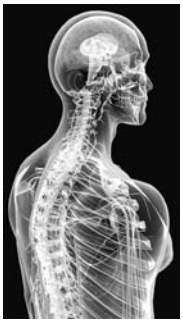
Chapter **32**

Neurological Disorders



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Historically, policy makers and researchers have used mortality statistics as the principal measure of the seriousness of diseases, based on which countries and organizations have launched disease control programs. Mortality statistics alone, however, underestimate the suffering caused by diseases that may be nonfatal but cause substantial disability. Many neurological and psychiatric conditions belong in this category. The absence of some neurological disorders from lists of leading causes of death has contributed to their long-term neglect. When the relative seriousness of diseases is assessed by time lived with disability rather than by mortality, several neurological disorders appear as leading causes of suffering worldwide.

World Health Organization data suggest that neurological and psychiatric disorders are an important and growing cause of morbidity. The magnitude and burden of mental, neurological, and behavioral disorders is huge, affecting more than 450 million people globally. According to the Global Burden of Disease Report, 33 percent of years lived with disability and 13 percent of disability-adjusted life years (DALYs) are due to neurological and psychiatric disorders, which account for four out of the six leading causes of years lived with disability (Mathers and others 2003).

Unfortunately, the burden of these disorders in developing countries remains largely unrecognized. Moreover, the burden imposed by such chronic neurological conditions in general can be expected to be particularly devastating in poor populations. Primary manifestations of the impact on the poor—including the loss of gainful employment, with the attendant loss of family income; the requirement for caregiving, with further potential loss of wages; the cost of medications; and the need for other medical services—can be expected to be particularly devastating among those with limited resources. In addition to health costs, those suffering from these conditions are also frequently victims of human rights violations, stigmatization, and discrimination. Stigmatization and discrimination further limit patients' access to treatment. These disorders, therefore, require special attention in developing countries.

This chapter addresses Alzheimer's disease (AD) and other dementias, epilepsy, Parkinson's disease (PD), and acute ischemic stroke. These conditions are current or emerging public health problems in developing countries, as assessed by high prevalence, large numbers of people who are untreated, and availability of inexpensive but effective interventions that could be applied on a large scale through primary care. Unfortunately, reliable population-based data from developing countries on the epidemiology of these and other neurological disorders are extremely limited. Some other important neurological conditions that cause high morbidity, such as headache, are not covered because of difficulties in recommending evidence-based interventions in developing countries.

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Dementia is a deterioration of intellectual function and other cognitive skills that is of sufficient severity to interfere with

social or occupational functioning. Of the many diseases that lead to dementia, AD is the most common cause worldwide among people age 65 and older, followed by vascular dementia, mixed dementia consisting of AD plus vascular dementia, and dementia caused by general medical conditions. Although distinguishing AD from other causes of dementia is important, particularly for treatment with acetylcholinesterase inhibitors, the burden from all causes of dementia is similar. Although the discussion in this chapter deals mostly with AD, the role of treatable dementias in developing countries is important as it can reduce the burden of caring in families.

Prevalence and Incidence Rate

More than 100 prevalence studies of AD and other dementias have been reported throughout the world. The prevalence of dementia has generally been found to double with every five-year increase in age, from 3 percent at age 70 to 20 to 30 percent at age 85 (Henderson and Jorm 2000). Studies in developing countries have shown a prevalence of dementia ranging from 0.84 to 3.50 percent (Chandra and others 1998; Hendrie and others 1995; Rajkumar, Kumar, and Thara 1997). Several studies have reported the incidence rate of AD and other dementias in Europe and the United States (Jorm and Jolley 1998). Compared with incidence rates in developed countries, very low age-specific incidence rates of AD and other dementias have been reported from developing countries (Chandra and others 2001; Hendrie and others 2001).

A comparison of data from developed and developing countries raises several important questions. The reported differences in the prevalence of AD and other dementias across countries could be due partly to methodological differences or could be due to genuine differences caused by variations in diet, education, life expectancy, sociocultural factors, and other risk factors. The low incidence reported from Ballabgarh, India, and Ibadan, Nigeria, raises the possibility of environmental factors or gene-environment interactions in the causation of AD. At the same time, multi-infarct dementia is more common than primary degenerative dementia in China (Li and others 1991), which also suggests variation in risk factors across countries.

Risk and Protective Factors and Survivorship

Three separate genes (APP, PS1, and PS2) are linked to early-onset, familial AD. Another gene (APO E4) is a risk factor for late-onset, nonfamilial cases (Henderson and Jorm 2000). Other genes have been implicated but not confirmed in large studies. Other risk factors reported in the literature include increasing age, positive family history of dementia, female gender (but this factor is controversial), lower level of education, several medical conditions, and exposure to such environmental factors as organic solvents and aluminum (Henderson and Jorm 2000).

Protective factors reported in the literature include a higher level of education, a specific gene (APO E2), the intake of antioxidants, and the use of some anti-inflammatory medications (Henderson and Jorm 2000). The use of estrogen supplements for women was believed to be a protective factor for AD (Henderson 1997), but a recent study of women taking a combination of estrogen and progesterone showed that these women had twice the risk of developing dementia than women taking a placebo (Shumaker and others 2003).

Studies from developed countries have reported median survival after the onset of dementia symptoms ranging from 5.0 years to 9.3 years (Walsh, Welch, and Larson 1990). In developing countries, the reported median survival was 3.3 years for all demented subjects and 2.7 years for those with AD (Chandra and others 1998).

Burden of Disease

Burden of disease estimates of AD and other dementias include vascular dementia, unspecified dementias, and other unclassified degenerative diseases of the nervous system. Mathers and others (2003) estimate DALYs for all dementias as 17,108,000, with the burden being almost twice as much for females (11,016,000) as for males (6,092,000). Because dementia is a disease of older ages, the burden from dementia is generally greater in high-income countries, where life expectancy is higher, diagnosis is better, and better treatment leads to increased longevity. Note, however, the relatively high burden in East Asia and the Pacific and South Asia relative to their level of economic development (table 32.1).

The bulk of care for those with dementia in developing countries is provided by the family at home, where the main caregivers are spouses (36 percent) and children (42 percent) (Prince 2000). Women in both developed and developing countries are usually the main caregivers (Prince 2000). Studies in developed countries indicate that caregivers' psychological well-being is a key factor in patients' admission to nursing or residential care (Levin, Moriarty, and Gorbach 1994).

In estimating the overall costs of care for dementia, one must emphasize the value of reducing the burden on caregivers. Caregiving can result in social isolation, psychological stress, and high rates of depression (Buck and others 1997). However, the methodology for estimating the costs of informal care needs to be standardized.

Interventions

As of now, there is no cure for AD, but some measures can provide symptomatic relief to patients and caregivers.

