, cleft palate, congenital heart disease, and neural tube defects. The risk increases with the number of AEDs used during pregnancy, which makes a strong case for monotherapy. However, more than 90% of women with epilepsy treated during pregnancy can be expected to have an uneventful pregnancy and a normal healthy baby.

Although women with epilepsy who are taking AEDs excrete these drugs in their milk, this is not a contraindication to nursing. Nursing babies should be watched, however, to make sure that there is no sedative effect that suppresses the nursing reflex.

Eclampsia is the occurrence of seizures in women (with no prior history of epilepsy) during pregnancy in a setting of pre-eclampsia (proteinuria, edema, and high blood pressure after the 20th week of gestation). The causes of eclampsia and seizures during that period are poorly understood and are believed to be multifactorial. If seizures during eclampsia are not controlled quickly, there is significant maternal as well as fetal mortality. Eclampsia is a common cause of maternal and fetal mortality in developing countries because most of the pregnancies and subsequent deliveries are still not conducted under the supervision of trained personnel. The diagnosis of eclamptic seizures is mainly established by the clinical setting. When evaluating a patient thought to have eclampsia, it is important to ask explicit questions privately of the family members to confirm that indeed the patient does not have a history of prior epileptic seizures, because a history of epilepsy may not have been disclosed to those delivering obstetrical care, especially among women recently wed who have not revealed their seizure disorder to their husband's family. Magnesium sulfate has been the standard treatment for both pre-eclampsia and eclampsia. Magnesium sulfate acts by various mechanisms, but is not effective in seizures due to epilepsy. Magnesium sulfate can cause sedation in the mother, and hypotonia and lethargy in the newborn.

Other drugs that have been used in eclampsia include phenytoin and diazepam. Phenytoin can be used for status epilepticus (15 mg per kg loading dose followed by maintenance dose). The best treatment for eclampsia, however, is delivery of the baby.

Sexually active women who do not wish to become pregnant should know that many enzyme-inducing AEDs (carbamazepine, oxcarbazepine, phenytoin, primidone, and phenobarbital) can decrease the efficacy of oral contraceptives taken by women with epilepsy. This problem can partially be overcome by taking a contraceptive pill with higher estrogen content. Barrier methods are particularly useful adjuncts to oral contraception. Benzodiazepines, gabapentin, lamotrigine, levetiracetam, tiagabine, and valproate do not influence the efficacy of oral contraceptives.

### Status Epilepticus

Status epilepticus (SE) was defined and classified in Chapter 2. Generalized convulsive SE is one of the most life-threatening neurologic emergencies. Rapidly recurring or continuous generalized convulsive seizures without return of consciousness between ictal events are associated with irreversible neuronal damage leading to substantial morbidity and mortality. As a common neurologic emergency requiring rapid response from the frontline care provider, one important function of neurologists in developing countries is to work with the primary care providers serving hospitals, clinics, and casualty departments to establish appropriate algorithms of care to be followed when patients present in SE. An ideal algorithm is shown in Table 5.3, along with algorithms for treatment of nonconvulsive (complex partial and absence) status, refractory status, and unilateral status. These algorithms will need to be considerably modified from location to location depending on resource availability. Serial convulsive seizures, which are frequent events with return of consciousness, are also a medical emergency and can signify impending status, but treatment with IV phosphenytoin or phenytoin is preferred in order to preserve consciousness.

Standard texts typically describe the management of SE to include ventilation, if

needed. Because ventilators are not generally available in developing regions outside of academic centers, the reality for most care providers in these settings is the need to manage SE without recourse to ventilation. This means treading a fine line between undertreating seizures (and therefore exposing the patient to long-term neurologic sequelae from SE-medicated brain damage) and extinction of seizures utilizing various medications that produce significant respiratory depression (and, therefore, placing the patient at risk of acute respiratory failure and/or aspiration).

When working with the primary health-care providers in your countries to develop appropriate protocols for the management of SE, keep in mind that healthcare personnel will respond most effectively to emergencies when they have a few simple instructions on how to proceed.

Some general considerations when developing algorithms for SE evaluation and treatment are listed below.

### *Initial Assessment and Treatment*

Ensure patent airway and adequate ventilation; assess vital signs and complete a rapid physical examination assessment for gross trauma, pregnancy, and comorbidity. If the patient is being treated for epilepsy, continue the previous treatment, by gastric tube if necessary, unless there is evidence that the medications caused an increase in seizure frequency.

If the patient is pregnant, eclampsia should be considered. Special attention should be given to looking for other evidence of eclampsia (e.g., hypertension). Magnesium sulfate may be used as the long-acting antiseizure medication; 2 g given IM, then continuous administration of 2 g per hour in 5% dextrose. Because magnesium sulfate is also a muscle relaxant, it can mask continuing status when EEG is not available; thus, deep tendon reflexes should be monitored and the rate decreased if reflexes cannot be elicited. Maximum of 40 g per 24 hours. Rapid delivery of the infant should be considered.

Establish an IV line with normal saline. If this cannot be achieved rapidly, treat the patient with one of the rapid acting anti-

### KEYPOINTS

- One important function of neurologists in developing countries is to work with the primary care providers serving hospitals, clinics, and casualty departments to establish appropriate algorithms of care to be followed when patients present in SE.
- Because ventilators are not generally available in developing regions outside of academic centers, the reality for most care providers in these settings is the need to manage SE without recourse to ventilation.
- Healthcare personnel will respond most effectively to emergencies when they have a few simple instructions on how to proceed.
- Because magnesium sulfate is also a muscle relaxant, it can mask continuing status when EEG is not available; thus, deep tendon reflexes should be monitored.

**TABLE 5.3** Ideal Therapeutic Algorithms for Status Epilepticus**Generalized Convulsive SE**

**Indications:** 5 minutes of continuous generalized convulsive seizures OR: 15 minutes of intermittent generalized convulsive seizures without full recovery of consciousness between seizures.

**Treatment:** First maintain airway and blood pressure, start an IV line, draw blood, and inject 50 ml of 50% DW and 100 mg thiamine. Take Hx of allergy if possible, then inject anticonvulsants:

IV fosphenytoin 20 mg/kg PE and IV midazolam 0.2 mg/kg bolus followed by 10 µg/kg/hr for 1 hr.

**Unless:** Hx of drug intolerance (e.g., allergy to phenytoin or benzodiazepine): replace by IV phenobarbital 20 mg/kg.

**Unless:** Acute intermittent porphyria: avoid P450 inducers, replace by NG gabapentin (if possible) or by IV valproate.

**Unless:** Hx of PME or JME: phenytoin/fosphenytoin harmful in PME, ineffective in JME. Replace by IV phenobarbital 20 mg/kg, or by IV valproate.

**Unless:** Tonic SE with Lennox-Gastaut syndrome: avoid benzodiazepines, replace by IV phenobarbital 20 mg/kg.

**Unless:** Focal SE without impairment of consciousness: IV treatment not indicated. Stop seizures by loading anticonvulsants PO or rectally (diastatic 15–20 mg).

**Generalized Nonconvulsive SE**

**Indications:** 15 minutes of continuous clinical or electrographic nonconvulsive seizures OR: two complex partial seizures without recovery of function between seizures.

**Treatment:**

**Complex partial SE:** IV fosphenytoin 20 mg/kg and IV midazolam 0.2 mg/kg bolus followed by 10 µg/kg/hr for 1 hr. If SE is refractory to those agents, bring fosphenytoin to 30 mg/kg and proceed with treatment as in CGSE.

**Unless:** Hx of drug intolerance: avoid specific antigen.

**Unless:** CPSE associated with PME or JME: IV midazolam and phenobarbital 20 mg/kg or IV valproate. Avoid hydantoins.

**Unless:** Acute intermittent porphyria: avoid all P450 inducers. If mild, NG gabapentin, otherwise IV valproate.

**Absence SE:** IV midazolam followed if necessary by IV valproate for childhood, juvenile, or atypical absence epilepsy, or epilepsy with myoclonic absences.

**Unless:** Hx of intolerance to those drugs: avoid specific antigen.

**Unless:** Lennox-Gastaut with tonic SE: omit benzodiazepines, go directly to IV valproate.

**Unless:** Associated with PME or JME: IV midazolam and IV phenobarbital 20 mg/kg or IV valproate. Avoid hydantoins.

**Unless:** Acute intermittent porphyria: avoid all P450 inducers. If mild, NG gabapentin, if severe IV valproate.

**Electrical SE with impaired consciousness:** IV fosphenytoin and midazolam.

**Electrical SE without impairment of consciousness:** no need for IV treatment. Load PO or rectally.

**Electrical SE during sleep:** No need for IV treatment.

**Refractory SE****Convulsive or complex partial seizures persist at end of infusion:**

**First maximize anticonvulsant dosage:** Intubate, use low dose pressors to maintain BP >90 if necessary.

Bring IV fosphenytoin up to 30 mg/kg PE. If still seizing 30 minutes after the end of the infusion:

**Option 1:** Depakote IV 30 mg/kg IV at 20 mg/min.

**Option 2:** Propofol 1.5 mg/kg followed by IV drip at 5–10 mg/kg/hr. If still seizing after 1 hr: CT scan to rule out structural sources of increased intracranial pressure and if none is found switch to

**Option 3:** Ketamine 1–1.5 mg/kg/hr (usually 100 mg). R/O increased ICP. If still seizing after 1 hr:

**Option 4:** Pentobarbital anesthesia: 15 mg/kg loading dose, maintenance ≥1.5 mg/kg/hr, adjust to obtain burst suppression pattern, stop IV every morning and monitor seizures, if they recur, commit to another 24 hours of anesthesia.

**Unilateral SE**

15 minutes of continuous clinical and/or EEG seizures: No need for IV treatment unless seizures spread.

Load PO, aim for high therapeutic/low toxic levels of multiple anticonvulsants.

Simple partial hemiconvulsions: The risk of generalization indicates treatment similar to generalized convulsive SE.

From Wasterlain C, and Treiman D (eds.). *Status Epilepticus: Mechanisms and Management*. Boston: MIT Press, 2004, with permission.

seizure medications listed below via rectal or intramuscular route.

Treat with a rapidly acting antiseizure agent. Two coadministered agents are recommended in the ideal situation: IV fosphenytoin because it is easier to give and does not cause tissue damage if the IV infiltrates, and midazolam because it has a shorter half-life than lorazepam or diazepam and allows more flexibility when used together with fosphenytoin. These drugs are expensive, however, and not likely to be available in developing world situations. Consequently, a more standard approach is to choose:

lorazepam 0.05 mg/kg IV or PR

OR

diazepam 0.2 mg/kg IV or 0.4 mg/kg PR

OR

paraldehyde 0.1 mg/kg IM (*do not* leave solution in plastic syringe. Draw up only what is needed and discard the syringe after each dose.)

With an established IV, deliver 1 cc/kg of IV glucose push. If available, consider IV administration of 100 mg of thiamine. This is especially critical during times of famine and/or if heavy, chronic alcohol use is suspected.

Send laboratory assessments for blood smear (in malarial regions), glucose, hemoglobin (if severe anemia is suspected), and any other available metabolic assessments that seem reasonable.

*If the patient continues to convulse 5 to 10 minutes after initial treatment, repeat a dose of the rapidly acting antiseizure agent used above.*

Initiate oxygen therapy if available, position patient to allow oral secretions to clear without aspiration, suction airway, and place bite block if needed.

*If the patient continues to convulse 5 to 10 minutes after the second dose of rapidly acting antiseizure medication.*

Assess respiratory rate for a full minute. Count respirations. Do not estimate. If the respiratory rate is at least 8 breaths per minute for adults or 10 breaths per minute for children, give the third dose of the rap-

idly acting antiseizure agent and prepare to administer a long-acting agent. If the respiratory rate is less than 8 breaths per minute in adults or 10 breaths per minute for children, proceed directly to the use of the long-acting agent without giving a third dose of the short-acting agent. If the respiratory rate is severely depressed (<4 breaths per minute), delay delivery of the long-acting agent for 30 minutes and provide supplementary oxygen and respiratory support by manual bagging during this time. If a ventilator is available and status is refractory, general anesthesia is indicated, as in Table 5.3.

Long-acting antiseizure medications for SE:

phenytoin 15 mg/kg IV over four hours

It is critical to have a well-functioning peripheral IV site when utilizing this agent.

If the IV site infiltrates tissues during phenytoin administration, severe necrosis may result. Phenytoin should never be administered IM.

OR

phenobarbital 15 mg/kg IV over four hours

This may also be given IM in four divided doses simultaneously if IV access is problematic.

OR

If IV formulations for phenobarbital or phenytoin are not available, give a third dose of the rapidly acting agent, place a nasogastric tube, and administer a half of the loading dose of phenobarbital or phenytoin orally. Deliver the second half three hours later.

*When the seizures are under control and/or maximally tolerated, therapy has been initiated.*

Conduct a more thorough history and examination to attempt to discern the possible cause of SE. Common causes of SE to be assessed include cerebral malaria, meningitis, alcohol withdrawal, abrupt discontinuation of antiseizure medications in a person known to have epilepsy, and poisonings, especially with organophosphates. Status in

**KEYPOINTS**

- Status in a febrile child poses a common diagnostic dilemma, particularly in malaria-endemic areas. In this situation, convulsive status must be regarded as a medical emergency and treated as discussed above.

a febrile child poses a common diagnostic dilemma, particularly in malaria-endemic areas, as noted in the earlier section on febrile seizures. In this situation, convulsive status must be regarded as a medical emergency and treated as discussed above.

If EEG is available and the patient remains unconscious, consider using EEG to assure the seizures have been controlled.

For infants and children, the administration of rectal diazepam should first be considered (0.5 mg/kg as a total dose, given in 15 to 30 seconds) if no IV is available, particularly outside the hospital facility. This dose may be repeated within 30 minutes if not effective. If IV is available, diazepam can be given (0.5 mg/30 sec, until the seizure stops, not exceeding 0.5 mg/kg). Clonazepam is then administered (0.05 mg/kg IV, followed by a slow infusion of 0.5 mg/kg/6 hours). Repeat seizures require phenytoin IV, 15 mg/kg. Blood level monitoring is necessary to determine if further acute administration is appropriate.

For newborns, pyridoxine dependency first needs to be ruled out by administering pyridoxine 50 mg IV very slowly. Then, phenobarbital (0.5 mg/kg) is the best option. Phenytoin is indicated if repeat seizures are not responding to phenobarbital.

The indication for artificial ventilation is very restricted, both in infants and in children: In practice it is indicated in cases of respiratory failure due to the underlying brain damage, not in order to administer respiratory-depressing compounds such as general anesthesia.

**Aggravation of Seizures by AEDs**

Certain AEDs may worsen seizures whose pathogenesis is negatively affected by the action of the drug. Absence, myoclonic, and atonic generalized seizures may worsen with AEDs that interfere with inward sodium currents, usually prescribed for treatment of partial seizures, including carbamazepine, oxcarbazepine, phenytoin, and phenobarbital, and also with GABAergic compounds such as vigabatrin and gabapentin. Furthermore, myoclonic seizures may be provoked “de novo” by some of these drugs, even in patients with partial epilepsies. This has been already documented for carba-

mazepine and oxcarbazepine. Toxic doses of these drugs can also exacerbate partial and secondarily generalized seizures. Spike-and-wave activity during sleep and some myoclonus can be worsened by lamotrigine, and infantile spasms are accentuated by carbamazepine, phenytoin, and phenobarbital.

AED-related seizure worsening is not a common occurrence, but should be considered when seizure frequency actually increases following the introduction of a given AED. This problem assumes a greater relevance in developing countries where most patients depend on AED dispensation through the public health system. Not uncommonly, a shortage of one type of AED will lead to substitution by another drug, which may occasionally worsen the clinical picture by aggravating or leading to de novo seizures.

**Pharmacokinetic Considerations in Pediatric and Geriatric Age Group**

Epilepsy management at extremes of age needs special attention. Drug trials usually have excluded these groups. Some AEDs affect children and adults differently. For example, phenobarbital can cause younger children to become hyperactive, but cause sedation in older patients. The increased half-life of most AEDs in the immature brain was discussed earlier in this chapter. With the onset of puberty, the drug-metabolizing patterns resemble that of adults. AED treatment in children must be followed more closely than in adults, with estimation of serum levels when indicated and available.

The general principles of AED treatment for the elderly are similar to those for other adults, but some differences in the pharmacokinetics need to be remembered when treating the elderly. Older patients are at risk of having toxic AED levels because of reduced hepatic metabolism and reduced renal clearance of certain AEDs. This population is also at greater susceptibility to cognitive and other neurotoxic side effects due to concurrent illnesses like Alzheimer's disease. Reduced protein binding and hypoalbuminemia can lead to increased free fraction of highly bound drugs. Most of the elderly population will be on other medications for various medical problems, and drug

interactions along with the basic medical conditions become a very important management issue.

### AED Prophylaxis

Severe head trauma, particularly associated with a depressed skull fracture, cerebral contusion, or intracerebral bleeding, as well as brain surgery, particularly involving vascular malformations and bleeding, are associated with a high risk of epileptic seizures and AED prophylaxis, particularly with phenytoin, has been recommended. However, although this drug has been shown to be effective against early post-traumatic/postoperative seizures, it does not prevent the late seizure development of post-traumatic epilepsy. Consequently, in such patients who are at high risk for early epileptic seizures, phenytoin can be given for a few weeks to reduce the chance of ictal events that might compromise convalescence, but there is no justification for prolonged prophylaxis over 1 or 2 years to prevent the development of an epileptic condition.

### CONCLUSIONS

The principal treatment of epilepsy is AEDs, and approaches to pharmacotherapy in the developing world are largely dependent on cost and availability. The threshold for

beginning treatment after a single seizure should be high, in order to avoid unnecessary financial burden. When treatment is necessary, the older, less expensive drugs, in monotherapy, are generally as effective as the newer ones, and both phenobarbital and phenytoin can be initiated with a loading dose if necessary. Most people with epilepsy have seizures that will be easy to treat, and very low doses of a single AED may suffice. For difficult-to-control seizures, sophisticated diagnostic and therapeutic approaches available only at major medical centers may be necessary. Where such facilities are absent, or when seizures persist despite the best available treatment, management consists of balancing seizure control with side effects and supportive care. This requires an understanding of the pharmacokinetics of AEDs and recognition of their adverse effects. When seizures are controlled by pharmacotherapy for several years, it is particularly advantageous for people in developing countries to determine whether it is possible to discontinue treatment, again to avoid unnecessary financial burden. Febrile seizures, particularly in malaria-endemic regions, pregnancy, SE, and pharmacokinetic variations at the extremes of age require specialized approaches to treatment.

### KEYPOINTS

- After head trauma, there is no justification for prolonged prophylaxis over 1 or 2 years to prevent the development of an epileptic condition.

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## ANTIEPILEPTIC DRUGS

Most people with newly diagnosed and chronic epilepsy in the developed countries will be treated with one or another antiepileptic drug (AED) and followed up at regular intervals. AEDs are the mainstay in the long-term management of people with epilepsy. The usual practice of initiating treatment with AEDs in the developed countries does not necessarily apply in the developing nations, especially among the people with epilepsy living in rural and far-flung areas.

The neurologists responsible for treating people with epilepsy in developing countries certainly need to know about the state-of-the-art approaches to the management of individual cases of epilepsy. On the other hand, it is equally important for them to be able to modify the ideal treatment schedules to suit their own socioeconomic milieu. While planning treatment programs for people with epilepsy in developing countries, it is important to ensure that these are simple, cost-effective, and also take into account the traditional views and attitudes toward epilepsy. Further, the treatment programs need to be tailored as per the regulations and resources of an individual country so that the AEDs recommended are actually available to the population with provisions that allow facilities for long-term follow-up, counseling, and education about the role of early treatment of people with epilepsy.

This chapter reviews the important aspects of currently available conventional and new AEDs, and the basic principles of choosing AEDs, the most suitable AED for a specific condition with contingency solutions, and examples of a few typical situations.

### MECHANISMS OF ACTION OF AEDS

Most AEDs work through different, multiple mechanisms while the exact mechanism of

action of a few of the drugs is not known. Some AEDs act on sodium channels, others potentiate the effect of  $\gamma$ -aminobutyric acid (GABA—a naturally occurring inhibitory neurotransmitter), while AEDs that are effective against absence seizures act by inhibiting calcium channels. A few other AEDs act by antagonizing the effect of the excitatory amino acid glutamate on one or more of its receptors.

