Introduction

- The data are presented for the four commonly used AEDs: phenobarbital, phenytoin, carbamazepine and valproic acid. The respondents were asked about their inclusion in essential lists of drugs, government policy on licensing, and the costs of the commonly used strength of the AEDs in local currency. For purposes of comparison, the costs are presented in international dollars as at 2000.

Salient findings

- Inclusion of the first-line AEDs in the country's list of essential drugs varies. Phenobarbital is included in 95.4%, carbamazepine in 93.1%, phenytoin in 86.1% and valproic acid in 86.7% of the responding countries.
- In low-income countries, inclusion in the list of essential drugs varies for first-line AEDs. Phenobarbital is included in 96%, carbamazepine in 82.6%, phenytoin in 68.2% and valproic acid in 62.5% of the responding countries.
- Phenobarbital is included in the list of essential drugs in more than 90% of the responding countries in all the regions except South-East Asia, where it is included in 80% of the responding countries. In contrast, valproic acid is included by two thirds of the responding countries in Africa and South-East Asia.
- A government policy regarding availability of the first-line AEDs only by prescription (from either a general practitioner or a specialist) exists in more than 90% of the countries.
- The median cost of the daily defined dose (DDD) of the first-line AEDs in international dollars varies. While the median cost of phenobarbital is 0.14 international dollars, it is three times more for phenytoin, 11 times for carbamazepine and 16 times for valproic acid.
- The median cost in international dollars for the first-line AEDs is variable across WHO regions. The cost of carbamazepine and valproic acid in Europe and the Western Pacific is almost half that of other regions. The cost of phenobarbital is 2.7 times higher in South-East Asia than in Europe. The median cost of phenytoin in international dollars is five times more in the Americas than in the Western Pacific.
- In international dollars the median cost of treatment of epilepsy is three and half times higher for carbamazepine, phenytoin and valproic acid and two times higher for phenobarbital in low-income countries than in high-income countries.

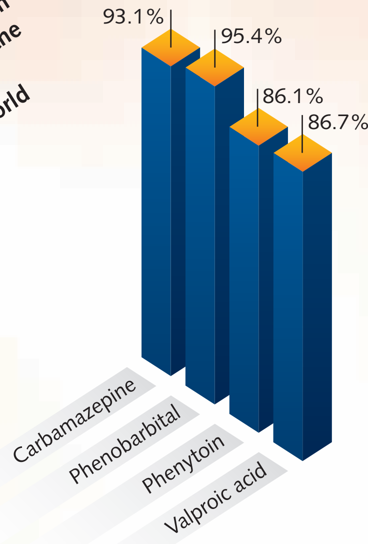
Limitations

- The data are available from only half the responding countries. However, the data represent 75% of the world's population.
- It is possible that a drug might be included in the country's essential drug list but that it is not available at all times and in the appropriate dosage in publicly provided services.
- Sometimes an essential drug list exists but it does not guide the purchasing and management of public sector drug supplies.
- The dose used for some of the people with epilepsy and children is lower than the DDD in many instances. The above-mentioned costs are therefore overestimated.

Conclusions

- Presence of AEDs in the essential drug list can enhance their availability and public provision. This is an important measure to narrow the treatment gap for epilepsy.
- In some high-income countries, drug formularies rather than essential drug lists exist, which are detailed lists of drugs that are approved or recommended for health providers and supply systems. Factors such as safety, effectiveness and cost-effectiveness are assessed before drugs are included in the formularies. This is important, especially for the newer AEDs.
- Inequity in the cost of first-line AEDs across regions, countries and income categories needs to be specifically tackled.
- Procedures must be adopted to decrease the pharmaceutical expenditure as it is a major component of the direct cost of epilepsy. This could be done by improving selection, open and transparent purchasing procedures and competitive purchasing.