Population-Based Interventions. No firm evidence indicates that any form of population-based intervention can prevent AD or that the progression of cognitive decline in old age can

Table 32.1 Disability-Adjusted Life Years by Cause and Region, 2001
(thousands)

Condition	Global total			East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	High-income countries
	Both sexes	Males	Females							
AD and other dementias	17,108	6,092	11,016	4,110	1,612	1,215	292	1,955	450	7,468
Epilepsy	6,223	3,301	2,922	1,303	354	737	248	1,741	1,373	464
PD	2,325	1,124	1,202	435	228	90	81	303	100	1,086
Cerebrovascular disease	72,024	35,482	36,542	25,832	12,616	3,936	1,948	13,184	5,125	9,354

Source: Mathers and others 2006.

be halted or reduced. However, growing inferential evidence suggests that reducing the risk of brain trauma in earlier life, for example, by mandating seat belt and crash helmet use, may help prevent dementia in later life (Gentleman, Graham and Roberts 1993).

Personal Interventions. There is a reduction in brain levels of the neurotransmitter acetylcholine in patients suffering from AD. Drugs that inhibit acetylcholinesterase, the enzyme responsible for metabolizing acetylcholine, cause an increase in brain acetylcholine. Evidence from randomized trials has confirmed that, for patients with mild to moderate AD, cognitive performance benefits, at least in the short term, from the use of acetylcholinesterase inhibitors (Foster and others 1996). Despite this benefit to patients, the practical benefits of treatment with acetylcholinesterase inhibitors are mainly attributable to the lowered caregiver burden. The benefits of using acetylcholinesterase inhibitors for other dementias have yet to be proven.

The behavioral and psychological symptoms of dementia are a major source of stress to family members providing care to patients. Training family caregivers in behavioral management techniques, including problem solving, memory training, and reality orientation, has been shown to reduce the level of agitation and anxiety in people with dementia (Brodaty and Gresham 1989; Haupt, Karger, and Janner 2000). Use of low doses of antipsychotic medications, which calm the patient and reduce symptoms such as aggression and wandering, have been shown to reduce caregiver stress, but these improvements have not been quantified (Melzer and others 2004).

Interventions that have specifically targeted stress and depression among caregivers and have shown positive results include caregiver training, counseling and support for caregivers, and cognitive and behavioral family interventions (Marriott and others 2000). Limitations to the implementation of such strategies include the need for training by specialists, which makes these strategies less suitable for developing countries. The challenge for developing countries is to develop culturally appropriate interventions that can be delivered within existing resources, such as supporting families in their role as caregivers.

Treating underlying disease and risk factors for cardiovascular disease can help prevent future cerebrovascular disease that could lead to multi-infarct dementia. Other conditions, such as hypothyroidism or vitamin B_{12} deficiency, which could lead to or aggravate dementia, are easily treatable, and the costs of treatment are much lower than the costs of dementia care.

In Western countries, the model of care for patients with moderate to severe dementia is based on skilled, long-term care in institutions. However, such long-term care institutions do not exist in developing countries, and if they were set up, they would be extremely expensive and beyond the reach of most patients and their families. Thus, the model of care in developing countries should be based on home care, along with providing training and support for family caregivers.

Interventions that should not be pursued include the use of multiple medications, which can be detrimental in older age groups, particularly unproven medications such as cerebral activators and neurotropic agents. In addition, in many developing countries, dementia is still equated with "madness," and patients are sometimes taken to traditional healers. Community education has a role to play in eliminating such practices.

EPILEPSY

Epilepsy is a common brain disorder characterized by two or more unprovoked seizures. Seizures are discrete events caused by transient, hypersynchronous, abnormal neuronal activity. Seizures may occur in close temporal association with a variety of acute medical and neurological diseases, such as acute stroke, sepsis, or alcohol withdrawal. However, the vast majority of seizures have no immediate identifiable cause.

Epilepsy can be broadly divided into three categories: idiopathic epilepsy (for example primary generalized childhood-onset absence epilepsy), which is thought to have a

genetic basis; secondary or symptomatic epilepsy, which is caused by a known central nervous system injury or disorder, such as infection, stroke, traumatic brain injury, or cerebral dysgenesis; and cryptogenic epilepsy, for which there is no clear evidence of an etiological factor. Idiopathic and cryptogenic cases represent approximately 70 percent of epilepsy cases; the remaining 30 percent are symptomatic (secondary).

Prevalence, Incidence Rate, Remission, and Mortality

The generally accepted estimate of the prevalence of active epilepsy globally is in the range of 5 to 8 per 1,000 population, but investigators from African and Latin American countries report at least double the prevalence reported elsewhere (Leonardi and Ustun 2002).

The incidence rate of epilepsy in developed countries is approximately 43 per 100,000 (Kotsopoulos and others 2002). In developing countries, the incidence rate of epilepsy is higher, with a median of 69 per 100,000 (Kotsopoulos and others 2002).

Based on follow-up of patients under treatment by general practitioners in the United Kingdom, Cockerell and others (1997) report that after nine years 86 percent of epilepsy patients had achieved a remission of three years, and 68 percent had achieved a remission of five years. Thus, data from developed countries suggest a good outcome of seizure control in most patients with treatment. In developing countries, although many people with new onset seizures do not receive treatment, some proportion of patients go into spontaneous remission even without treatment (Mani and others 1993). However, the actual remission rate in developing countries is yet to be documented in population-based studies.

The risk of premature death in people with epilepsy is two to three times higher than for the general population. In addition to sudden unexplained death, which occurs in up to 1 in 100 patients with severe refractory epilepsy, additional mortality results from accidents and suicide. However, the exact cause of the increased risk is not known in most cases.

Risk Factors

A reported risk factor for idiopathic (presumed genetic) epilepsy is family history of epilepsy. Reported risk factors for symptomatic epilepsy include prenatal or perinatal causes (obstetric complications, prematurity, low birthweight, neonatal asphyxia). Recent data suggest that the effect of obstetric complications or neonatal asphyxia may have been overemphasized. Prematurity, low birthweight, and neonatal seizures may be independent risk factors as well as markers of underlying disease. Other causes include traumatic brain injuries, central nervous system infections, cerebrovascular disease, brain tumors, and neurodegenerative diseases. Developmental disabilities are not a risk factor for epilepsy in themselves, but they may be associated with seizure disorder (Casetta and others 2002; Leone and others 2002).