### CURRENTLY AVAILABLE AEDS

#### Drugs Commonly Used in Developing Countries (Conventional or First-Line Drugs)

##### *Phenobarbital (PB)*

PB is the oldest of the currently available AEDs (it was first used in 1912) and even today remains the most commonly prescribed AED in terms of volume. It is a remarkable and effective drug for partial and generalized tonic-clonic seizures. PB can be used for all seizure types except absence seizures and spasms, as it is known to worsen absences. In addition to its being effective in most seizure types, it is still the cheapest AED and is available almost universally.

Because PB is still a commonly used AED and very often the first AED to be used in many developing countries, knowledge about its actions and interactions is necessary for the neurologists and other physicians using this drug. PB acts not only by limiting the spread of seizure activity, but also raises the seizure threshold. It has been shown to have actions on the sodium, potassium, and calcium channels, GABA receptors, and even modify the glutamate excitability. It has the longest half-life com-

### KEYPOINTS

- While planning treatment programs for people with epilepsy in developing countries, it is important to ensure that these are simple, cost-effective, and also take into account the traditional views and attitudes toward epilepsy.
- PB can be used for all seizure types except absence seizures and spasms, as it is known to worsen absences. In addition to its being effective in most seizure types, it is still the cheapest AED and is available almost universally.

**KEYPOINTS**

- In developing countries, phenobarbital should still be seriously considered as a first-line AED due to its low cost and efficacy.

pared to any of the available AEDs except zonisamide, and has the advantage of being available as oral preparation for routine use (tablet and elixir) and intramuscular and intravenous injection for use in emergency situations. When used orally, it can be conveniently given once daily, usually at bed time, since that can, to some extent, reduce the impact of its sedative side effect.

PB has a number of drug interactions that are of particular importance in developing countries. Phenytoin, valproate, and felbamate inhibit metabolism of PB, causing an increase in its levels. Rifampin, a commonly used antitubercular drug, is a powerful enzyme inducer and lowers the PB levels. In developing countries, many patients have epilepsy secondary to tuberculosis of the brain or may have concomitant extra-central nervous system tuberculosis and such patients receive treatment with rifampicin. PB is also a potent hepatic enzyme inducer and can increase the metabolism of many commonly used drugs like estrogen-containing oral contraceptives, steroids, and aminophylline. The metabolism of the other commonly used AEDs like carbamazepine, valproate, diazepam, and clonazepam can also be enhanced by the concomitant use of PB. Theoretically, there are many possibilities, but in clinical practice, the drug interactions of PB in a given individual are perhaps not that severe and, in the general population, not that commonly seen because these are often a result of a combined effect of many inhibitory and excitatory actions.

Although PB has been extensively used in clinical practice, few studies compare its efficacy and side effects with the other commonly used AEDs. In a multicenter double-blind trial, the overall efficacy for the control of partial and secondarily generalized seizures with PB was equal to that with phenytoin and carbamazepine. Although PB has been out of favor in many developed countries, mainly due to its reported side effects, the trial interestingly found PB to be associated with the lowest incidence of motor and gastrointestinal side effects and idiosyncratic reactions. A few other open-label studies have reported comparable efficacy and side effects of PB with valproate and carbamazepine. In developing coun-

tries, phenobarbital should still be seriously considered as a first-line AED due to its low cost and efficacy.

The most common side effects of PB are impairment of cognition and alteration of behavior, particularly in children. It should be used with caution in children because of its potential for paradoxical excitement and hyperactivity. Being a barbiturate, PB can cause physical dependence, and abrupt cessation of the drug can result in withdrawal seizures. Occasionally, children born to mothers receiving PB during pregnancy can also suffer from withdrawal seizures during the neonatal period. Chronic intake of PB has been associated with coarsening of features, Dupuytren's contracture, osteomalacia and rickets, folate deficiency, and rarely a megaloblastic anemia. PB has a relatively good safety profile with regard to idiosyncratic reactions. Generalized hypersensitivity is rare, but may include exfoliative dermatitis. Occasionally, hepatitis that is believed to be immunologically mediated has also been reported.

***Carbamazepine (CBZ)***

CBZ is widely preferred for generalized tonic-clonic and partial (with or without secondarily generalized) seizures. It is ineffective against, and may worsen, absence and myoclonic seizures. Its efficacy in partial and tonic-clonic seizures is equal to that of other commonly used AEDs like phenytoin (PHT) and phenobarbital (PB), but it is less likely to cause sedation than PB and does not cause cosmetic side effects like PHT. CBZ is useful in children and adults and needs to be given in divided doses. It is known to worsen absences and myoclonic jerks in some patients, and a higher incidence of spina bifida has been reported among children born to mothers taking CBZ during pregnancy. CBZ is available as tablets of various strengths and as syrup in most countries. Sustained-release preparations are also available in many countries, but no parenteral preparations are currently available.

***Phenytoin (PHT)***

PHT is still commonly used for all seizure types except generalized absence and myoclonic seizures and spasms and is an effective AED for all ages. Oral preparations

are of limited value during the first few months of life when bioavailability is very poor. It is best avoided among young women because of its cosmetic side effects. There is no definite evidence that PHT is any more teratogenic than other AEDs. It is not a very easy drug to use because of its nonlinear dose and serum level relationship and a narrow therapeutic range. PHT is available as tablets and capsules of various strengths, as syrup, and as intravenous injection. It should not be given as intramuscular injection because of its local toxicity, but a more expensive preparation, fosphenytoin, can be given intramuscularly.

#### ***Sodium Valproate (VPA)***

VPA is most frequently used for generalized absences, myoclonic jerks, and also generalized tonic-clonic seizures. Since this drug is effective in controlling all seizure types seen in the idiopathic generalized epilepsies (IGEs), it has emerged as the first-line drug for most of the IGEs. It is also effective in other seizure types, but needs to be used with caution among very young children due its hepatic toxicity. Hepatotoxicity may be as much as 100 times greater in infants as in adults. Among the conventional AEDs, VPA has been reported to have the most teratogenic potential. It is usually available as tablets of various strengths, as elixir, and as intravenous injections and microgranules in some countries.

#### ***Primidone (PRM)***

After oral consumption, PRM is rapidly broken into its two metabolites, phenobarbital (PB) and phenylethylmalonamide (PEMA)—both have antiepileptic activity in addition to that of PRM. Since the predominant effect is due to PB, both the antiepileptic and side effects of PRM are similar to those of PB. PRM is not the first choice drug for any seizure type. It is associated with a high incidence of toxicity at the time of initiation, causing significant sedation, ataxia, dizziness, and depression. Chronic therapy is associated with impaired cognition and psychiatric problems in many patients; the latter is not seen with PB. It is available as tablets and has been used for all seizure types except absence seizures.

#### ***Ethosuximide (ESM)***

ESM has very limited use because it is effective only for typical absence seizures. It is available as a capsule and as a suspension. This drug does not have any serious side effects. ESM is not available in many countries.

#### **Drugs Less Commonly Used in Developing Countries (New AEDs)**

##### ***Clobazam (CLB)***

This drug is related to diazepam and is used mainly as add-on therapy for partial as well as generalized seizures. It is rarely used alone and tolerance to the antiepileptic effect has been reported, but many patients do continue to have benefit with long-term therapy. It is available as tablets of different strengths.

##### ***Clonazepam (CZP)***

This drug is mostly used as add-on therapy for atypical absence, atonic, and myoclonic seizures. It is also effective in typical absence seizures, but is rarely used alone because of its sedative and cognitive side effects and development of tolerance to the antiepileptic effect. It is available as tablets of different strengths.

##### ***Felbamate (FBM)***

Felbamate is effective in the treatment of partial and secondarily generalized tonic-clonic seizures and is also useful for the Lennox-Gastaut syndrome. Felbamate has been associated with a high risk of potentially fatal bone marrow and liver failure, restricting its use to patients in whom the benefit is expected to be greater than the risk, particularly those with frequent drop attacks. It is available as tablets and as an elixir for children.

##### ***Gabapentin (GBP)***

GBP is chemically related to GABA, but its mechanism of action remains controversial. It is effective for partial and secondarily generalized seizures, but is not as effective for primary generalized seizures. GBP has minimal side effects and no significant drug interactions. These properties make it useful among patients on multiple other drugs, par-

ticularly the elderly. Because GBP is not metabolized in the liver and depends on the kidneys for elimination, it will accumulate in patients with chronic renal failure. It is available as capsules of different strengths.

#### **Lamotrigine (LTG)**

Lamotrigine is commonly used in adults for partial and secondarily generalized seizures. It has also been approved for use in children with Lennox-Gastaut syndrome. LTG also appears to be effective for generalized seizures including absence and atonic seizures and juvenile myoclonic epilepsy. LTG can cause skin rash, especially in patients concurrently taking VPA. Very slow titration, particularly when used with VPA, reduces the risk of rash. Occasionally, the rash may be life-threatening (Stevens-Johnson syndrome). It is available as tablets of various strengths.

#### **Levetiracetam (LEV)**

LEV, a piracetam analogue, is unique among the newer AEDs because it is effective starting with the initial dose. Its mechanism of action appears to be different from that of other AEDs and, like GBP, its tolerability and pharmacokinetics are very attractive, with minimum drug interactions. Sedation and behavioral problems are the most common side effects. It has mostly been used as add-on therapy for partial and secondarily generalized seizures and photosensitive epilepsy.

#### **Oxcarbazepine (OXC)**

OXC is chemically related to CBZ and is equally effective in controlling partial and generalized tonic-clonic seizures. Its side effect profile is better than CBZ and it is better tolerated. It has recently become available in the form of tablets in many countries.

#### **Tiagabine (TGB)**

TGB is a safe and well tolerated drug that is useful for treating partial and secondarily generalized seizures. The experience with this drug is limited. There are anecdotal reports of precipitating absence status in idiopathic generalized epilepsy.

#### **Topiramate (TPM)**

TPM is used as add-on therapy for the treat-

ment of adults with partial onset seizures, children with partial seizures, Lennox-Gastaut syndrome, and both adults and children with primary generalized tonic-clonic seizures. Side effects include sedation, word-finding difficulties, weight loss, parasthesias, and renal stones. TPM is available as tablets of various strengths. It has a bitter taste, so the tablets should not be broken.

#### **Vigabatrin (VGB)**

VGB has mainly been used to treat complex partial and secondarily generalized tonic-clonic seizures that do not respond to the first-line drugs. It has also been recommended as a first-line drug for the treatment of infantile spasms. Because it is effective in infants and can be rapidly titrated, VGB is useful in partial seizures in infancy. Recent reports of visual field deficits in 40% of patients taking VGB have limited its use for chronic treatment.

#### **Zonisamide (ZNS)**

ZNS has been used to treat all seizure types including atonic seizures and certain types of progressive myoclonic epilepsy. Common side effects include anorexia, dizziness, somnolence, confusion, poor concentration, and renal stones.

The most commonly accepted mechanism(s) of action and some important features of AEDs are summarized in Table 6.1.

### **BASIC PRINCIPLES FOR CHOOSING AEDs**

The decision to initiate treatment with AEDs is a unique one because of the impact it can have with regard to self confidence of the affected individual, education, employment, marriage, and other societal responsibilities and obligations. The benefits of therapy are obvious and include the reduced risk for future seizures and potential injury and even death, besides the psychosocial benefits to the individual and family members of the person not having seizures. Treatment with AEDs has potential shortcomings in the form of side effects of drugs, cost, inconvenience, and the societal stigma. Further, the side effects of chronic long-term therapy are obvious only after many years of treatment and many times are unfortunately irreversible. The decision to treat should always

**TABLE 6.1** Important Pharmacokinetic Features of the First Line and Second Line AEDs

Drug	Mechanism(s) of action	Daily maintenance dose range in adults (mg)	Dosage interval (times per day)	Important side effects
Carbamazepine	1	400–2400	3–4	Dizziness, ataxia, water retention, skin rash, seizure increase in infants and children
Clobazam	1,2	10–40	1–2	Tiredness, unsteadiness, irritability, tolerance (reduction of its antiepileptic activity)
Clonazepam	1,2	2–8	1–3	Drowsiness, ataxia, skin rash
Ethosuximide	3	500–2000	1–2	Nausea, vomiting, loss of appetite, weight loss, bone marrow depression
Felbamate	5	1800–4800	3–4	Decreased appetite, weight loss, insomnia, potentially fatal bone marrow or liver failure
Gabapentin	8	1200–4800	3–4	Tiredness, dizziness, weight gain, irritability
Lamotrigine	1,4	100–800*	1–2	Dizziness, unsteadiness, rash (occasionally Stevens-Johnson syndrome)
Levetiracetam	8	1000–4000	2–3	Somnolence, asthenia, dizziness, psychosis
Oxcarbazepine	1	900–2700	3–4	Tiredness, dizziness, headache, unsteadiness, rash, water retention
Phenobarbital	1,2	60–240	1	Tiredness, depression, memory problems, impotence, hyperactivity (in children), skin rash
Phenytoin	1	100–700	1–2	Tiredness, dizziness, memory problems, gum hypertrophy, hirsutism, acne, facial coarsening, skin rash, decreased bone density, cerebellar atrophy
Primidone	1,2	250–2500	3–4	Tiredness, depression, memory problems, psychosis, impotence, hyperactivity (in children), skin rash
Tiagabine	1,6	20–60	2–4	Dizziness, light-headedness, slow response
Topiramate	1,2,4,7	100–1000	2	Drowsiness, dizziness, impaired memory, weight loss, renal stones, seizure worsening, word-finding difficulty
Valproate	1,2	500–3000	3–4	Anorexia, nausea, liver damage, weight gain, hair loss, polycystic ovarian disease, thrombocytopenia
Vigabatrin	6	2000–7000	1–2	Drowsiness, fatigue, dizziness, weight gain, hyperactivity, visual field deficits
Zonisamide	1,3	400–600	1–2	Dizziness, anorexia, memory problems, weight loss, renal stones, skin rash

1: Sodium currents

2:  $\gamma$ -aminobutyric acid-A (GABA-A) receptor currents

3: T-calcium currents

4: Glutamate and/or AMPA/kainate receptor antagonist

5: Interaction at N-methyl-D-aspartate (NMDA) receptor

6: Inhibitor of GABA transaminase (GABA-T)/blocking the reuptake of GABA

7: Calcium current inhibitor

8: Unknown

\*300–800 without valproate, 100–400 with valproate

**KEYPOINTS**

- Very often, ideal treatment schedules cannot be practiced in developing countries due to the poor availability of drugs and the costs involved. Therefore, flexibility on the part of the treating physician is important for planning contingency alternatives.
- There are real-life situations in developing countries where the cost of AEDs becomes the most important adverse effect.

be individualized, keeping in mind the total picture of an individual's problem. The benefits of therapy should be weighed against the potential harmful effects.

It is most useful to formulate a treatment plan at the time of each patient's initial evaluation. In order to be successful, the treatment plan should allow for flexibility in view of either a change in the clinical situation or the availability of the first choice AED. The clinicians need to be fully conversant with the ideal drug for a condition and should be ready with contingency or alternative plans, if the ideal drugs are not available.

**Symptomatic Focal Epilepsies**

*Ideal situation:* Carbamazepine is generally the drug of choice for symptomatic focal epilepsies in the industrialized world, and the extended release form is preferred because twice-a-day dosing is possible. Although phenytoin is as effective and can be given once a day, it is less often prescribed because of the cosmetic side effects and saturation kinetics. Oxcarbazepine is similar to carbamazepine and is being increasingly used as a first-line drug. Other drugs that are commonly tried if the first-choice drug fails, in no particular order, include valproate, lamotrigine, topiramate, levetiracetam, and zonisamide. Because efficacies are similar, decisions are based more on side effect profiles and dosage regimens acceptable to each individual patient. Tiagabine is less commonly used, and drugs that are sedating, such as phenobarbital, primidone, and the benzodiazepines, are usually avoided. Felbamate and vigabatrin are extremely effective antiepileptic drugs with serious toxicity, so they are generally considered a last resort, to be used with full patient disclosure. Not all of these drugs are available in every country, and regulations vary with respect to use as monotherapy, or as adjunctive medications for some of the newer drugs.

*Contingency situation:* Very often, ideal treatment schedules cannot be practiced in developing countries due to the poor availability of drugs and the costs involved. Therefore, flexibility on the part of the treating physician is important for planning con-

tingency alternatives. In developing countries with limited resources, an alternative contingency strategy (though not ideal) could be to begin with phenobarbital, and if that fails, go on to use phenytoin, carbamazepine, or valproate. While commonly used AEDs (PHT, PB, CBZ, and VPA) have been shown to have differential efficacy in comparative studies, there is no conclusive evidence that these and other AEDs have differential efficacy against partial seizures arising from different parts of the brain.

PB is no longer used as a first-line drug by most people in developed countries due to its adverse cognitive and behavioral effects, but may be the drug of choice for developing countries, especially for patients who are struggling for subsistence. There are real-life situations in developing countries where the cost of AEDs becomes the most important adverse effect. Very often the issue at stake is whether to treat epilepsy or provide food and clean water. Clinicians in developing countries could follow the simple strategy to initiate treatment with PB and be ready to change to other AEDs in case of disabling adverse effects with PB.

**Idiopathic Generalized Epilepsies**

*Ideal situation:* Valproate is commonly preferred as the drug of choice for patients with primary generalized epilepsies that do, or can, manifest with multiple seizure types, because it is effective against generalized tonic-clonic seizures, absences, and myoclonic jerks. Other wide-spectrum antiepileptic drugs that can be used to control all seizure types with a single medication include lamotrigine, levetiracetam, zonisamide, and topiramate. When these drugs fail, polytherapy is necessary for patients who have generalized tonic-clonic seizures and either absences or myoclonic jerks. Absences can be treated with ethosuximide, and myoclonic jerks with clonazepam and, rarely, primidone. Care must be taken when combining medications to avoid pharmacokinetic and pharmacodynamic interactions that increase the likelihood of adverse events.

*Contingency situation:* Even while treating IGEs, PB could have an important role as the alternative drug for treatment of different

seizures associated with IGEs in developing countries, since this may be the only available AED. Additionally, while CBZ is well known to worsen myoclonic jerks, the use of PHT as a first-line AED in IGEs (as in partial epilepsies) is associated with problems of its adverse effects. Further, both CBZ and PHT are not effective against absence seizures.

### Idiopathic Focal Epilepsies

*Ideal situation:* These conditions, typified by benign childhood epilepsy with centrotemporal spikes, are often so mild that no treatment is necessary. When seizures are recurrent, particularly during the day, the approach to treatment is essentially the same as that for symptomatic focal epilepsies. Here the clinicians need to be aware of the possibility of seizure worsening due to CBZ among patients with benign childhood epilepsy with centrotemporal spikes. Because CBZ can precipitate continuous spike-and-wave during slow sleep, it can be a problem in situations where EEG is not available. Under ideal conditions, VPA is possibly the drug of choice even for treating seizures seen in most of the benign focal epilepsies, but the other AEDs are also as effective. Very often, AEDs in low dose are effective for the treatment of idiopathic childhood focal epilepsies.

*Contingency situation:* The treatment of idiopathic focal epilepsies in developing countries also has to be tailored on the pattern described above. When a decision to treat is arrived at, most such epilepsies would respond to any of the commonly used AEDs. The AED used in developing countries would largely depend on its availability and affordability.

### Symptomatic Generalized Epilepsies

*Ideal situation:* Patients with diffuse brain damage and epileptic seizures usually experience multiple seizure types, including generalized tonic-clonic seizures, atypical absences, myoclonic jerks, and drop attacks. The Lennox-Gastaut syndrome typifies this group of conditions. When multiple seizure types occur, valproate is often the drug of choice, but commonly polytherapy is neces-

sary, and often seizures cannot be completely controlled. Drop attacks are particularly refractory to pharmacotherapy, although felbamate, lamotrigine, topiramate, and zonisamide may be of some benefit. Because these patients are almost always intellectually compromised, drugs that further impair cognitive function, like the barbiturates and benzodiazepines, should be avoided.