11.1 Carbamazepine, Phenobarbital, Phenytoin and Valproic acid in the list of essential drugs in the world
N=86



Carbamazepine
Phenobarbital
Phenytoin
Valproic acid

11.2 Median cost of daily defined dose (DDD) of Carbamazepine, Phenobarbital, Phenytoin and Valproic acid in WHO regions and the world
(in International Dollars)

Carbamazepine
Phenobarbital
Phenytoin
Valproic acid

Africa N=13
2.22
0.12
0.5
3.14

America N=13
2.33
0.25
0.81
3.46

South-East Asia N=4
2.25
0.41
0.43
3.68

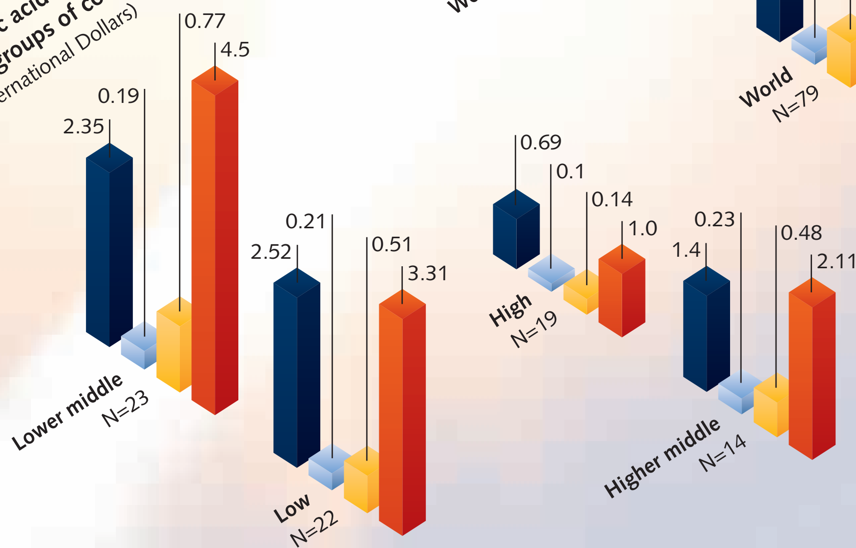
Europe N=30
1.1
0.15
0.23
1.63

Eastern Mediterranean N=8
1.95
0.08
0.39
2.7

Western Pacific N=11
1.04
0.09
0.15
1.55

World N=79
1.59
0.14
0.46
2.2

11.3 Median cost of daily defined dose (DDD) of Carbamazepine, Phenobarbital, Phenytoin and Valproic acid in different income groups of countries
(in International Dollars)



Prof Amadou Gallo Diop

A consensual definition of the so-called "treatment gap" was adopted by international experts gathered together by the ILAE: "The difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated in a given population at a given point in time, expressed as a percentage" (*2*). It is estimated that 80% of the global health burden represented by epilepsy is borne by the developing world, where 80% of people with epilepsy reside and do not receive modern treatment, or are not even identified (*66*). Poor infrastructure, insufficient availability of drugs and scarcity of trained medical personnel are relevant factors in this situation (*67*). Some potential causes could be the level of health-care development, cultural beliefs, economy, distance from health-care facilities and supply of AEDs, and a lack of prioritization in national health policies.

Epilepsy is one of the major brain disorders worldwide. The condition is characterized by repeated seizures or "fits" which take many forms, ranging from a very short lapse of attention to severe and frequent convulsions. Epilepsy is responsible for an enormous amount of suffering affecting about 50 million people around the world (*68*), yet in the developing countries the large majority of people with epilepsy remain excluded from receiving care and are consequently maintained in the shadow of the treatment gap.

Both cultural and structural factors underpin the treatment gap. In many developing countries, epilepsy is perceived as a manifestation of supernatural forces, caused by ancestral spirits or attributed to possession by evil spirits (*69, 70*). The levels of literacy and knowledge influence cultural beliefs and treatment choices. Usually the family and the patient first consult the traditional healers and follow their recommendations for a long period of time (*71, 72*). The mean duration before seeking modern medical care can be several years and depends on the area of residence (urban or rural), the impact of cultural belief and the financial means; for example, reports from some countries reveal that this period can last 6–14 years (*72*).

People with epilepsy are often stigmatized, which discourages them from seeking the diagnoses and care they need and deserve (*73*). Another burden is the discrimination experienced by people who have seizures, who are able to work but are unemployed or underemployed. In some societies the fear of "contamination" by the breath, blood, sperm and genital secretion of people with epilepsy, and who are not treated, leads to unacceptable responses such as rushing away from a person experiencing a seizure without offering any help (*70*). Death, drowning, burning and other injuries may result from such situations. Children with epilepsy, victims of the treatment gap, often face discrimination and isolation at school, resulting in low self-esteem and underachievement. Surveys conducted in schools revealed a high rate of social withdrawal among children with epilepsy.