Treatment Gap

Epilepsy affects about 50 million people worldwide, of whom approximately 80 percent live in developing countries (WHO 2000). The difference between the number of people with active epilepsy and the number who are being appropriately treated in a given population at a given point in time is known as the *treatment gap*. Meinardi and others (2001) estimate that 90 percent of people with epilepsy in developing countries are inadequately treated. Possible reasons for the high treatment gap include fear of stigmatization, cultural beliefs, lack of knowledge about the medical nature of epilepsy, illiteracy, economic issues, distance to health facilities, inadequate supply of antiepileptic drugs (AEDs), and lack of prioritization by health authorities (Wang and others 2003). Even in the developed world, patients who live in isolated rural regions or inner-city slums and those who are isolated from the majority because of cultural factors may suffer a treatment gap.

Faith Healers

Many people with epilepsy seek treatment from faith healers, to whom they pay large sums in cash or in kind for treatment with no beneficial medical effects. Karaagac and others (1999) find that in Silivri, Turkey, 65 percent of 49 people with epilepsy had visited religious figures at the onset or during the course of the disease. A study from rural India revealed that 44 percent of children with epilepsy had sought help from traditional practitioners, whereas approximately 33 percent had received help from both qualified and traditional practitioners (Pal and others 2002). Native Americans still seek traditional healing ceremonies for epilepsy instead of—or in addition to—Western medicine.

Patient Compliance

In a study in rural Thailand, only 57 percent of people with epilepsy were 100 percent compliant with treatment, possibly because of misunderstanding of the instructions (48 percent), forgetfulness (16 percent), and economic limitations (13 percent) (Asawavichienjinda, Sitthi-Amorn, and Tanyanont 2003). To improve compliance in a rural African community, medical personnel visited the community every 6 months and provided a long-term supply of medications; this effort led to a substantial increase in compliance at 20 months (Kaiser and others 1998). In India, Desai and others (1998) demonstrate the dependency of compliance on access to free treatment. Inadequate communication between doctors and patients influences compliance negatively (Gopinath and others 2000).

Burden of Disease

The burden of disease (BOD) estimates for epilepsy include epilepsy and status epilepticus. Mathers and others (2003) estimate the DALYs for epilepsy as 6,223,000, with slightly higher rates for males (3,301,000) than for females (2,922,000). Many risk factors for epilepsy are linked with a lower level of economic development; thus, the burden is highest in South Asia followed by Sub-Saharan Africa (table 32.1). A notable observation is the reportedly low burden in the Middle East and North Africa, despite parts of that region being relatively underdeveloped. Epilepsy imposes a large economic burden on patients and their families. It also imposes a hidden burden associated with stigmatization and discrimination against patients and even their families in the community, workplace, school, and home. Social isolation, emotional distress, dependence on family, poor employment opportunities, and personal injury add to the suffering of people with epilepsy.

Interventions

Currently, there are no preventive measures for idiopathic or cryptogenic epilepsy; however, much can be done to prevent secondary seizures.

Population-Based Interventions. Public health policies, such as better perinatal care by well-trained birth attendants (particularly in rural areas) and strategies to control severe head injuries (for example, by means of laws requiring motorcyclists to wear helmets and prohibiting drunk driving), can modify risk factors for epilepsy and thereby reduce the incidence and prevalence of epilepsy. Policies to control neurocysticercosis (for instance, building latrines in rural areas) can serve to prevent such infections. Mass deworming for neurocysticercosis has not been shown to be effective in the long term (Pal, Carpio, and Sander 2000) but was effective in a campaign in Ecuador (M. Cruz, personal communication, 2004).

Estimates indicate that 70 to 80 percent of people in developing countries live in rural and remote areas and have no easy access to skilled medical care. Strategies that involve training community-based health care providers who practice in these communities to identify and manage patients with epilepsy should be considered.

Policies are needed to ensure the continuous availability of cheap and efficacious medications, such as phenobarbital, to all epilepsy patients. Campaigns to educate communities about the medical nature of epilepsy and to dispel myths and misconceptions about epilepsy could reduce stigma against epilepsy and thereby encourage patients to seek medical treatment.

Personal Interventions. Researchers, primarily in high-income countries, have tested (a) the efficacy of both older AEDs (such as phenobarbital, phenytoin, carbamazepine, and valproic acid) and newer AEDs (such as lamotrigine, oxcarbazepine, and topiramate) in controlling seizure frequency and (b) the safety of these AEDs when prescribed alone or in combination. Some, but not all, of the new AEDs may be better tolerated in monotherapy and have fewer long-term adverse effects than older AEDs. However, no study has shown any difference in efficacy between the older and newer medications (Aldenkamp, De Krom, and Reijs 2003). Newer medications are more expensive and, for people in most developing countries, are practically impossible to access. In some low-income countries, however, even older AEDs are not available, and when they are, their supply is irregular.

Newer AEDs are generally recommended as add-on or adjunctive drugs for better seizure control in patients with refractory epilepsy already on AEDs. The first AED will render approximately 50 percent of patients seizure free. Approximately 20 to 40 percent of patients who do not respond to the first AED will respond to the introduction of a second AED, with a greater than 50 percent decrease in seizure frequency (Schapel and others 1993).

The Global Campaign against Epilepsy, which is jointly sponsored by the World Health Organization, International League against Epilepsy, and International Bureau for Epilepsy, advocates using phenobarbital to close the high treatment gap in low-income countries. As a first step, all patients with epilepsy should be given phenobarbital, so that the majority of patients responsive to phenobarbital will be appropriately treated. In resource-poor countries, phenobarbital can be provided for as little as US$5 to US$10 per year. Phenobarbital has extremely low abuse potential. Its side effects—predominantly sedation, possible mild cognitive impairment, and depression—have limited its use in industrial countries. In developing countries, however, side effects are less important than uncontrolled seizures, and they can be diminished by using the lowest possible effective doses. Thus, phenobarbital is the drug of choice for large-scale, community-based programs, particularly in rural and remote areas of developing countries.

In recent years, some centers in both developed and developing countries have been performing surgery on cases of *refractory epilepsy,* that is, on patients who do not respond to any AEDs. Before centers can undertake such surgery, however, they must have the requisite expertise, facilities, and equipment, including a skilled neurosurgeon. Proper selection of patients—for example, those with mesial temporal pathology on MRI—is extremely important. A meta-analysis of studies of people who underwent epilepsy surgery in developed countries shows that 58 percent are seizure free and 10 to 15 percent have reduced seizure frequency (Engel and others 2003). After surgery, even if patients are seizure free, medication should be continued for one to two years (Engel and others 2003).

PARKINSON'S DISEASE

PD is characterized by bradykinesia, resting tremor, cogwheel rigidity, postural reflex impairment, progressive course, and good response to dopaminergic therapy. Other distinct forms of parkinsonism include relatively rare genetic forms and the less common neurodegenerations with multiple system involvement or significant striatal lesions (for example, progressive supranuclear palsy or multiple system atrophy). Parkinsonism secondary to external causes, such as manganese poisoning or carbon monoxide poisoning, although now rare, is referred to as secondary parkinsonism. Because the burden of these diseases to the patient is similar to or greater than that for PD and there is no evidence for addressing these disorders separately, they will not be distinguished here.

