

## 3.6 Neurological disorders associated with malnutrition

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**In low income countries, inadequate amounts of food (causing conditions such as child malnutrition and retarded growth) and inadequate diversity of food (causing deficiency of vital micronutrients such as vitamins, minerals or trace elements) continue to be priority health problems. Malnutrition in all its forms increases the risk of disease and early death. Nearly 800 million people in the world do not have enough to eat. Malnutrition affects all age groups, but it is especially common among poor people and those with inadequate access to health education, clean water and good sanitation. Most of the malnutrition-related neurological disorders are preventable.**

Chronic food deficits affect about 792 million people in the world (1). Malnutrition directly or indirectly affects a variety of organ systems including the central nervous system (CNS). A number of nutritional conditions are included in the Global Burden of Disease (GBD) study, such as protein–energy malnutrition, iodine deficiency, vitamin A deficiency, and iron deficiency anaemia. Over 15% of the disability-adjusted life years (DALYs) lost globally are estimated to be from malnutrition (2).

This section focuses on neurological disorders associated with malnutrition. In addition, it touches briefly on the ingestion of toxic substances in food or alcohol, as these also contribute to neurological disorders.

Most of the malnutrition-related neurological disorders can be prevented and therefore they are of public health concern. Raising awareness in the population, among leaders and decision-makers and in the international community is important in order to adopt an appropriate health policy.

### ETIOLOGY, RISK FACTORS AND BURDEN

The major dietary nutrients needed by living organisms, especially human beings, can be grouped into macronutrients and micronutrients. The macronutrients are the energy-yielding nutrients — proteins, carbohydrates and fat — and micronutrients are the vitamins and minerals. The macronutrients have a double function, being both “firewood” and “building blocks” for the body, whereas the micronutrients are special building items, mostly for enzymes to function well. The term “malnutrition” is used for both macronutrient and micronutrient deficiencies. Macronutrient and micronutrient problems often occur together, so that the results in humans are often confounded and impossible to separate out. Table 3.6.1 outlines which of the nutrients may contribute to neurological disorders if not provided in sufficient amounts, together with their recommended daily allowances. Table 3.6.2 outlines some of the

neurological consequences attributable, in certain circumstances, to ingestion of toxic substances in food and alcohol.

Table 3.6.1 Neurological disorders caused by nutrient deficiency

Nutrient	RDA <sup>a</sup>	Neurological disorder when deficient
<b>Macronutrients</b>		
<b>Total energy</b>	2200 (kcal)	In childhood: long-term mental deficit
<b>Vitamins</b>		
<b>Vitamin B1 Thiamine</b>	1.1 mg	Beri-beri, polyneuropathy, Wernicke's encephalopathy
<b>Vitamin B3 Niacin</b>	15 mg NE	Pellagra including dementia and depression
<b>Vitamin B6 Pyridoxine</b>	1.6 mg	Polyneuropathy
<b>Vitamin B12 Cobalamine</b>	2.0 µg	Progressive myelopathy with sensory disturbances in the legs
<b>Folate</b>	180 µg	Neural tube defects (myelomeningocele) of the fetus, cognitive dysfunction in children and elderly?
<b>Minerals</b>		
<b>Iodine</b>	150 µg	Iodine deficiency disorders
<b>Iron</b>	15 mg	Delayed mental development in children
<b>Zinc</b>	12 mg	Delayed motor development in children, depression
<b>Selenium</b>	55 mg	Adverse mood states

<sup>a</sup> Recommended daily allowance for an adult.

Table 3.6.2 Potentially toxic food compounds that may contribute to neurological disorders

Food compound	Potential neurological disorder when ingested
<b>Alcohol</b>	Fetal alcohol syndrome, retarded mental development in childhood, Wernicke's encephalopathy, visual problems (amblyopia), peripheral neuropathy
<b>Lathyrus sativus</b>	Spastic paraparesis (lathyrism)
<b>Cyanogenic glucosides from insufficiently processed cassava roots</b>	Konzo, tropic ataxic neuropathy

## MAIN NEUROLOGICAL COMPLICATIONS OF MALNUTRITION

### Macronutrient deficiency (general malnutrition)

The nervous system develops in utero and during infancy and childhood, and in these periods it is vulnerable to macronutrient deficiencies. As a rule, general malnutrition among adults does not cause specific neurological damage, whereas among children it does.

Undernutrition can be assessed most commonly by measurement of the body weight and the body height. With these two measurements, together with age and sex, it will be possible to evaluate the energy stores of the individual. The aims of the anthropometric examination are:

- to assess the shape of the body and identify if the subject is thin, ordinary or obese;

■ to assess the growth performance (this applies only to growing subjects, i.e. children).

A person who is too thin is said to be “wasted” and the phenomenon is generally called “wasting”. Children with impaired growth are said to be “stunted” and the phenomenon is called “stunting”. Both these conditions may cause neurological disturbances in children.

The percentage of wasted children in low income countries is 8%, ranging from 15% in Bangladesh and India down to 2% in Latin America (3). Different kinds of disasters may raise the figures dramatically in affected areas. This presents a disturbing picture of malnutrition among children under five years of age in underprivileged populations. These children should be an important target group for any kind of nutritional intervention to be undertaken in these countries.

Stunting is also widespread among children in low income countries. Its prevalence ranges from 45% in Bangladesh and India to 16% in Latin America. The global average for stunting among children in low income countries is 32% (3). Increasing evidence shows that stunting is associated with poor developmental achievement in young children and poor school achievement or intelligence levels in older children. “The causes of this growth retardation are deeply rooted in poverty and lack of education. To continue to allow underprivileged environments to affect children’s development not only perpetuates the vicious cycle of poverty but also leads to an enormous waste of human potential. . . . Efforts to accelerate economic development in any significant long-term sense will be unsuccessful until optimal child growth and development are ensured for the majority” (3).

### Long-term effects of malnutrition

Apart from the risk of developing coronary heart disease, diabetes and high blood pressure later in life owing to malnutrition in early life, there is now accumulating evidence of long-term adverse effects on the intellectual capacity of previously malnourished children. It is methodologically difficult, however, to differentiate the biological effects of general malnutrition and those of the deprived environment on a child’s cognitive abilities. It is also methodologically difficult to differentiate the effect of general malnutrition from the effect of micronutrient deficiencies, such as iodine deficiency during pregnancy and iron deficiency in childhood, which also cause mental and physical impairments. Malnourished children lack energy, so they become less curious and playful and communicate less with the people around them, which impairs their physical, mental and cognitive development.

Two recent reviews highlight the evidence of general malnutrition per se causing long-term neurological deficits (4, 5). An increasing number of studies consistently show that stunting at a young age leads to a long-term deficit in cognitive development and school achievement up to adolescence. Such studies include a wide range of tests including IQ, reading, arithmetic, reasoning, vocabulary, verbal analogies, visual-spatial working memory, simple and complex auditory working memory, sustained attention and information processing. Episodes in young childhood of acute malnutrition (wasting) also seem to lead to similar impairments. The studies also indicate that the period in utero and up to two years of age represents a particularly vulnerable time for general malnutrition (4).

In addition to food supplementation, it has been nicely demonstrated that stimulation of the child has long-term beneficial effects on later performance. One such study is from Jamaica, where stunted children who were both supplemented and stimulated had an almost complete catch-up with non-stunted children (6), see Figure 3.6.1.

### Treatment of severe malnutrition

If a child becomes seriously wasted, this in itself is a life-threatening condition. Even if the child is brought to hospital, the risk of dying still remains very high. WHO has issued a manual for the management of severe malnutrition that is available on its web site (7). An important element, in

addition to initial treatment similar to intensive care, is to stimulate the child in order to prevent the negative long-term effect on the cognitive capacity of the child.

### Micronutrient deficiencies

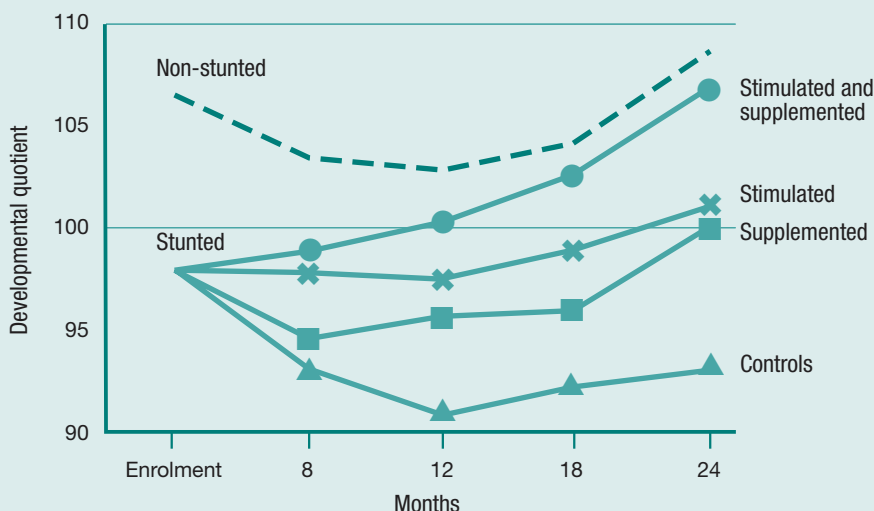
Micronutrients is the term used for those essential nutrients that are needed in small amounts for human growth and functioning. They are essentially used as cofactors for enzymes engaged in various biochemical reactions. They comprise vitamins, fat-soluble as well as water-soluble, and trace elements (= minerals). Iron, vitamin A, zinc and iodine are most discussed today, but other important micronutrients are vitamin C and the vitamin B complex. Diets that supply adequate energy and have an acceptable nutrient density will usually also cover the needs for micronutrients. When the diet is otherwise monotonous, however, it is recommended to supplement it with micronutrient-rich foods. Food preservation methods, high temperature and exposure to sunlight can reduce the activity of many vitamins. Most of these deficiencies are strongly linked to poverty and human deprivation. Some of these conditions are much more significant with regard to their global occurrence and their impact on the nervous system than other micronutrient deficiencies, so this section focuses on deficiencies of vitamin A, vitamin B complex, iodine and iron.

### Vitamin A deficiency

Vitamin A assumes two types of function in the body: systemic functions (in the whole body) and local functions in the eye.

Vitamin A is very important for the mucous membranes as it is needed for the proper production of mucopolysaccharides, which help to protect against infections. If vitamin A is deficient, the wetness of the mucous membranes will decrease and the membranes will become more like skin than mucous membranes. This can be seen in the eye as xerophthalmia (dry eye in Greek). Inside the eye, vitamin A is used in the rods (the receptors for low intensities of light). If there is too little vitamin A, the person will not be able to see in low light intensity: he or she will become night-blind. Vitamin A deficiency has long been identified as the major cause of nutritional blindness. This is still an important problem around the world: it is estimated that 250–500 000 children are blinded each year because of eye damage brought about by severe vitamin A deficiency. It is the single most important cause of blindness in low and middle income countries.

Figure 3.6.1 Mean developmental quotients of stunted<sup>a</sup> and non-stunted<sup>b</sup> children: results of intervention over two years



<sup>a</sup> Adjusted for initial age and score.

<sup>b</sup> Adjusted for age only.

Source: (6).

Vitamin A deficiency does not only cause eye damage: it also increases mortality owing to increased vulnerability and impaired immune function, especially to diarrhoeal diseases and measles. Vitamin A deficiency develops quite quickly in children with measles, as infections make the body consume its vitamin A stores much more quickly. Children between six months and four years old are most vulnerable to vitamin A deficiency. An estimated 100 million pre-school children globally are estimated to have vitamin A deficiency and 300 000 are estimated to die each year because of vitamin A deficiency.

In order to prevent child deaths and childhood blindness, many low income countries have integrated vitamin A supplementation into their immunization programmes. Children at risk are given vitamin A capsules every six months. The cost of the capsules is low (currently US\$ 0.05 each).

### **Vitamin B complex deficiencies**

The B vitamins generally are coenzymes in the energy metabolism in the body. Vitamin B deficiencies have occurred in extreme situations in the past, such as in the 19th century when the steam mills in South-East Asia started to provide polished rice. Suddenly, people had enough energy but insufficient supply of B vitamins and developed beri-beri, a Sinhalese word for “I cannot”. It may also occur today in refugee populations, if they are provided with a very limited choice of food items with enough energy but deficient in B vitamins. Similarly, it may also happen to alcoholics and people with other types of very monotonous diets.