As far as structural factors are concerned, in several countries health insurance is poorly developed and the population consequently has to pay for health care. In such countries general economy, health and education expenditures are low while malnutrition and morbidity are dramatically high. Many aspects of health care have become unaffordable for the patient because of health system reforms conducted in the majority of the countries: one of the reasons invoked by the population for not seeking medical treatment is financial.

Epilepsy is a clear-cut example of a neurological disorder for which several pharmacological and alternative treatments are available. Recent studies in both the developing and the developed world revealed that, if properly treated, up to 70% of people with this condition could live productive and fulfilling lives, free from seizures (*68*). The AEDs most often prescribed in the developing world are phenobarbital and phenytoin. These two drugs are the cheapest and are prescribed in 65–85% of treated epileptic patients (*68*). They are available in most health establishments but are not accessible to the large majority of people with epilepsy (*74, 75*).

Another form of treatment gap is related to non-medicinal therapy for severe epilepsy in developed and developing countries. When people with epilepsy continue to have frequent seizures despite multiple drug therapy, epilepsy surgery may be indicated (*76*). In some parts of the world, epilepsy centres are performing surgery routinely, with minimal resources and good results in those selected from the 25% of people with epilepsy who do not benefit from drug therapy and who are candidates for such operations. Surgery could represent a significant improvement in the quality of life for some of the 20–30% of people with epilepsy who continue to have seizures while taking appropriate medication. Another alternative, especially in children with drug-resistant epilepsy, is the use of a ketogenic (very high fat content) diet. Although it is expensive and difficult to tolerate, reduction in the frequency of seizures has been consistently reported. There are no reports on the use of this method in Africa. An alternative to surgery is vagus nerve stimulation; as this involves implantation of an expensive device, its present applicability is limited to the developed world.

Bridging the treatment gap

In order to solve progressively the huge challenge of reducing the treatment gap, professionals from various sectors managing every aspect of the lives of people with epilepsy will need to take action in a multidisciplinary approach, coordinating health, education, social and professional activities and psychology. These trained health and social workers must cooperate with patients and families, communicators, community leaders and opinion leaders, with the support of governments, national and international institu-

tions and nongovernmental organizations, bilateral and multilateral agencies and pharmaceutical companies. This need is summed up in ILAE/IBE/WHO Global Campaign Against Epilepsy publications (*68, 77*). The main actions recommended to bridge the epilepsy treatment gap are:

- fostering political commitment;
- improving access to care for epilepsy;
- arranging educational and training programmes on epilepsy for medical practitioners, nurses and midwives, social workers, and schoolteachers;
- developing adapted guidelines for epilepsy management;
- considering the cultural environment in any epilepsy health plan;
- facilitating collaboration with traditional healers and community leaders;
- ensuring the integration of epilepsy prevention in public health interventions;
- providing appropriate support and care.

In conclusion, the main problems are the lack of knowledge about epilepsy and the limited human and material resources in the majority of countries. In other words, the treatment gaps are widest where there is a lack of available, accessible and affordable health care – and part of good care is awareness raising and eradicating stigma. People with epilepsy in the developing world can wait years from the moment of their first seizure before they consult modern medical services and benefit from the progress achieved. The opportunity offered by the international collaborative initiative set up by the Campaign should progressively transform the situation and eliminate any possibility of a person with epilepsy not receiving treatment.

Introduction

- The respondents were asked about the availability of various services such as epilepsy surgery, social rehabilitation, special education, sheltered work and special equipment. They were asked whether these services were available free of charge or without special conditions when covered by insurance.