Prevalence, Incidence Rate, and Mortality

Prevalence estimates vary widely across populations (Tanner and Goldman 1996; Zhang and Roman 1993). Recent reports, contrary to previous reports, suggest that the prevalence in developing and developed countries may be similar (Marras and Tanner 2002). Few incidence studies have been performed, and none in developing countries. Van Den Eeden and others (2003) report the incidence rate of PD in the United States as approximately 13 per 100,000 person-years. Men are affected more commonly than women (Tanner and Goldman 1996). Lower PD incidence in African Americans—and by extension Africans—has been suggested but is controversial (Van Den Eeden and others 2003). Most mortality estimates available for developed countries show about a twofold overall increased mortality, independent of age, in those with PD (Berger and others 2000).

Causes and Risk Factors

The cause of PD is unknown. A specific environmental risk factor has not been identified. Pure genetic forms account for 10 to 15 percent of cases or fewer. Increasing age and male gender are risk factors worldwide (Marras and Tanner 2002). Exposure to toxins, head trauma, frequent infections, diets high in animal fat, and midlife adiposity have been reported to increase PD risk, but none do so consistently (Tanner and Goldman 1996). The most consistent association is an inverse association with cigarette smoking and caffeine consumption, suggesting a protective effect (Ascherio and others 2001).

Burden of Disease

The BOD estimates for PD include Parkinson's disease and secondary parkinsonism. Mathers and others (2003) estimate the DALYs for PD as 2,325,000, with the burden being slightly higher in females (1,202,000) than males (1,124,000). Though male gender is a risk factor for PD, the higher burden in females may reflect their longer life span. As PD is a disease of older ages, the burden from PD is generally higher in high-income countries, where life expectancy is higher, diagnosis is better, and better treatment leads to increased longevity. However, the burden is high in East Asia and the Pacific and South Asia relative to that in other regions (table 32.1).

The economic burden of PD includes direct costs, such as for medication, physicians, hospitals, and chronic care facilities. Estimated indirect costs resulting from the loss of labor of both patients and caregivers typically exceed direct costs. The quality of life of both patients and caregivers is adversely affected.

Interventions

Treatment of PD is based on symptomatic relief, except for preventing secondary parkinsonism caused by neurotoxins.

Population-Based Interventions. No determinants of PD amenable to population-based interventions have been identified.

Personal Interventions. Specific curative or neuroprotective treatments for PD have not been established. Interventions are primarily directed at palliation of symptoms and include pharmaceuticals, surgery, physical therapy, and—in some countries—traditional medicines.

Levo-dopa (l-dopa), l-dopa/decarboxylase inhibitor is the most widely used therapy for PD. It provides partial relief of all PD symptoms. Despite its benefits, chronic side effects after long-term use can cause significant morbidity.

Researchers in developing countries have studied the use of traditional medicines for PD. Clinical trials have shown that the seeds of *Mucuna pruriens,* which contain l-dopa, are a safe and effective treatment for PD (Parkinson's Disease Group 1995), and in animal studies, they are two to three times more effective than synthetic l-dopa dose per dose (Hussain and Manyam 1997). This substance is available in ayurvedic formulations in India at a much lower cost than that of synthetic antiparkinsonian drugs. Another traditional medicine is derived from *Banisteriopsis caapi,* which tribal societies of the Amazonian jungle use to make a potent hallucinogenic brew. It reportedly showed dramatic positive effects on rigidity and akinesia in 15 patients with postencephalitic parkinsonism (Lewin and Schuster 1929). A third traditional option is tai chi, a basic exercise in traditional Chinese medicine that may help with some of the motor deficits of PD.

Surgical treatment for PD by deep brain stimulation is generally recommended to address the loss of efficacy of dopaminergic drugs. For most patients, it is not effective independent of drugs. Although a few will have dramatic improvement and

may be able to reduce or stop drugs, this effect is generally temporary. Criteria for selection of patients for deep brain stimulation include those with advanced disease who are responsive to l-dopa, not demented, and in good general health. Additional considerations are the high cost of the equipment, the need for trained personnel to program the device, and—in most cases—the need for several visits to a medical center to program the stimulator correctly, with periodic returns to adjust the settings.

STROKE

Stroke, also known as *cerebrovascular accident* or *brain attack,* is a syndrome caused by an interruption in the flow of blood to part of the brain caused either by occlusion of a blood vessel (*ischemic stroke*) or rupture of a blood vessel (*hemorrhagic stroke*). The interruption in blood flow deprives the brain of nutrients and oxygen, resulting in injury to cells in the affected vascular territory of the brain. The occlusion of a blood vessel can sometimes be temporary and present as a reversible neurological deficit, which is termed a *transient ischemic attack.* Even though stroke is a clinical diagnosis, brain imaging is required to distinguish ischemic stroke from hemorrhagic stroke. When imaging is unavailable, clinical scores can be useful to identify patients with intracerebral hemorrhage (Allen 1983; Poungvarin, Viriyavejakul, and Komontri 1991).

Frequency of Types of Strokes, Prevalence, Incidence Rate, Mortality, and Disability after Stroke

In most parts of the world, about 70 percent of strokes are due to ischemia, 27 percent are due to hemorrhage, and 3 percent are of unknown cause (Gunatilake, Jayasekera, and Premawardene 2001). Approximately 25 percent of all ischemic strokes are due to cardioembolic causes, with the proportion being higher among younger individuals. In some parts of the world—for instance, China and Japan—hemorrhagic strokes account for a greater proportion of all strokes, ranging from 17.1 to 39.4 percent in China (Zhang and others 2003) to 38.7 percent in Japan (Fukiyama and others 2000).

Comparable data do not exist for all parts of the world. Most morbidity data from Southeast Asian countries, for example, are hospital based and are, thus, likely to be underestimates, because many stroke patients die before they are brought to the hospital. Mortality data are also likely to be underestimates, because verifying the cause of death is usually difficult.

In India, the prevalence of stroke has been estimated at 203 per 100,000 population older than 20 (Anand and others 2001). The male-to-female ratio was one to seven. In Taiwan, China, the crude point prevalence was 592 per 100,000 (Huang, Chiang, and Lee 1997).

He and others (1995) report the age-adjusted stroke incidence of 117 per 100,000 population in China. The annual incidence of stroke in China is reported to have increased in both men and women, with an average annual percentage change of 4.5 and 4.2 percent, respectively (Wang, Zhao, and Wu 2001). In Japan, the age-adjusted annual incidence of stroke was 105 per 100,000 (Fukiyama and others 2000). Wide variation within these countries and a high risk of death after the first stroke in the first year in Japan have been reported. Investigators believe that those observations are due to variations in the prevalence of hypertension and the consequent larger proportion of hemorrhagic stroke (Kiyohara and others 2003).