The different deficiency syndromes of vitamin B overlap and are sometimes very difficult to distinguish from one another. A recent example is the Cuban neuropathy in the mid-1990s, in which over 50 000 people suffered from a gait and visual disturbance, technically a polyneuropathy (8, 9). Massive research resources were put in to find the exact cause. It is now known that the population that experienced the epidemic had an extreme diet (tea with sugar as the main source of energy; which is likely to generate a vitamin B deficiency) and the epidemic stopped as soon as universal distribution was made of tablets with vitamin B complex. This led the scientists to conclude that it was a vitamin B complex deficiency, without being able to distinguish the vitamins from each other. From a public health perspective, therefore, the B vitamins may as well be treated together, the only exceptions being vitamin B12 and folate.

*Vitamin B1 (thiamine).* Beri-beri is one form of vitamin B1 deficiency, and the main symptom is a polyneuropathy in the legs (10). In severe cases, one can suffer from cardiovascular complications, tremor, and gait and visual disturbances. An acute form of the syndrome seen in alcoholics is Wernicke’s encephalopathy (discussed in the section on alcohol). It is characterized by a serious confusion, unsteadiness and eye movement disorders. It can be rapidly reversed if correctly diagnosed and immediately treated with high-dose thiamine.

*Vitamin B3 (niacin).* Deficiency of niacin leads to “pellagra”, an Italian word for “rough skin”, which was common in Italy and Spain in the 19th century when large populations were sustained on a maize diet. In its classic form it appears with three Ds: dermatitis, diarrhoea and dementia; that is with cutaneous signs, erythema, pigmentation disorders, diarrhoea and neuropsychiatric disturbances such as confusion and psychomotor agitation.

*Vitamin B6 (pyridoxine).* Vitamin B6 is involved in the regulation of mental function and mood. Neuropsychiatric disorders including seizures, migraine, chronic pain and depression have been linked to vitamin B6 deficiency (11). Some studies have suggested that neurological development in newborns could be improved by supplementation in pregnancy, but this is still a hypothesis (12). Vitamin B6 deficiency may occur especially during intake of some drugs which antagonize with the vitamin (i.e. isoniazid, penicillamine).

*Folate.* Folate (or folic acid) plays an important role for rapidly dividing cells such as the blood cells, and a folate deficiency causes a special type of anaemia called megaloblastic anaemia which is reversible when folate is given. In recent years, it has been found that folate deficiency during

pregnancy increases the risk of fetal malformation in the form of neural tube defects (NTDs = myelo-meningocele) (13). Folate supplementation for women at the time of conception protects against neural tube defects (13). Supplementation of folate in wheat flour is therefore common in Europe and North America, with the objective of reducing the risk of neural tube defect (14–16). In Canada, Chile and the United States, mandatory fortification of flour substantially improved folate and homocysteine status, and neural tube defect rates fell by between 31% and 78% (17). Nevertheless, many countries do not choose mandatory folic acid fortification, in part because expected additional health benefits are not yet scientifically proven in clinical trials, in part because of feared health risks, and because of the issue of freedom of choice. Thus additional creative public health approaches need to be developed to prevent neural tube defects and improve the folate status of the general population.

**Vitamin B12 (cobalamine).** The vitamin B12 or cobalamine is — like folate — important in the formation of blood cells, particularly the red blood cells. Vitamin B12 is different from the other B vitamins because it needs an “intrinsic factor” produced by the gut in order to be absorbed. This means that people with gut disorders and also elderly people may experience vitamin B12 deficiency. Vitamin B12 deficiency also causes a megaloblastic anaemia which is reversible when vitamin B12 is given. What is worse is an insidious irreversible damage to the central and peripheral nervous systems. In a severe form it may also cause a psychiatric disorder with irritability, aggressiveness and confusion. It has been suggested that vitamin B12 deficiency might contribute to age-related cognitive impairment; low serum B12 concentrations are found in more than 10% of older people (18) but so far there is insufficient proof of beneficial effects of supplementation. The most serious problem with vitamin B12 deficiency still seems to be the irreversible progressive myeloneuropathy, which is difficult to diagnose.

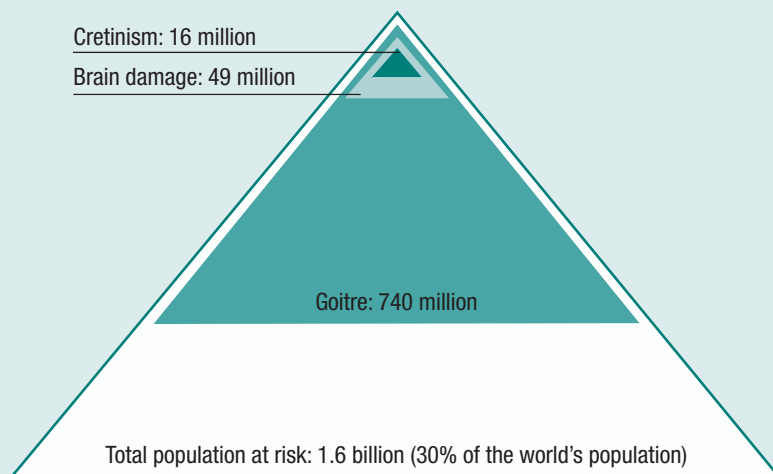
### Iodine deficiency disorders

Iodine deficiency does not cause one single disease, but many disturbances in the body. These are denoted by the term iodine deficiency disorders: their effects range from increased mortality of fetuses and children, constrained mental development — in its worst form, cretinism — to impaired school performance and socioeconomic development, as detailed in Table 3.6.3.

WHO has estimated that 1.6 billion people in 130 countries live in areas where they are at risk of being deficient in iodine. Goitre — indicated by a swelling of the thyroid gland — is present in 740 million people, and some 300 million suffer from lowered mental ability as a result of a lack

of iodine. Iodine deficiency disorders today constitute the single greatest cause of preventable brain damage in the fetus and infant and retarded psychomotor development in young children. At least 120 000 children every year are born cretins — mentally retarded, physically stunted, deaf-mute or paralysed — as a result of iodine deficiency. In addition, an estimated annual total of at least 60 000 miscarriages, stillbirths and neonatal deaths stem from severe iodine deficiency in early pregnancy, as shown in Figure 3.6.2 (19).

Figure 3.6.2 Toll of iodine deficiency worldwide



Source: adapted from (19).

Table 3.6.3 Spectrum of disorders caused by iodine deficiency

Iodine deficiency disorder	Effect
Goitre	Enlargement of the thyroid gland
Hypothyroidism	Decreased production of thyroid hormones
Miscarriages	Early death of fetuses in the womb
Stillbirths	Late death of fetuses (the child is dead at birth)
Perinatal mortality	Increased number of deaths among newborn children
Congenital abnormalities	Abnormalities of the newborn child
Cretinism	Severe mental retardation, growth retardation, deaf-mutism and physical disability
Decrease in IQ	
Impaired educability	Lower school performance
Impaired social and human development	

At the World Summit for Children in 1990, the problem of iodine deficiency disorders was highlighted and a strong political will to eliminate them was demonstrated. At that time, the scale and severity of the iodine problem was only just being realized. Since then, several surveys have shown even more severe damage than was estimated from this deficiency in many regions of the world. Work to eliminate iodine deficiency disorders has made enormous progress and is becoming a success story in the prevention of a nutritional deficiency. WHO has issued a useful guide to help programme managers assess the problem and monitor progress towards its elimination (20).

The main intervention strategy for control of iodine deficiency disorders is universal salt iodization. Salt was chosen as the commodity to be fortified for a number of reasons: it is widely consumed in fairly equal amounts by most people in a population, it is usually produced centrally or in a few factories, and the cost of iodizing is low (about US\$ 0.05 per person per year). Over the last decade, extraordinary progress has been made in increasing the number of people consuming iodized salt. In 1998, more than 90 countries had salt iodization programmes. Now, more than two thirds of households living in countries affected by iodine deficiency disorders consume iodized salt. Universal salt iodization ranges from 63–90% in Africa, the Americas, South-East Asia and the Western Pacific, whereas in Europe it is only 27%, thus leaving Europeans at risk of iodine deficiency disorders. Because of active programmes of salt fortification, iodine deficiency disorders are rapidly declining in the world. In 1990, 40 million children were born with mental impairment attributable to iodine deficiency and 120 000 cretins were born, which was substantially more than just seven years later. WHO has estimated that the number of people with goitre will decrease to 350 million by the year 2025 as a result of iodine enrichment and supplementation programmes. A challenge is to enforce the legislation that has been passed in all but seven of the countries of the world with a recognized iodine-deficiency public health problem. All the salt producers, from large industries to small-scale producers, need to be encouraged to use the more expensive procedure to fortify their salt production, and the consumers also need to be informed. Quality control and monitoring of the impact of the procedures are other continuing tasks related to the world's most widespread preventable cause of mental impairment (20).

### Iron deficiency anaemia

Iron deficiency anaemia affects more than 3.5 billion people globally, making it the most frequent micronutrient deficiency in the world. Iron deficiency seems to be the only micronutrient deficiency that high income and low income countries have in common. Of the total burden of disease in

DALYs, over 2% is attributable to anaemia. Iron deficiency anaemia depresses human productivity by tiredness, breathlessness, decreased immune function and impaired learning in children. The effect of iron deficiency on learning is difficult to study because iron deficiency is also closely related to poverty and socioeconomic disadvantage. The indirect productivity effects of improved iron status are on cognitive ability and achievement, through impact on mental and motor skills in infants and on cognition, learning and behaviour in children and adolescents. An early severe chronic iron deficiency leads to poorer overall cognitive functioning and lower school achievements (21, 22). Thus, macronutrient, iodine and iron deficiencies all have a substantial negative effect on cognition, behaviour and achievement; in all three cases, the effects produced by chronic deficiencies in the early years are manifested later in life (23). The estimated losses of GDP attributable to iron deficiency in three countries are considerable (Figure 3.6.3).

The most affected populations are children in the pre-school years and pregnant women in low and middle income countries. In these populations, deficiencies of dietary iron are aggravated by repeated episodes of parasitic diseases such as malaria, hookworm infestation or schistosomiasis in children, and by menstruation, repeated pregnancies or blood loss at delivery in women. A low dietary intake of iron and the influence of factors affecting absorption also contribute to iron deficiency. About 40% of the women in low and middle income countries and up to 15% in high income countries suffer from anaemia.

Better nutrition, iron supplementation or fortification, child spacing and the prevention and treatment of malaria and hookworms can all prevent iron deficiency. Iron is found naturally in meat, fish, liver and breastmilk. Vitamin C increases iron absorption, and coffee and tea decrease absorption. Correction of iron deficiency anaemia is cheap, but a functioning health service is needed to promote the measures among the most vulnerable groups. There is, however, some evidence to suggest that iron supplementation at levels recommended for otherwise healthy children carries the risk of increased severity of infectious disease in the presence of malaria and/or undernutrition. It is therefore advised that iron and folic acid supplementation be targeted to those who are anaemic and at risk of iron deficiency. They should receive concurrent protection from malaria and other infectious diseases through prevention and effective case management (25).

### **Zinc deficiency**

There is a close connection between zinc deficiency and stunting. In addition, zinc supplementation of young children in low income countries improves their neurophysiological performance (26), also in combination with iron supplements (27). Some behavioural abnormalities in adults also seem to respond favourably to zinc supplementation, such as mood changes, emotional lability, anorexia, irritability and depression (28).

### **Selenium deficiency**

Selenium deficiency has been linked to adverse mood states (29). Selenium supplementation together with other vitamins has been found beneficial in the treatment of mood lability (30). Generally, the scientific information about selenium and neurological disorders remains scarce.

## **TOXICONUTRITIONAL DISORDERS**

In the 19th century, medical science successfully revealed the causation of several neurological disorders that occurred in localized epidemics or endemic foci. There are, however, still a number of obscure neurological disorders occurring in localized epidemics or endemic foci in tropical countries. Most of these syndromes consist of various combinations of peripheral polyneuropathy and signs of spinal cord involvement. The term “tropical myeloneuropathies” has been used to group these disorders of unknown etiology; to reduce the confused clinical terminology, Román distinguishes two clinical groups which he calls tropical ataxic neuropathy, with prominent sensory

ataxia, and tropical spastic paraparesis, with predominantly spastic paraparesis with minimal sensory deficit (31).