Salient findings

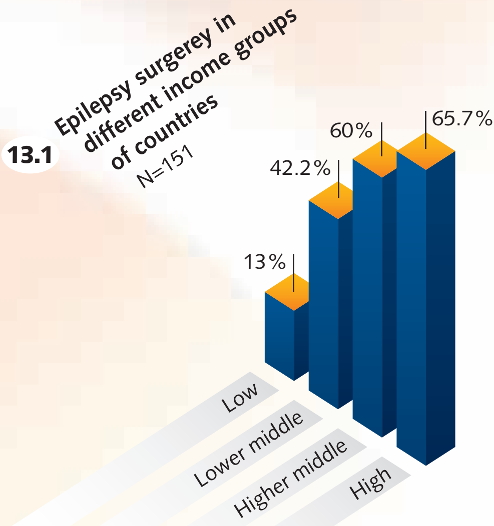
- Epilepsy surgery is available in 40.9% of the responding countries.
- Epilepsy surgery is not available in 88.6% of the responding countries in Africa, 68.2% in the Western Pacific, 66.7% in South-East Asia, 50% in the Americas and the Eastern Mediterranean, and 33.3% in Europe.
- Epilepsy surgery is not available in 87% of low-income countries. The facility for epilepsy surgery is also absent in 34.3% of high-income countries.
- Facilities for social rehabilitation are available in 56.5% of the responding countries. In about half of them, social rehabilitation is available to people with epilepsy free of charge or without any special condition.
- No social rehabilitation services are available in 68.2% of the responding countries in the Western Pacific, 66.7% in South-East Asia, 57.1% in the Eastern Mediterranean, 37.8% in Europe, 37.1% in Africa, and 25% in the Americas.
- Some special equipment is available free of charge or without any special condition in 19.3% of the responding countries.
- Facilities for special education are available in 62.3% of the responding countries. In two thirds of them it is available to people with epilepsy free of charge or without any special condition.
- Special education facilities are available in 45.7% of low-income countries and in one third of them they are available free of charge. Such facilities are present in 77.1% of high-income countries and are available free of charge in three quarters of them.
- Facilities for sheltered work are available in 25.5% of the responding countries. In two thirds of them, sheltered work is available to people with epilepsy free of charge or without any special condition.
- Sheltered work facilities are available in 50% of the responding countries in the Americas, 42.2% in Europe, 9.1% in the Western Pacific, 8.6% in Africa, and 7.1% in the Eastern Mediterranean. They are not present in any of the responding countries in South-East Asia.
- Sheltered work facilities are not available in 93.5% of low-income countries. They are also absent in 37.1% of high-income countries.

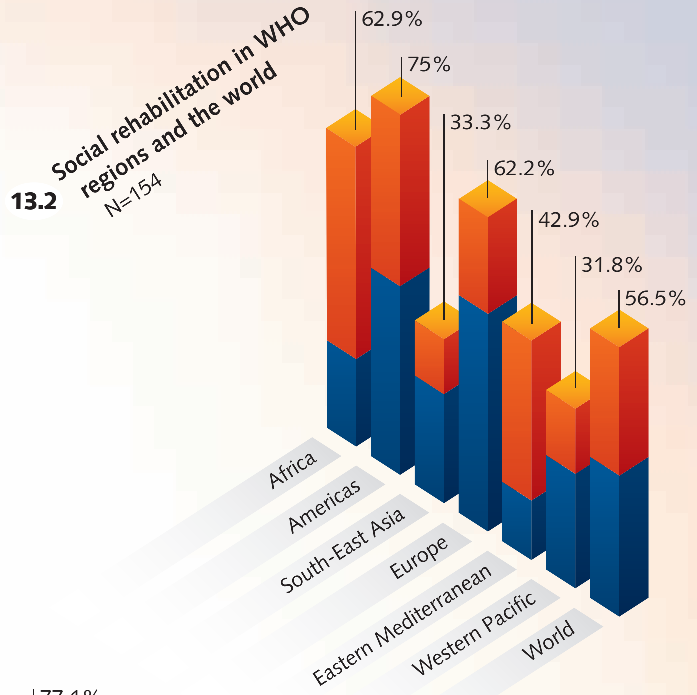
Limitations

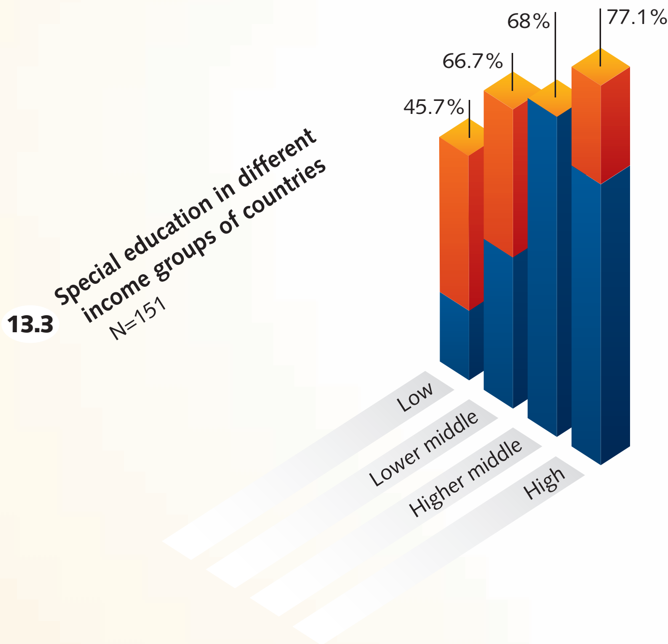
- Respondents may have replied positively to the question of availability of sub-specialized services for epilepsy in the country even if only a very limited number of such facilities are available in a few large cities.
- Because the sources of information in most countries were key persons working in the area of epilepsy, the data pertain mainly to countries where individuals with an interest in providing epilepsy care exist. It is therefore possible that the above figures are overestimated.
- Some respondents may have replied in the affirmative even if the sub-specialized services are part of the general services. It is also not clear what percentage of these services is available and utilized by people with epilepsy.