Walker and others (2000) report the yearly age-adjusted mortality rate per 100,000 for age group 15 to 64 ranged from 35 to 65 in men and 27 to 88 in women in Tanzania. When compared with the rates in England and Wales—11 for men and 9 for women—these rates are extremely high. The authors postulate that the high rates in Tanzania are due to untreated hypertension. Many developed countries have experienced a steep decline in stroke mortality in recent decades, but the rate of decline has fallen substantially in recent years (Liu, Ikeda, and Yamori 2001; Sarti and others 2000). Mortality from stroke has increased in some Eastern European countries (Sarti and others 2000).

Approximately 15 percent of patients die shortly after a stroke. Of the remaining 85 percent, approximately 10 percent recover almost completely, and 25 percent recover with minor impairments (National Stroke Association 2002). Thus, approximately 40 percent experience moderate to severe impairments that require special rehabilitative care. About 10 percent will require care in a nursing home or other long-term facility.

Risk Factors

Risk factors for stroke in general are similar to those for cardiovascular disease. Moreover, risk factors for first stroke and recurrence of stroke are also similar if they remain uncontrolled after the first attack (see chapter 33).

Increasing age, particularly after 55, is one of the most important risk factors for stroke (Thorvaldsen and others 1995). Although stroke is more prevalent among men, stroke-related fatality rates are higher among women (Goldstein and others 2001). Hypertension is the most important modifiable determinant of both first and recurrent stroke (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998). The association between blood pressure and stroke in East Asian populations seems stronger than in Western populations (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998). Other risk factors include smoking, environmental exposure to tobacco smoke, dyslipidemia, atrial fibrillation, diabetes and impaired glucose

tolerance, generalized and abdominal obesity, physical inactivity, excess alcohol consumption, increased homocysteine levels, drug abuse, hemostatic factors, and existing cerebrovascular disease (Goldstein and others 2001).

In developing countries, rheumatic heart disease leading to embolic stroke is also a major cause. This risk factor is declining in importance with the control of rheumatic fever. Dehydration in postpartum women can lead to a stroke, particularly in remote areas where deliveries are conducted at home.

Burden of Disease

The BOD estimates for stroke include subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and sequelae of cerebrovascular disease. Mathers and others (2003) estimate the DALYs for cerebrovascular disease as 72,024,000, with the burden being almost similar for females (36,542,000) and males (35,482,000). The burden is highest in East Asia and the Pacific, followed by South Asia and by Europe and Central Asia (table 32.1). The burden in Sub-Saharan Africa is higher than in the Middle East and North Africa, which may suggest an etiology for stroke other than atherosclerotic disease.

Health experts anticipate that the number of stroke cases will increase, particularly in developing countries, because of aging populations and increased exposure to major risk factors. Corresponding to this increase in the number of stroke cases will be an increase in the number of people with disabilities surviving after stroke.

Interventions

Several intervention strategies are available for stroke, but only a few can be applied in developing countries.

Population-Based Interventions. Public health policies to address risk factors for stroke include tobacco and alcohol control, laws to provide labels showing the fat content of foods, and public education about the harm caused by high-fat foods. Public health programs to control rheumatic fever will reduce rheumatic heart disease and the subsequent risk of embolic strokes. Better training of birth attendants will reduce the risk of peripartum hemorrhage, which leads to puerperal strokes.

Personal Interventions. Modification of adverse lifestyle and major risk factors such as hypertension, diabetes, high lipid levels, smoking, and alcohol abuse is beneficial both for primary prevention and recurrence of stroke. Some evidence indicates that the decline in the incidence of stroke observed in many countries is due to better management of hypertension (MacWalter and Shirley 2002). Special consideration should be given to the profile of risk factors in developing countries, which include not only recognized risk factors in developed countries but also locally relevant risk factors, such as rheumatic heart disease and puerperal stroke.

Treatment strategies for acute ischemic stroke include the following:

- *General management.* Overall medical care of patients with an acute stroke is important. Attention to complications such as bronchoaspiration, fluid and electrolyte imbalance, and control of blood sugar, as well as prevention of deep vein thrombosis, is crucial. Experience in developed countries suggests that specialized stroke units provide the best care for acute stroke patients (Smaha 2004), but in developing countries, particularly in rural areas, where hospital beds are scarce and most patients are attended by general physicians, such units are impractical.
- *Platelet antiaggregants.* Aspirin can prevent early stroke recurrence if given during the acute phase of stroke (within 48 hours) (Chinese Acute Stroke Trial Collaborative Group 1997; International Stroke Trial Collaborative Group 1997). The adverse effects of aspirin (cerebral hemorrhage and gastrointestinal complications) appear to be dose related, and most agree that using a low dose of aspirin is prudent (Antithrombotic Trialists' Collaboration 2002). Since aspirin can aggravate a hemorrhagic stroke, simple guidelines for the use of platelet antiaggregants should be developed and could be based on scales such as the Siriraj score to rule out hemorrhage (Poungvarin, Viriyavejakul, and Komontri 1991).
- *Thrombolytic therapy.* Tissue plasminogen activator and recombinant tissue plasminogen activator (rt-PA) can be used to halt a stroke by dissolving the blood clot that is blocking blood flow to the brain (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). Thrombolytic therapy can increase bleeding and must be used only after careful patient screening, with a CT scan of the brain within three hours of stroke symptom onset, to exclude an intracranial bleed. It also requires appropriately trained physicians to administer the medication. These prerequisites for the administration of thrombolytic agents restrict its use to selected centers in developing countries.

Strategies for prevention of recurrence of stroke apply equally to individuals who have experienced a transient ischemic attack and to those who have experienced a complete stroke. These strategies include the following:

- *Platelet antiaggregants.* Aspirin therapy is effective in preventing recurrence of stroke, with low daily doses being at least as effective as higher daily doses (Antithrombotic Trialists' Collaboration 2002). When compared with aspirin,

clopidogrel has a slight benefit among those who have had a previous stroke, myocardial infarction, or symptomatic peripheral arterial disease. Clopidogrel is an effective and safe alternative for patients who do not tolerate aspirin. Although clopidogrel may be slightly more effective than aspirin, it is also more expensive. Antiplatelet combination therapy using agents with different mechanisms of action, such as the combination of extended release dipyridamole and aspirin, has been shown to reduce the risk of stroke over aspirin alone (Sacco, Sivenius, and Diener 2005). In contrast, combination therapy with aspirin and clopidogrel offers no advantage over aspirin alone and also increases the risk of hemorrhage (Diener and others 2004).