### Syndromes of ataxic polyneuropathy

Reports on a form of ataxic polyneuropathy described by Strachan and later by Scott led to the recognition of a tropical neurological syndrome characterized by painful polyneuropathy, orogenital dermatitis and amblyopia, known as Strachan's syndrome. It was linked with malnutrition and reported from Africa. During the Second World War, prisoners of war in tropical and subtropical regions suffered from similar syndromes with "burning feet", numbness and loss of vision with pallor of the temporal border of the optic disks. Spastic paraplegia was also seen in these highly variable conditions (32). Since the Second World War, ataxic polyneuropathies have been reported from many tropical and subtropical areas (31).

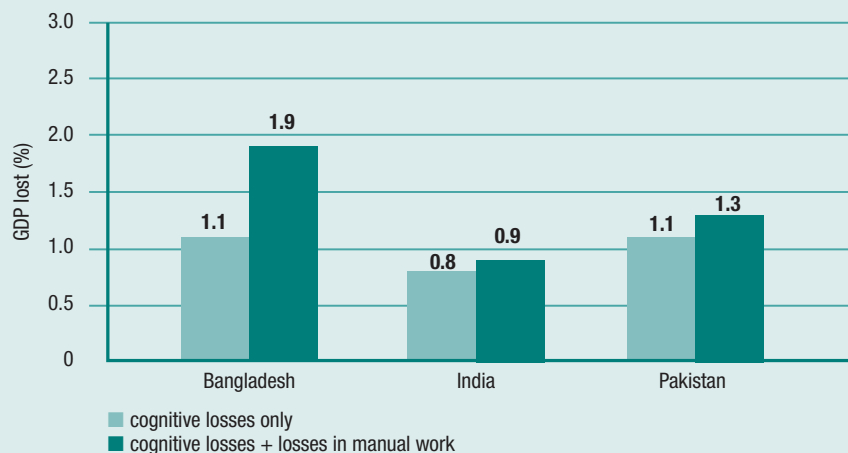
In the 1930s, Moore described, in an institution in Nigeria, a syndrome of visual loss, sore tongue, stomatitis and eczema of the scrotum in adolescent boys. Their cassava-based diet was suggested to be the cause, as the students improved during holidays. The cyanide-yielding capacity of bitter cassava and its toxic effects were described at that time. This syndrome of painful polyneuropathy, ataxia and blurred vision was extensively studied in Nigeria by Osuntokun (33). The diagnostic criteria used for this tropical ataxic neuropathy were the presence of two of the following: myelopathy, bilateral optic atrophy, bilateral sensorineural deafness, and symmetrical peripheral polyneuropathy. Men and women were equally affected, with a peak incidence in the fifth and sixth decades of life. The prevalence in certain areas of Nigeria ranged from 1.8% to 2.6% in the general population. When discussing the neurological syndromes resembling Nigerian ataxic neuropathy described from different parts of the world, Osuntokun pointed out that it is unlikely that the same specific etiological factor is involved in all places. In Nigeria, tropical ataxic neuropathy has been shown to persist also into this millennium (34).

### Syndromes of spastic paraparesis

The second clinical group of tropical myeloneuropathies proposed by Román (31) is comprised of syndromes with spastic paraparesis as the main feature. Besides paraparesis as a sequel of extrinsic cord compression resulting from trauma or tuberculosis, several syndromes with spastic paraparesis have been reported in epidemics or endemic foci throughout the world.

The classic form of locally occurring spastic paraparesis, mentioned already by Hippocrates, is lathyrism (35), caused by excessive consumption of grass pea, *Lathyrus sativus* (36). The clinical picture is an acute or sub-acute onset of an isolated spastic paraparesis, with increased muscle tone, brisk reflexes, extensor plantar responses and no sensory signs. It has been known since ancient times and has occurred in Europe (37) and North Africa but is today known as a public health problem in only Bangladesh, India (38) and Ethiopia (39). An excitotoxic amino acid in the grass pea, beta-N-oxalylamino-L-alanine is held responsible for the disease (36).

Figure 3.6.3 Loss of gross domestic product (GDP) attributable to iron deficiency



Source: (24).

A second form of spastic paraparesis, nowadays called HTLV-I associated myelopathy/tropical spastic paraparesis, has been found in geographical isolates in different parts of the world (40). It is now proved to be caused by the human T-lymphotropic virus type I (HTLV-I) and is unrelated to nutrition.

A third form of spastic paraparesis with abrupt onset has been reported in epidemic outbreaks in Africa. Clinically and epidemiologically it is similar to lathyrism but without any association with consumption of *L. sativus*. This disease is now called konzo (41). Konzo has been reported only from poor rural communities in Africa; it is characterized by the abrupt onset of an isolated and symmetric spastic paraparesis which is permanent but non-progressive. The name derives from the local designation used by the Congolese population affected by the first reported outbreak in 1936. Konzo means “tied legs”, and is a good description of the resulting spastic gait. Outbreaks of konzo are described from Cameroon, the Central African Republic, the Democratic Republic of the Congo, northern Mozambique and the United Republic of Tanzania. Konzo has been associated with exclusive consumption of insufficiently processed bitter cassava in epidemiological studies (42).

### Toxic optic neuropathy

Toxic optic neuropathy, also called nutritional amblyopia, is a complex, multifactorial disease, potentially affecting individuals of all ages, races, places and economic strata (43). It may be precipitated by poor nutrition and toxins (especially smoking and alcohol) but genetic predisposal is also an important factor. Most cases of nutritional amblyopia are encountered in disadvantaged countries (9). Typically, toxic and nutritional optic neuropathy is progressive, with bilateral symmetrical painless visual loss causing central or cecocentral scotoma. There is no specific treatment for this disorder. Nevertheless, early detection and prompt management may ameliorate and even prevent severe visual deficit.

### Alcohol-related neurological disorders

Alcohol and other drugs play a significant role in the onset and course of neurological disorders. As toxic agents, these substances directly affect nerve cells and muscles, and therefore have an impact on the structure and functioning of both the central and peripheral nervous systems. For example, long-term use of ethanol is associated with damage to brain structures which are responsible for cognitive abilities (e.g. memory, problem-solving) and emotional functioning. In people with a history of chronic alcohol consumption the following abnormalities have been observed: cerebral atrophy or a reduction in the size of the cerebral cortex, reduced supply of blood to this section of the brain which is responsible for higher functions, and disruptions in the functioning of neurotransmitters or chemical messengers. These changes may account for deficits in higher cortical functioning and other abnormalities which are often symptoms of alcohol-related neurological disorders.

### Fetal alcohol syndrome

The role of alcohol in fetal alcohol syndrome has been known for many years: the condition affects some children born to women who drank heavily during pregnancy. The symptoms of fetal alcohol syndrome include facial abnormalities, neurological and cognitive impairments, and deficient growth with a wide variation in the clinical features (44). Not much is known about the prevalence in most countries but, in the United States, available data show that the prevalence is between 0.5 and 2 cases per 1000 births (45). Though there is little doubt about the role of alcohol in this condition, it is not clear at what level of drinking and during what stage of pregnancy it is most likely to occur. Hence the best advice to pregnant women or those contemplating pregnancy seems to be to abstain from drinking, because without alcohol the disorder will not occur.

### Alcohol-related polyneuropathy

A typical example of a toxiconutritional disorder, alcohol-related polyneuropathy is elicited by a combination of the direct toxicity of alcohol on the peripheral nerve and a relative deficiency of vitamin B1 and folate. In its usual form it starts in an insidious, progressive way with signs located at the distal ends of the lower limbs: night cramps, bizarre sensations of the feet and the sufferer is quickly fatigued when walking. Examination reveals pain at the pressure of the muscular masses. This polyneuropathy evolves to a complete form with permanent pain in the feet and legs. The signs of evolution of alcoholic polyneuropathy are represented by the deficit of the leg muscles leading to abnormal walk, exaggerated pain (compared to burning, at any contact) and skin changes. At the latest stage, ulcers may occur (46). The onset of the peripheral neuropathy depends on the age of the patient, the duration of the abuse and also the amount of alcohol consumed. The excessive abuse of this substance determines the central and/or peripheral nervous lesions.

### Wernicke's encephalopathy

Wernicke's encephalopathy is the acute consequence of a vitamin B1 deficiency in people with severe alcohol abuse. It is due to very poor diet, intestinal malabsorption and loss of liver thiamine stores. The onset may coincide with an abstinence period and is generally marked by somnolence and mental confusion; which gradually worsens, together with cerebellar signs, hypertonia, paralysis and/or ocular signs. The prognosis depends on how quickly the patient is given high-dose vitamin B1 (by intravenous route, preferably). A delay or an absence of treatment increases the risk of psychiatric sequelae (memory disorders and/or intellectual deterioration). If the treatment is too late, the consequences could be an evolution to a Wernicke–Korsakoff syndrome, a dementia.

### Alcohol and epilepsy

Alcohol is associated with different aspects of epilepsy, ranging from the development of the condition in chronic heavy drinkers and dependent individuals to an increased number of seizures in people already with the condition. Alcohol aggravates seizures in people undergoing withdrawal and seizure medicines might interfere with tolerance for alcohol, thereby increasing its effect. Though small amounts of alcohol might be safe, people suffering from epilepsy should be advised to abstain from consuming this agent.

After an episode of weeks of uninterrupted drinking, sudden abstinence may lead to epileptic seizures and severe coma, "delirium tremens". Detoxification should be under medical supervision and possibly with medication to decrease the risk of this potentially life-threatening condition.

In terms of relative risk, much more is known about alcohol and epilepsy than other conditions. There is little difference between abstainers and light drinkers in the risk for chronic harmful alcohol-related epilepsy. Risk is highest at levels of consumption which exceed 20 g of pure alcohol (or two drinks) per day for women and 40 g for men. For example, the WHO project on comparative risk assessment has shown more than a sevenfold increase in risk among those who consume these high volumes or are dependent on alcohol when compared with abstainers for both male and female drinkers (47).

## PREVENTION OF NUTRITIONAL DEFICIENCIES

The neurological disorders discussed in this chapter stem from three main causes:

- general malnutrition in childhood leading to macronutrient deficiency;
- micronutrient deficiencies caused by insufficient supply or increased consumption (sometimes called "hidden hunger");
- ingestion of toxic compounds.

The prevention of neurological complications attributable to the first two causes is, in theory, very simple: achieve Millennium Development Goal No. 1 by eradicating extreme poverty and hunger. Most people encountering a nutritional deficiency do so because of poverty. Acknowledging that eradicating poverty is easier said than done, there are some strategies that can be used to prevent some of the micronutrient deficiencies. There are three principal ways of approaching a potentially micronutrient-deficient diet:

- Diversification — include other micronutrient-rich food items in the diet.
- Supplementation — add a supplement of the micronutrient, for instance as a pill. This method is used with vitamin A in a large number of low income countries, linked to the immunization programme.
- Fortification — add more of the micronutrient to a common food commodity. Universal salt iodization is an example where this strategy has been used.

Worldwide efforts to cope with the most appalling micronutrient deficiencies are ongoing. Adding iodine to all salt has been a very successful way of preventing neurological complications caused by iodine deficiency. Supplementation of vitamin A for children under five years of age is another successful strategy to prevent blindness as a result of vitamin A deficiency. In societies with more resources and more centralized food distribution, fortification of flour with folate has been shown to decrease the occurrence of neural tube defects. In populations with restricted food choice, such as refugee populations in camps surviving on food rations, surveillance is needed to detect and correct vitamin deficiencies.

The toxic exposures need different approaches. For *L. sativus*, supplementation of cereals during acute food shortages in lathyrism-endemic areas can reduce its consumption. Another possibility is the development of a genetically modified atoxic variety that could prevent the problem. In the case of insufficiently processed toxic cassava, this solution does not seem so attractive, as low-toxic varieties are not as reliable in producing food for the family; the approach should concentrate on the proper processing of cassava. For alcohol, the focus needs to be on restricting alcohol consumption, at least during pregnancy.

The large majority of the malnutrition-related neurological disorders can be avoided by simple measures, such as the following recommended actions for policy-makers.