*Contingency situation:* As pointed out earlier, these syndromes constitute the difficult-to-treat epilepsies even under optimal situations. While treating such patients, the efforts of the clinicians in developing countries are hampered not only by the refractory nature of the seizures but also by the limited availability of AEDs. The choice of AEDs while treating such patients in developing countries will be limited to those drugs that are available, and many times, the drugs used are not necessarily the ideal ones. Rectal diazepam (if available) could prove to be a very handy drug in case of recurrent and breakthrough seizures and even managing status epilepticus before the patient can be shifted to a hospital or even at a hospital with limited facilities.

### Special Syndromes

*Ideal situation:* Management of febrile seizures is a topic by itself and is discussed elsewhere (Chapter 5). The treatment of neonatal seizures is usually directed primarily at the cause, and that usually requires extensive investigations. Hypoglycemia, hypocalcemia, hypomagnesemia, and pyridoxine deficiency need to be treated energetically with specific replacements. When the decision to use AEDs is arrived at, PB is generally the drug of choice, with PHT being the second-line drug. A loading dose is usually given, followed by a maintenance dose for variable periods. The treatment of choice for infantile spasms in the industrialized world is ACTH or vigabatrin, although some success has also been achieved with VPA. Lennox-Gastaut syndrome is another condition with seizures that are usually not responsive to treatment. VPA and benzodiazepines (clobazam and clonazepam) are the commonly used AEDs that are effective against different seizure types. ACTH and

**KEYPOINTS**

- In developing countries, the management of epilepsy syndromes mentioned above largely depends on the availability of AEDs. While managing patients with resistant seizures, there is a tendency to increase the dose of an individual drug and also to increase the number of drugs. Such high-dose polytherapy with AEDs can often result in worsening of seizures, especially absences and tonic seizures.

corticosteroids have also been used with limited success. Trials with lamotrigine, felbamate, and topiramate have all shown a reduction in seizure frequency. Ketogenic diet has also been shown to be effective, especially in young children.

*Contingency situation:* In developing countries, the management of epilepsy syndromes mentioned above largely depends on the availability of AEDs. While managing patients with resistant seizures, there is a tendency to increase the dose of an individual drug and also to increase the number of drugs. Such high-dose polytherapy with AEDs can often result in worsening of seizures, especially absences and tonic seizures. PB and other benzodiazepines can additionally worsen the overactivity and aggressive behavior that is commonly associated with many of these syndromes, particularly those secondary to a brain insult. Rectal diazepam, when available, can be very helpful in emergency situations.

#### **ANTIEPILEPTIC DRUG CHOICE FOR SPECIFIC CONDITIONS**

The guidelines for choosing AEDs and initiating treatment are summarized in Tables 6.2 and 6.3, while Table 6.4 lists the commonly used first- and second-line AEDs for different seizure types. The details of practical approaches to treatment of seizures and epilepsy are listed in Chapter 5.

#### **DRUG INTERACTIONS AND OTHER ASPECTS OF PARTICULAR CONCERN IN DEVELOPING COUNTRIES**

Many developing countries are still endemic areas for malaria, HIV infection, tuberculosis, and parasites. They have, at the same time, the highest rates of incidence and prevalence epilepsy rates, mainly due to many of the secondary (and often preventable) causes of epilepsy. Many situations in the management of these disorders can directly or indirectly either precipitate seizures for the first time or result in the worsening of pre-existing seizures.

The increase of the incidence of tuberculosis has led to the increased use of isoniazid (INH). Acute intoxication by isoniazid is known to cause seizures, especially in

**TABLE 6.2** Guidelines for Choosing and Initiating Treatment with AEDs among Patients with Newly Diagnosed Epilepsy

1. Establish the seizure type(s) and, when possible, syndrome and etiology with the help of a good clinical evaluation and relevant investigations.
2. Start treatment with the first-choice single AED (Table 6.4). Start with a low dose and increase gradually to the acceptable maintenance dose.
3. If seizures are not controlled, increase the dose and check serum levels of the drug (if facility is available).
4. If seizures are controlled, continue the AED in the minimum effective dose. Almost two-thirds of patients will have good seizure control with a single appropriate AED.
5. In case of poor seizure control, try another drug (alternative monotherapy). First introduce the second drug with gradual dose increments until a therapeutic dose is reached, and then slowly taper off the first drug that had failed to control the seizures.
6. Refer the patient to a specialized center if seizures are not controlled with the second drug regimen. Infants and small children should also be referred if there is pre-existing developmental delay, abnormal neurologic examination, or the patient does not exhibit features of a recognizable syndrome.

**The common reasons for poor seizure control among patients with newly diagnosed epilepsy are: incorrect diagnosis (either missing an epilepsy syndrome or patient has nonepileptic seizures), poor drug compliance, poor bioavailability of cheaper 'generic drugs', failure to increase dose to the recommended level in the absence of side effects, and failure to introduce drug slowly, resulting in side effects and poor AED compliance.**

infants, accompanied by lactic acidosis, coma, and even death. This antitubercular drug raises the steady-state serum levels of primidone and phenytoin. Isoniazid-induced valproic-acid toxicity, or vice versa, has also been reported. For the same reasons, one

**TABLE 6.3** Guidelines for the Treatment in Patients with Chronic Epilepsy in an Epilepsy Center

1. Carefully review the history (if possible try to speak with a person who has seen the seizures), EEGs, CT/MRI scans, and other relevant investigations.
2. Try to classify the 'epilepsy syndrome' and also the seizure type(s). Rule out nonepileptic seizures by recording a few seizures with EEG (long-term video-EEG). Many times, epileptic seizures may coexist with nonepileptic seizures.
3. Ensure AED compliance (determine serum levels of AEDs) and construct a table of all the AEDs previously used with their maximum doses (ensuring that maximum doses have been used), beneficial effects, and side effects.
4. Find out about any other drugs that the patient may be taking that could cause drug interactions.
5. Try the second-line (new) AEDs as add-on therapy.
6. Evaluate the patient for epilepsy surgery, especially if patient has intractable partial seizures.

**Remember that a small percentage of patients with seizures have truly intractable seizures and current AED therapy has a limited role in such situations.**

needs to be careful when using isoniazid with carbamazepine and do a regular clinical and biological surveillance. Pyridoxine given early is the only effective antidote, in a dose equivalent to the amount of INH ingested. Rifampicin interacts with phenytoin and decreases the serum level of phenytoin by increasing its hepatic metabolism. Pyrazinamide is hepatotoxic and requires biological surveillance before and during treatment with AEDs.

New-onset seizures are a frequent manifestation of central nervous system disorder among patients infected with human immunodeficiency virus (HIV). Seizures are more common in advanced stages of the dis-

ease, although they may occur early in the course of illness. The majority of patients have generalized seizures, and status epilepticus is not uncommon because the associated metabolic abnormalities increase the risk for status epilepticus. Opportunistic infectious and/or tumor-like cerebral lesions can also lead to partial and/or generalized seizures in HIV-infected patients. Several new anti-retroviral drugs have been produced during the last 10 years. Some have been shown to have a clear-cut neurotoxicity including peripheral effects. Some are too new to prove their eventual undesirable effects, while others may have pharmacologic interactions with AEDs. For these reasons, one needs to be very cautious when facing situations necessitating a long-term use of AEDs and anti-retroviral drugs.

Malaria is a common problem in many developing countries. The high fever in malaria can itself cause seizures, and chloroquine used commonly for the treatment of malaria can also rarely cause seizures. Among the new antimalarial drugs, mefloquine has been reported to increase seizure frequency in epileptic patients and should not be administered to patients with a history of convulsions, those with history of epilepsy in first-degree relatives, or those having serious psychiatric disorders. On the whole, the risk of mortality due to malaria is much more than the risk of single or recurrent seizures due to malaria except while using mefloquine.

Although PB has been in clinical use for almost a century, its efficacy and side effects among people living in developing countries have never been determined. Genetic, dietary, or other environmental factors could greatly alter pharmacokinetic and pharmacodynamic activities in these populations, and affect the efficacy and side effects of this and other drugs. It is not an uncommon clinical experience that PB used in smaller doses is an effective and safe AED among people with epilepsy in developing countries. There is a strong case to study the efficacy and safety profile of this cheap AED among populations in developing countries. Backed by supportive data, PB could be a very good candidate for the first-line single AED for use at the community level in developing coun-

#### KEYPOINTS

- It is not an uncommon clinical experience that PB used in smaller doses is an effective and safe AED among people with epilepsy in developing countries.

**TABLE 6.4** Recommended AEDs for Different Seizure Types

Seizure Type	First-line	Second-line	Third-line
<b>Generalized Seizures</b>			
Absence (typical and atypical)	Valproate	Ethosuximide Lamotrigine	Levetiracetam Zonisamide
Myoclonic	Valproate	Topiramate Levetiracetam Lamotrigine Zonisamide	Clobazam Clonazepam Phenobarbital
Tonic-clonic	Phenobarbital Phenytoin Carbamazepine Valproate	Lamotrigine Oxcarbazepine	Topiramate Levetiracetam Zonisamide
Atonic	Valproate	Lamotrigine Topiramate	Felbamate
<b>Partial Seizures</b>			
Simple and complex partial with or without secondary generalization	Phenobarbital Phenytoin Carbamazepine	Valproate Oxcarbazepine Lamotrigine Topiramate Levetiracetam Zonisamide	Gabapentin Tiagabine Vigabatrin Felbamate

tries. Similar studies are required for other commonly used AEDs also so that their correct place in clinical usage could be ascertained.

Irregular supply and the availability of spurious drugs in many of the developing countries are important issues especially while using drugs like PB. Many generic brands are available in most of the developing countries that are usually much cheaper compared to the brand name drugs. Bioavailability of the generic drugs can be variable and not reliable, resulting in breakthrough seizures or sudden appearance of adverse side effects.

It should also be remembered that many people with epilepsy in developing countries use traditional medicines even while on modern AEDs. These traditional medicines could contain substances with potential antiepileptic effects, and this is another aspect that needs to be investigated very seriously. As neurologists, we should not necessarily discourage the use of traditional medicines, particularly when the seizures are controlled and these medicines are not

causing any side effects. The use of yoga, different forms of meditation, and other such physical measures have been shown to be effective in reducing the seizures in isolated studies and this issue also needs to be addressed in a more organized and scientific manner.

## CONCLUSIONS

Neurologists practicing in developing countries, even more than in the industrialized world, need to be aware of the important pharmacokinetic properties that permit available AEDs to be used most effectively, with minimum side effects and drug interactions, in order to make the best use of limited resources. Irregular supply of the available AEDs resulting in breakthrough seizures is also a major problem in many developing countries. Besides the effectiveness of a particular drug, its cost becomes an important issue in developing countries when selecting AEDs. In this context, PB could still be used as the first-line AED despite its reported adverse effects. Clinicians in developing countries would still

have the option of switching over to other first-choice AEDs in case of problems with PB. Interestingly, the efficacy as well as the adverse drug reactions of the AEDs among people with epilepsy in developing countries could be significantly different compared to that among those in the industrialized world due to genetic, dietary, or environmental factors. Hardly any trials on the usefulness and safety of conventional and

new AEDs have been conducted among populations in developing countries despite the fact that most of the people with epilepsy today live in developing countries. The pharmaceutical industry needs to correctly estimate the marketing potential of AEDs in the developing countries, and should invest more in developing nations when planning future trials with AEDs.

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## ALTERNATIVE TREATMENTS

About 20% to 30% of epileptic patients have seizures that are not completely controlled with medication, and this figure has remained stable over the last 20 years, despite the introduction of many new and expensive antiepileptic drugs (AEDs). Current research suggests that seizures not controlled with adequate trials of two first-line drugs in monotherapy, nor with one or two rational drug combinations, should be considered medically refractory. There is no fixed time frame for the sequential trials of medications because this depends on age and seizure frequency.

The proportion of refractory patients varies significantly among the various epilepsy syndromes. For instance, the proportion of medically refractory patients with post-traumatic or post-stroke epilepsies is smaller than with temporal lobe epilepsy due to hippocampal sclerosis or with focal cortical dysplasia. Syndromic and etiologic diagnoses, therefore, are helpful in determining which patients are likely to continue to have seizures despite adequate pharmacotherapy. For these patients, timely and successful use of alternative treatments, particularly epilepsy surgery, can spare them years of suboptimal quality of life and prevent irreversible cognitive, psychosocial, and occupational disability. Thus, early recognition of pharmacoresistance and application of available alternative treatments is crucial to a good outcome.

Alternative treatments, particularly those that do not require sophisticated and expensive technology, are more important in the developing world than in the industrialized world, where refractory epilepsy is more common because effective AEDs are unavailable, or the supply is unreliable. In these situations, avoidance of precipitating

factors and appropriate use of traditional healers can greatly improve chances that seizures will be reduced or eliminated.

### RESECTIVE SURGICAL TREATMENT OF EPILEPSY

The second half of the 19th century witnessed the first modern neurosurgical procedures to alleviate pharmacoresistant seizures. However, epilepsy surgery progressed in a stepwise fashion rather than at a steady pace, because concerns with efficacy and safety, as well as the development of AEDs during the 20th century, have often challenged the procedure. The attainment of the current situation, where epilepsy surgery has a firm place in the neurological therapeutic armamentarium, depended on a number of advances in functional neuroanatomy, neurophysiology, and neuroimaging. The introduction of high-resolution MRI in the past decade has now simplified presurgical evaluation sufficiently for some patients to make surgical treatment for epilepsy a reality in the developing world.

### Approaches to Resective Surgical Treatment in the Developing World

The fairly recent concept of surgically remediable epilepsy syndromes is key to the view that surgical intervention can be a practical alternative therapy in many developing countries. Surgically remediable syndromes are conditions with known pathophysiology and natural history, characterized by disabling seizures that are highly likely to be pharmacoresistant if the first few trials of AEDs fail, but have a 70% to 90% chance of being eliminated by an appropriate surgical resection. Surgery for these conditions is cost-effective because the epileptogenic region to be resected can be localized nonin-

### KEYPOINTS

- About 20% to 30% of epileptic patients have seizures that are not completely controlled with medication, and this figure has remained stable over the last 20 years, despite the introduction of many new and expensive antiepileptic drugs.
- Alternative treatments, particularly those that do not require sophisticated and expensive technology, are more important in the developing world than in the industrialized world, where refractory epilepsy is more common because effective AEDs are unavailable, or the supply is unreliable. In these situations, avoidance of precipitating factors and appropriate use of traditional healers can greatly improve chances that seizures will be reduced or eliminated.
- The fairly recent concept of surgically remediable epilepsy syndromes is key to the view that surgical intervention can be a practical alternative therapy in many developing countries.

**KEYPOINTS**

- The prototype of a surgically remediable epilepsy syndrome is mesial temporal lobe epilepsy, the most common form of epilepsy, and one of the most resistant to AEDs.
- MRI is the single most important tool in the identification of surgically remediable syndromes.
- In most developing countries, the identification of the surgically remediable syndrome and the determination of surgical candidacy will both be performed at the referral center where MRI is available. The crucial role of the neurologist working in the community is the timely identification of pharmacoresistance and suspicion of a surgically remediable syndrome.
- For most who have surgically remediable syndromes, sophisticated technology is not needed for evaluation and surgery, provided adequately trained and experienced personnel can optimize the use of the available resources.

vatively, usually by identification of a structural abnormality with high-resolution magnetic resonance imaging (MRI), which is confirmed to be epileptogenic by electroencephalogram (EEG). Patients with surgically remediable epilepsy syndromes commonly have normal, or near-normal, functional capacity at the outset, apart from their epileptic seizures, but progressive psychological and social problems, or developmental delay in children, ensue if seizures are not completely controlled. Consequently, early surgical intervention can rescue a patient from a lifetime of disability and dependence on family and society for support.

The prototype of a surgically remediable epilepsy syndrome is mesial temporal lobe epilepsy, the most common form of epilepsy, and one of the most resistant to AEDs. Patients with focal seizures due to easily accessible discrete neocortical lesions, as well as infants and young children with catastrophic epilepsy due to diffuse lesions limited to one hemisphere, such as extensive Sturge-Weber malformations and hemimegacephaly, also have surgically remediable syndromes. All of these conditions can be easily diagnosed by appropriately trained personnel using MRI and EEG. If epilepsy surgery practice is limited to this fairly significant portion of the population with medically refractory epilepsy, the results will be excellent and the cost will be significantly less than that of long-term medical care and welfare support.

MRI is the single most important tool in the identification of surgically remediable syndromes. In patients with medically refractory epilepsies, the convergence of clinical and EEG abnormalities to a cortical region harboring a resectable structural lesion should immediately lead to consideration of surgical candidacy. In regions where MRI is not available, a suspicion of a surgically remediable syndrome is the first step toward referral to more specialized centers. Patients with recurrent partial seizures unresponsive to medication should be considered as potential surgical candidates until proven otherwise. In particular, a clinical history compatible with complex partial seizures of temporal lobe origin (see Chapter 2) associated with epileptiform EEG abnormalities in

one or both temporal lobes should prompt referral to a center where MRI is available, to determine the presence of the single most common surgically remediable syndrome, namely temporal lobe epilepsy due to hippocampal sclerosis. In most developing countries, the identification of the surgically remediable syndrome and the determination of surgical candidacy will both be performed at the referral center where MRI is available. The crucial role of the neurologist working in the community is the timely identification of pharmacoresistance and suspicion of a surgically remediable syndrome.

Technological advances in long-term video-EEG monitoring, intracranial electrode recordings, functional imaging, and intraoperative monitoring as part of the surgical armamentarium are the rule in industrialized countries. Epilepsy surgery in this context is a highly sophisticated procedure; safer resections of epileptogenic regions close to eloquent cortex are now possible through neuronavigation and intraoperative MRI. These procedures, however, are necessary for only a small fraction of the patients who are potential surgical candidates. For most who have surgically remediable syndromes, sophisticated technology is not needed for evaluation and surgery, provided adequately trained and experienced personnel can optimize the use of the available resources.

Surgical candidacy is determined by identification of an epileptogenic region that can be safely resected with a high probability of seizure control and a low probability of introducing new, unacceptable neurologic deficits. History and careful description of the ictal semiology provides important clues regarding the site of seizure generation. For patients with surgically remediable syndromes, it is then necessary to demonstrate the presence of a structural lesion in the suspected brain area, usually by MRI. Finally, the epileptogenic nature of this lesion must be confirmed by EEG, preferably by long-term video-EEG monitoring of ictal onsets. Where such facilities are available, however, a single, well-localized interictal EEG spike focus will suffice for many patients. Interictal focal functional deficits further help to identify the brain area that is persistently abnormal, and provides confidence that it can be

removed without producing additional neurologic disturbances. The neurologic exam can be used for this purpose when the epileptogenic region is in primary cortical areas. For the more common mesial temporal lobe epilepsies, careful neuropsychologic evaluation is necessary to document verbal learning and memory problems with lesions in the language-dominant hemisphere, and visual-spatial problems when the lesion is in the nondominant hemisphere. Given the results of this presurgical evaluation, an experienced epilepsy surgery team, with specialized expertise in epileptology, clinical neurophysiology, neuroradiology, neuropsychology, and neurosurgery can provide the patient with a realistic surgical

prognosis with respect to seizure outcome, subsequent quality of life, and risk of additional deficits. In the industrialized world, when results of this noninvasive presurgical evaluation are equivocal, more detailed studies can be carried out using intracranial depth or grid electrodes to record ictal events; however, the development of facilities for this purpose is not likely to be cost-effective for most developing countries. Intraoperative interictal electrocorticography (ECoG), however, can still be used to answer residual questions in some patients.

A reasonable first step for centers in developing countries is to focus on the surgical treatment of mesial temporal lobe epilepsy and of certain types of neocortical lesion-

#### KEYPOINTS

- A reasonable first step for centers in developing countries is to focus on the surgical treatment of mesial temporal lobe epilepsy and of certain types of neocortical lesional epilepsies. Besides constituting the largest proportion of surgically remediable epilepsies, these syndromes have the additional advantage of not being too demanding in terms of technological requirements.