- *Anticoagulant therapy.* Anticoagulation with warfarin should be considered in stroke patients with atrial fibrillation, because of its clear efficacy in preventing embolic strokes, provided that patients are appropriately monitored (European Atrial Fibrillation Trial Study Group 1993; Mohr and others 2001). Anticoagulant therapy also reduces the risk of embolic stroke in patients with rheumatic heart disease. However, anticoagulation can be hazardous in developing countries because of the lack of monitoring facilities.
- *Surgical treatment.* In patients with symptomatic carotid disease with stenosis of 70 percent and in asymptomatic patients with high-grade stenosis, carotid endarterectomy has been shown to be more beneficial than medical care alone (Asymptomatic Carotid Atherosclerosis Study 1995; Asymptomatic Carotid Surgery Trial Collaborative Group 2004; North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991). However, inappropriate selection of patients or high intraoperative complications could obviate such benefits. Carotid angioplasty has been suggested as an alternative to carotid endarterectomy in management of severe internal carotid artery disease, but its advantages and disadvantages have yet to be clearly established (Naylor, London, and Bell 1997). Carotid endarterectomy for stroke prevention is available at only a few centers in developing countries, which makes its widespread use impractical.

The goal of rehabilitation after a stroke is to enable individuals who have experienced a stroke to reach the highest feasible level of independence as soon as possible. Successful rehabilitation depends on the extent of brain damage, skill of the rehabilitation team, length of time before rehabilitation is started, and support provided by caregivers. Because each stroke patient has specific rehabilitation needs, customizing the rehabilitation program is important. Rehabilitation therapies include several complementary approaches:

- physical therapy, which helps stroke patients relearn simple motor activities, such as walking
- occupational therapy, which helps patients relearn everyday activities, such as eating and drinking
- speech therapy, which helps patients relearn language and speaking skills
- counseling, which can help alleviate some of the mental and emotional problems that result from stroke.

Comprehensive rehabilitation in a multidisciplinary stroke unit reduces deaths, disability, and the need for long-term institutional care (Smaha 2004), but such facilities are extremely limited in developing countries. Home-based rehabilitation services can prevent long-term deterioration in activities of daily living, although the absolute impact is relatively modest (Outpatient Service Trialists 2002). However, in developing countries, the vast majority of patients will be treated either at home by a general physician or in a small community hospital where no skilled rehabilitation therapist is available.

COST-EFFECTIVENESS OF INTERVENTIONS IN DEVELOPING COUNTRIES

We determined incremental cost-effectiveness ratios (ICERs) for selected interventions for each condition by calculating total DALYs lost by a population because of the condition with and without treatment and then dividing the difference by the treatment cost. The disability weights used are presented in table 32.2. All analyses in this section followed the volume editors' standardized guidelines for economic analysis, region-specific age structures, and underlying mortality rates. We converted nontradable inputs into U.S. dollars at the market exchange rate. We assumed that the costs of tradable inputs were internationally consistent, as were costs associated with surgical treatments. Table 32.3 presents the costs of drugs and medical services. No fixed costs were assumed; therefore, our results are not linked with the extent of treatment coverage.

Table 32.2 Disability Weights Used in ICER Analysis

Weight	AD and other dementias	Epilepsy	PD	Acute stroke	Recurrent stroke
Untreated	0.627	0.15	0.392[a]	0.278[b]	0.556
Treated	0.627[c]	0	0.316	0.235[b]	n.a.[d]

Source: Mathers and others 2006.
n.a. = not applicable.
a. Treatment for PD is assumed to be effective for a maximum of 10 years. We also assume that a patient reverts to the untreated disability weight after 10 years.
b. Disability is assumed to last a maximum of 10 years; then we assume the patient recovers fully.
c. The patient is assumed to experience no benefit from treatment. Benefits are in the form of reduced caregiver hours.
d. Treatment does not change the disability weight following a recurrent stroke; only the likelihood of experiencing a second stroke is reduced.

Table 32.3 Input Requirements for Interventions by Condition

Condition	Visits to primary health care doctor in outpatient department		Primary health care worker visits to patient in home or patient visits to see the worker in outpatient department		Specialist care in outpatient department		Inpatient care		Annual drug costs (US$)
	Patients using the service[a] (percent)	Visits per year	Patients using the service (percent)	Visits per year	Patients using the service (percent)	Visits per year	Patients using the service (percent)	Length of stay	
AD and other dementias									
Acetylcholinesterase inhibitors	100	4	100	12	100	2	5	7	638
Antipsychotics	100	12	100	12	25	6	5	7	10
Epilepsy									
Phenobarbital	100	2	100	6	10	2	1	3	1
Lamotrigine[b]	100	2	100	6	10	2	1	3	144
Surgery	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2,600[c]
PD									
Levodopa/carbidopa	100	3	100	6	100	2	1	5	71
Ayurvedic preparations	100	3	100	6	100	2	1	5	19
Deep brain stimulation	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	37,000
Stroke (acute attack)									
Aspirin	n.a.	n.a.	100	1	100	1	100	14	3
Heparin	n.a.	n.a.	100	1	100	1	100	14	691
rt-PA	n.a.	n.a.	100	1	100	1	1	7	1,777[d]
Stroke (prevention of recurrence)									
Aspirin	100	4	100	6	100	1	n.a.	n.a.	3
Dipyridamole and aspirin	100	4	100	6	100	1	n.a.	n.a.	64
Carotid endarterectomy	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	6,216

Source: Authors.

n.a. = not applicable.

a. Percentage of patients receiving the specified treatment.

b. Nondrug treatment costs for lamotrigine are not included in the cost-effectiveness analyses because they are accounted for in the phenobarbital treatment costs. Lamotrigine is taken in addition to phenobarbital.

c. Epilepsy surgery also requires screening at a cost of US$600 per screened patient. Because only half of screened patients are eligible for surgery, the cost amounts to US$1,200 per treated patient.

d. This treatment requires testing for eligible patients. The costs of screening ineligible patients include all the same hospital and doctor costs as treatment, as well as 80 percent of the drug cost to account for the diagnostic CT.

AD and Other Dementias

We analyzed the use of acetylcholinesterase inhibitors in the treatment of AD on the basis of the following assumptions: first, only patients who were older than 60 at the time of onset were considered; second, the treatment has no long-term benefits—that is, it does not reduce patient disability and has no effect on mortality.

We computed the benefits of reduced caregiver hours on the basis of reports that the improvement in cognitive function in AD patients associated with treatment using acetylcholinesterase inhibitors was a 1.2 point change in the global assessment scale for cognitive function, as measured by the Mini Mental State Examination. A 1 point improvement in the score was associated with a 0.56 hour per day reduction in caregiver hours, or roughly 205 hours per year (Marin and others 2003).