- Support efforts towards universal salt iodization.
- Support vitamin A supplementation among children under five years of age, if judged necessary.
- Consider strategies to decrease childhood malnutrition.
- Consider folate fortification of flour, if affordable and possible.
- Oversee the distribution of food rations to refugee populations, in order to detect and correct vitamin deficiencies.
- Promote the proper processing of toxic cassava.
- Restrict alcohol consumption, especially during pregnancy.

A preventive approach should include adapted communication with the aim of changing behaviour, strengthening capacities and reducing the incidence of some chronic diseases such as frequent neurological complications. The following activities are possible examples:

- specific nutritional programmes for children and pregnant and nursing women;
- rapid diagnosis of nutritional deficiencies in vitamins and minerals that could have a severe impact on mother and child and alter their mental and physical status and development;
- nationwide measures such as those for the prevention of iodine deficiency and its consequences.

Early interventions could reverse the deleterious tendencies. In many countries, the mass interventions against iron, vitamin A and iodine deficiencies among children (those under five years of age and older ones as well) and pregnant and nursing women, must be reinforced. At the other end of the scale, much remains to be done for adults and elderly people.

## **A PUBLIC HEALTH FRAMEWORK**

### **Political aspects**

Within the context of the fight against poverty, malnutrition would benefit from strong political commitment to improve and develop an integrated approach of various ministries. Improving the dialogue between public and private sectors should be an important approach to emphasize in every country. Efforts remain to be made for a comprehensive salt iodization as recommended by international organizations. This implicates obligatory reinforcement of policies for legislation, standards, application and control. Regulations on the advertising of beers, wines, other alcoholic drinks and tobacco must be reinforced, especially during sports and cultural events. Nigerian President Olusegun Obasanjo has lent his support to the goal of reducing death from chronic disease: “Governments have a responsibility to support their citizens in their pursuit of a healthy, long life. It is not enough to say: ‘we have told them not to smoke, we have told them to eat fruit and vegetables, we have told them to take regular exercise’. We must create communities, schools, workplaces and markets that make these healthy choices possible.”

### **Management and provision of care**

The management of neurological disorders related to malnutrition — attributable to direct causes or secondary induced effects of metabolic diseases — is a challenge that requires a pragmatic approach in order to be effective. Setting up pilot interventions that are feasible and realistic would be a useful demonstration to WHO Member States concerned by this public health problem. Lessons learnt from other integrated programmes (for both noncommunicable and communicable diseases) could serve as a model for neurological disorders associated with malnutrition.

It is essential to set up a multidisciplinary task force surrounding neurologists and nutritionists. This team should be supplemented by clinicians who are concerned with the secondary causes of neurological diseases related to nutrition, i.e. cardiologists, endocrinologists, specialists in internal medicine and paediatricians. Social scientists would also have an important role, for a better understanding of knowledge, attitudes and practices. Specialists in communication would be involved in the initiative, so as to reach, educate and sensitize the population. Other sectors such as education, private and public sectors, civil society, community leaders and nongovernmental organizations will all have a part to play to contribute to the concretization and reinforcement of the strategies and interventions.

CONCLUSIONS AND RECOMMENDATIONS	
1	Malnutrition, micronutrient deficiencies and ingestion of toxic compounds continue to be priority public health problems. Most of the neurological disorders associated with them are preventable.
2	Priorities need to be identified for the actions needed to deal with neurological disorders associated with malnutrition, micronutrient deficiencies, or the ingestion of toxic compounds.
3	The strategy of communication should use appropriate and diversified channels for better sensitization and social mobilization. It should target the general population, health professionals and social workers. Schools constitute a favourable environment because they provide access to teachers and pupils who can carry the message home at household level.
4	The interrelationship between neurological disorders and nutrition must be stressed in the training of general practitioners, paramedical staff and social workers. The capacities of nongovernmental organizations, community organizations and the education sector must be reinforced and developed so as to target the prevention of nutritional problems.
5	Development and review of training manuals, counselling guidelines and training curricula is a necessary part of capacity-strengthening whose contents need to be centred on specific subjects in accordance with needs assessment, the gaps to be filled and the interventions to be implemented in the community.
6	Educative support to the health services must be elaborated to develop tools of education and counselling for primary and secondary prevention and to develop guidelines and support to facilitate management of the targeted diseases and secondary complications, including disabilities and rehabilitation.

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- The Micronutrient Initiative web site (<http://www.micronutrient.org/>) includes links to the most important Internet sites regarding the individual micronutrients discussed in this chapter.

## 3.7 *Pain associated with neurological disorders*

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**Pain can be a direct or an indirect consequence of a neurological disorder, with physical and psychological dimensions that are both essential for its correct diagnosis and treatment. Pain — acute and chronic — is a major public health problem that poses significant challenges to health professionals involved in its treatment. Chronic pain may persist long after initial tissue damage**

**has healed: in such cases, it becomes a specific health-care problem and a recognized disease. Adequate pain treatment is a human right, and it is the duty of any health-care system to provide it.**

The current and most widely used definition of pain was published by the International Association for the Study of Pain (IASP) in 1979, which states that pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or, is described in terms of such damage” (1). This definition was qualified by the Taxonomy Task Force of the association in 1994 (2): “Pain is always subjective. Each individual learns the applications of the word through experiences relating to injuries in early life”.

The physiological effect of pain is to warn of tissue damage and so to protect life. Pain is classified as nociceptive if it is caused by the activation of nociceptors (primary sensory neurons for pain). Nociceptive pain can be somatic (pain originating from the skin or musculoskeletal system) or visceral (pain originating from visceral organs). The sensory system itself can be damaged and become the source of continuous pain. This type of pain is classified as neuropathic. Chronic neuropathic pain has no physical protective role as it continues without obvious ongoing tissue damage. Pain without any recognizable tissue or nerve damage has its cause classified as idiopathic pain. Any individual pain state may be a combination of different pains. A clinician’s duty is to diagnose, treat and support pain patients, which means the identification of pain type(s) and their causative disease(s). It is also to provide adequate treatment aimed at the cause of the pain and symptomatic relief which should include psychosocial support. As the definition of pain reveals, pain has both a physical and a psychological element. The latter plays an important part in chronic pain disorders and their management. Adequate pain treatment is a human right and organization of it involving all its dimensions is the ethical and legal duty of society, health-care professionals and health-care policy-makers.

## TYPES OF PAIN ASSOCIATED WITH NEUROLOGICAL DISORDERS

Pain can be a direct or an indirect consequence of a neurological disorder. The former is seen in neurological conditions where there has been a lesion or disease of pathways that normally transmit information about painful stimuli either in the peripheral or in the central nervous system (CNS). These types of pain are termed neuropathic pains. Pain can also be an indirect consequence of a nervous disease when it causes secondary activation of pain pathways. Examples of these types of pain include musculoskeletal pain in extrapyramidal diseases such as Parkinson's disease, or deformity of joints and limbs due to neuropathies or infections.

It is useful to distinguish between acute and chronic pain. Pain begins frequently as an acute experience but, for a variety of reasons — some physical and often some psychological — it becomes a long-term or chronic problem. According to the IASP classification of chronic pain, this term refers to any pain exceeding three months in duration.

### Pain directly caused by diseases or abnormalities of the nervous system

#### Neuropathic pain

In contrast to nociceptive pain which is the result of stimulation of primary sensory nerves for pain, neuropathic pain results when a lesion or disruption of function occurs in the nervous system. Neuropathic pain is often associated with marked emotional changes, especially depression, and disability in activities of daily life. If the cause is located in the peripheral nervous system, it gives rise to peripheral neuropathic pain and if it is located in the CNS (brain or spinal cord) it gives rise to central neuropathic pain.

*Peripheral neuropathic pain.* Painful diabetic neuropathy and the neuralgia that develops after herpes zoster are the most frequently studied peripheral neuropathic pain conditions. Diabetic neuropathy has been estimated to afflict 45–75% of patients with diabetes mellitus. About 10% of these develop painful diabetic neuropathy, in particular when the function of small nerve fibres is impaired. Pain is a normal symptom of acute herpes zoster, but disappears in most cases with the healing of the rash. In 9–14% of patients, pain persists chronically beyond the healing process (postherpetic neuralgia). Neuropathic pain may develop also after peripheral nerve trauma as in the condition of chemotherapy-induced neuropathy.

The frequencies of many types of peripheral neuropathic pain are not known in detail but vary considerably because of differences in the frequency of underlying diseases in different parts of the world. While pain caused by leprosy is common in Brazil and parts of Asia, such pains are exceedingly rare in Western parts of the world. Because of an explosion in the frequency of diabetes as a result of obesity in many industrialized countries and in South-East Asia, the likely result of this will be an increase in painful diabetic neuropathy within the next decade.

*Central neuropathic pain, including pain associated with diseases of the spinal cord.* Central post-stroke pain is the most frequently studied central neuropathic pain condition. It occurs in about 8% of patients who suffer an infarction of the brain. The incidence is higher for infarctions of the brainstem. Two thirds of patients with multiple sclerosis have chronic pain, half of which is central neuropathic pain (3).

Damage to tissues of the spinal cord and, at times, nerve roots, carries an even higher risk of leading to central neuropathic pain (myelopathic pain). The cause may lie within the cord and be intrinsic, or alternatively, be extrinsic outside the cord. Intrinsic causes include multiple sclerosis and acute transverse myelitis, both of which may result in paraplegia and pain. In certain developing countries, for example in sub-Saharan Africa, intrinsic damage may be attributable to neurotoxins — as in the case of incorrectly prepared cassava, which leads to tropical spastic

paresis. Lathyrism resulting from consumption of the grass pea (*Lathyrus sativus*) may cause a spinal disorder and, in both cases, pain is a significant symptom (see also Chapter 3.6).

Extrinsic causes of cord damage and pain are numerous. Spinal cord injuries result in pain in about two thirds of all patients (4). Other causes include compressive lesions, for example tumours and infections, especially tuberculosis and brucellosis. The former group comprises both primary CNS tumours (e.g. neurofibroma and meningioma) and secondary tumours from breast, lung, prostate and other organs, together with lymphomas and leukaemias.

### **Pain indirectly caused by diseases or abnormalities of the nervous system**

Pain arises as a result of several distinct abnormalities of the musculoskeletal system, secondary to neurological disorders. These can be grouped into the following categories:

- musculoskeletal pain resulting from spasticity of muscles;
- musculoskeletal pain caused by muscle rigidity;
- joint deformities and other abnormalities secondary to altered musculoskeletal function and their effects on peripheral nerves.

#### **Pain caused by spasticity**

Pain caused by spasticity is characterized by phasic increases in muscle tone with an easy predisposition to contractures and disuse atrophy if unrelieved or improperly managed. In developed countries, the main causes of painful spasticity are strokes, demyelinating diseases such as multiple sclerosis, and spinal cord injuries. With an ageing population, especially in the industrialized countries, and rising numbers of road traffic accidents, an increase in these conditions, and therefore pain, is to be expected in the future.

Strokes and spinal cord disease are also major causes of spasticity in developing countries, for example stroke is the most common cause of neurological admissions in Nigeria.

#### **Pain caused by muscle rigidity**

Pain can be one of the first manifestations of rigidity and is typically seen in Parkinson's disease, dystonia and tetanus. Apart from muscle pain in the early stages of Parkinson's disease, it may also occur after a long period of treatment and the use of high doses of L-Dopa causing painful dystonia and freezing episodes. Poverty of movement and tremors may also contribute to the pain in this disorder.

Tetanus infection, common in developing countries, is characterized by intense and painful muscle spasms and the development of generalized muscle rigidity, which is extremely painful. During intense spasm, fractures of spinal vertebrae may occur, adding further pain.

#### **Pain caused by joint deformities**

A range of neurological disorders give rise to abnormal stresses on joints and, at times, cause deformity, subluxation or even dislocation. For example "frozen shoulder" or pericapsulitis occurs in 5–8% of stroke patients. Disuse results in the atrophy of muscles around joints and various abnormalities giving rise to pain, the source of which are the tissues lining the joint. In addition, deformities may result in damage to nerves in close proximity resulting in neuropathic pain of the "evoked" or spontaneous type.

The literature does not give data for the prevalence and incidence of the pain associated with the disorders mentioned.