#### CASE STUDY

**Presentation:** A 27-year-old woman complained of difficulties maintaining jobs, being repeatedly fired due to “inadequate behavior at work.” She had been working as a secretary, and often became “spaced out” during phone calls, did not register important appointments, and failed to deliver messages to her colleagues and chiefs. In addition, her colleagues would mention strange behaviors during which she would stare fixedly ahead and purposelessly remove all objects from her tabletop, or else lick her lips repeatedly, producing a strange sound. After a minute or so, movements would stop, and she would slowly recover, without recollection of what had happened, except that she probably had had a seizure. She had a diagnosis of epilepsy, which she omitted in job interviews. She had been treated with many different combinations of AEDs, for more than 10 years, but seizures were not controlled. She had had two prolonged febrile convulsions during a benign viral meningitis at age 2 and was kept on AEDs for about a year after that. She then remained free of seizures up to mid-adolescence. At present, she was taking carbamazepine 1,200 mg/day and clonazepam 6 mg/day.

**Evaluation:** General medical and neurologic examinations were normal. She had a stack of EEGs performed over the years, and they all showed epileptiform and slow-wave abnormalities over the right temporal lobe, only occasionally being independently recorded on the left side. A CT scan was normal, and doctors had told her that her epilepsy probably was caused by some abnormality during delivery. She was sent to an epilepsy center in her region, where an MRI showed atrophy and increased signal in the right hippocampus. The diagnosis of hippocampal sclerosis in a woman with medically refractory seizures and significantly negative psychosocial impact, led to the discussion of the possibility of epilepsy surgery. She was then referred to a tertiary center to undergo preoperative evaluation. The latter could be streamlined due to a consistent clinical, interictal EEG, and imaging picture. A 24-hour prolonged 16-channel EEG showed an abundance of spikes and irregular slow waves over the right anterior and basal temporal lobes. Neuropsychology showed preservation of most cognitive abilities, except for visual memory.

**Treatment and outcome:** The patient underwent an anterior temporal lobectomy. She has been maintained with carbamazepine 1,200 mg/day, and is now seizure free for 2.5 years.

**Comment:** This woman suffered from delayed diagnosis of a common and surgically remediable epilepsy syndrome, namely mesial temporal lobe epilepsy due to hippocampal sclerosis. The delay in diagnosis allowed this often curable disorder to negatively impact her professional life. Important points illustrated by this case are the occurrence of a prolonged febrile convulsion with several years of a “latent period,” followed by the appearance of complex partial seizures, which eventually become difficult to control and prone to interfere with personal and professional activities. A common scenario, also illustrated by this woman, is the use of many different combinations of AEDs, until a point is reached where no doubts remain that the disorder will not be controlled by medication alone. Unfortunately for this woman, such realization occurred in her late 20s, although the clinical picture was fully established a decade earlier. Current evidence suggests that a period of 1 to 2 years may be enough to determine medical refractoriness. Surgical treatment for this disorder is now available in many developing countries. When indicated, it can help control seizures in more than 80% of patients.

**KEYPOINTS**

- Thus, the challenge for specialized epileptologists in these countries is to develop realistic protocols, and to continuously re-evaluate surgical results in order to improve presurgical and operative approaches.

al epilepsies. Besides constituting the largest proportion of surgically remediable epilepsies, these syndromes have the additional advantage of not being too demanding in terms of technological requirements. Many candidates for temporal lobe surgery can undergo surgery with excellent results on the basis of interictal EEG epileptiform abnormalities, neuropsychologic assessment, and MRI. When evidence of hippocampal sclerosis is present and the other data are concordant for the same anterobasal temporal lobe region, surgery is usually successful, irrespective of the data provided by scalp ictal EEG. Presurgical evaluation without ictal EEG recordings, however, will demand even greater experience on the part of the diagnostic team, which is why “skilled personnel” are the most essential component of an epilepsy surgery center where resources are limited. A 16-channel EEG machine with a video recorder plus a 1.5T MRI and very good neuropsychology is all that is required to operate on many surgical candidates with mesial temporal lobe epilepsy (as well as

certain types of neocortical lesional epilepsies and surgically remediable catastrophic epilepsies of infancy and early childhood). Thus, the challenge for specialized epileptologists in these countries is to develop realistic protocols, and to continuously re-evaluate surgical results in order to improve presurgical and operative approaches.

A valid question in this era of ever-increasing, high-technology approaches to diagnosis and treatment is whether *minimum requirements* for epilepsy surgery are changing. The answer is: probably not. Technological progress allows patients with more complex epilepsy to be adequately evaluated and occasionally operated on in epilepsy surgery centers in the industrialized world, but is not contributing much to management of the “easy” surgical candidates. The ability to operate on additional patients in these high-tech centers is, of course, important, but their numbers are small in comparison with the number of patients who have mesial temporal lobe epilepsy and other surgically remediable epilepsy syn-

**CASE STUDY**

**Presentation:** An 11-year-old girl had left school 2 years before presentation because of multiple epileptic seizures during sleep. She was a good student until seizures began 3 years earlier, when she had a dramatic decrease in school performance. She would have between 10 and 30 seizures per night, all stereotyped: the left arm would extend, her head would rotate to the left, and the right arm would flex at the elbow. She would then have difficulties breathing, awaken, and after a few minutes would again fall asleep. During the day she would be somnolent and irritable, and her concentration was poor. Behavioral abnormalities and low grades led her to drop out of school. Multiple AEDs, in mono- and polytherapy, failed to control or even reduce the frequency of the nightly attacks. When evaluated, she was taking carbamazepine 1,000 mg/day, valproic acid 1,500 mg/day, and clobazam 20 mg/day. History disclosed no presumed etiology for the epilepsy.

**Evaluation:** General medical and neurologic examinations were normal. EEGs showed frequent bilateral synchronous frontal spikes, without lateralization. A CT scan was normal. She was referred to an epilepsy center, where an MRI revealed an area of increased cortical thickness and abnormal signal in the right superior frontal gyrus, about 4 cm in front of the precentral gyrus. One night-time prolonged video-EEG recording sufficed to record 14 seizures, all starting in the right anterior quadrant, with fast generalization. After additional testing, she was referred to epilepsy surgery.

**Treatment and outcome:** The patient underwent resection of the lateral and medial surfaces of the right superior frontal gyrus, under ECoG guidance. The lesion appeared to be completely resected. Focal cortical dysplasia was confirmed on pathologic examination. There were no complications. She has been maintained on carbamazepine 1,200 mg/day and clobazam 20 mg/day. Despite this, she continues to have one to three sleep-related seizures per month. However, because she now can go for weeks without any seizures, she has been able to successfully resume school activities.

**Comment:** This girl illustrates the severe partial epilepsies that can be associated with malformations of cortical development, and particularly with focal cortical dysplasia. The frontal lobe seizures occurred so often that they caused prolonged sleep deprivation, with a negative impact on cognition and behavior. Malformation of cortical development should be suspected in patients with such severe epilepsies, even when cognition is uncompromised. Even though surgical outcome for this disorder is not as universally beneficial as it is for mesial temporal lobe epilepsy, a surgical approach can still be cost-effective in developing countries where epilepsy surgery centers exist.

## CASE STUDY

**Presentation:** This 34-year-old woman, with recurrent seizures since age 8, presented to the epilepsy clinic after having failed epilepsy surgery 2 years earlier. Her history was remarkable for a prolonged febrile convulsion at 6 months of age. Her current attacks began with nonspecific dizziness, progressing to disconnection from the environment and dystonia of the left hand. Secondary generalization was uncommon, and the partial seizures recurred at least twice a week. Neither semiological features nor seizure frequency were modified by operation, which consisted of a right anterior temporal lobectomy, including resection of the mesial structures.

Review of the notes of the preoperative evaluation showed that abundant interictal spikes were recorded from the right sphenoidal, anterior, and mid-temporal electrodes, and that ictal recordings consistently showed seizure onset over the entire right temporal lobe. Computed tomography (CT) disclosed three small calcifications, respectively, in the right posterior temporal, right parietal, and left occipital regions. MRI hinted at these small lesions, but was remarkable for a reduced volume of the right hippocampus, without abnormal signal intensity. Neuropsychologic evaluation had shown abnormal visual memory. Postoperative histopathology was not available. Presently, she was taking carbamazepine 1,600 mg/day and clobazam 30 mg/day.

**Evaluation:** IgG, but not IgM, immunoassays for cysticercosis were positive. Repeat video-EEG monitoring disclosed spikes and ictal onsets from the right mid and posterior temporal regions. MRI showed the extent of previous resection and the void signal related to the calcifications shown on CT.

**Treatment:** After discussing with the patient and relatives the risks inherent in reoperations and the potential for a visual field defect, a right mid- and posterior temporal lobectomy was performed under electrocorticographic monitoring. Very frequent spikes were recorded from the cortex surrounding the posterior temporal calcified cyst.

**Outcome:** Seizures were completely controlled, and have not recurred after 30 months of follow-up. A left superior quadrantanopia can be detected by clinical examination. The patient is currently taking carbamazepine 1,200 mg/day and clobazam 20 mg/day.

**Comment:** This woman had seizures related to a calcified cysticercotic temporal lobe cyst and surrounding epileptogenic cortex, whose role in seizure generation was initially neglected. The presence of an atrophic ipsilateral hippocampus and a history of prolonged febrile convulsions directed the attention to the anteromesial temporal lobe structures. Although both interictal spikes and ictal onsets also involved the anterior temporal regions, they were much more widespread over the right temporal lobe. These EEG findings, the nonspecific semiological features, and the lack of an abnormal signal intensity of the atrophic hippocampus should have raised a red flag in regard to an anteromesial localization of the ictal generators.

Some patients with calcified cysts and refractory epilepsy may also have hippocampal sclerosis. The hippocampus was not likely to have been epileptogenic in this woman, because improvement after the first operation—directed at the mesial temporal structures—was virtually nil. An important issue to be clarified through further studies is why some calcified cysticercotic cysts are epileptogenic and others are not—such as the right parietal and the left occipital cysts in this patient.

dromes. Furthermore, satisfactory surgical results are much more dependent on the clinical skills of relevant specialists than on cutting-edge advances in neuroimaging or clinical neurophysiology. In addition, there is the obvious need to optimize the allocation of limited technological resources. In practice, this means that potential candidates for epilepsy surgery must have access to MRI and video-EEG monitoring in countries where inequalities of medical care restrict availability of costly procedures to those who need them most.

### Justification for Resective Epilepsy Surgery in the Developing World

Approximately 80% of persons with epilepsy live in developing countries. Thus, 80%

of patients who could potentially benefit from surgical treatment live in these regions. It is hardly acceptable that the majority of individuals who could benefit from any particular form of treatment cannot receive it. The challenge is to reconcile the need for careful presurgical evaluation with the need to make epilepsy surgery widely available. Developed countries, with all their technology and experience, should help developing countries design simpler, but effective strategies to evaluate patients for surgery. Efforts in the industrialized world to support and disseminate advances that make epilepsy surgery more cost-effective will aid millions of people in developing countries who need not suffer the consequences of medically refractory seizures.

### KEYPOINTS

- Approximately 80% of persons with epilepsy live in developing countries. Thus, 80% of patients who could potentially benefit from surgical treatment live in these regions. It is hardly acceptable that the majority of individuals who could benefit from any particular form of treatment cannot receive it. The challenge is to reconcile the need for careful presurgical evaluation with the need to make epilepsy surgery widely available.

**KEYPOINTS**

- For patients with pharmaco-resistant seizures, who are the greatest consumers of AEDs and are in the most need of other health care resources, elimination of disabling seizures by surgery could have an enormous beneficial impact on the cost of their care.
- Reintegration into society, not only of patients, but also of their caregivers, also justifies the costs of implementing epilepsy surgery.
- Because an expensive presurgical evaluation is not required, corpus callosotomy could be offered cost-effectively in developing countries with neurosurgical facilities.

The best model will involve a creative partnership between specialists trained abroad and their local colleagues to develop regional or national epilepsy surgery programs. The next step will be to train people locally and legitimize the concept of regionally relevant approaches.

The economic feasibility of surgical treatment in countries with limited resources is readily apparent. Data from Colombia show that epilepsy surgery can be performed at one-tenth the cost of that in developed countries, and countries like Brazil, India, and Turkey have reported a similar experience. In contrast, AEDs are often unavailable, unaffordable, or irregularly distributed in the developing world. Eighty percent of the pharmaceutical market is focused on the 20% of persons with epilepsy living in industrialized countries. For patients with pharmaco-resistant seizures, who are the greatest consumers of AEDs and are in the most need of other health care resources, elimination of disabling seizures by surgery could have an enormous beneficial impact on the cost of their care. The realistic goal to reduce or eliminate the need of AEDs in many patients should be considered in both the ethical and economic arguments for epilepsy surgery in developing countries.

Because opportunities for education and work are considerably more limited in developing countries, the handicap imposed by uncontrolled epilepsy is almost certainly greater than in areas where schooling and employment are easier to obtain. About half the people unemployed before epilepsy surgery can find a job after operation, provided the patient is not mentally retarded and seizures are satisfactorily controlled by the procedure. Psychological and social rehabilitation, however, is dependent on the preoperative educational and vocational status of the patient, indicating the need for an earlier and more aggressive approach to surgical intervention. For nonwealthy states, losing a job, or not obtaining one in the first place, can be catastrophic for the lifetime of the individual (see Chapter 5). Reintegration into society, not only of patients, but also of their caregivers, also justifies the costs of implementing epilepsy surgery.

**PALLIATIVE PROCEDURES**

A sizable proportion of patients with medically refractory seizures have epilepsy syndromes that are not surgically remediable. They do not have a single, resectable epileptogenic zone, and often have a diffuse epileptic encephalopathy, in which disabling seizures coexist with generalized or multifocal EEG abnormalities and intellectual disability. A number of palliative procedures have been developed to alleviate the condition in these patients, including corpus callosotomy, vagal nerve stimulation, and ketogenic diet. All these procedures target cortical epileptogenicity in a nonspecific fashion, do not involve resection of cortical tissue, and act through mechanisms that are not fully understood.

**Corpus Callosotomy**

A section of the corpus callosum interferes with interhemispheric synchronization of epileptic activity, thus reducing the probability of occurrence of generalized seizures dependent on such synchronization. As such, the procedure aims at reducing tonic, atonic, and myoclonic drop attacks, as well as generalized tonic-clonic seizures. Partial seizures are often unaffected or even increased by the procedure. Preoperative evaluation must exclude a resectable epileptogenic zone, but is usually straightforward. Long-term outcome after corpus callosotomy is variable. Because there is a risk of motor and cognitive complications, the pros and cons of corpus callosotomy should be balanced on an individual basis. However, because an expensive presurgical evaluation is not required, corpus callosotomy could be offered cost-effectively in developing countries with neurosurgical facilities.

**Ketogenic Diet**

The increase in ketone bodies associated with a diet rich in lipids and low in carbohydrates decreases seizure frequency in a significant percentage of patients with pharmaco-resistant epilepsy. The mechanisms through which the ketogenic diet exerts its antiepileptic effect are not fully understood. Open studies report that some patients may become seizure free and that more than 50% achieve a significant reduction in seizure fre-

quency. The need for absolute compliance with the diet and gastrointestinal side effects are the main deterrents to its use. Although a multidisciplinary support team of diet specialists, clinicians, and psychologists is usually considered necessary for effective implementation of the ketogenic diet in the industrialized world, this alternative therapy has been successfully and cost-effectively used in developing countries without such support.

### Vagus Nerve Stimulation

Evidence that subcortical structures may modulate cortical epileptogenicity and pathways of seizure propagation led to the development of vagal nerve stimulation. This technique involves implantation of electrodes on the cervical portion of the vagus nerve and of a subcutaneous stimulator, which costs several thousands of dollars. Stimuli are delivered at a given frequency, travel through the nerve toward relay nuclei in the medulla and pons, and from there, interfere diffusely with cortical and subcortical excitability. A reduction of about 50% of the seizure frequency in 50% of patients seems to be the uniform result in most series. Thus, vagal nerve stimulation is not a cost-effective alternative treatment for countries with limited resources.

### DEALING WITH PRECIPITATING FACTORS

The management of seizure-precipitating factors usually does not include AEDs, and it may be appropriate to discuss this issue in the context of alternative treatments (see also Chapter 5). Many of these factors can lead to seizures even in patients without epilepsy, and all can precipitate seizures in epileptic patients. With a few exceptions, change of habit is key to dealing with these factors, but this may prove difficult to achieve. Patients often come to accept that epilepsy demands the use of pills, but are much less prone to accept that the condition may require the change of habits or attitudes that are perceived as part of their lives. Thus, the first step is to provide a simplified explanation to the patient and relatives about the mechanisms through which these precipitating factors can lead to seizures, making it clear that avoiding them (whenever possible) is the logical thing to do.

### Menses

Seizure precipitation by menses is common in women with partial epilepsies and is related to reduced progesterone levels during this period. There are different ways to deal with the increase in seizures just before and during menses, and individualized approaches are the rule. A rather nonspecific approach is to simply augment the daily dosage of AEDs, thus increasing protection during the whole month. Another way is to increase AED dosages or add rapidly acting drugs such as benzodiazepines only in the week around menses, provided regular periods are the rule. Finally, for more severe epileptic disorders, hormonal therapies based on restoring progesterone levels can be administered.

### Sleep-Wake Cycles

For the purpose of dealing with persons with increased seizure susceptibility, the sleep wake cycles can be divided into four states: full wakefulness, deep sleep, the transition between sleep and wakefulness, and that between wakefulness and sleep. Different epilepsy syndromes tend to generate seizures in specific states of the sleep-wake cycles, and this should be recognized and managed accordingly. Approaches vary from adjusting the schedule of AED dosages to promote higher serum levels during the more vulnerable states, to the anticipation of an increased risk of seizures in specific situations related to the sleep-wake cycle, thus leading to the implementation of protective measures to avoid injuries during seizures. For instance, patients with some primary generalized epilepsy syndromes whose seizures tend to occur upon awakening should be advised to avoid driving in the first 2 or 3 hours of the day if they had few hours of sleep the night before. The role of sleep deprivation in seizure occurrence is an important issue for discussion with patients, particularly adolescents. Management options include encouraging a small nap before going out in the evening or the administration of an extra dosage of the usual AED before going into sleep. The relevance of sleep-wake cycles for seizure precipitation is illustrated in the following case report.

### KEYPOINTS

- Although a multidisciplinary support team of diet specialists, clinicians, and psychologists is usually considered necessary for effective implementation of the ketogenic diet in the industrialized world, this alternative therapy has been successfully and cost-effectively used in developing countries without such support.
- Thus, the first step is to provide a simplified explanation to the patient and relatives about the mechanisms through which these precipitating factors can lead to seizures, making it clear that avoiding them (whenever possible) is the logical thing to do.
- The role of sleep deprivation in seizure occurrence is an important issue for discussion with patients, particularly adolescents.

**CASE STUDY**

**Presentation:** A 15-year-old girl was noted to be convulsing during sleep at about 7 a.m. She had tonic-clonic jerking of all four limbs with blood-tinged frothing from the mouth. She had passed urine in her clothes and vomited once after a few minutes. She then slept for the next 2 hours and complained of headache and body aches on awakening. She also noticed that she had bitten her tongue. The previous two nights, she was awake till 3 a.m. and 5 a.m. in a cousin's wedding.

**Evaluation:** Her neurologic evaluation revealed a normal examination. She had no previous history of seizures or any neurologic insult. There was no family history of seizures. An EEG and CT scan of the head were performed and were normal.

**Treatment and outcome:** The issue of her risk for seizure recurrence was discussed with her and the family members. It was suspected that sleep deprivation for two consecutive nights could have provoked the seizure. It was thought safe to keep her under observation, and she was not prescribed any treatment. She was advised to change her lifestyle and observe regular habits and was seizure free when last seen about 2 years after her first seizure.

**Comment:** The management of patients presenting with a single seizure will continue to be a dilemma for clinicians. It is estimated that 5% to 10% of the population will have a single seizure during their lifetime. Sleep deprivation, hypoglycemia, alcohol withdrawal, high fever, and many other acute metabolic insults are some of the factors known to provoke seizures. This girl had a single provoked seizure and should not be classified as having epilepsy (by definition, a diagnosis of epilepsy requires two or more unprovoked seizures). People with a single provoked seizure need not be treated with AEDs except when there are associated factors that increase the risk for seizure recurrence, or a history of previous events that were unrecogized seizures (see Chapter 3 for details).

**KEYPOINTS**

- People who do not have a history of epilepsy, but present with seizures clearly related to alcohol or sedative drug withdrawal, need not be managed chronically with AEDs, although these may be prescribed for a short period of time.