The cost of using acetylcholinesterase inhibitors per hour of caregiver time saved averaged US$13 across low- and middle-income countries (LMICs) and was at least US$11 in specific regions (the regions are the same as those in table 32.1). This amount is substantially more than the wage rate in these regions, which would generally not exceed US$1 to US$1.50 per hour, even for hired caregivers specifically trained to care for AD patients. We, therefore, conclude that the use of acetylcholinesterase inhibitors in developing countries is not efficient from an economic perspective. Calculating the cost per DALY averted for acetylcholinesterase inhibitors would not be meaningful, because we assume no benefit to the patient. Finally, the use of acetylcholinesterase inhibitors is uncommon in developing countries; therefore, reducing its use is not an important concern.

Epilepsy

We analyzed the cost-effectiveness of phenobarbital in the treatment of epilepsy, and the results are shown in table 32.4. We assumed that phenobarbital was provided to all patients. The cost of using phenobarbital per DALY gained in LMICs was US$89. Table 32.4 shows that the benefits of phenobarbital are large relative to its cost.

We did not look at other AEDs, such as phenytoin or carbamazepine, because the costs of those medications are much greater than that of phenobarbital, but their effectiveness is essentially the same (Aldenkamp, De Krom, and Reijs 2003). Although their use may be justified for specific medical reasons, phenobarbital is much more cost-effective.

We analyzed treatment options for patients who are refractory to treatment with phenobarbital. We assumed that such cases were treated either with a combination of phenobarbital and lamotrigine or with a combination of phenobarbital and surgery. We used the cost for epilepsy surgery of US$2,600, in accordance with a study from Colombia, and applied it to all regions (Malmgren and others 1996; Tureczek, Fandino-Franky, and Wieser 2000). We assumed that roughly half of surgery recipients experience no more seizures and that the remaining half continue to take phenobarbital despite undergoing surgery. Our evaluation of the surgical option included the costs of diagnostic services and the costs associated with screening patients who ultimately may not be eligible for surgery. For patients in LMICs who are refractory to phenobarbital, the ICER of the add-on drug lamotrigine was US$3,000, and the ICER of the surgical option plus phenobarbital was US$3,100. The difference between phenobarbital and the other two options was significant in all regions.

Among refractory epilepsy patients eligible for surgery and according to postoperative outcome studies conducted in developed countries, surgery may be of comparable cost-effectiveness to treatment with a combination of phenobarbital and lamotrigine. Because effectiveness data for developing countries are not available, this calculation is based on cost estimates from a study in Colombia and estimates of the effectiveness of surgery from developed countries. If the surgical outcome in developing countries were worse than in developed countries, the cost-effectiveness of surgery would be lower. Furthermore, we note a number of limitations to the use of surgery in refractory epilepsy, particularly in developing countries, along with the lack of long-term follow-up data on the outcome of surgery. We stress that the primary treatment of epilepsy is with phenobarbital, and effective treatment of epilepsy lies in more efficient use of this highly cost-effective medication to close the treatment gap.

Parkinson's Disease

We evaluated three interventions for PD: a combination of l-dopa and carbidopa, traditional medicines such as the ayurvedic treatment used in India, and deep brain stimulation. We assumed that treatment for all three modalities was effective for 10 years from the onset of treatment. The ICERs in LMICs for these three modalities were US$1500, US$750 and US$31,000, respectively (table 32.4). On the basis of the cost of medication and evidence from clinical trials of effectiveness (Parkinson's Disease Group 1995) and from animal studies (Hussain and Manyam 1997), we found that ayurvedic treatment was the most cost-effective option. The relatively favorable ICER for ayurvedic treatment is due to the extremely low medication cost of this intervention. The relatively high ICER for deep brain stimulation was largely attributable to the extremely high cost of surgery. Table 32.4 shows DALYs gained for US$1 million of health expenditure.

Stroke

We evaluated two sets of interventions for stroke: treatment of acute stroke and prevention of secondary stroke. We assumed

Table 32.4 Results from Cost-Effectiveness Analysis of Interventions for Alzheimer's Disease, Epilepsy, Parkinson's Disease, and Stroke, by World Bank Region

Condition	Low- and middle-income countries	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa
AD							
Cost per care hour reduced using acetylcholinesterase inhibitors (US$)	11	11	12	13	12	11	11
Epilepsy							
Incremental costs of DALYs gained per year of treatment compared with no treatment (US$)							
Phenobarbital	89	78	122	261	165	54	25
Phenobarbital and lamotrigine	2,994	3,306	2,945	4,301	3,344	2,872	1,490
Phenobarbital and surgery	3,060	3,411	3,049	3,477	2,904	3,097	1,788
Number of DALYs gained per US$1 million per year							
Phenobarbital	11,262	12,799	8,185	3,828	6,072	18,581	39,632
Phenobarbital and lamotragine	334	302	340	232	299	348	671
Phenobarbital and surgery	327	293	328	288	344	323	559
PD							
Incremental costs of DALYs gained per year of treatment compared with no treatment (US$)							
Levodopa/carbidopa	1,512	1,398	1,760	2,254	1,944	1,311	1,281
Ayurvedic preparation	751	638	1,000	1,494	1,184	551	520
Levodopa/carbidopa and deep brain stimulation	31,114	26,941	29,310	29,444	30,770	31,347	34,069
Number of DALYs gained per US$1 million per year							
Levodopa/carbidopa	662	715	568	444	514	763	781
Ayurvedic preparation	1,331	1,568	1,000	669	845	1,815	1,922
Levodopa/carbidopa and deep brain stimulation	32	37	34	34	32	32	29

Stroke (treatment of acute attack)							
Incremental costs of DALYs gained per year of treatment compared with no treatment (US$)							
Aspirin	149	109	104	574	534	118	112
Heparin	2,675	2,185	1,318	4,952	5,443	2,967	2,940
rt-PA	1,278	1,169	648	2,158	2,516	1,630	1,623
Number of DALYs gained per US$1 million per year							
Aspirin	6,691	9,209	9,633	1,742	1,873	8,463	8,942
Heparin	374	458	759	202	184	337	340
rt-PA	783	856	1,543	463	398	613	616
Stroke (prevention of recurrence)							
Incremental costs of percent recurrence risk averted after 2 years of treatment (US$)							
Aspirin	4	3	6	9	7	2	2
Dipyridamole and aspirin	5	5	6	8	7	4	4
Carotid endarterectomy	87	87	87	87	87	87	87
Incremental costs of DALYs gained per 2 years of treatment compared with no treatment (US$)							
Aspirin	70	60	59	233	196	52	34
Dipyridamole and aspirin	93	95	63	194	186	96	69
Carotid endarterectomy	1,458	1,614	836	2,001	2,234	1,759	1,284
Number of DALYs gained per US$1 million per 2 years of treatment							
Aspirin	14,313	16,569	16,866	4,285	5,093	19,348	29,373
Dipyridamole and aspirin	10,752	10,555	15,969	5,150	5,384	10,369	14,572
Carotid endarterectomy	686	620	1,197	500	448	568	779

Source: Authors.

that stroke sufferers have fully recovered 10 years after their last stroke.