### **Complex painful disorders**

Complex regional pain syndrome (CRPS) refers to several painful disorders associated with damage to the nervous system including the autonomic nervous system. CRPS Type I was previously

known as reflex sympathetic dystrophy, with the cause or preceding event being a minor injury or limb fracture. CRPS II, formerly known as causalgia, develops after injury to a major peripheral nerve. The symptoms exceed both in magnitude and duration those which might be expected clinically given the nature of the causative event. Also, patients often experience a significant reduction in motor function. The pain is spontaneous in type with allodynia and hyperalgesia. Other features of the syndrome include local oedema or swelling of tissues, abnormalities of local blood flow, sweating (autonomic changes) and local trophic changes. Both conditions tend to become chronic. They are a cause of significant psychological and psychiatric disturbance, and treatment is a major problem.

### **Headache and facial pain**

Any discussion of pain arising from disorders of the nervous system must include headache and facial pains: these conditions are discussed in Chapter 3.3. They have been the subject of considerable research and been carefully classified by the International Headache Society. Epidemiological studies have focused primarily on migraine and tension-type headaches (primary headache disorders). Secondary headache disorders are also described (see Box 3.3.1).

### **ASSESSMENT OF PAIN**

Pain has physical and psychological dimensions, both of which may be measured; they form an important aspect of the diagnosis of painful disorders and are essential for the correct application of treatment and its assessment. Pain is a subjective experience but physiological changes that accompany it may be measured: they include changes in heart rate, muscle tension, skin conductivity and electrical and metabolic activity in the brain. These measures are most consistent in acute rather than chronic pain and they are used primarily in laboratory studies. Clinically, pain assessment includes a full history of the development, nature, intensity, location and duration of pain. In addition to clinical examination, self-report measures of pain are often used.

The use of words as descriptors of pain have permitted the development of graded descriptions of pain severity. For example, mild pain, moderate pain, severe pain and very severe pain, to which numerical values may be attached (1–4), may be graded on a numerical scale from 0 to 4 indicating the level of pain being experienced. In clinical practice, however, there is widespread use of a 0–10 scale, a visual analogue scale, which is easy to understand and use and is not affected by differences in language. Such measures are often repeated at intervals to gain information about the levels of pain throughout the day, after a given procedure or as a consequence of treatment. More sophisticated verbal measures use groups of words to describe the three dimensions of pain, namely its sensory component, the mood-related dimension and its evaluative aspect. This technique was devised by Melzack and others and is best seen in the Short-Form McGill Pain Questionnaire (5). The questionnaire requires the patient to be well acquainted with the words used. Often because of age, not having English as a first language or as a result of some form of mental impairment, the scale cannot be used. In its place it is possible to use a “faces scale” in which recognizable facial images representing a range of pain experiences from no pain to very severe pain are readily understood. Such scales are often used with children. In the case of patients with pain generated as a result of a lesion within the nervous system (neuropathic pain) specific measures have been devised to distinguish between that type of pain and pain arising outside the nervous system (6). In the assessment of a patient with neuropathic pain, the evaluation of sensory function is crucial and can be carried out at the bedside with simple equipment.

Another technique used in clinical assessment includes pain drawings, which allow the patient to mark the location of pain and its qualities using a code on a diagram of the body. A pain diary is used by patients to record levels of pain throughout the day, using a visual analogue scale. This reveals the pattern of pain severity in relation to drug therapy and activity levels. Finally, pain behaviour is

often used to aid diagnosis. It is especially useful for determining the extent to which psychological factors influence pain. For example, a wide discrepancy between the behaviour exhibited in the clinic and what might be expected, given the nature of the disorder, is a valuable clue to a person's emotional state, ability to cope with pain and conscious or unconscious desire to communicate distress non-verbally to the clinician. Pain assessment should take account of the patient's sex and ethnic and cultural background, all of which tend to influence the clinical presentation.

## PUBLIC HEALTH ASPECTS OF PAIN DISORDERS

Pain — acute and chronic — is a ubiquitous experience and it is also a major public health problem that poses significant challenges to health professionals involved in its treatment. Reliable data about the prevalence and incidence of pain, however, are limited, with available studies being based on either regional surveys of a broad spectrum of painful disorders, or specific pain states.

In a collaborative study of pain in a primary care setting, WHO revealed that persistent pain afflicted between 5.3% and 33% of individuals resident in both developing and developed countries. The lowest frequency was reported in Nigeria and the highest in Santiago, Chile. The study revealed that persistent pain was associated with depression, which affected the quality of life and reduced the level of daily activity of the sufferers (7). It was concluded that the essential need to work and to earn income might be a reason why many people in developing countries tolerate pain rather than reporting to doctors or hospitals. Therefore, lack of an adequate social and health-care support network, cost implications and job security must influence the extent to which people living in developing countries and suffer pain fail to seek help.

A detailed study of the prevalence, severity, treatment and social impact of chronic pain in 15 European countries was carried out recently (8). The prevalence of chronic pain ranged between 12% and 30%, figures similar to those in the WHO study. The most common sites for pain were the head and neck, knees and lower back. Of the respondents, 25% had head or neck pains (migraine headaches, 4%; nerve injury from whiplash injuries, 4%). Although back pain may have a neurological cause, the likelihood was that in the great majority pain was the result of musculoskeletal disorders or back strain. The authors concluded that one in five Europeans suffer from chronic pain which is of moderate severity in two thirds and severe in the remainder. The study also reveals that, in the opinion of 40% of the respondents, their pain had not been treated satisfactorily and 20% reported that they were depressed. In economic terms, 61% were less able or unable to work outside their homes, 19% had lost their jobs because of pain and another 13% had changed their jobs for the same reason.

A large-scale survey in Australia (9) of just over 17 000 adults with pain daily for at least three months (chronic pain) yielded a prevalence rate of 18.5%; in a comparable survey in Denmark, a prevalence rate of 19% was obtained (10). It is therefore evident from the three surveys that a prevalence rate for chronic pain of 18–20% is to be expected in adult populations selected at random from developed countries. Unfortunately, these figures do not give any detail about pain arising from the nervous system, except for the information about head and neck pain in the European survey.

Certain neurological disorders causing pain have been examined in terms of the incidence of pain. For example Kurtzke (11) estimated that the annual incidence of herpes zoster infection in the United States was 400 per 100 000 of the population. A study of the incidence of post-herpetic neuralgia in 1982 revealed a figure of 40 per 100 000 (12). Further information from Bowsher (13) indicated that the number of individuals with post-herpetic neuralgia increases with age so that 40% of people over 80 years of age who acquire acute herpes zoster will suffer from chronic post-herpetic neuralgia. In populations in which ever greater numbers are living to 80 years and more, there is likely to be a significant increase in individuals suffering from post-herpetic neuralgia.

The earlier study by Ragozzino et al. (12) gave figures for the anatomical distribution of the neuralgia that was present in 56% in the thoracic region, 13% in the face and 13% in the lumbar regions; 11% had pain in the cervical region. One third of patients with multiple sclerosis develop neuropathic pain states, of whom trigeminal neuralgia occurs in 5%, and another one third develop other forms of chronic pain (3). There is an increase in the incidence of trigeminal neuralgia in patients with cancer and other diseases that impair the immunological systems.

It is significant that one third of cancer patients have a neuropathic component to their pain as do a similar proportion of patients with prolonged low back pain (14).

It should be noted that stump pain arises from a severed nerve in the limb and may be caused by a local neuroma or by tethering of the severed nerve to local tissues. In either case the pain is of the peripheral neuropathic type. In contrast, phantom limb pain is central neuropathic pain and more difficult to treat.

Central stroke pain is defined as neuropathic pain that follows an unequivocal episode of stroke. It is associated with partial sensory loss in all but a few cases. A prospective study by Andersen et al. (15) revealed a one-year incidence of 8%, with symptoms being severe in 5% and mild in 3%. For most patients the pain develops gradually during the first month but delays of many months have been recorded. The pain is incapacitating, distressing and often even more so than other symptoms.

Headache disorders have also been the subject of intensive epidemiological research (see Chapter 3.3).

Poor relief of acute pain is a recognized risk factor for the development of chronic pain after various forms of surgery, for example herniotomy, mastectomy, thoracotomy, dental surgery and other forms of trauma. In part, this is the result of nerve injury which presents as acute neuropathic pain in 1–3% of patients. The majority of such patients experience persistent pain one year after the causative event, indicating that acute neuropathic pain is a very definite risk factor for chronic pain. Prompt treatment of early nerve pain is therefore important (16).

Hernia repair is followed by moderate to severe pain in 12% of patients one year postoperatively and is of the somatic or neuropathic type (17). Breast surgery of various types gives rise to the experience of phantom breast and pain with or without a phantom.

Information about the incidence and prevalence of pain generally, and neurologically related pain in particular, is almost totally lacking for developing countries, although there is no reason to believe that conditions that give rise to pain such as stroke, multiple sclerosis, various forms of headache and other disorders vary in nature. There may well be differences, however, in the extent to which some disorders are present, for example multiple sclerosis is less common in developing countries, whereas others are not encountered in the Western world, such as certain forms of poisoning by neurotoxins from foods, and leprosy which is a cause of neuropathic pain.

HIV/AIDS is a major cause of neuropathic pain in the later stages of the disease: 70% of AIDS sufferers develop this form of pain, which is severe and comparable with the severe pain experienced in cases of advanced cancer. The incidence of severe pain must, therefore, be high in countries where AIDS is a major health problem.

### Box 3.7.1 Signs and symptoms of chronic pain

- Immobility and consequent wasting of muscle, joints, etc.
- Depression of the immune system causing increased susceptibility to disease
- Disturbed sleep
- Poor appetite and nutrition
- Dependence on medication
- Overdependence on family and other caregivers
- Overuse and inappropriate use of health-care providers and systems
- Poor performance on the job, or disability
- Isolation from society and family
- Anxiety and fear
- Bitterness, frustration, depression and suicide

The figures quoted in this section show that a significant number of individuals suffer from chronic and incapacitating pain as a result of diseases of the nervous system, or as a result of damage to peripheral nerves at the time of surgery and other forms of trauma. The nature of the pain, which is often neuropathic in type, means that the sufferer has a disabling condition that in time may be primarily the result of pain, which is difficult to relieve. As such, it poses a significant health problem in terms of its personal, social and economic consequences.

## **DISABILITY AND BURDEN**

Anyone involved primarily in the management of chronic pain is aware that it may persist long after the initial tissue damage has healed. Pain reflects pathophysiological changes in the nervous system and they, together with changes that usually occur in patients' emotions and behaviour, have led to the conclusion that, in such cases, chronic pain is a specific health-care problem and a disease in its own right. This diagnostic category is not fully accepted among clinicians because many continue to believe that pain must be a symptom of an ongoing disease or injury. Current research reveals, however, that the pathophysiological changes mentioned persist when signs of the original cause for pain have disappeared. The signs and symptoms of chronic pain, once it has evolved into a disease, are listed in Box 3.7.1. The combination of these features of the condition reveal the potential for physical impairment, disability and handicap which collectively form the basis of significant degrees of burden for both the patient and the family.

## **TREATMENT AND CARE**

### **Barriers to effective pain relief**

#### **Educational barriers**

Despite the wide availability of teaching aids for educating professional groups who are heavily engaged in pain management (18), relatively little attention has been given to their use in developed countries. They are used to an even lesser extent in developing countries. Therefore many doctors, nurses and others dealing with patients in pain enter their professional careers inadequately equipped to deal with the most common symptom and cause of considerable suffering worldwide.

#### **Politicoeconomic barriers**

The availability of drugs for the treatment of pain is a problem in over 150 countries. Frequently, pain management has a low priority, because the chief focus of attention is infectious diseases and, often, there are exaggerated fears of dependence with very restrictive drug control policies. In addition, in developing countries, the cost of medicines generally and therefore problems in their procurement, manufacture and distribution, add further barriers to their use.

#### **A treatment gap**

In many countries, therefore, there is a treatment gap, meaning that there is a difference between what could be done to relieve pain and what is being done. That gap exists in a number of developed countries, primarily because of poor pain education and the often limited and patchy nature of specialized facilities for pain treatment. Additionally, in developing countries these problems are far greater and the gap is far wider because of the lack of education, access to appropriate drugs for pain relief and facilities for pain management.