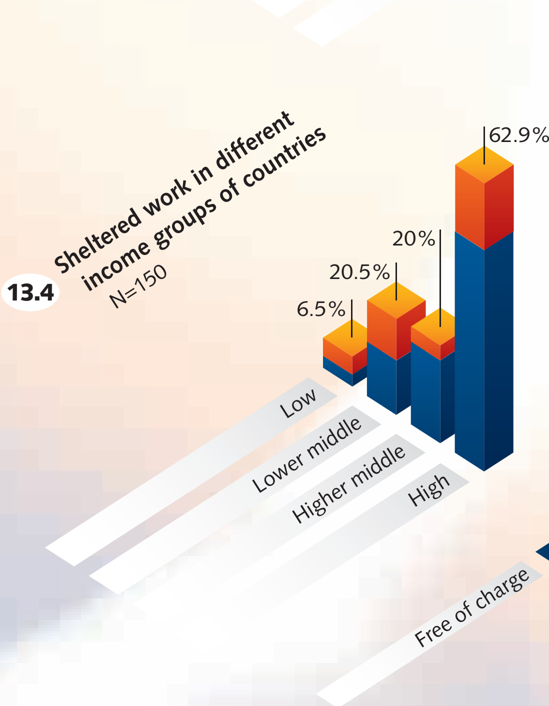
Conclusions

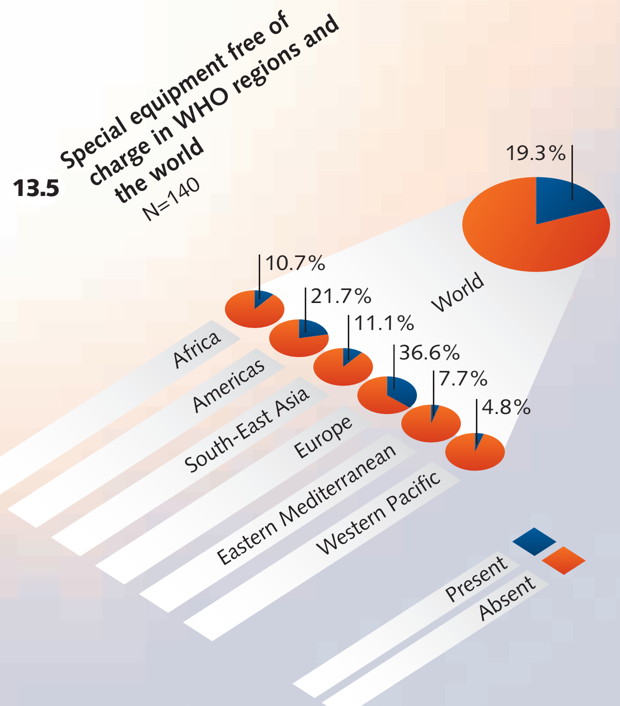
- Epilepsy surgery is an important treatment option for patients with intractable epilepsy and may reduce the need for long-term drug treatment.
- Severe social problems may occur in people with poorly controlled seizures, e.g. fewer social contacts, friends and leisure activities. Special social rehabilitation units aim to facilitate independent lifestyles and to reduce psychosocial disabilities.
- Special equipment is important for the rehabilitation of a subcategory of people with epilepsy to allow them a better quality of life and improved general social functioning.
- It is important to include as many children with epilepsy in mainstream schools as possible. Specialist units need to be established within countries to cope with the special educational needs of children with associated learning difficulties.
- Sheltered workshops allow the development of vocational competence, train for competitive employment and provide appropriate job placement.
- The inequity in the availability of sub-specialized services across regions and income groups of countries needs to be dealt with. The availability of these services needs to be improved even in high-income countries.