**Alcohol and Sedative Drug Withdrawal**

Seizures can occur upon sudden alcohol and sedative drug withdrawal, particularly when these drugs have been used for prolonged periods. Although this is much more common in people with epilepsy, seizures in this context can also occur in people without epilepsy. When planned in advance, the period of alcohol withdrawal should be accompanied by the temporary administration of benzodiazepines, which will control not only the anxiety state induced by alcohol discontinuation, but will also increase seizure threshold. The approach to the safe discontinuation of sedative drugs is different, and requires decrease of dosages over a long period of time. In people with epilepsy, rapid withdrawal of barbiturates or benzodiazepines are well known seizure precipitants, and the discontinuation of these drugs should be done over weeks or months. When epilepsy is more severe, there is a definite risk of an increase in seizures even with slow discontinuation of barbiturates, and thus small dosages of a benzodiazepine can be admin-

istered temporarily. People who do not have a history of epilepsy, but present with seizures clearly related to alcohol or sedative drug withdrawal, need not be managed chronically with AEDs, although these may be prescribed for a short period of time.

**Stimulant Drugs**

Stimulant drugs can facilitate seizure occurrence in people both with and without epilepsy. Even small doses of cocaine or crack, and drugs such as amphetamines, methylphenidate, or sympathomimetic drugs for asthma can decrease seizure threshold sufficiently to cause seizures in susceptible individuals. Should an increase in seizure frequency occur in these contexts, preventive measures, including discontinuation of the precipitating drug or increase of AED dosages, should be taken. In some highly sensitive patients, even the use of caffeine should be discouraged. There are some regions of developing countries in which the ingestion of stimulants is a routine, including chewing or brewing coca leaves in the Andes and drinking *mate* (a stimulant herb)

in the South American Pampa. These habits may need modification in some persons with epilepsy in these regions.

### Toxic Metabolic Insults

Electrolyte imbalance, hypo- or hyperglycemia, and other toxic metabolic insults may lead to or facilitate the occurrence of seizures. Correction of the underlying systemic insult is the most important therapeutic measure, and AEDs are usually not indicated in those without a history of unprovoked seizures. Prolonged periods of excessively hot temperatures as well as endemic parasitic disorders in developing countries frequently lead to dehydration, vomiting, and diarrhea. In these situations, the possibility of electrolyte imbalance should be considered in epileptic patients with an otherwise unexplainable increase in seizure frequency.

### Sensory Stimulation

Seizures may be precipitated by a variety of sensory stimuli, particularly in certain specific epilepsy syndromes. Most common are patients with primary (idiopathic) generalized epilepsies who display photosensitivity. Intermittent photic stimulation from video games, stroboscopic lights, or a variety of alternating dark/light patterns may induce myoclonic jerks or generalized convulsions in these patients. Photosensitive-related seizures are at times self-induced by intellectually disabled patients. Rare reflex epilepsies are associated with seizures precipitated by a variety of complex stimuli such as eating, reading, music, and water baths. Somatosensory- or movement-induced seizures can occur in patients with epileptogenic zones in perirolandic regions, while ictal episodes associated with any modality of startle can occur with epilepsies due to extensive brain damage.

The vast majority of these patients also have spontaneous seizures, but the possibility that some episodes may be due to specific types of sensory stimulation should be actively pursued through clinical history, because avoidance of offending stimuli offers a nonpharmacologic means to reduce seizure frequency.

## THE PLACE OF TRADITIONAL MEDICAL TREATMENTS

Long-held cultural views about epilepsy and the failure of public health systems in developing countries to systematically identify and adequately treat recurrent seizures leaves room for traditional medical treatments. Educational campaigns led by governments and the World Health Organization (WHO), and non-governmental organizations (such as International League Against Epilepsy and IBE), continuously attempt to promote an understanding of epilepsy as a brain disorder with recognized causes and specific modes of treatment. Still, there is a long way to go as far as education is concerned.

Perhaps a bigger problem than the failure of people in developing countries to understand modern medical concepts of epilepsy is the failure of the allopathic medical establishment to understand and respect traditional beliefs of their patient population. Even in developing countries, it is the rule rather than the exception that allopathic physicians and healthcare workers are either not of the same ethnic group as the majority of their patients, or are so far removed from the traditional culture that they are no longer able to empathize with patients' and their families' concerns about specific diagnoses and recommended treatment plans. The perceived arrogance of allopathic medical practitioners and cross-cultural mismatches undoubtedly account for a considerable percentage of treatment failures in developing countries, as well as avoidable disasters, as was movingly documented by Anne Fadiman in her book, *The Spirit Catches You and You Fall Down*, about the tragic outcome of treatment offered to a Hmong child at a modern hospital in California. Both the physicians and healthcare workers on the one hand, and the Hmong community on the other, did their best to help this child, but failed to communicate adequately with each other, not only because they did not share a common language, but because they did not share a common culture. Interpreters are necessary who will not only translate words, but philosophies, and who will ensure that both parties to the discussion are treated with equal respect and understanding. The most common strategy used to

### KEYPOINTS

- Perhaps a bigger problem than the failure of people in developing countries to understand modern medical concepts of epilepsy is the failure of the medical establishment to understand and respect traditional beliefs of their patient population.
- The perceived arrogance of medical practitioners and cross-cultural mismatches undoubtedly account for a considerable percentage of treatment failures in developing countries.
- Interpreters are necessary who will not only translate words, but philosophies, and who will ensure that both parties to the discussion are treated with equal respect and understanding.

overcome cross-cultural obstacles to optimal patient care employs eight questions, designed by Arthur Kleinman, to elicit an explanatory model of the patient and the patient's family. These are:

1. What do you call the problem?
2. What do you think has caused the problem?
3. Why do you think it started when it did?
4. What do you think the sickness does? How does it work?
5. How severe is the sickness? Will it have a short- or long-term course?
6. What kind of treatment do you think the patient should receive? What are the most important results you hope to receive from this treatment?
7. What are the chief problems the sickness has caused?
8. What do you fear most about the sickness?

Although these questions might seem simpleminded and obvious at first, they set a tone that prevents the allopathic physician from blindly and dogmatically asserting opinions and making requests that are totally incompatible with the patient's and the patient's family's cultural context. Cross-cultural discrepancies can then be easily identified, and compromises can be reached based on informative discussions that are predicated on mutual respect and understanding.

Most traditional medical treatments for people with epilepsy are scientifically unproven, but at least provide some comfort to patients and relatives, with a favorable psychological impact that can be beneficial. Although these treatments can be harmful if they delay, or interfere with, standard medical attention that could provide more adequate diagnosis and treatment, or if traditional healers advise against allopathic medicine, they cannot be dismissed out of hand. A collaborative relationship should be developed between traditional and allopathic approaches to treatment.

Traditional medical approaches are discussed in more detail in Chapter 8; however, it is useful to provide some overview here. Most traditional healers utilize a holis-

tic approach, beginning with a diagnostic evaluation, for instance using cowries, sand, stones, animal sacrifices, interpretation of dreams, and dialogue with supernatural persons and forces. Next, treatment often recommends, transforms, or forbids the use of various animal, vegetable, mineral, and liquid substances, depending on their presumed benefit or potential harm to the patient. Their utilization can take the form of amulets, eating or drinking, inhalation, or bathing. In some societies, scarifications are practiced. During mystical celebrations, supernatural forces are "invited" by the healer to visit the patient if they are protective, or to withdraw from the body and soul if they are negative. The blood from sacrificed animals may be offered to the patient's family and ancestors, as well as to supernatural forces. Often the family is asked to make a specific donation, perhaps to the children, a religious group, or people in need. While these interventions can be highly effective as an adjunct to appropriate allopathic medical therapy, it is important to understand the traditional practices in their area, and gently discourage those that might have a detrimental effect because of known toxicities or other unhealthful consequences, such as malnutrition. On the other hand, it is not unlikely that some substances used by traditional healers could, in fact, have antiepileptic properties, and further scientific investigation would be appropriate.

## CONCLUSIONS

AEDs are not always effective in controlling epileptic seizures. Alternative forms of treatment, however, can often be useful to control seizures or reduce their frequency. While the identification and removal of precipitating factors is an effective nonpharmacologic intervention for some patients, many will have truly medically refractory seizures. Where epilepsy surgery facilities exist, it is crucial to suspect a surgically remediable epilepsy syndrome and refer promptly for further evaluation and surgical treatment. Epilepsy surgery as an alternative treatment in developing countries has been shown to be both feasible and cost-effective. More than technological sophistication, a positive attitude of skilled personnel is the basis of a

successful epilepsy surgery program in the developing world. Other alternative treatments, such as the ketogenic diet, can be effectively used, but vagus nerve stimulation

is less practical for developing countries. There are potential benefits from collaboration with traditional healers.

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## PSYCHOSOCIAL ISSUES

Epilepsy has been associated with centuries-old stigma that is so deeply rooted in society that modern diagnostic and therapeutic advances have not been able to nullify the psychosocial burden of the disorder, particularly in developing countries. The majority of people with epilepsy have their first seizure when they are still young. The problems for a person with epilepsy can begin while still at school and very often continue throughout life, limiting opportunities for education, employment, marriage, and children. The situation is complicated by the fact that in the majority of developing countries, the sociocultural environment of chronic disorders often leads to the dual utilization of modern and traditional medicines by most people. This duality exists due to the belief that chronic illness is “necessarily” the primary result of supernatural forces. Fostered by the family and local society, such a supernatural concept of disease has a dramatic negative impact on the epileptic patient’s life in terms of consultation, treatment compliance, follow-up, and burden. Efforts of nongovernmental organizations (NGOs), like the Global Campaign against Epilepsy, are expected to play a vital role in reducing the peculiar psychosocial burden posed by epilepsy.

### THE EPILEPTIC PATIENT

#### The Predicament

People with epilepsy most often come to the attention of health workers, whether modern or traditional, not because they have seizures, but because the seizures are interfering with their lives. If their seizures did not interfere with their lives, they would perhaps not seek help. It is, therefore, the health worker’s responsibility not only to

stop or reduce the seizures, but to understand how and why the seizures interfere with the patients’ lives and help them deal with this. The disability caused by the seizures constitutes the predicament. For health workers and neurologists to appropriately care for the person with epilepsy, it is necessary to fully understand all of the issues that contribute to the patient’s predicament, which include the need to consider traditional remedies, the stigma caused in part by beliefs in a supernatural power, and the adverse consequences of such misconceptions.

#### Traditional Healing

Unfortunately, modern allopathic medicine is too often in conflict with traditional practices. In such circumstances, traditional healers can interfere with timely and appropriate medical interventions, causing unnecessary disability.

On the other hand, the unpredictable nature of epilepsy causes a psychological tension borne by the individual, the family, and the group, and this stress is often better managed by the traditional healers than the modern doctors. The time and quality of listening to the patient and relatives is generally better in the mysterious traditional healers’ huts than at the crowded modern hospitals. Modern treatment, even when well applied, may not seem to be sufficient for the patient. Consequently, collaboration between modern physicians and traditional healers often provides the best opportunity for effective treatment.

The traditional treatment of epilepsy is still widely used in many developing countries and needs to be placed into its sociocultural context utilizing a holistic approach. The diagnosis is based on the history of the

### KEYPOINTS

- The problems for a person with epilepsy can begin while still at school and very often continue throughout life, limiting opportunities for education, employment, marriage, and children.
- For health workers and neurologists to appropriately care for the person with epilepsy, it is necessary to fully understand all of the issues that contribute to the patient’s predicament, which include the need to consider traditional remedies, the stigma caused in part by beliefs in a supernatural power, and the adverse consequences of such misconceptions.
- Collaboration between modern physicians and traditional healers often provides the best opportunity for effective treatment.

**CASE STUDY**

**Presentation:** A 29-year-old man has been experiencing sudden bursts of laughing since the age of 9, which can occur any-time or anywhere. Some laughing episodes are followed by loss of consciousness for less than 2 minutes and then full recovery. He has never been seen in a modern health center, but rather cared for by traditional healers who “diagnosed” him as “possessed by the devil.” Prescriptions of sacrifices, ritual baths, and amulets to wear have been respected, but the episodes continued. When he was 29, his mother heard on TV a documentary produced by the National League against Epilepsy stressing that these spells might be gelastic seizures.

**Evaluation:** The next morning, his mother, who used to ask prayers to help him “become more serious and attentive, rather than laughing and not listening to people who talked to him,” went to the only neurology service in the country and described what her son had been experiencing for 20 years, which was very similar to what she had learned the day before on TV. An electroencephalogram (EEG) revealed spikes and slow waves predominant over the left frontotemporal area.

**Treatment:** A prescription of carbamazepine was given.

**Outcome:** Two months later, only two events had occurred, compared to more than eight per month during the last 20 years.

**Comment:** This case illustrates the long delay before modern management is sought due to misconceptions of epileptic seizures in some cultural environments. It also demonstrates the effectiveness of public education about epilepsy.

**CASE STUDY**

**Presentation:** Since the age of 8, this 37-year-old man experienced bizarre symptoms, which led his mother to consult a traditional healer. Eleven years later, the healer recommended that she take him to a modern medical center. He has a sister with “seizures” who never consulted a medical doctor, but recovered 6 years after, without any specific treatment. The patient’s symptoms started at age 8, with complex absence seizures associated with brief jerks of both arms. Because they often occurred in the classroom, the teacher asked his parents to keep him at home to avoid “contaminating” the other children with the devil’s manifestations. He was cared for by a traditional healer who tried several techniques to “wash his spirit and body from the supernatural forces.” He improved, but was not allowed to attend school. At the age of 16, when his father died, the symptoms became worse, with delirium and aggressive behaviors, in addition to myoclonic absences and some tonic seizures with prolonged loss of consciousness. After the healer treated him with ritual baths, inhalation, amulets, long talks, and mystical incantations, his “psychiatric” symptoms improved, but the jerks and prolonged absences continued. At the age of 28, the healer recommended that his mother consult a neurologist. Antidepressant drugs were prescribed, but did not improve his status.

**Evaluation:** All investigations performed after his first consultations with the neurologist were normal. A diagnosis of epileptic and nonepileptic seizures was made.

**Treatment and outcome:** Despite a normal EEG, the neurologist tried carbamazepine and clonazepam. The jerks and prolonged absence improved, but when he does not consult the healer regularly, the psychiatric symptoms re-emerge.

**Comment:** This case is a rare one because there are very few traditional healers who are informed enough to accept that some symptoms and diseases are out of their area of expertise. In this case, the patient suffered from comorbidity, a reactive psychopathologic condition aggravated by his father’s death (responding to a traditional approach) and a clear-cut epileptic pattern responding to carbamazepine (which also probably had an effect on his mood) and clonazepam. The collaboration of modern and traditional approaches provided excellent care for his mental and physical problems.

illness, “complementary exploration” via search with cowries, sand, stones, animal sacrifices, interpretation of dreams, contact, and dialogue with supernatural personages

and forces. The treatment usually utilizes the different life elements: animal, vegetable, mineral, and liquid. Following indications, these natural means will be utilized, trans-

formed, or forbidden, depending on their supposed benefit or their disadvantages for the patient. If they are diagnosed as positive forces for the patient, they will be worn in different forms such as amulets for example, eaten, utilized for bath, drink, or breathed. Supernatural forces will be “invited” during special mystical celebrations, to visit the patient if they are protective, or withdrawn from his or her body and soul, if they are negative. These rituals are often public and crowded, accompanied with religious songs and dances. The themes of these evocations generally focus on the patient’s family and ancestors. Blood from sacrificed animals may be used to satisfy evil forces or to calm devils.

Just as for allopathic medicine, traditional healers can be specialized in a domain of action or treatment. Specific means for diagnosis and treatment can be strictly derived from pure traditional culture or from holy religious texts. Honest healers are able to direct their patient to medical doctors at an early stage, if they are convinced that the problem is not amenable to their abilities. Some traditional healers are reticent to manage epileptic patients, because they are afraid of transmitting “contagious epilepsy” to their own family or descendants. Others, for financial reasons and very often for the sake of prestige, persist in telling the family to follow their prescription only and not to mix it with antiepileptic drugs (AEDs). The family expenses in the traditional network are often higher than the annual cost of modern AEDs. Patients who have not been directed to allopathic medicine often adopt resignation and consequently accept the decision of God. On the other hand, patients with provoked seizures or benign syndromes can at times be spared inappropriate long-term pharmacotherapy by consulting a healer rather than a physician who would misdiagnose their condition. Some countries are attempting to maximize the beneficial services of honest traditional healers by developing standards for certification that, in turn, permit government reimbursement.

Very often, the methods and practices used in traditional healing leave a long-lasting impact not only on the minds of the patient and family members but, more

importantly, observers are impressed and overly influenced by such rituals. When negative, the message then spreads by word of mouth, worsening the predicament for people with epilepsy and for society. The practice of using traditional healing methods for the treatment of epilepsy is so rampant and deep rooted in society, especially among the rural and uneducated living in the far flung areas of developing countries, that any attempt to oppose these directly and aggressively could prove counterproductive. Epilepsy caregivers and health planners in developing countries need to understand this aspect of societal behavior and first aim to improve the public awareness and availability of modern treatment for people with epilepsy. Once seizures become controlled with modern medicines, the belief in and dependence on, faith healers may decline, while the role of modern medicine in epilepsy treatment gains acceptance by society.

### Stigma

In addition to the burden of the disease itself, epileptic patients must cope with the stigma attached to this disorder. Epilepsy is still classified with mental illnesses in the health care structure of many countries. This leads to further discriminative attitudes against people with epilepsy. Considered contagious in many cultural contexts, the epileptic patient is kept away from several family and social activities and functions. In many regions of the developing world, negative supernatural powers are considered to be the cause of seizures, resulting in fear and repulsion toward those afflicted with epilepsy. In some rare contexts, the positive aspects of these supernatural powers are evoked, leading also to fear, but also a certain degree of respect. Neurologists in developing countries must be aware of these real-life situations when managing patients with epilepsy because they contribute significantly to the societal stigma attached to this disorder.

### Safety Issues Relevant to Developing Countries

Some rituals practiced by faith healers in developing countries, such as scarification and tattooing, are associated with risks.

### KEYPOINTS

- Some countries are attempting to maximize the beneficial services of honest traditional healers by developing standards for certification that, in turn, permit government reimbursement
- The practice of using traditional healing methods for the treatment of epilepsy is so rampant and deep rooted in society, especially among the rural and uneducated living in the far flung areas of developing countries, that any attempt to oppose these directly and aggressively could prove counterproductive.
- Neurologists in developing countries must be aware of these real-life situations when managing patients with epilepsy because they contribute significantly to the societal stigma attached to this disorder.

**KEYPOINTS**

- Ridiculing the traditional beliefs of patients and their families is not the solution because it can offend their cultural and/or religious sensitivity and develop defensive behavior leading to nonacceptance of modern treatment.
- In most developing countries, there are no uniform rules concerning driving and epilepsy. As a result, most people with epilepsy hide their condition and continue to drive their own private and even public transport vehicles.
- When the decision to seek modern medical care is made and this happens, the health personnel must avoid making the families feel guilty about their delay because such feelings may dissuade them from continuing with modern medicines.

Ridiculing the traditional beliefs of patients and their families is not the solution because it can offend their cultural and/or religious sensitivity and develop defensive behavior leading to nonacceptance of modern treatment. Rather, the health professional should spend time and explain, with simple and understandable words, the epileptic disorder, its determinants, its management, and why the advantages and safety of modern treatment requires it to be continued for a long period. It may be helpful for the neurologist to accept some of the proposed traditional treatments, such as ritual baths, amulets, animal sacrifices, and prayers; methods that are less dangerous than the use of oral preparations and certain physical measures.

The use of generic drugs that have variable bioavailability compared to brand name medications, the irregular supply of commonly used AEDs, and improperly prepared or out-of-date drugs are common problems in developing countries that pose risks not only for an occasional breakthrough seizure, but also for grave emergencies like status epilepticus.

In most developing countries, women still cook around open fires and fetch drinking water from deep wells and fast-moving streams. Similarly, men who are fishermen go out into the seas and rivers each day in search of their livelihood. Whether or not such people with epilepsy are taking AEDs, they are always at risk for injury or even death, due to burns or drowning, as a result of a seizure. Even those who are on treatment with modern medicines are not without risk.