The treatment gap can be reduced worldwide by improving pain education, increasing facilities for pain treatment and access to pain-relieving drugs. In the case of opioid analgesics, an increase in their availability and the employment of correct protocols is a matter of urgency. Improvements of this kind are possible if use is made of the guidelines published by WHO, together with the

International Narcotics Control Board, on achieving balance in a national opioids control policy, which are available in 22 languages on the web site of the WHO Collaborating Centre for Policy and Communications in Cancer Care (19). Also, no stricter measures should be enacted than those requested by the international drug conventions and international recommendations (20) on the use of opioid medicines. WHO is developing a programme to assist countries in improving access to medications controlled under the drug conventions (see Box 3.7.2) (19).

### Management of pain of neurological origin

The range of treatments available for pain directly caused by diseases of the nervous system includes pharmacological, physical, interventional (nerve blocks, etc.) and psychological therapies. Treatments for pain are used in association with other forms of treatment for the primary condition, unless of course pain is itself the primary disorder. IASP definitions of pain treatment facilities and services are given in Box 3.7.3.

There are many studies of the medical treatment of peripheral neuropathic pain (21). There are far fewer studies published on the treatment of central neuropathic pain, for example post-stroke pain. Neuropathic pain does not respond well to non-opioid analgesics such as paracetamol, acetylsalicylic acid and ibuprofen — a non-steroidal anti-inflammatory drug. Opioids have been shown to have some efficacy in neuropathic pain but there are specific contraindications for their use.

Topical agents may give local relief with relatively little toxicity; they include lidocaine and, to a lesser extent, capsaicin cream, particularly in the treatment of post-herpetic neuralgia. In selected cases, electrical stimulation techniques such as transcutaneous electrical stimulation or dorsal column stimulation may be used, but the latter in particular is expensive which clearly limits its use. Pain associated with spasticity and rigidity is treated with muscle relaxants. In the case of baclofen, it can be administered systemically or intrathecally. However, the latter route requires administration by a trained specialist and therefore is unlikely to be freely available in developing countries.

Pain arising from joints secondarily damaged by the effects of neurological disorders is usually controlled using simple analgesics, for example paracetamol or a non-steroidal anti-inflammatory drug (NSAID).

## Box 3.7.2 Access to Controlled Medications Programme

In many parts of the world, patients suffering severe pain face immense challenges in obtaining pain relief, because the opioids that could provide such relief have been categorized as “controlled substances”. They are therefore subject to stringent international control and rendered inaccessible.

Severe under-treatment is reported in more than 150 countries, both developing and industrialized. They account for about 80% of the world population. Annually, up to 10 million people suffer from lack of access to controlled medications. Nearly one billion of the people living today will encounter this problem sooner or later. Most of them are pain patients.

The future Access to Controlled Medications Programme, initiated by WHO, will address the main causes for impaired access. These causes stem essentially from an imbalance between the prevention of abuse of controlled substances and the use of such substances for legitimate medical purposes.

For almost 50 years the focus was on the prevention of

abuse, which led to too strict rules in many countries that do not allow medical use. In relation to that, prejudice has developed consisting of an unjustified fear of psychological dependence of patients on opioid medication and an unjustified fear of death caused by opioids. Many countries have neglected their obligation to provide sufficient analgesia given in the United Nations drug conventions and as called for by many international bodies (the International Narcotics Control Board, the United Nations Economic and Social Council, the World Health Assembly, etc.)

The programme, as proposed, will focus on regulatory barriers, the functioning of the estimate system for importing/exporting by the countries, and the education of health-care professionals and others involved. It will organize regional workshops where health-care providers, legislators and law enforcers will exchange their views and the problems they encounter. It will train civil servants responsible for submitting estimates and, in doing so, train health-care providers in the rational use of opioids. Furthermore, it will develop other activities, including advocacy.

Psychological techniques — and cognitive/behaviour therapy in particular — are used to help patients cope with pain and maximize their social, family and occupational activities. Research reveals that such therapies are effective in the reduction of chronic pain and absenteeism from work (22).

Physical therapy carried out by physiotherapists and nurses is an important part of the management of many patients with neurological diseases, painful or not, including strokes, multiple sclerosis and Parkinson's disease, to name but a few. Relaxation techniques, hydrotherapy and exercise are helpful in the management of painful conditions that have a musculoskeletal component. In fact, in the case of CRPS type I and II they form the first line of treatment when used together with analgesics. There is good evidence that multimodal treatment and rehabilitation programmes are effective in the treatment of chronic pain (23, 24).

All health-care workers who treat pain, especially chronic pain, whatever its cause, can expect about 20% of patients to develop symptoms of a depressive disorder. Among patients attending pain clinics, 18% have moderate to severe depression when pain is chronic and persistent. It is known that the presence of depression is associated with an increased experience of pain whatever its origin and also reduced tolerance for pain. Therefore the quality of life of the patient is significantly reduced, and active treatment for depression is an important aspect of the management of the chronic pain disorder.

### Service delivery

The management of neurological diseases is primarily a matter for specialist medical and nursing staff, both in developed and developing countries. In contrast, specific facilities for pain management, especially chronic pain management outside neurological centres, are much less well organized and are often absent, especially in developing countries. The relief of pain should be one of the fundamental objectives of any health service. Good practice should ensure provision of evidence-based, high quality, adequately resourced services dedicated to the care of patients and to the continuing education and development of staff. In 1991, an IASP Taskforce on Guidelines for Desirable Characteristics for Pain Treatment Facilities issued definitions of the various types of service in existence for the management of pain by pain clinicians (25). They are given in Box 3.7.3.

## Box 3.7.3 Definitions of pain treatment services

Pain treatment facility	A generic term describing all forms of pain treatment facilities without regard to personnel involved or types of patient served.
Multidisciplinary pain centre	The centre comprises a team of professionals from several disciplines (e.g. medicine, nursing, physiotherapy, psychology) devoted to the analysis and management of pain, both acute and chronic. The work of the centre includes teaching and research. The centre may have both inpatient and outpatient facilities.
Multidisciplinary pain clinic	The clinic is a health-care delivery facility with a team of trained professionals who are devoted to the analysis and treatment of pain. The clinic may have both inpatient and outpatient facilities.
Pain clinic	Pain clinics vary in size and staffing complements but should not be run single-handed by a clinician. The clinic may specialize in specific diagnoses (e.g. neuropathic pain) or pains related to a specific area of the body (e.g. headache).
Modality-orientated clinic	The clinic offers a specific type of treatment and does not conduct comprehensive assessment or management. Examples include clinics dealing with nerve block, transcutaneous electrical nerve stimulation (TENS), acupuncture and hypnosis.

Source: (25).

During the past 15–20 years, the ideals for pain management in general, and services in particular, have increasingly been met in developed countries. They are met to a much lesser extent in developing countries, where other health priorities, costs of treatment and availability of trained personnel are all contributing factors to the relative lack of resources. Nevertheless, strenuous efforts to improve services for people in pain are being made in many developing countries. Even though services for neurological disorders are better provided, many patients with pain of neurological origin may never reach such centres. There is therefore a great need for health-care providers to devote more resources to pain relief in general, which in turn will bring about an improvement in the treatment facilities available for neurological patients with pain.

## RESEARCH

Worldwide, research on pain takes place within the disciplines of experimental neurosciences (molecular biology, anatomy, physiology), clinical neurosciences (neurology, neurosurgery, psychiatry), psychology and psychosomatic medicine, anaesthesiology, orthopaedic surgery, public health and community medicine, physical therapy and nursing. The IASP is an interdisciplinary scientific society that fosters interactions between these diverse lines of research via its triennial World Pain Congresses, its scientific journal *Pain*, and books published by IASP Press (18). Its Special Interest Group on Neuropathic Pain provides a forum for scientific exchange on neuropathic pain and other types of pain that are related to neurological disorders (26).

## TRAINING

At present, pain medicine and algesiology are recognized as medical specialties in only a small number of countries (for example Finland, Germany, Turkey and the United Kingdom). Therefore, most medical doctors interested in treating patients for pain spend their residency in one of the existing medical disciplines — particularly anaesthesiology but also orthopaedic surgery, neurology or, more rarely, psychiatry or psychosomatic medicine.

Pain treatment fellowships are offered by some countries, and IASP has postgraduate training positions. In Germany, a medical subspecialty, specialized pain therapy, is supervised by a licensed training centre and carried out after finishing a residency in one of the traditional medical specialties. More general training in pain management does exist but it is very variable within and between specialist medical areas and between countries.

Training programmes for nurses who will specialize in pain management are growing steadily. Such programmes exist mainly in relation to palliative care, post-operative pain management and the work of pain clinics in developed countries but, increasingly, also in countries in the developing world.

Physiotherapy is a discipline in which pain management is an integral part of the working day and therefore should be a major aspect of the training of all physiotherapists.

Clinical psychologists have a major role in the treatment of chronic pain patients. Usually they specialize in pain management after a period of postgraduate training in general clinical psychology and practise either independently or in specialist pain centres. Very few clinical psychologists are available for work with patients in pain, whether attributable to neurological conditions or not, in developing countries. However, specialist training in pain management for medical practitioners who work in hospitals or the community in developing countries is spreading gradually. IASP has provided a core curriculum for professional education in pain that forms the basis for growing numbers of pain education programmes and is available via open access (27).

**CONCLUSIONS AND RECOMMENDATIONS**

<b>1</b>	Pain is associated with neurological disorders in three ways: as neuropathic pain resulting from diseases, infections or injuries of the central and peripheral nervous system, as musculoskeletal pain secondary to neurological disorders, and as complex regional syndromes in which both the somatic and autonomic nervous systems are involved.
<b>2</b>	Chronic pain may develop from poorly treated or neglected acute pain as a result of changes in the function of the CNS: the pain persists and as such has become a disorder of the nervous system.
<b>3</b>	Pain is a significant symptom in several neurological disorders or after injuries to the nervous system, adding significantly to physical and emotional suffering and often to disability. Neurologists and non-neurologists who have responsibility for patients with neurological disorders should ensure that pain is assessed carefully and recorded in terms of its origins, nature and severity as part of an overall clinical assessment prior to diagnosis and management.
<b>4</b>	There is an urgent need for the inclusion of specific pain education programmes in undergraduate curricula for doctors, nurses and other health professionals likely to deal with pain problems. Postgraduate training is also neglected in many countries, though specialization in pain management is increasing steadily, particularly in developed countries. There is a need to continue and expand postgraduate training in pain management and to develop specialized pain management centres.
<b>5</b>	A treatment gap, which is greatest in developing countries, results from inadequate pain education, the low priority given to pain relief compared with other medical problems such as infectious diseases, and poor access to the most powerful analgesics.
<b>6</b>	A fear of addiction, coupled with unnecessarily restrictive legal controls and limitation of access by cost and availability of other pain-relieving drugs, significantly reduces the potential for pain relief. Recognized international guidelines for the use of powerful analgesics should be observed and unduly restrictive regulations should be suitably modified to ensure availability on a reasonable basis. Guidelines should be made available on the use of co-analgesic drugs and other treatments used to relieve or control very severe pain.
<b>7</b>	There is an urgent need for more research into chronic pain of neurological origin.

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## 3.8 Parkinson's disease

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**Parkinson's disease is a chronic progressive neurodegenerative disorder of insidious onset, characterized by the presence of predominantly motor symptomatology (bradykinesia, rest tremor, rigidity, and postural disturbances). It is also associated with a diversity of non-motor symptoms, which, together with late-onset motor symptoms (such as postural instability and falls, freezing of gait, speech and swallowing difficulties), are presently one of the most difficult challenges the treating physician is faced with when dealing with patients with a long duration of the disease.**

In addition to the motor symptomatology of Parkinson's disease (PD) (1), some non-motor symptoms such as hyposmia, rapid eye movements, sleep behaviour disorder, personality changes, pain, paresthesias and depression may be present and may even manifest before the motor symptoms (2). Urinary disturbances, orthostatic hypotension and neuropsychiatric disturbances (dementia, hallucinations and delirium) usually become evident and troublesome after several years in the course of the disease (3). Overt dementia is a late complication that most frequently affects older patients with prolonged disease duration (4). Late-onset motor symptoms include postural instability and falls, freezing of gait, speech and swallowing difficulties.