13.1
Epilepsy surgerey in different income groups of countries
N=151
13%
42.2%
60%
65.7%
Low
Lower middle
Higher middle
High


13.2
Social rehabilitation in WHO regions and the world
N=154
62.9%
75%
33.3%
62.2%
42.9%
31.8%
56.5%
Africa
Americas
South-East Asia
Europe
Eastern Mediterranean
Western Pacific
World


13.3
Special education in different income groups of countries
N=151
45.7%
66.7%
68%
77.1%
Low
Lower middle
Higher middle
High
Free of charge


13.4
Sheltered work in different income groups of countries
N=150
6.5%
20.5%
20%
62.9%
Low
Lower middle
Higher middle
High
Free of charge


13.5
Special equipment free of charge in WHO regions and the world
N=140
19.3%
10.7%
21.7%
11.1%
36.6%
7.7%
4.8%
World
Africa
Americas
South-East Asia
Europe
Eastern Mediterranean
Western Pacific
Present
Absent

Prof Jerome Engel Jr

Healers have entered the intracranial space for thousands of years to treat various illnesses. Ancient neurosurgical therapies, however, were based on beliefs of supernatural causes of disease and a need to release evil spirits. The modern approach to surgical treatment for epilepsy began in the late 19th century with the advent of scientifically based concepts of natural causes of epilepsy and the technical development of brain surgery (*78*). Initially, epilepsy surgery was based on identification of a visible, resectable lesion in the cerebral cortex, usually caused by head trauma resulting in an obvious skull fracture or scalp wound. Surgeons were also guided to the location of the epileptogenic brain area by the initial behavioural features of the epileptic seizures (*79*). By the early 20th century, potentially epileptogenic disturbances in the brain could be visualized by neuroradiological techniques such as pneumoencephalography and cerebral angiography. The discovery of electroencephalography (EEG) in the mid-20th century, however, made it possible to localize an epileptogenic region for surgery based entirely on focal epileptiform EEG abnormalities, permitting effective surgery even in the absence of visible structural pathology (*80, 81*). Surgery, particularly for temporal lobe epilepsy, thus became an important alternative treatment for epilepsy in the industrialized world.

The application of epilepsy surgery again advanced significantly towards the end of the 20th century as a result of greatly improved neuroimaging, specifically magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT), which further improved the ability to identify resectable epileptogenic brain lesions that were not apparent with previous diagnostic tools (*82, 83*). For the first time, hippocampal sclerosis, perhaps the most common cause of human epilepsy, could be reliably identified noninvasively, and the visualization of a variety of malformations of cortical development greatly enhanced opportunities for surgical treatment of catastrophic epilepsies of infancy and early childhood.

Today, as a result of continuing improvement in presurgical diagnostic technology, as well as microsurgical techniques, epilepsy surgery is a safe and effective alternative treatment for a wide variety of epileptic conditions that are not adequately treated by AEDs. Because surgical treatment is presently the only therapy that can actually cure epilepsy, and because complete elimination of epileptic seizures can prevent or reverse the severe psychological and social consequences of epilepsy, as well as developmental delay in some childhood epilepsy conditions, its timely application offers the potential to rescue people with epilepsy from a lifetime of disability.

Despite the introduction of many new AEDs over the past two decades, 30–40% of people with epilepsy who have access to such medications have seizures that cannot be completely controlled by pharmacotherapy. It is estimated that one quarter to one half of people with medically refractory seizures are potential candidates for surgical therapy, or about 10% of the entire population of people with epilepsy. There is, therefore, a great need to facilitate the identification of potential surgical candidates, and to expand facilities for performing surgical therapy. A major impediment to timely and effective surgical intervention, however, has been the prevalent misconception that epilepsy surgery should be a last resort, considered only after treatment with all available AEDs has failed. There are now so many different AEDs available in the industrialized world that it would literally take a lifetime to try them all in every conceivable combination. In countries where many pharmacotherapeutic alternatives exist, it is necessary to develop guidelines to determine when to stop additional drug trials and consider surgical intervention.