Some rituals in developing countries last throughout the night (e.g., marriages, religious congregations, political rallies), which increases the likelihood of seizure occurrence because of sleep deprivation and the fact that many patients forget their medicines during such events.

In most developing countries, there are no uniform rules concerning driving and epilepsy. As a result, most people with epilepsy hide their condition and continue to drive their own private and even public transport vehicles. Although it is safe for people with epilepsy whose seizures are

controlled to drive, those with epilepsy who continue to drive when their seizures are not controlled, or even treated, pose a risk to themselves and society. Similarly, people employed in high risk jobs like construction work and railway track maintenance who are not on effective treatment can experience severe injuries and death as a result of seizures at work.

**THE FAMILY**

In developing countries, management of epilepsy is not limited to the patient. The individual is part of a large group of people, including the family circle and the community. Individuals are not isolated in traditional societies. Members of the family are always involved in the patient's management process. Any treatment plan must take this fact into account and incorporate the entire family, social group, or community, rather than the individual.

Families of patients with chronic disorders such as epilepsy often move from one healer to another before becoming sufficiently dissatisfied to visit a modern medical center to try modern medicines. This process can take many years. When the decision to seek modern medical care is made and this happens, the health personnel must avoid making the families feel guilty about their delay because such feelings may dissuade them from continuing with modern medicines.

In consultations, it is common to encounter caregivers who do all the talking and answer every question posed to the patient, even if the patient is mentally able to do so. It is important to identify these situations because they reflect excessive, and consequently harmful, overprotection. This behavior, although well-intended, progressively becomes an obstacle to any initiative on the part of the patient. Some patients react by purposely forgetting to take their drug and inducing seizures. Others develop psychogenic seizures when they want to put their parents or the family under stress. When confronted with such families, the treating physician should set aside some private time during the consultation with just the patient. It is also necessary to have a session with the parents only, to encourage

them to have more confidence in the patient.

Epilepsy in a child profoundly affects the parents. Having a child with seizures can lead to a feeling of guilt for many parents. Their expressed or unexpressed questions are: “Did I do something wrong to deserve this punishment from God? Am I paying for previous misbehavior? Did I take adequate care of this child? Were we right to have him or her? Do we harbor a bad gene that we have given to our child?” Every seizure is stressful, especially generalized tonic-clonic events that can evoke fear of death due to the loss of consciousness. This fear leads to overprotection. Outpatient consultations provide opportunities to discuss these issues with parents. The support of a psychologist can be useful to develop positive and more constructive attitudes on the part of the parents as well as the patient. On the other hand, the sociocultural milieu in most developing countries results in parents keeping children with poorly controlled seizures at home and not in institutions. As a result, the life of at least one parent (usually the mother) is devastated, but he or she will continue to sacrifice anything to be able to look after the ill child. Additionally, families often must make severe compromises to be able to afford the cost of AEDs prescribed to their children.

Siblings suffer when a child with epilepsy is given undue attention by parents, whether or not seizures are controlled. Furthermore, the needs of unaffected siblings are often unmet when parents spend limited resources on AEDs.

### **PUBLIC KNOWLEDGE, ATTITUDES, AND PERCEPTIONS**

Negative attitudes toward people with epilepsy are the result of misconceptions about the nature of epilepsy. Although governments in most developing nations recognize the importance of epilepsy as a health care problem, they remain preoccupied with the struggle to provide clean drinking water, immunizations, and other such basic health needs to their people. Poverty, illiteracy, and improper use of limited resources continue to hamper efforts to educate the general public about conditions such as epilepsy.

### **Belief in Contagion**

In many parts of Africa and Asia, epilepsy is considered to be contagious. Consequently, epileptic patients may not be attended to during or after seizures, because people are afraid of being contaminated by their sweat, urine, saliva, flatus, and even breath. Air is often evoked as a way of entry of the devil into the body, especially for pregnant women whose newborn could be affected by this presumed epileptogenic influence. Very often, family members of persons with epilepsy ask if they should share food with others in the house. Elimination of this single misconception would not only reduce anxiety and unnecessary complication, but prevent a considerable percentage of morbidity and mortality associated with epilepsy in developing countries. The authority of the chief of the village may be necessary to confirm that epilepsy is not contagious and that a patient can be cared for without any danger to the caregivers.

### **Belief in Possession**

Epilepsy is often perceived as a supernatural ailment, caused by ancestral spirits or attributed to possession by evil spirits. It is also thought to be due to witchcraft and “poisoning.” Under Christian missionary teaching, epilepsy may have come to be considered demoniac possession or divine punishment for sins, in accordance with biblical examples. Amalgamation of indigenous traditions with Judeo-Christian or Islamic doctrines influence popular attitudes toward epilepsy. Low levels of literacy and limited possibilities for people to acquire medical information contribute to the persistence of these negative cultural beliefs and resultant harmful behaviors.

### **Fear of Inheritance**

In some countries, like the Indian subcontinent, there may be no problem with marriage if the boy has epilepsy, but a girl with epilepsy usually finds it impossible to get married after disclosing her disorder. As a result, parents of most girls with epilepsy will not reveal this information to a potential marriage prospect (most marriages are still arranged in this region). Very often, these women have a seizure soon after the mar-

### **KEYPOINTS**

- Every seizure is stressful, especially generalized tonic-clonic events that can evoke fear of death due to the loss of consciousness. This fear leads to overprotection.
- In many parts of Africa and Asia, epilepsy is considered to be contagious. Consequently, epileptic patients may not be attended to during or after seizures, because people are afraid of being contaminated by their sweat, urine, saliva, flatus, and even breath.
- Epilepsy is often perceived as a supernatural ailment, caused by ancestral spirits or attributed to possession by evil spirits. It is also thought to be due to witchcraft and “poisoning.”
- Low levels of literacy and limited possibilities for people to acquire medical information contribute to the persistence of these negative cultural beliefs and resultant harmful behaviors.

**CASE STUDY**

**Presentation:** A 25-year-old girl had a history of three generalized tonic-clonic seizures at age 15, 17, and 20 years. One seizure occurred in sleep while the remaining two occurred while she was awake during the day. She had no previous history of seizures, myoclonic jerks, or absences. No family member was affected with seizures.

**Evaluation:** Her neurologic examination was normal. The EEG done after the third seizure showed brief generalized spike-wave discharges “at a few places” and CT scan of the head was reported to be normal.

**Treatment and outcome:** She was treated with carbamazepine (600 mg per day) and subsequently remained seizure free. It was decided to taper off the carbamazepine after a seizure-free interval of 3 years, and finally, the medicine was stopped. She then became engaged to a boy chosen by her parents. While waiting for the marriage to take place, she experienced another seizure about 2 months after stopping carbamazepine. The girl’s family disclosed her seizure history to the boy’s family, and the boy’s parents canceled her engagement. The girl was restarted on carbamazepine, but became depressed. With proper counseling, she returned to a normal life.

**Comment:** Even today, epilepsy carries a heavy stigma both in developing and developed countries. In many countries like in the Indian subcontinent, a girl with epilepsy suffers greater discrimination than a boy with epilepsy. On the one hand, many girls are declared not suitable for marriage due to epilepsy, while on the other, paradoxically, young girls with epilepsy may be forced into marriage due to the belief that epilepsy will be cured by marriage. While managing such cases, it should be emphasized that the majority (>90%) of women with epilepsy can lead a normal married life and can have normal children while on AEDs. Additionally, people can develop seizures at any time—even after marriage. Epilepsy can neither be cured by marriage nor is it a bar to marriage.

**KEYPOINTS**

- People with epilepsy are discriminated against when seeking employment, for want of any rules and regulations pertaining to epilepsy and unemployment in most developing countries.

riage (due to missed medicines, the stress of marriage, and sleep deprivation since most marriages are all night affairs), with drastic consequences. Clear information about the genetic risks of epilepsy should help alleviate this problem.

**Restrictions on Activities of Daily Life**

Due to stigma, misconceptions, and over-protection, many activities are forbidden for the epileptic patient. These include family tasks, schooling, employment, and leisure activities, even simple sports. Young persons with epilepsy are often excluded from normal childhood activities because their playmates believe they suffer from a contagious illness or a psychiatric disturbance. Most health care givers do not understand that sports can be an excellent means to integrate children with epilepsy into their peer group.

People with epilepsy are discriminated against when seeking employment, for want of any rules and regulations pertaining to epilepsy and unemployment in most devel-

oping countries. As a result, most people hide their epilepsy while applying for jobs or selecting careers. On the other hand, many persons with epilepsy have jobs that present a risk of injury because of their seizures. A vigorous effort is needed at the government and local community levels to integrate people with epilepsy into society, to make them feel as useful and productive as possible.

There are no universal driving regulations for people with epilepsy. Every country has its own laws. Many developing countries that have driving laws consider epilepsy, whether or not seizures are controlled, to be incompatible with ever obtaining a driver’s license.

In many developing countries, there is a high rate of school dropout due to poor seizure control or ongoing subclinical seizure activity, leading to poor scholastic performance. Also, parents can be ashamed to send their child with seizures to school, to disturb the class, or reveal that they have someone with epilepsy in their family.

Often, teachers ask parents to keep their child at home because they are not willing to take responsibility for seizures that might occur in class. These factors contribute to the education gap between people with epilepsy and the general population, which aggravates the burden of epilepsy and negatively impacts the integration of people with epilepsy into society.

### FAILURE TO SEEK HELP

Even where there are adequate means for treatment of epilepsy, the majority of people suffering from this disorder in many developing countries are not treated. Large parts of the population who can, geographically and financially, reach modern medical facilities are treated intermittently. Either because their poverty does not allow them to afford the cheapest drugs, or they have not been well health-educated about the necessity of a long-term treatment, it is now estimated that the treatment gap (related to modern medications) is 80% of the population suffering from epilepsy in developing countries. In Ethiopia, a prospective study identifying 139 people with previously diagnosed epilepsy reported that 39% were receiving AED treatment (phenobarbital); 19% were using only traditional treatment; and 42% did not receive any—modern or traditional—treatment.

### PSYCHIATRIC COMORBIDITY IN DEVELOPING COUNTRIES

Two main situations occur in developing countries regarding eventual neuropsychiatric comorbidity. The first is the association of epileptic seizures with a psychiatric condition. The main examples of this are epileptic encephalopathies. In this context, consanguineous marriages are responsible for a familial distribution of such conditions. The family then is considered to be “possessed” and becomes feared and discriminated against. The second situation results from

the fact that people with epilepsy are more often referred to psychiatrists than neurologists, because there are fewer of the latter and because a large part of the population considers the clinical manifestations of many seizure types as “psychic.” The result can be helpful when the epilepsy is intractable and the behavioral problems are more easily managed; however, the prognosis is usually not good. In most developing countries, there are no centers or programs for dealing with such cases. Better cooperation between relevant specialists, such as neurologists, neurosurgeons, psychiatrists, psychologists, and social workers, is needed to provide help in these very difficult situations.

### CONCLUSIONS

In many developing countries, epilepsy is not considered to be a medical disorder. People with epilepsy are subjected to stigmatization, rejection, discrimination, and restrictions in social functions. A very heavy burden is borne in medical, social, and economic spheres. The major causes of the patient's predicament could be ameliorated by improving general knowledge and creating a bridge between traditional and modern worlds. There are many cultural obstacles to the application of modern medical practice. Patients can spend more than 20 years in traditional therapies before seeking consultation in a medical facility. However, it is not in the interest of the patient to consider the two practices mutually exclusive. In addition to modern pharmacological treatment, traditional healers can help patients use their own cultural background to deal with related psychological stress. These cultural factors, which not only contribute to disability, but can also exacerbate seizures, include stigma, issues of safety, concerns of a large family circle, knowledge, attitudes, and perceptions of the community and the public in general, failure to seek help, and the impact of psychiatric comorbidity.

### KEYPOINTS

- Often, teachers ask parents to keep their child at home because they are not willing to take responsibility for seizures that might occur in class.
- Better cooperation between relevant specialists, such as neurologists, neurosurgeons, psychiatrists, psychologists, and social workers, is needed to provide help in these very difficult situations.

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## PUBLIC HEALTH ISSUES

The appropriate role for the neurologist working in developing countries differs somewhat from that of most other medical care providers. Regions with limited neurologic expertise are unfortunately also areas in which the burden of neurologic disorders is heaviest and most medical care is provided by nonphysician practitioners. In such an environment, the neurologist needs to function as a medical educator and patient advocate rather than simply a clinician. Through medical education of general physicians, clinical officers, nurses, midwives, and other nonphysician care providers, the neurologist in developing countries will be able to improve quality of care for a much greater population of patients—a population extending far beyond the number of people who could effectively be managed by a single physician or clinic. By active patient advocacy through interactions with policy makers and hospital administrators, the neurologist can impact the very healthcare system people with epilepsy must access and utilize for effective treatment. The role of the neurologist in developing countries as a public health advocate cannot be overstated.

The World Health Organization (WHO) defines a “public health issue” as a problem, which occurs frequently, carries a substantial risk of death or disability, and places burden upon the individual, family, community, and/or society. Certainly epilepsy meets these criteria. As discussed in Chapter 3, epilepsy represents a prevalent condition, particularly in developing regions. For many individuals, especially those suffering from uncontrolled seizures, the burden of epilepsy includes substantial physical disability. Even among people with fairly infrequent seizures, health-related quality of life is substantially decreased. The cost of the disease includes

the direct costs of utilizing medical care and even greater expense associated with lost human resource potential and decreased work productivity. The psychosocial and economic effects of epilepsy impact the person with epilepsy, their family, and their community. And much of the global burden of epilepsy results from preventable causes. As such, epilepsy from a public health perspective deserves some consideration.

### EPILEPSY AND SEIZURE PREVENTION

#### Primary Prevention

Epilepsy represents the most common chronic neurologic disorder in the developing world, and preventable causes of epilepsy abound there. Limited medical services and unstable drug supplies, as well as epilepsy-associated stigma, further increase the urgency of epilepsy prevention. Focused public health interventions and improved access to and quality of specific medical services could substantially decrease the burden of epilepsy in most developing countries.

In poverty-ridden regions, chronic malnutrition and limited access to prenatal and antenatal medical services negatively impact maternal health and substantially increase the risk of birth injury and neonatal infections. Improved nutrition for women of childbearing years and increased access to prenatal clinics would assist in decreasing these early central nervous system (CNS) injuries. Perinatal care should be optimized with the use of trained traditional birth attendants (TBAs) and TBAs must have access to a secondary referral source that can provide surgical intervention, if needed. A greater number of TBAs are needed, especially in rural regions, to support the evaluation and

### KEYPOINTS

- Regions with limited neurologic expertise are unfortunately also areas in which the burden of neurologic disorders is heaviest and most medical care is provided by nonphysician practitioners. In such an environment, the neurologist needs to function as a medical educator and patient advocate rather than simply a clinician.
- The role of the neurologist in developing countries as a public health advocate cannot be overstated.

## KEYPOINTS

- Healthcare providers must be made aware of opportunities for prevention and should have a heightened appreciation for the earliest signs of CNS involvement when otherwise routine pediatric conditions present.
- Neurocysticercosis (NCC), the number one cause of epilepsy in Latin America and the likely culprit for much epilepsy in other regions, can potentially be prevented with improved sanitation measures and higher standards of food preparation.

monitoring of pregnant women well before their delivery. This will facilitate the timely identification of problems so preemptive measures can be taken before birth trauma or perinatal infections occur. Optimal prenatal care will also identify potentially devastating infectious disorders, such as syphilis and gonorrhea, averting damage to the child, the mother, and her partner. Actions taken to improve birth outcomes would not only decrease the burden of epilepsy and cerebral palsy, but also would improve women's health and decrease infant mortality.

Children who escape early CNS injuries remain at risk due to high rates of childhood CNS infections, such as bacterial meningitis and cerebral malaria that undoubtedly contribute to epilepsy development. Appropriate vaccination measures, bed net usage, malaria prophylaxis when indicated, and ready access to adequately trained and equipped healthcare providers who can offer expedient treatment for these life-threatening events are all critical for averting such epilepsy-inducing injuries. When common childhood illnesses go untreated, complications, such as bronchopneumonia with hypoxia and measles encephalitis, may ensue. Chronic otitis media or tonsillitis may progress with meningeal seeding to secondary meningitis. Failure to manage less severe infections can allow prolonged fevers with recurrent complex febrile seizures. Adequate, affordable health services for children are of paramount importance, since these services can avert many of the epilepsy-inducing events. Parents and community leaders need education regarding the signs of serious CNS infections, and feasible care options must be available to them. Health care providers must be made aware of opportunities for prevention and should have a heightened appreciation for the earliest signs of CNS involvement when otherwise routine pediatric conditions present.

Among adults and children alike, traumatic brain injury predisposes to epilepsy in developing regions. The circumstances associated with head injury, including domestic and societal violence, wars, and motor vehicle accidents, all can be decreased if ample public and governmental support exists. The state of public roads and the vehicles travel-

ing these roads are especially appalling in many low-income countries. Motor vehicle occupants, as well as thousands of pedestrians and bicyclists, are injured every year by cars and trucks lacking such basic features as brakes and headlights. The health implications of poor roads and road safety must be made clear to public officials. The use of seat belts should be encouraged, possibly required. Public education and ancillary funding is needed to increase helmet usage by bicyclists and motorcyclists. Much can be gained through public education, social marketing, and lobbying of government agencies.

Cerebrovascular disease, a key cause of epilepsy in the older population of developed countries, may soon become a significant contributor to the burden of epilepsy in the developing world. In urban regions, the arrival of fast food, high in fat and salt, is promoting an epidemic of malnourished obesity accompanied by hypertension and diabetes. Tobacco companies are increasingly marketing their wares in low-income regions where nicotine abuse and addiction are on the rise even among the poorest members of society. Public officials must be made aware of the long-term health implications of these market forces. Health centers struggling to provide urgent medical services must be encouraged and rewarded for supplying preventive services through the screening and treatment of hypertension and diabetes. Rapid action is necessary to quell the inevitable epidemic of cerebrovascular disease that will undoubtedly be followed by increasing rates of stroke-associated epilepsy.

Neurocysticercosis (NCC), the number one cause of epilepsy in Latin America and the likely culprit for much epilepsy in other regions, can potentially be prevented with improved sanitation measures and higher standards of food preparation. Regions with endemic cysticercosis have a population prevalence of 6% to 10% for systemic exposure to *T. solium* and an estimated 400,000 people suffer from epilepsy due to NCC. Expensive, complicated immunizations are not needed; simple provision and usage of latrines that limit animal (primarily pig) access to human waste could break the cycle of cysticercosis. Improved personal

hygiene and safer sources of drinking water would decrease the human fecal-oral spread of infective ova that result in CNS infection. To date, immunization and mass chemotherapeutic measures have not shown long-term effectiveness for cysticercosis control, but since NCC-induced epilepsy often presents years after infestation, intervention studies using human and porcine chemotherapy will not show improvements in epilepsy rates for several years, even if effective.

The necessary public health interventions are not trivial—less than half of the developing world's inhabitants have access to safe water and sanitation. But decreasing the transmission of cysticercosis would be accompanied by decreases in other waterborne illnesses. The potential health benefits of improved water and sanitation extend far beyond the prevention of epilepsy.

#### **Potentially Heritable Causes: Marriage and Childbearing for People with Epilepsy**

Despite much evidence to the contrary, common beliefs regarding the heritability of epilepsy remain a source of stigma in many developing countries. These concerns and beliefs should be addressed in an open forum with public education. As discussed in Chapter 3, genetic epilepsies are rare and epilepsy should not be considered a reason for preventing marriage and/or childbearing. In Egypt, 22% of people with epilepsy had a family history of epilepsy, but parental consanguinity was found in 65% of the total sample, and mental subnormality also resulted from such intrafamilial unions. Although epilepsy is certainly not grounds for the prohibition of marriage and/or childbearing, consanguineous marriages should be discouraged regardless of the presence or absence of epilepsies within families.

#### **Seizure and Injury Prevention**

Although antiepileptic drugs (AEDs) comprise a critical component of epilepsy care, AEDs will not “cure” epilepsy. However, some lifestyle interventions can assist with seizure control and injury prevention. In addition to encouraging patient compliance with medications, healthcare providers caring for people with epilepsy should recom-

mend maintenance of a regular, adequate sleep schedule. People with epilepsy should also be cautioned against excessive intake of alcoholic beverages or stimulants, as these can precipitate seizure activity. Candid advice regarding safety issues should be given. People with active seizures should be cautioned against driving or operating heavy or dangerous equipment, and in general, these individuals should not be placed in vulnerable positions that could result in injury if a seizure occurs.