The pathophysiology of PD involves the progressive loss of dopamine-containing neurons of the pars compacta of the substantia nigra leading to denervation of the nigrostriatal tract and significant reduction of dopamine at the striatal level. The consequence of this denervation process is an imbalance in the striato-pallidal and pallido-thalamic output pathways, which is responsible for the major motor deficits (5). Genetic predisposing factors in combination with environmental factors are thought to be responsible for the cellular changes leading to progressive neuronal degeneration in which mitochondrial dysfunction, oxidative mechanisms and failure of the protein degradation machinery at the cellular level are probably involved (6). The presence of Lewy bodies (cytoplasmic proteinaceous inclusions) in surviving dopaminergic neurons is the pathological hallmark of PD.

### DIAGNOSIS

As there are no definitive biological or imaging markers, diagnosis is at present made through the use of stringent clinical criteria such as those developed by the Brain Bank of the Parkinson's Disease Society in the United Kingdom (7). These criteria are used worldwide and provide for a definite

diagnosis with a high degree of accuracy. Clinicopathological studies based on brain bank material from Canada and the United Kingdom have shown that clinicians diagnose the disease incorrectly in about 25% of patients. In these studies, the most common reasons for misdiagnosis were presence of essential tremor, vascular parkinsonism and atypical parkinsonian syndromes (8).

Although, as previously mentioned, the diagnosis is made exclusively on a clinical basis, there are new diagnostic tools that can be used to confirm the presence of dopaminergic denervation at the striatal level, thus lending support to the clinical diagnosis. These include fluorodopa positron emission tomography (FDOPA-PET) and dopamine transporter imaging with radionuclide tracers by means of single photon emission tomography (DAT-SPECT). Both methods are still used as investigational tools and not for the routine diagnosis of PD.

Most cases of Parkinsonism are attributable to primary Lewy body PD. “Parkinsonism-plus” syndromes (which include progressive supranuclear palsy, multisystem atrophy, corticobasal degeneration) and secondary parkinsonisms (mainly drug induced, flunarizine and cinnarizine still being important culprits particularly in Latin American countries where these drugs are misused frequently for the prevention of cerebrovascular disorders) account for a small proportion of cases of parkinsonism seen in clinical practice.

## ETIOLOGY AND RISK FACTORS

Current theories on the etiology and pathogenesis of PD consider this disorder to be multifactorial and the result of a genetic predisposition possibly interacting with environmental factors. That genes play a role in the etiology of PD is supported at present by the discovery of at least 11 forms of genetic parkinsonism that share clinical features and possibly pathogenetic mechanisms with the more common, as yet, sporadic form of the disease (9). The quest for environmental exogenous triggering factors has remained elusive and supported only through indirect evidence gathered from numerous and extensive epidemiological studies. Age, sex, dietary habits, infections, environmental toxins and trauma are among the factors considered by these studies (10).

## EPIDEMIOLOGY AND MAGNITUDE

Parkinson’s disease is a universal disorder, with a crude incidence rate of 4.5–19 per 100 000 population per year. The wide variation in incidence estimates probably reflects differences in methodology and case ascertainment as well as age distribution of the sample population. Age-adjusted rates provide a more realistic figure and range from 9.7 to 13.8 per 100 000 population per year. As this is a chronic disorder with a prolonged course, prevalence is much higher than incidence. Crude prevalence estimates vary from 18 per 100 000 persons in a population survey in Shanghai, China, to 328 per 100 000 in a door-to-door survey of the Parsi community in Bombay, India. Age-adjusted rates give a more restricted range of 72–258.8 per 100 000 persons. The majority of studies reporting overall crude prevalence (including males and females across the entire age range) fall between 100 and 200 per 100 000 persons (11). Differences in prevalence have been suggested to be related to environmental risk factors or differences in the genetic background of the population under study. There is no evidence that any increase in the number of new patients being diagnosed each year has to do with variations in causative factors, but more probably with increased awareness and earlier recognition of the disease. Although the disease usually begins in the fifth or sixth decade of life, recent evidence shows increased incidence with advancing age (12). It has long been recognized that a small proportion of patients develop the disease at an early age. Patients presenting with the disease before 40 years of age are generally designated as having “early-onset” PD. Among them, those beginning between 21 and 40 years are called “young-onset” PD while those beginning before the age of 20 years are called “juvenile Parkinsonism”. Contributions from the field of genetics have demonstrated that a large proportion

of “young-onset”, and “juvenile” cases are of genetic origin, while the majority of the remaining cases are presently considered to be sporadic. Some of the late-onset PD cases are also found to have a genetic component. Although PD has been traditionally considered to affect individuals from both sexes equally, data recently published show a higher proportion of males to be affected by this disorder, with a male to female ratio of 1.9 (12).

### Global and regional distribution

Parkinson’s disease affects individuals globally. Regional figures showing differences in both incidence and prevalence probably reflect the existence of factors that may be demographic (variations in life expectancy across countries), health-care-related (lack of proper and widespread recognition of the disorder, variations in access to health care), genetic, and environmental, together with methodological differences. Examples of regional variations abound, and some of them were commented upon above. In addition, early studies had shown variations in prevalence at the international level attributed to ethnic differences across regions. Higher rates were reported for Caucasians in Europe and North America, intermediate rates for Asians in China and Japan, and the lowest rates for Blacks in Africa. However, more recent studies from Asia do not show significant differences in prevalence compared with studies in Caucasians (11).

### COURSE AND OUTCOME

Parkinson’s disease runs a chronic slowly progressive course, being extremely variable in patients. During the initial years of the disease, motor disability may not be significant as symptoms are usually unilateral and mild. If left untreated, after several years it causes significant motor deterioration with loss of independence and ambulation. As the disease progresses, the increasing motor disability affects the activities of daily living. This is further complicated by the development of motor fluctuations and dyskinesias (owing to long term levodopa therapy) (13). The gait disturbances — especially freezing of gait and postural instability — lead to frequent falls, with increased risk of fractures. Dysarthria and hypophonia lead to difficulties in communication, while deglutition disorders increase the risk of aspiration pneumonia. In the later stages of the disease, patients usually need increased assistance for most activities of daily living such as feeding, personal hygiene, dressing, turning in bed, rising from the sitting position and walking (2, 14).

Mortality in PD is increased compared with a control population, though figures vary considerably from one study to another. Before the discovery of levodopa as the rational therapy of PD the observed mortality vs expected mortality ratio was approximately 3:1 (15). The introduction of levodopa has resulted in significant improvement in quality of life and reduction in mortality. The standardized mortality ratio for the PD group in a recent study was 1.52 compared with the controls (16). The cause of this increased mortality is attributable to incidental complications related to motor disability (immobility, prostration, deglutition disorders) and autonomic dysfunction leading to falls, fractures, pneumonia, urinary tract infections, etc. (17). With an increase in life expectancy, the disease, at present, runs a more prolonged course. As a result, long-term motor complications, both attributable to the disease and treatment-related, and a host of non-motor manifestations mentioned earlier are seen more frequently and account for significant morbidity (18).

### BURDEN ON PATIENTS, FAMILIES AND COMMUNITIES

The definition of burden, in the case of PD as in any other chronic disabling disorder, varies according to whether it is analysed from the perspective of the patient, the family, or the community. In the case of the patient, burden carries the meaning of a heavy, worrisome and emotionally disturbing load. For the family, the burden also takes into account the plight of the caregivers: it involves the caregiver’s appraisal of the balance between level of care demands, resources available, and quality

of giver–recipient relationship. For the community, burden entails both the impact related to social responsibility as well as economic costs. Some of these aspects are covered below.

The impact of receiving a diagnosis of a disease such as PD causes an initial emotional burden on the patient and family: they face an uncertain future living with a chronic disabling disorder — for which there is no cure and which entails significant social stigmatization. After the initial impact and with proper counselling, the patient learns to cope with the disease. As the effect of medications initially, and for a considerable time, produces significant benefit, there ensues what is usually called a honeymoon period, during which an acceptable state of health is achieved. Most patients carry on with their activities and lead an almost normal life for several years without the need of special assistance if they complement their pharmacological treatment with proper physical activity and psychological support.

With the progression of the disease, there is increasing motor impairment and disability. The patient may lose significant autonomy as the severity of the symptoms increases. Motor fluctuations and dyskinesias are compounding factors that further add to the patient's disability and interfere with everyday life. Moreover, with advanced disease the increased prevalence of gait and balance disorders reduces the capacity for independent ambulation. In this scenario, patients begin to need increasing help in everyday activities, and the burden on the caregivers increases in parallel (19). Depending on the individual patient, the degree of dependence may vary. In instances in which the disease runs a benign course, the need for special care and assistance may be limited, while in those with a more aggressive course, they may become totally dependent on external help. Designing and creating a more apt housing environment is therefore a necessary consequence that adds to the burden of the family.

An additional burden for the family is indirectly related to the functional impact of the disease. Progressive motor impairment and disability leads the majority of patients still in their active years to lose their jobs, therefore causing a significant reduction of the total household income.

In an ideal setting, the burden on the community may be reflected in many aspects. This burden may be absorbed by the private sector, nongovernmental organizations and government institutions if they provide the necessary funds and efforts for:

- removal of architectural barriers to provide for easier accessibility;
- public transport with disabled access;
- institutions and programmes that provide comprehensive care for the patients and family (establishment and ongoing support);
- subsidized medication programmes;
- compensation for loss of employment benefits;
- research support.

## TREATMENT, MANAGEMENT AND COST

The discovery of the dopaminergic deficit was the major turning point in the development of rational pharmacotherapeutic approaches to PD leading to the introduction of levodopa and later dopamine agonists. With the exception of anticholinergics and amantadine, all other drugs subsequently developed (dopa-decarboxylase inhibitors, monoamine oxidase inhibitors, catechol-O-methyl transferase inhibitors) act indirectly through dopaminergic mechanisms (1, 19). Functional surgery, developed many years ago as a palliative approach to the therapy of PD, has more recently become an important therapeutic option (19, 20).

There have been newer developments in the field of PD pharmacotherapy in an attempt to intervene at different levels of the biochemical machinery of the basal ganglia beyond the dopamine agonist receptor. Drugs acting at the adenosine, glutamate, adrenergic, and serotonin receptors are at present under scrutiny as potentially beneficial at different stages of the disease (27).

Initiation of therapy depends on the age and mental status of the patient and the severity of the disease. In young patients, there is evidence supporting the postponement of more potent medications such as levodopa to prevent early development of motor complications. In older patients, not only the risk of motor complications is less, but the safety profile of levodopa is better within a higher age range. Initially, patients are generally medicated with a single drug but as disease progresses multiple medications may be required (22).

In addition to the primary medications used for symptomatic treatment of the specific motor symptoms of PD, there is also a need for complementary medication to treat the diverse non-motor symptoms (constipation, urinary incontinence, sexual dysfunction, orthostatic hypotension, sleep disorders, psychiatric symptoms such as depression, psychosis and behavioural disorders, and cognitive disturbances) that affect a significant number of patients with PD in the advanced stages.

Functional surgery, both lesional or deep-brain stimulation, also plays an important role in the treatment of the complicated PD patient with drug-refractory disease, as this resource has become increasingly useful in the management of motor complications (motor fluctuations and dyskinesias) (20). Three different brain targets for surgery are presently used, depending on the characteristics of the patient.

The comprehensive management of the disease requires, in addition to medical and surgical treatment, the participation of numerous other medical disciplines and health-related professionals, including physical therapist, specialized nurse, occupational therapist, speech and deglutition disorders specialist, psychologist, psychiatrist, urologist and gastroenterologist.

It is also important to deal with the issues related to cost of the disease for the patient, family and society. Unfortunately, available information is limited, and almost restricted to Europe and North America, which makes it difficult to extrapolate it to other regions of the world. It is perhaps better to analyse it in relative terms compared with a control population than to make absolute currency estimates. In a recently published study from the United States, the annual utilization of health services and cost for the PD cohort was significantly higher than for a control population. On an annual basis, PD patients spend approximately two more days in hospital, 43 more days in long-term care institutions, and fill more than 20 more prescriptions than do the controls. The total annual cost is more than double that of the control population, even before adding indirect costs (uncompensated care, productivity loss, etc.). Prescription drugs account for roughly 5% of total costs, followed by outpatient care 7.5%, uncompensated care 19%, and inpatient care 20%, while productivity loss is by far the largest share of the total cost reaching almost 50%. Figure 3.8.1

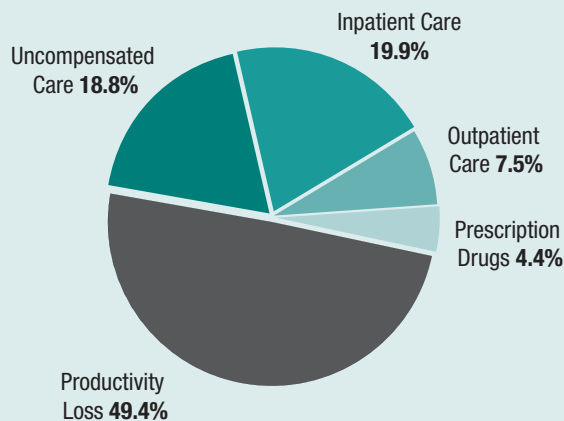
provides a breakdown of cost distribution in Parkinson's disease according to a study by Huse et al. (23).