The concept of surgically remediable epilepsy syndromes has been a major advance in this regard (*84*). Surgically remediable epilepsy syndromes are well-defined conditions with known pathophysiologies and natural histories. For these conditions, failure of two or three appropriate AEDs at adequate doses predicts subsequent pharmacoresistance with a high degree of confidence, whereas the likelihood of a seizure-free outcome with surgery, by definition, is 70–80%. Surgically remediable syndromes can be easily diagnosed noninvasively in most patients, and early surgical intervention is not only associated with seizure freedom in these patients but can prevent the development of irreversible psychological and social disabilities. The prototype of a surgically remediable epilepsy syndrome is mesial temporal lobe epilepsy. Patients with focal epilepsy due to discretely localized brain lesions also have surgically remediable epilepsy syndromes, as do infants and young children with catastrophic epilepsies attributable to diffuse brain disturbances limited to one hemisphere.

Surgically remediable syndromes can be easily identified by history, including an accurate description of the clinical seizures, routine EEG, and neuroimaging, preferably MRI. Presurgical evaluation usually requires inpatient video/EEG monitoring in order to capture and characterize habitual seizures and localize their site of origin in the brain. For some surgically remediable epilepsies, such as temporal lobe epilepsy, neuropsychological evaluation is important, often including an intracarotid amobarbital procedure to confirm that the contralateral hemisphere can support memory following mesial temporal lobe resection. Where sufficient resources exist, additional diagnostic techniques, such as intracranial video/EEG monitoring with intracerebral depth or subdural electrodes, PET, SPECT, functional MRI and magnetoencephalography (MEG) can also be used to help determine the area of brain to be resected. These diagnostic approaches, however, are usually only necessary when

patients present with difficult diagnostic problems, and not for those with the typical surgically remediable epilepsies. A psychiatric assessment is also recommended as part of the presurgical evaluation, to predict potential postoperative behavioural problems and help to deal with them. Patients operated on early in the course of their disorder are usually easily rehabilitated, but those who have had epilepsy for long periods of time may have difficulty adjusting to their seizure-free state.

Temporal lobe epilepsy is usually treated with an anterior mesial temporal resection, and localized cortical lesions are treated with limited resections, which may require additional functional mapping to ensure that essential cortex is not damaged in the process. Published reports indicate that 60–90% of patients receiving these treatments can expect to become free of disabling seizures (*85, 86*). Complications, including infections, and unexpected neurological deficits occur in approximately 6% of patients, but half of these are transient. Surgical mortality is negligible. Infants and young children with catastrophic epilepsy are treated with hemispherectomy, hemispherotomy, or multilobar resections, and 60–80% become free of disabling seizures (*87*). Because these children usually already have hemiparesis with a useless hand, the surgery does not introduce additional neurological deficits. In fact, contralateral motor function can improve slightly, and developmental delay is often reversed. Surgical mortality, however, is somewhat higher than with the more focal resections. Many other types of epilepsy that are not the typical surgically remediable syndromes can also be treated surgically, but they require a more extensive presurgical evaluation; prognosis for a seizure-free outcome may range from 30% to 60%, and surgical complications are more likely. The risk–benefit ratio for surgery in these conditions is considerably greater, therefore, than for the surgical remediable epilepsy syndromes, and these are not cost-effective procedures for countries with limited resources.

Whereas the treatment gap for epilepsy is of considerable concern in the developing world, there is a marked treatment gap with respect to epilepsy surgery even in industrialized countries, where perhaps only 5% of potential surgical candidates are ever referred to an epilepsy surgery centre. This is largely attributed to misinformation about the risks and benefits of surgery, particularly with respect to recent advances in diagnostic and surgical approaches that have greatly improved safety and efficacy. Until recently, epilepsy surgery was not available in countries with limited resources, but epilepsy surgery programmes are now prominent in Brazil, China, India and Turkey and are being developed in many other countries with limited resources where it is recognized as a more cost-effective treatment for surgically remediable syndromes than continued pharmacotherapy (*88, 89*). The success of epilepsy surgery programmes in countries with limited resources depends more on a well-trained clinical team, including a neurologist, neurosurgeon, clinical neurophysiologist, neuropsychologist, neuroradiologist and psychiatrist, than on high-level diagnostic and surgical technology. By investing in the appropriate clinical expertise, countries with limited resources can operate on patients with surgically remediable epilepsy syndromes and achieve results identical to those in the industrialized world, with only video/EEG and MRI. Because of the relatively high prevalence of surgically remediable epilepsy syndromes, particularly mesial temporal lobe epilepsy, investment in such epilepsy surgery centres, even in the poorest regions of the world, could greatly reduce the economic and human burden of epilepsy.