People with epilepsy and their families must be counseled regarding the risk of exposure to bodies of water through fishing, fetching water, or swimming alone. These activities must also be avoided in the presence of people unlikely to assist if a seizure occurs. Working over or around open fires or kerosene heaters should be discouraged. Often, household chores can be reallocated to other members of the family to spare women with active epilepsy prolonged periods of standing over open flames. People with epilepsy should also be cautioned against climbing heights and traveling into unpopulated regions alone. These instructions may seem very obvious to trained neurologists, but other medical care providers will almost certainly fail to offer such advice unless explicitly trained to do so. All of these issues should be considered when a patient is initially diagnosed with epilepsy. As seizure control is gained, restrictions may be gradually lifted.

#### **THE ECONOMIC IMPACT OF EPILEPSY**

The direct costs associated with epilepsy include medical expenses associated with medications, hospitalization, and outpatient clinic fees. Costs not typically considered in studies of developed countries include medical services rendered for seizure-related injuries (e.g., burns) and the high cost of simply reaching a clinic equipped to deal with seizure disorders. Such expenses should be included when assessing the direct cost of epilepsy in developing regions. In Italy, the direct costs of epilepsy result primarily from hospital admissions in people with severe epilepsy and AEDs in the general population of people with epilepsy. In the US, new cases of epilepsy are associated

#### **KEYPOINTS**

- People with epilepsy and their families must be counseled regarding the risk of exposure to bodies of water through fishing, fetching water, or swimming alone.
- Working over or around open fires or kerosene heaters should be discouraged.

**KEYPOINTS**

- Although novel AEDs have been developed, the high cost of these new agents dictates that older AEDs will figure prominently in the epilepsy care regimens of developing countries.
- Given the limited number of physicians and specialists in rural regions, many patients require referral to more urban areas for assessment. The difficulties these referrals pose for families and patients should not be underestimated.
- Several problems contribute to the treatment gap, including cultural interpretations of the seizures, insufficient anticonvulsant drug supplies, poor drug distribution systems, and a lack of physician and paramedical personnel. Ironically, developed countries, especially the US and UK, solve their medical staff shortage by hiring physicians and nurses from developing regions. This practice results in developing countries bearing the financial burden of medical education for developed ones.

with a cost of ~\$5,400/case in the initial year after diagnosis. Studies in India indicate that among patients in a tertiary care center, direct costs alone could consume up to 0.5% of the gross domestic product, if the expenditures from these individuals were representative of the general population of people with epilepsy. Where recently developed AEDs are available and highly technological diagnostic services are accessible, these tend to drive the overall direct cost of epilepsy care.

Although novel AEDs have been developed, the high cost of these new agents dictates that older AEDs will figure prominently in the epilepsy care regimens of developing countries. The AEDs most commonly used in sub-Saharan Africa are: phenobarbital (prescribed in 65%–90%); carbamazepine (5%–25%); phenytoin (2%–25%); and valproate (2%–8%). Estimated annual costs for these medications in sub-Saharan Africa are: phenobarbitone \$25–50; carbamazepine \$200–300; and valproate \$300–500. Where the average laborer earns less than \$1 a day, drug costs may present a significant barrier to care.

According to the World Bank, in 2001, the total annual healthcare expenditures (including public and private funding) for developing countries ranged from \$21–74 per capita. Sources of epilepsy care funding include governmental budgets, donations from international agencies and nongovernmental organizations, social or compulsory health insurance funds, private insurance, out-of-pocket spending, charitable donations, and direct payments by private corporations. To date, few studies have been published that formally evaluate the economic aspects of epilepsy in the developing world, and no such work has been undertaken in Africa. Specifically, studies to estimate the cost of epilepsy care, cost-effectiveness of AEDs and epilepsy surgery, and lost economic opportunities are needed.

Chronic, disabling, stigmatizing disorders such as epilepsy are characterized by incurring much higher indirect than direct costs, and many of the indirect costs cannot be accurately captured by simple economic figures. Indirect costs should encompass lost wages and decreased productivity of the

people with epilepsy and their care providers. No validated measures exist to assess lost opportunities for education, social advancement, and employment, although such lost human resource potential certainly occurs in regions where epilepsy is heavily stigmatized.

Given the limited number of physicians and specialists in rural regions, many patients require referral to more urban areas for assessment. The difficulties these referrals pose for families and patients should not be underestimated. User fees, the cost of transport, and the costs of supporting family members who accompany the patients while in the city require substantial resources from rural dwellers, who may utilize a noncurrency, bartering system for most of their needs. Most traditional cultures require the dead to be buried in or near their home villages. Therefore, for acutely ill patients, the families may also need to consider the exorbitant cost associated with transporting a deceased family member from the city back to the village. Under such circumstances, local healthcare workers are often reluctant to suggest such distant referrals. This reluctance can be exacerbated by consulting physicians who fail to give proper feedback to the referring healthcare providers. Keep in mind that the referring healthcare worker, whether a physician, nurse, or clinical officer, will ultimately be the person caring for the patient. They need detailed instructions about management, prognosis, when to refer, and medication adjustments.

**DELIVERY OF CARE IN COUNTRIES WITH LIMITED RESOURCES**

Eighty-five percent of the world's population of people with epilepsy resides in developing regions. Unfortunately, this great burden of disease is accompanied by an 80% to 85% treatment gap—meaning less than 20% of people requiring treatment for epilepsy are receiving treatment. Several problems contribute to the treatment gap, including cultural interpretations of the seizures, insufficient anticonvulsant drug supplies, poor drug distribution systems, and a lack of physician and paramedical personnel. Ironically, developed countries, especially the US and UK, solve their medical staff

## CASE STUDY

**Presentation:** A 23-year-old male with well-characterized focal seizures and secondary generalization presented with an ocular injury resulting in loss of the right eye. He had experienced a generalized seizure while setting barbed-wire fencing and had fallen forward onto the roll of fencing, with subsequent eye and facial injuries. The ward nurses felt somewhat unsympathetic toward the patient. His outpatient records reported good seizure control when he was taking phenobarbital, but he only came for medical review and medications intermittently. This seizure-related injury had occurred off medications.

**Evaluation:** The physician and social worker met with the patient together to discuss issues of treatment adherence given the dire consequences of his recent seizure. The patient pointed out that he lives 20 km from the hospital and there is no regular transport available to the hospital. When he came for his medications, he was typically given only a 30-day supply (a general hospital policy that could be overridden if the physician writes a letter explaining why). To come to the hospital required a day's travel in each direction. Although there was a rural clinic nearer to his village, the supplies box provided included only very basic drugs and did not include phenobarbital. One reason phenobarbital was not included in the basic drug box was that the clinical officer staffing the rural health clinic had never been trained in how to use this drug.

**Treatment:** The patient was restarted on phenobarbital and discharged with a 3-month supply. Later discussions with the Rural Health Clinic staff throughout the district revealed that this was a common problem. Many of them had people with epilepsy come to their clinics seeking phenobarbital.

Clinical officers were asked to provide a list of the people with epilepsy in their catchment areas, and estimates were made for the quantity of phenobarbital that each would need. Training sessions were held so clinical officers could maintain treatment for people already determined by local physicians to have epilepsy. They were also trained in how to recognize possible cases of epilepsy for referral to the hospital. The number of people with active epilepsy receiving treatment increased substantially after the local healthcare workers were provided with the training and medications needed.

**Comments:** Access to medications can be blocked by geographic barriers as well as simple economic barriers. Neurologists in developing regions can implement simple programs that may have a major impact on the population of people with epilepsy in their countries. The role of the neurologist as a medical educator and patient advocate in such environments cannot be overstated!

shortage by hiring physicians and nurses from developing regions. The medical personnel rarely return to practice in their native country. Understandably, professionals in resource-poor regions seek better circumstances for themselves and their families. But it must be recognized that, in essence, this practice results in developing countries bearing the financial burden of medical education for developed ones.

Strong traditional belief systems combined with limited access to formal healthcare lead many people with epilepsy to seek care through traditional healers. People with epilepsy admitted to a medical facility for seizure-associated burns or injuries often never bring their underlying disorder to the attention of medical staff. Neurologists must provide strong advocacy support to place epilepsy care on the healthcare agenda for developing countries. This will be particularly challenging where health system resources already strain under the impact of HIV.

## Models of Epilepsy Care

Clearly, the model for epilepsy care delivery used in developed countries where patients are managed by physicians, often epileptologists in tertiary care centers, is neither feasible nor desirable in resource-poor settings. Even in those developing regions where tertiary care centers are available, these epilepsy services will be limited to the minority of patients. No single model for epilepsy care delivery can be applied to all developing countries, but a few general principles may help formulate appropriate local and national health policies.

Epilepsy care should be included in the basic health services offered in most developing countries. Medical care providers, regardless of their level of expertise, must be familiar with epilepsy symptoms and presentations, since only through their diagnostic suspicion will people with epilepsy come to the attention of more sophisticated practitioners. Nurses and clinical officers staffing rural and primary care centers should be educated to recognize possible cases of

## KEYPOINTS

- Medical care providers, regardless of their level of expertise, must be familiar with epilepsy symptoms and presentations, since only through their diagnostic suspicion will people with epilepsy come to the attention of more sophisticated practitioners.

**KEYPOINTS**

- Adherence to treatment improves substantially for patients when care is provided closer to home.
- In environments with limited resources, epilepsy can be diagnosed clinically. Extensive testing is not required unless diagnostic uncertainty prevails. Less expensive medications that are more likely to be available and much more affordable for the patients should be first-line therapies.
- By working in collaboration with traditional healers, physicians might be better able to access people with epilepsy early, and could potentially offer opportunities to modify certain harmful practices.

epilepsy and be provided with appropriate referral options when potential cases come to their attention. In countries such as India, specialized expertise in epilepsy is available in major cities, either through trained neurologists or generalists with particular interest in epilepsy. In these countries, more efficient use of limited specialty skills can be made if a clear referral system is developed that utilizes a screening system whereby people with possible epilepsy are first seen by their local physician before seeking higher-level diagnostic services. If limited neurologic services are available without such a filtration system, more vulnerable persons who require such expertise will be less likely to access needed care. Of course, such a system will only function properly if the primary care physicians screening referrals are adequately educated regarding neurologic assessment and triage.

In regions such as sub-Saharan Africa, where neurology-specific training is sparse and neurologists are extremely rare, personnel in rural and primary care clinics should have recourse to physician-level referral whenever possible. Physicians can then provide confirmatory diagnosis (including any indicated and available diagnostic services); assess patients to assure there is no ominous, treatable underlying etiology for new seizure disorders; initiate treatment; and provide local medical personnel with a treatment maintenance plan that can be easily followed by the healthcare providers to whom patients have ready access.

Distance from health care facilities is often a problem, especially for rural dwellers. Nonphysician primary healthcare workers, when properly trained, can provide appropriate care for people with epilepsy. Adherence to treatment improves substantially for patients when care is provided closer to home. If resources are available to establish local specialty clinics dedicated to epilepsy care, patients may benefit substantially from the dedicated services of nonphysician providers who have received additional neurologic training. Nurse-led noncommunicable disease services have been established in South Africa and allow district hospitals to transfer patients with chronic disorders to these

nurses for long-term management. Otherwise, epilepsy care may be vertically integrated into the existing primary healthcare programs. Ample experience indicates that without additional training and public support, primary healthcare workers will be reluctant, possibly even resistant, to providing care for people with such a misunderstood and stigmatized condition.

Even physicians need to be better educated in the cost-effective treatment of epilepsy. In environments with limited resources, epilepsy can be diagnosed clinically. Extensive testing is not required unless diagnostic uncertainty prevails. Less expensive medications that are more likely to be available and much more affordable for the patients should be first-line therapies. Polypharmacy is not necessary in many cases, and with more drugs comes greater expense, more side effects, and decreased compliance. These basic principles should be reiterated to primary care physicians and frequently reinforced. In India, one tertiary care center found that proper treatment allowed up to one-third of patients on polypharmacy to be maintained on monotherapy, with considerable savings.

**Health-Seeking Strategies**

An intact and efficient referral and healthcare delivery system for epilepsy will only be effective if people with epilepsy access the formal healthcare system. Because traditional beliefs dub epilepsy a supernatural affliction in many regions of the developing world, the majority of the patients will initially or exclusively consult an indigenous or traditional healer. This care-seeking choice often results in long delays before consultation with the modern medical system. By working in collaboration with traditional healers, physicians might be better able to access people with epilepsy early, and could potentially offer opportunities to modify certain harmful practices. Developing such collaborative associations may be very difficult, particularly where the physician-indigenous healer relationship has historically been one of competition and animosity. But to best serve people with epilepsy in many developing countries, efforts must be made to resolve this conflict. The possibility that

locally available plants may possess anticonvulsant properties certainly should also be considered.

Utilization of other members of the community as assistants in the distribution of drugs and active community participation will optimize local support for people with epilepsy and their families. The key to success for any national epilepsy care program is education—of the individual, the family, and the community, as well as healthcare professionals at all levels of training and expertise. Since the estimated treatment gap for epilepsy care in most developing countries is >80%, we have much room for improvement. Today, new opportunities for social marketing exist through mass media (newspaper, radio), and medical personnel can benefit from medical education through new telemedicine technologies and the Internet.

### Funding Epilepsy Care Services

Fiscal resources for funding even basic health services are frequently insufficient to meet the needs of people in the developing world. Regardless, efforts must be made to make public policy makers aware of the burden of this treatable disease. Even the poorest countries may offer lower clinic fees and medications to people with certain chronic conditions (e.g., hypertension, diabetes). Epilepsy should be included among these recognized and subsidized disorders. Incorporating epilepsy care into the primary clinics will best suit those countries or regions with the least resources available, since marginal costs will be least under this system. Optimal health policy planning for epilepsy care requires reviewing the healthcare system's resources and recognizing the population's geographic, social, and financial barriers to accessing these services.

Cost-sharing, especially by individuals with the resources to seek more technologically advanced care, may be an important means of financial sustainability for an epilepsy care program. But many people with epilepsy experience economic hardships related to their disorder, and every effort should be made to ensure that financial barriers do not prevent patients from seeking care and maintaining compliance.

### INFORMATION AND EDUCATION

Educating the public can be difficult, given the high rates of illiteracy in many regions, which range from 29% to 60%, with females disproportionately affected. These limitations make it especially important to utilize avenues such as radio (available for 160 per 1,000 in Africa) and television (60 sets per 1,000 people). Local languages and dialects should be used whenever possible. As several studies have confirmed grave misconceptions regarding epilepsy even among educated persons in developing countries, newspapers are also worthwhile avenues for public advocacy.

The Global Campaign against Epilepsy is a prominent movement that aims to increase public awareness and education regarding epilepsy, identify the needs of people with epilepsy, and encourage governments to address these needs. Such patient-oriented social interventions can substantially benefit people with epilepsy through improved compliance and quality of life.

### Professional Development

Every neurologist and most physicians in developing regions will at times feel overwhelmed by the burden of disease they encounter and the limited resources available for care provision. Furthermore, outside of academic centers, intellectual endeavors may be difficult to identify that will help ongoing professional development. All of these issues undoubtedly contribute to the “brain drain,” whereby health professionals from developing regions migrate to developed countries. It should be recognized that professor exchanges, local continuing medical education programs, and research opportunities do exist to help overcome some of these academic lapses. Such opportunities can be found through the World Federation of Neurology ([www.wfneurology.org](http://www.wfneurology.org)), the U.S. Fulbright Program (<http://www.cies.org/>), and the U.S. National Institutes of Health ([www.nih.gov](http://www.nih.gov)), among others.

### CONCLUSIONS

As highly trained physicians, neurologists in developing countries carry substantial “social capital.” Because there are too few

### KEYPOINTS

- Many people with epilepsy experience economic hardships related to their disorder, and every effort should be made to ensure that financial barriers do not prevent patients from seeking care and maintaining compliance.

neurologists in most developing regions to personally deliver services directly to the entire population of people with epilepsy, neurologic specialists should direct a substantial proportion of their efforts toward public policy, patient advocacy, and medical education. Given the many preventable causes of epilepsy in the developing world, opportunities abound to educate and impact health policy. Higher quality maternal and child health services, better road conditions, improved water safety, and latrines could decrease the burden of epilepsy while providing multiple other positive health benefits to the public. Patient advocacy that elucidates the economic and psychosocial burden placed on the entire society by epilepsy may gain governmental support more effectively than the humanitarian appeals and education that are often effective in social

marketing. Neurologists in the developing world face a difficult but rewarding challenge if they choose to tackle these critical public health issues.

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[www.who.int/mental\\_health/management/globalepilepsycampaign/en/](http://www.who.int/mental_health/management/globalepilepsycampaign/en/)

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## “OUT OF THE SHADOWS”

ILAE/IBE/WHO

### GLOBAL CAMPAIGN AGAINST EPILEPSY

#### THE CAMPAIGN AT A GLANCE

A Global Campaign Against Epilepsy is much needed—the burden of epilepsy is underestimated and the means available to reduce it are underutilized.

The problem is too complex to be solved by individual organizations.

The three leading international organizations working in epilepsy have therefore joined forces to bring epilepsy “out of the shadows.”

The Campaign will assist governments worldwide to make sure that diagnosis, treatment, prevention, and social acceptability of epilepsy are improved.

#### The Campaign Strategy

Working along two parallel tracks, the Campaign will:

- Raise general awareness and understanding of epilepsy;
- Support Departments of Health in identifying needs and promoting education, training, treatment, services, research, and prevention in their countries.

#### The Campaign Tactics

- To generate Regional Declarations on Epilepsy, produce information on epilepsy for policy-makers, incorporate epilepsy care into National Health Plans, and facilitate the establishment of national organizations of professionals and lay persons who are dedicated to promoting the well-being of people with epilepsy.
- To help organize Demonstration Projects that illustrate good practice in the provision of epilepsy care.

The Global Campaign is managed by a Secretariat consisting of representatives of the three responsible organizations:

- World Health Organization (WHO)
- International League Against Epilepsy (ILAE), professionals
- International Bureau for Epilepsy (IBE), lay persons

#### WHY HAVE A GLOBAL CAMPAIGN AGAINST EPILEPSY?

A Global Campaign Against Epilepsy is necessary because the burden of epilepsy on individuals and communities is far greater than previously realized. The problem is too complex to be solved by individual organizations. The three leading international organizations working in epilepsy have therefore joined forces to bring epilepsy “out of the shadows.”

The Campaign is conducted by the World Health Organization (WHO) in partnership with the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). The aims of the Campaign are to provide better information about epilepsy and its consequences and to assist governments and those concerned with epilepsy to reduce the burden of the disorder.

#### What Is the Global Campaign?

##### *Campaign Strategy and Tactics*

The mission statement of the Campaign is: “To improve acceptability, treatment, services, and prevention of epilepsy worldwide.”

Major goals are to ensure that epilepsy care is incorporated into National Health Plans and to facilitate the existence in every

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country of organizations of professionals and lay people who are dedicated to promoting the well-being of people with epilepsy.

In order to increase awareness of the problems caused by epilepsy and the means available to deal with them, conferences have been organized between key persons in health care administration and government and experts in the field of epilepsy. These conferences were held in the six WHO regions (Africa, the Americas, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific) and have resulted in Regional Declarations on Epilepsy, White Papers, and regional reports.

In order to assist Departments of Health, which are looking for tools applicable in their country to realize the objectives of the Campaign, Demonstration Projects are organized in a number of countries in different regions. These Demonstration Projects offer models of how to identify needs; how to educate and train staff involved in diagnosis, treatment, services, prevention, and research; and how to promote education of the general public.

#### ***Management of the Campaign***

Three organizations collaborate in the Global Campaign Against Epilepsy: WHO (specialized agency of the United Nations, with 192 Member States), ILAE (with member organizations in more than 90 countries), and IBE (with member organizations in more than 60 countries). ILAE member organizations consist of professionals concerned with medical and scientific aspects of epilepsy, while those of IBE are concerned with social aspects and the quality of life of people with epilepsy.