We evaluated aspirin, heparin, and rt-PA for the treatment of acute stroke. The International Stroke Trial Collaborative Group (1997) reports that, within 14 days of the onset of stroke, mortality with heparin treatment is less than with a placebo; however, after six months, mortality is actually greater for patients treated with heparin than with a placebo—that is, there is a negative cost per DALY gained if this effect is incorporated. The estimates presented here are based on the change in the short-term mortality risk. For LMICs, the cost per DALY averted using aspirin was US$150 (table 32.4). The equivalent costs of interventions using rt-PA and heparin were US$1,300 and US$2,700, respectively. The costs of heparin are higher than the costs of rt-PA, despite the expensive equipment required for rt-PA, because of the lower effectiveness of heparin.

Table 32.4 presents DALYs averted for US$1 million of health expenditure for the three treatments. The cost per DALY gained using aspirin is a conservative estimate, because the use of aspirin has additional benefits in terms of preventing a recurrence of stroke.

Table 32.4 shows the costs of preventing a second stroke within two years of the first stroke. For LMICs, aspirin was the least expensive option at US$3.80 per single percentage point decrease in the risk of a second stroke within two years of the first. This rate translates to roughly US$70 per DALY gained (table 32.4). Combining dipyridamole with aspirin, because of higher cost, was slightly more expensive at roughly US$5.20 per single percentage point decrease in recurrent stroke risk for a single individual, or about US$93 per DALY. In contrast, carotid endarterectomy was US$87 for an equivalent decrease in individual recurrence risk or almost US$1,500 per DALY. The aspirin monotherapy option for preventing a recurrence of stroke was the most cost-effective approach only in South Asia and Sub-Saharan Africa, largely because of the relatively low costs of nontradable inputs, such as hospital and doctors' fees, in those regions. Low input costs of nontradables increase the relative importance of drug costs in determining the most cost-effective intervention; therefore, the cheaper drug, aspirin, was most cost-effective. Table 32.4 shows that, though US$1 million would be most effectively spent on aspirin alone in South Asia and Sub-Saharan Africa, investment in aspirin and dipyridamole treatment would result in a greater DALY gain in the other regions.

RECOMMENDATIONS

The use of acetylcholinesterase inhibitors for treating patients with AD, as assessed by the number of caregiver hours saved, suggests that this intervention is not cost-effective. This finding, combined with the limited efficacy of acetylcholinesterase inhibitors, suggests that they should not be widely used in developing countries. Instead, giving low doses of antipsychotic medication to patients with any form of dementia who also have behavioral problems may be a better option for reducing caregiver stress, although this possibility has not been systematically evaluated.

Phenobarbital is by far the most cost-effective intervention for managing epilepsy and should be recommended for widespread use in public health campaigns against epilepsy in LMICs. For those patients who do not respond to phenobarbital, the addition of lamotrigine is advisable rather than surgery, because of the resource-intensive evaluation and infrastructure required for epilepsy surgery.

Indigenous systems of medicine, such as the ayurvedic medicines used in India, are much more cost-effective than Western medications or surgical procedures for managing patients with PD. Other countries may wish to test and standardize such medications for their own use.

Aspirin is by far the most cost-effective intervention both for treating acute stroke and for preventing a recurrence of stroke. It is easily available in developing countries, even in rural areas.

RESEARCH AND DEVELOPMENT AGENDA

The populations of most developing countries are aging rapidly. Many neurological disorders frequently occur in the elderly, posing an emerging public health problem. As a result, developing countries should begin or expand their research and development agendas to address issues related to the prevention, identification, and management of neurological disorders. In the short term, they should focus on early identification, optimum treatment, and amelioration of distress and handicaps and on reduction of the social and economic burden on patients and their families. In the long term, they should develop and implement strategies for primary prevention of neurological disorders. Specific areas for research and development include the following:

- *Conducting population-based epidemiological studies in developing countries.* Population-based data from developing countries are insufficient, which limits evidence-based planning. In addition, such data may also suggest important hypotheses for research if they identify genuine differences across regions (for example, the reported difference in the incidence of AD in developed and developing countries). In addition, the identification of risk or protective factors would be useful in the primary prevention of such diseases.
- *Enhancing existing health care delivery systems.* In most developing countries, approximately 70 to 80 percent of patients live in rural areas, where medical care is frequently provided by nonphysician health care providers or, at best,

by a general physician. Limitations in the availability of health care have resulted in a huge treatment gap for many neurological disorders. For such situations, a simple model for the management of neurological disorders by existing community-based health care providers, trained to provide such services, would be helpful. Research is needed on optimum referral systems for more difficult cases that local communities will accept and can afford. Strategies for home-based care of patients need to be systematically evaluated.

- *Developing cheaper and more efficacious medicines.* Many currently available medications have significant side effects and are too expensive for many patients in developing countries. Newer medications need to be developed with lower costs, fewer side effects, better efficacy, and less frequent dose schedules.
- *Promoting the use of indigenous systems of medicine.* Many people in developing countries use local indigenous medicines. More research needs to be done on the pharmacological properties of those medications (see chapter 69).
- *Launching stigma removal campaigns.* The stigmatization of patients with neurological disorders and of their families is still prevalent, particularly in rural and remote areas, and it often prevents patients from seeking and obtaining appropriate medical care. Effective strategies to address this issue need to be developed and implemented on a large scale.

MISSED OPPORTUNITIES

Many research studies have reported that the incidence of AD is lower in developing countries than in Western countries. Migration studies, such as those looking at the migration of Africans to the United States, have shown a change in the risk for AD within one or two generations. This finding suggests that developing countries may have some protective factors that rapidly change on migration to developed countries. Despite this information being available for more than 25 years, no systematic efforts have been made to identify these protective factors. Given the rapid adaptation of Western lifestyles in developing countries, identifying these factors is important before the opportunity is permanently lost.

The successful use of phenobarbital for treating epilepsy was first described in 1912. Not only is it effective for many types of epilepsy, but it is also inexpensive. Nevertheless, despite its availability for more than 90 years and its modest cost, the treatment gap for epilepsy still exceeds 90 percent in many developing countries.

Indigenous systems of medicine, such as for the treatment of PD, have been used for centuries in developing countries. However, their utility has not been fully exploited.

Despite evidence of the benefit of control of hypertension in the primary prevention of stroke, most efforts in developing countries are directed at treatment of stroke. This approach not only is more expensive but also is less beneficial to the patient.

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