In June 1997, these three partners launched the Global Campaign Against Epilepsy simultaneously from Geneva, Switzerland, and Dublin, Ireland, during the 22nd World Congress on Epilepsy. A Secretariat was established consisting of a representative from each of the three organizations, which oversees the day-to-day running of the Campaign. The Secretariat is accountable to an Advisory Board composed of two representatives of each of the three bodies. Both the Secretariat and the Advisory

Board members are accountable to their respective organizations. WHO works through its regional offices and country representatives. IBE and ILAE work through their regional commissions, their resource-oriented and problem-oriented commissions, and their national member organizations.

The Campaign structure and activities are outlined in Figure 1.

### **General Activities of the Global Campaign**

#### ***Collaboration to Increase Awareness about Epilepsy***

Since WHO Cabinet approval in December 1999, collaboration with and support for the Campaign have been strengthened through the involvement of the Regional Offices of WHO. Regular contacts are maintained with various interested clusters and departments within WHO.

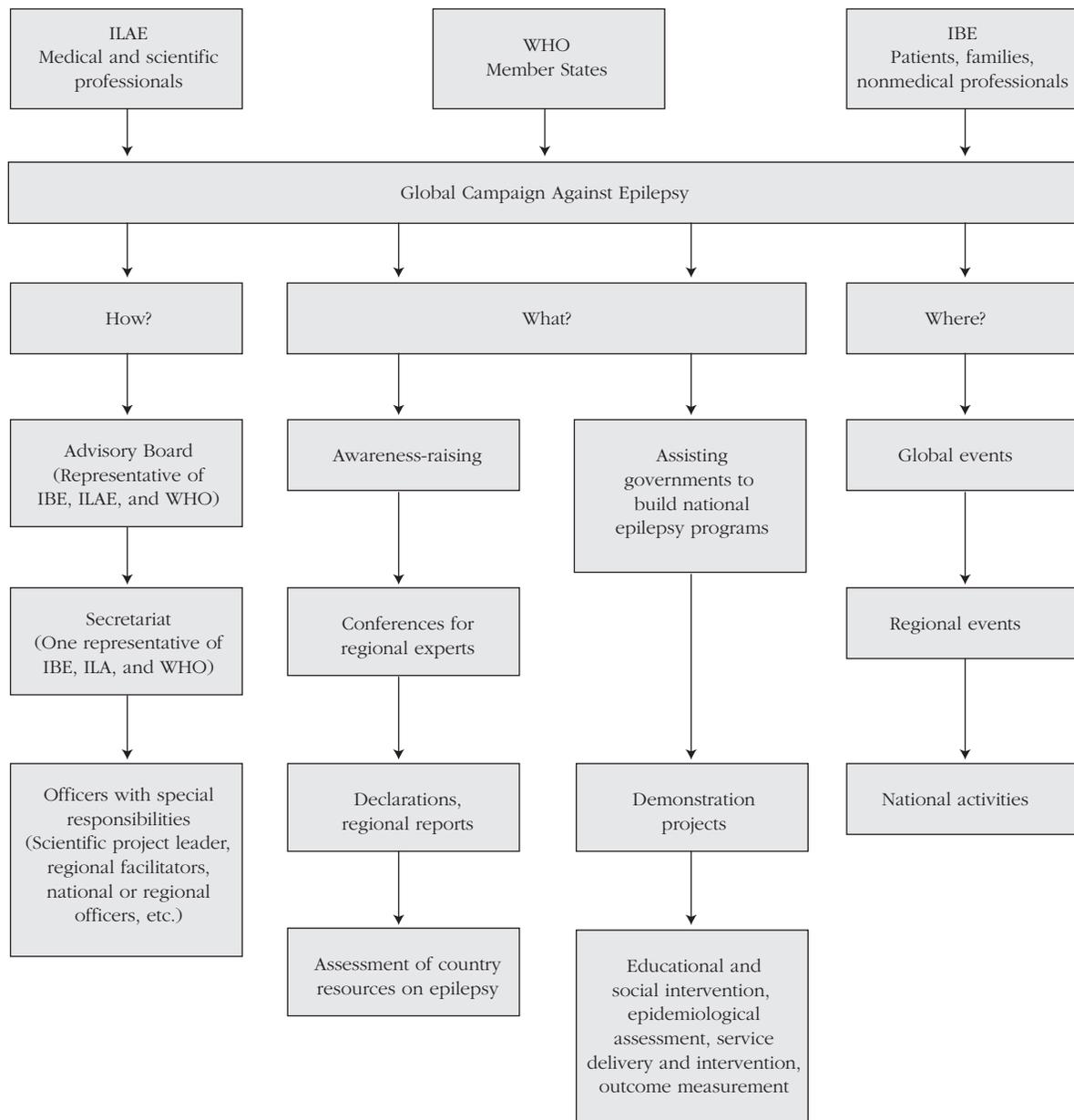
Support has been provided by the Global Health Forum for Health Research for a review of the evidence base for priority setting in epilepsy research. Furthermore, the applicability to epilepsy of the common format for priority setting was determined.

A number of IBE/ILAE Commissions are engaged in various developmental activities for the Campaign, for example, regarding a definition of the treatment gap and outcome measures for the Demonstration Projects.

#### ***Regional Conferences and Declarations***

As part of general awareness-raising, regional conferences on public health aspects of epilepsy were organized in the six WHO regions (Africa, the Americas, Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific).

At these regional conferences, delegates of epilepsy organizations of national and international lay persons (IBE) and professionals (ILAE) met with public health experts from governments and universities and representatives from WHO headquarters and regions. As the result of intensive discussion and examination of data presented by delegates, a Regional Declaration on Epilepsy was adopted after each conference, summarizing perceived needs and proposing actions to be taken. These declarations call



**FIGURE 1**

on governments and all health care providers to join in taking strong and decisive action to meet the objectives of the Global Campaign Against Epilepsy.

Following the European Conference, the WHO Regional Office for Europe, together

with all European member organizations of IBE and ILAE, strongly supported by WHO headquarters, agreed to submit the European Declaration on Epilepsy with an accompanying White Paper to the European Parliament and European Governments. This

event took place in March 2001, and was followed 8 months later by the establishment of a group of Parliamentary Advocates for Epilepsy, whose role is to place epilepsy on the health agenda of the European Union.

In other regions, the follow-up of the regional declarations will be tailored according to prevailing conditions.

### ***Regional Reports and Country Resources***

A questionnaire on country resources has been developed by a group of experts, in order to map the resources for epilepsy worldwide. All IBE and ILAE member organizations and all WHO Member States have been invited to complete the questionnaire.

Reports on the implementation of the GCAE are being prepared in a number of WHO regions, which will include the data collected through the questionnaires. These documents are intended to be tools for advocacy and instruments for dialogue with governments, health care providers, donors, and other partners. These reports are working papers and provide basic knowledge on epilepsy and basic facts about the epidemiologic burden, as well as propose the next steps to be taken.

### ***National Activities***

On a national level, the elements of the Global Campaign are adapted by the national member organizations to the needs specific to each country. The national organizations strive to implement the strategy of the Campaign through active engagement with their governments and local WHO offices. They also participate in planning the Campaign at an international level.

### ***Technical Consultative Meetings***

Technical consultative meetings were organized in a number of WHO regions by WHO Regional Offices in collaboration with the Campaign Secretariat. The main objectives were:

- To review the present state of epilepsy in the regions;
- To discuss regional reports on epilepsy;
- To review the implementation of the GCAE in the region, including the progress of Demonstration Projects;

- To develop a framework of action for countries.

The meetings brought together clinicians with expertise in the field of epilepsy, leaders of the Global Campaign Against Epilepsy, and senior staff from WHO. In addition, a number of technical consultative meetings were organized at WHO headquarters on the progress and prospects of the Campaign, at which, for example, it was agreed that epilepsy interventions should be sustainable and provide long-term care and that the outcomes should be measured.

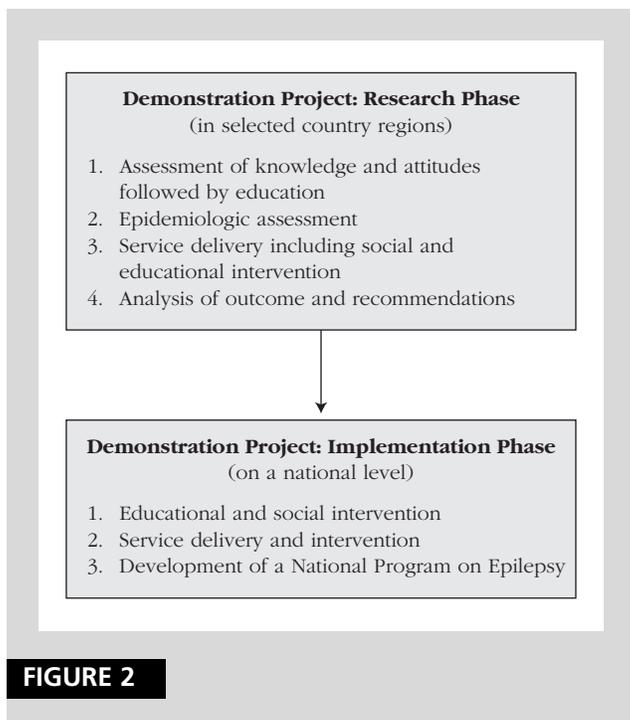
### **Specific Activities of the Global Campaign**

In April 1999, representatives of the three partners in the Campaign met in Geneva with epilepsy experts from industrialized and developing countries, to discuss the development and implementation of Demonstration Projects, which the Campaign encourages to be set up in a number of selected countries in different regions.

The counterparts of these projects at a country level will be the member organizations of IBE and ILAE, working in close collaboration with WHO country representatives. These local counterparts will be involved in raising awareness of the needs of people with epilepsy, as well as encouraging and supporting the provision of good treatment and services.

The Demonstration Projects will illustrate good practice in providing services to people with epilepsy and will be used as models of what can be achieved. When proven to be effective, similar projects will be implemented in the whole of the country in which they are situated, in neighboring countries and, finally, globally.

Demonstration Projects start in a representative region of limited size. This is the research phase: The aim is to investigate the impact of local conditions on general strategies to improve epilepsy care. Results of the research phase are used by National Health Authorities to plan and implement services and awareness-raising about epilepsy all over the country. Results of the subsequent implementation phase are assessed in order



**FIGURE 2**

to develop a National Program on Epilepsy. The components of these two phases are shown in Figure 2.

### **Demonstration Projects**

**Selection of location.** Criteria for country selection are:

- The likelihood that results of the Demonstration Project can be utilized by other countries;
- Availability of political and personal contacts;
- Willingness to participate;
- Availability of a WHO collaborative center or country representative;
- Presence of an IBE and an ILAE member organization, or groups that have the potential to form a member organization;
- A regular supply of basic antiepileptic drugs (AEDs);
- Facility of communications.

**Management structure of demonstration projects.** The Global Campaign partners coordinate the projects, working closely with the national IBE and ILAE member organizations, other nongovernmental organizations on neurology and neuroscience, WHO

Regional Offices, and country offices and local ministries.

The Demonstration Projects are the responsibility of the Campaign's Secretariat, which oversees the day-to-day running of the Campaign, providing governments and other partners with sufficient, clear information and ensuring adequate funding. External funds will be used to initiate Demonstration Projects; however, such funds will not be used to pay for services or drugs, because the provision of anything except minimal outside funding for these components would be likely to indicate that the project could not be locally sustainable.

Scientific supervision of the projects is delegated to a Scientific Project Leader, who liaises directly with local Principal Investigators and Regional Facilitators in helping to set up and monitor the projects. The Scientific Project Leader also liaises with local ILAE and IBE member organizations in order to foster local ownership and community participation and with the relevant WHO offices and Departments of Health.

The Scientific Project Leader is responsible for helping to design and evaluate the project protocols. An important aspect of the evaluation is ensuring that each Demonstration Project has sustainability built into its design and that outcomes are measurable. They are also responsible for monitoring the projects to see how they are performing, and for writing up this performance for scientific journals.

Principal Investigators have responsibility for the Demonstration Project in the country where it is held. They are responsible for constructing the project's protocol according to the guidelines of the Scientific Project Leader and local circumstances. Principal Investigators ensure that the protocol implementation keeps to its budget and timescales. The Principal Investigators are the focal points of the Campaign's relationship with the project and the people through whom information will flow. Ensuring that the project meets its outcome measures is central to their work.

Regional Facilitators, working in close relationship with the relevant WHO Regional Advisers, will support the Principal Investigators in the implementation of their projects.

An outline of the management structure of the Demonstration Projects is given in Figure 3.

**Design and activities of the demonstration projects.** In general terms, each Demonstration Project has four aspects:

1. Assessing whether knowledge and attitudes of the population are adequate, correcting misinformation and increasing awareness of epilepsy and how it can be treated (educational and social intervention)
2. Assessing the number of people with epilepsy and estimating how many of them are appropriately treated (epidemiologic assessment and case-finding)
3. Ensuring that people with epilepsy are properly served by health personnel equipped for their task (service delivery and intervention)
4. Analyzing the outcome and preparing recommendations for those who wish to apply the findings to the improvement of

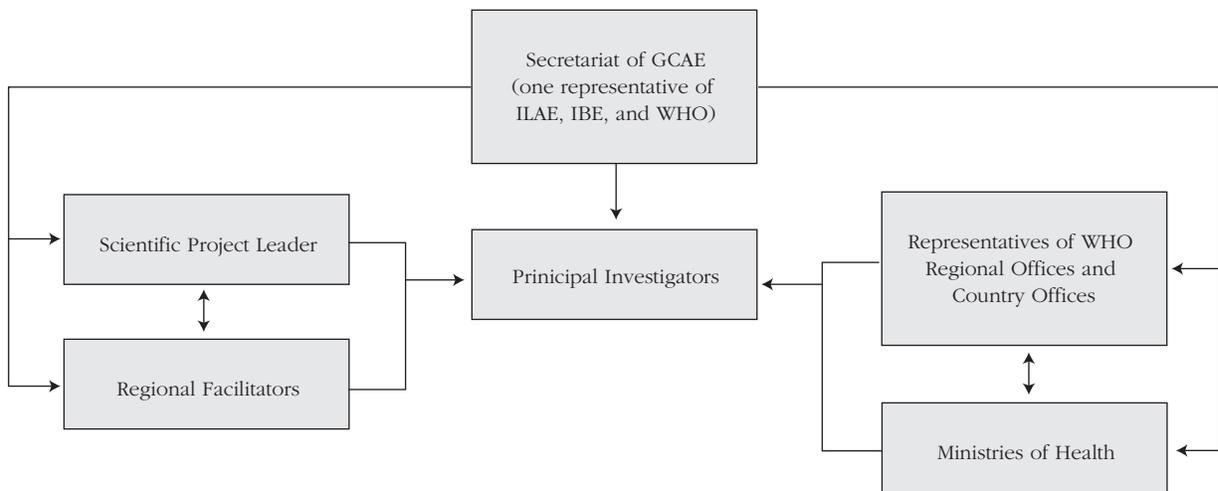
epilepsy care in their own and in other countries (outcome measurement)

**Step 1: Educational and Social Intervention**

Incorrect perceptions about epilepsy are often the reason why people with epilepsy are stigmatized; this can be an incentive to hide the fact of having epilepsy. Symptoms from which certain persons suffer may not be recognized as a sign of epilepsy, which is a disorder for which medication is available. Both these factors are a source of underestimation when assessing the prevalence of epilepsy.

The educational and social intervention will prepare the population for the epidemiologic study, but will also promote a change of attitude in the community, through the following activities.

- A representative sample of the population in the area will be surveyed to assess public awareness and understanding of epilepsy and attitudes toward people who suffer from the condition.
- An educational program to decrease social stigma, improve social relations and leisure activities, and open up realistic job opportunities will be targeted on



**FIGURE 3**

groups of key people in the communities, such as teachers at local primary and secondary schools.

- People will be informed about epilepsy through:
  - public address systems and the media;
  - distribution of materials on epilepsy;
  - posters.
- People will be informed about international and national professional and lay organizations concerned with epilepsy.

### Step 2: Epidemiologic Assessment and Case-Finding

Correctly identifying people with epilepsy is crucial to establishing the extent of a country's treatment gap and to ensuring that appropriate treatment is offered to those who need it. It is essential that staff involved in a survey—and also health personnel who care for patients with hitherto unrecognized epilepsy—have sufficient knowledge of epilepsy, so that conflict is not created when epilepsy is diagnosed in a survey while the person is receiving treatment for another, wrongly diagnosed condition.

- At the onset of the Demonstration Project, questionnaires to assess knowledge, attitudes, and practice regarding epilepsy are distributed to all health personnel in the study area; the questionnaires are self-administered.
- All physicians and a number of the primary health care personnel (village doctors) receive basic epilepsy training to correct deficiencies that were revealed by the questionnaires.
- Participation in the professional epilepsy society and support of the lay association are encouraged.
- A door-to-door survey is carried out in a representative part of the area:
  - a screening questionnaire is applied, designed to identify cases of epilepsy with convulsive seizures;
  - a village doctor then applies a diagnostic questionnaire to those patients preliminarily identified as possible cases of epilepsy with generalized tonic-clonic seizures, with or without occurrence of other seizure types;

- senior primary health care physicians then confirm the diagnosis; if there are doubts, local neurologists will be responsible for a final decision.

### Step 3: Service Delivery and Intervention

This stage covers quality of diagnosis, treatment, follow-up, and referral networks. In order to provide appropriate treatment, activities that ensure the supply of antiepileptic drugs and facilitate their use in treatment are necessary and will be put in place if not available.

- People with epilepsy who are under the care of the team involved in the Demonstration Project will be offered the possibility of participation in the study. If their epilepsy is not active, their previous treatment will be continued; if they still have seizures, their treatment will be adjusted according to the treatment protocol of the Demonstration Project. People who are diagnosed with epilepsy and are not receiving regular treatment will be offered treatment, provided they have had at least two convulsive seizures in the previous 12 months and if they and/or their guardian are able and willing to give informed consent.
- All people who follow the protocol will be assessed separately. For each patient included in the study, a standard entry form and a follow-up form will be prepared. The protocol is based on:
  - treatment with available first-line drugs;
  - provision of education that facilitates compliance with treatment and, if necessary, adaptation of lifestyle;
  - if seizures persist, referral to a local neurologist for reassessment and prescription of antiepileptic medication according to the findings.
- The staff involved in the Demonstration Project will receive:
  - a treatment protocol;
  - a chart to assist physicians in dealing with side effects;
  - written instructions on evaluation and how to boost compliance.
- Patients and their families will be educated about:

- the nature of epilepsy and its characteristics, causes, and prognosis;
- the nature and objectives of treatment, the way to use the drugs, possible side effects and how to deal with them, the duration of treatment, and the importance of compliance.
- general health measures, emergency treatment of seizures, and how to live with epilepsy.
- Patients and their families will be encouraged to join the local epilepsy organization for lay people.

#### Step 4: Outcome Measurement

Whether the Demonstration Projects are successful and provide suitable approaches for other countries to adopt will have to be confirmed by evidence. Their success or otherwise will be seen in terms of the decrease of the treatment gap and its consequences in the demonstration region.

In order to discern whether a project is achieving the desired results, its performance will be specifically measured by comparing the following before onset and after completion of the project:

- The number of people with epilepsy who received a correct diagnosis;
- The number of people successfully treated;
- The social situation of people of various age groups with epilepsy;
- Knowledge, attitudes, and practice of those interviewed at the onset.

#### Step 5: The Ultimate Goal

The ultimate goal of the Demonstration Projects is the development of a successful model of epilepsy control that will be integrated into the health care systems of the participating countries and regions and, finally, applied on a global level.

Furthermore it is hoped that the lessons learned from the Demonstration Projects will support the development of preventative measure strategies globally.

Anyone interested in following the progress of the Global Campaign and its Demonstration Projects will be able to do so from the regular updates on the relevant websites:

[who.int/mental\\_health/management/globalepilepsycampaign/en/](http://who.int/mental_health/management/globalepilepsycampaign/en/)

[www.ibe-epilepsy.org](http://www.ibe-epilepsy.org)  
[www.ilae-epilepsy.org](http://www.ilae-epilepsy.org)

Further information on the Global Campaign Against Epilepsy and how to help achieve the goals of the campaign in specific countries can be obtained from the addresses shown below.

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