Cost is also relative to accessibility to health delivery and medications, which is quite variable in different regions of the world. An indirect method to estimate cost is to review health spending in absolute terms and relative to the GNP, which will show major differences from one country to another. Of course, different countries have different health priorities, and depending on life expectancy the burden of PD may differ significantly.

## PREVENTION

At present there are no proven therapies for prevention of PD (7). Although there is evidence of the existence of risk and protective factors, these are not strong enough to warrant specific measures in an attempt to diminish risk or enhance protection.

Figure 3.8.1 Cost distribution in Parkinson's disease



Source: (23).

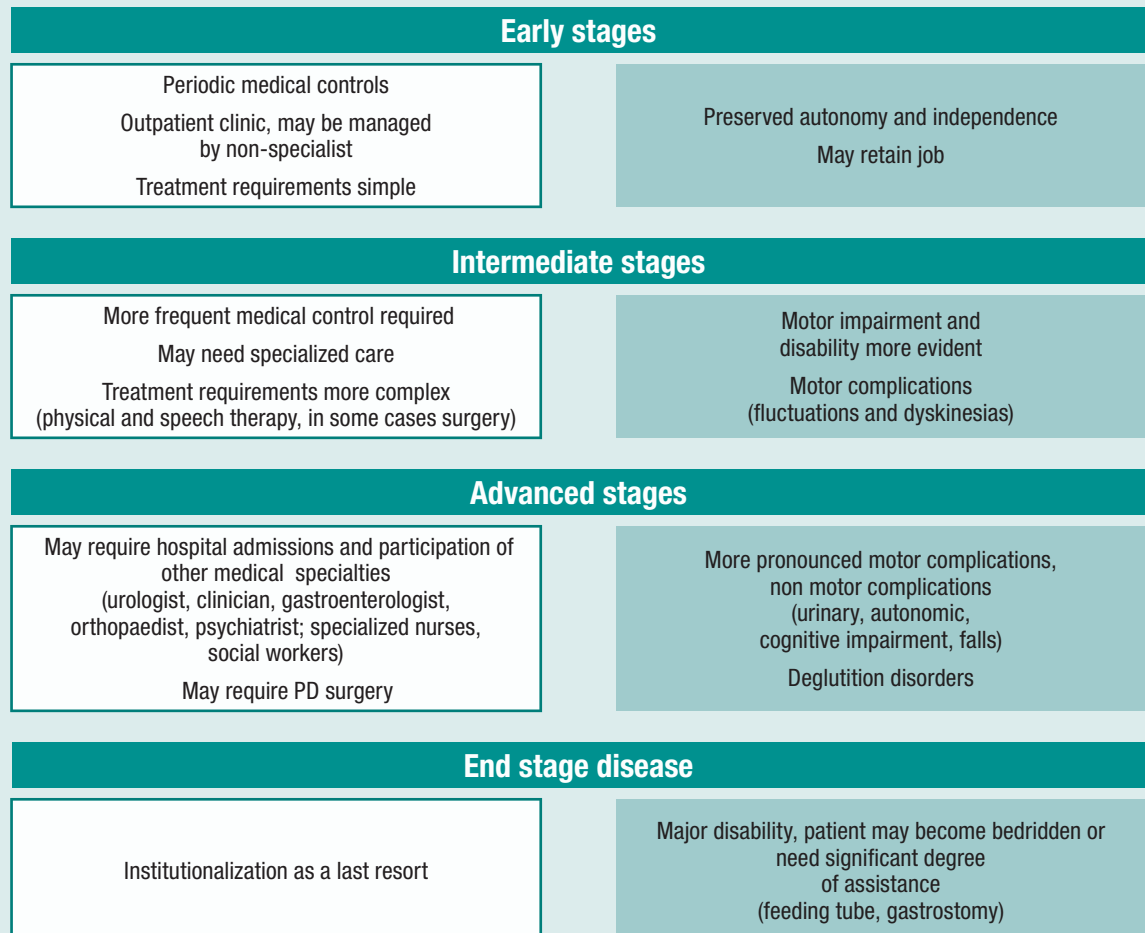
An important part of the present research effort in PD is targeted at understanding the pathogenesis of the disease, in particular the mechanisms involved in cell death. In parallel, drug development programmes, both in the pharmaceutical industry and in non-commercial research laboratories, are engaged in finding neuroprotective and neurorestorative therapies (27). If and when these drugs become available, early detection of the disease would be of paramount importance.

### INFRASTRUCTURE AND HUMAN RESOURCES

As the disease runs a progressive course going through different stages with changing needs according to each stage, the need for infrastructure and the involvement of human resources varies accordingly. Figure 3.8.2 provides an algorithm on health systems requirement as the disease progresses.

Special mention has to be made of the demand for human resources and infrastructure in the case of patients in whom pharmacological manipulations fail to modify long-term motor complications and who are considered candidates for stereotactic surgery (both lesional or deep-brain stimulation). Although the percentage of patients requiring these procedures is still small, the demand will probably grow until better pharmacological options are available. The cost of these procedures is quite high and the need for specialized personnel, infrastructure, and equipment is significant.

Figure 3.8.2 Progression of Parkinson’s disease and health system requirements



## DELIVERY OF CARE

Diagnosis and delivery of care for the uncomplicated patient can be performed by the general practitioner or family physician only if they are properly trained in the clinical diagnosis of PD and informed on the critical decisions at initiation of treatment which could affect long-term prognosis. In recent years there has been a shift in different regions of the world, in which PD or movement disorders specialists have become involved with delivery of primary care. This change has taken place for several reasons.

- Initiation of therapy involves crucial therapeutic decisions that may influence the future course of the disease, thus making it necessary for a more experienced physician to make these decisions.
- Awareness and education campaigns have brought PD to the forefront, making the patients more demanding in terms of the quality of medical care they seek.
- The worldwide launching of the Charter for People with Parkinson's Disease in 1997 by the WHO Working Group on Parkinson's Disease (with the support of the European Parkinson's Disease Association), on occasion of the commemoration of World Parkinson's Disease Day. The charter states: "People with PD should have the right to be referred to a doctor with special interest in Parkinson's disease" (24).

In the more advanced stages of the disease, it becomes necessary to resort to more specialized care: most patients are referred to a neurologist who can deal more efficiently with the complex issues involved. Depending on the medical customs or organizational aspects of medical care in different countries or regions of the world, consultation with the neurologist is performed at the request of the primary care physician but follow-up rests in the hands of the referring doctor with the occasional assistance of the specialist. In other instances the neurologist, specialized in PD or not, may at this point become the one responsible for the follow-up of the patient.

The complicated PD patient presenting with long term motor complications (fluctuations and/or dyskinesias; gait disturbances, and speech and deglutition disorders; autonomic dysfunction) will need to be referred to specialists working in a centre that has personnel and facilities for special investigation and treatment. It is also necessary at this stage to seek the help of other medical specialties and in some instances admit the patient to hospital, clinic or other health-care institution, either to perform more complex ancillary studies or specialized surgery, or provide for acute inpatient care. According to published data, almost 40% of advanced PD patients (at 15 years into the course of the disease) need to be admitted to long-term care facilities when the need for complex care exceeds the possibilities of the family or primary caregivers at home (3).

## Treatment gap

There are wide gaps in different aspects of PD care. The first has to do with education and awareness. Knowledge and information about PD is nowhere near as comprehensive as that available for vascular disease or cancer, despite being one of the most frequent neurodegenerative disorders affecting roughly 1% of the population over the age of 65 years. Another very important gap is that related to present limitations of therapy; lack of effective preventive treatments, lack of restorative treatments, and lack of effective therapies to prevent or symptomatically improve long-term complications, both motor and non-motor.

The third aspect has to do with the lack of universal access to the presently available wide range of PD medications, surgery and complementary therapies. This is particularly significant in the poorer or less developed regions of the world, where the lack of properly trained physicians, the high cost of medication and the small number of centres equipped to provide comprehensive management result in inadequate health-care delivery to PD patients.

In WHO's recently published Atlas of Country Resources for Neurological Disorders (25), availability of anti-Parkinson drugs in primary care is extremely variable in WHO regions. In the world as a whole, drug availability is only 60.6%, ranging from an extreme of only 12.5% in Africa to 79.1% in Europe. The same is true for rehabilitation, which is an important aspect of the treatment of PD. Worldwide availability of rehabilitation services is of the order of 73.2%, ranging from just 18.8% in Africa to 88.1% in Europe. No less problematic is the lack of neurologists in certain regions; there are 0.03 neurologists per 100 000 population in Africa and 0.07 per 100 000 in South-East Asia as the lowest extremes, compared with 4.84 per 100 000 population in Europe.

Finally, there is a paucity of comprehensive management programmes for PD throughout the world to provide the best standard of care for this disorder. Development of simplified treatment and management guidelines suitable for use in developing countries might be a step forward in closing this treatment gap.

Information on government policy specifically addressing the needs and requirements of PD patients in different regions of the world is scarce. In the majority of cases, wherever information is available, there is no legislation relating to the needs of patients with any type of disability or chronic disorders, including PD. Canada, the European Union and the United States are probably the only countries in the world in which legislation has been passed that consider PD in particular as a medical problem that requires specific policy.

## RESEARCH

Research in PD is carried out by different organizations. These include government institutions, government-supported research laboratories at universities and private not-for-profit research facilities, and as part of the research and development programmes of the pharmaceutical industry and private corporations. Even though millions of dollars are invested every year in different areas of research, there are few countries in which significant funds are assigned to research in PD as part of a concerted effort or carefully designed programme with proper supervision and clearly defined goals. Only the European Union and the United States have passed legislation or provided a regulatory framework towards obtaining tangible results in PD within a reasonable time frame.

Multiple areas of research are at present focused on finding the answer to the important questions facing the field of PD. They include research on genetics, pathogenesis, molecular biology and early diagnostic markers (clinical and non-clinical). Therapy is also a main area of research comprising pharmacological therapy as well as non-pharmacological methods (such as surgery, gene therapy, stem cell therapy and trophic factors).

An area of research that has not received proper attention is that related to health systems and service delivery. This subject is crucial in resource-poor countries, where the lack of adequate supervision and guidance in the allocation of funds may cause a distortion — such as being able to provide sophisticated surgical procedures to a minority of PD patients while more than 80% of them are unable to receive the more basic pharmacological agents.

## TRAINING

The core medical curricula in most medical schools throughout the world dedicate little time to providing information on PD and the complexities of its treatment and management. Where available, residency training programmes in neurology provide their trainees with more thorough information and training in this regard. In some parts of the world there are PD and movement disorders post-residency fellowships that allow for the development of more comprehensive education in this neurology subspecialty. In their scientific programmes, most local, regional and international neurology meetings have topics related to PD.

Unfortunately the training of health-care professionals towards a more effective health-care delivery for PD patients in resource-poor countries is lacking and constitutes a major challenge. These countries are the ones having the greatest need for trained professionals. Efforts should be made to establish training programmes in these regions to provide for at least:

- proper diagnostic skills for the primary care physician;
- rational use of available pharmacological treatments;
- training of nurses and carers in the complex management issues affecting the long-term complicated PD patient;
- increasing the availability of trained professionals in the areas of physical rehabilitation, speech and deglutition therapy.

## PARTNERSHIPS WITHIN AND BEYOND THE HEALTH SYSTEM

Fortunately, the number of nongovernmental organizations, advocacy groups and private foundations with a special interest in PD has grown considerably throughout the world. In the majority of cases these organizations, working together or independently of the health and education systems, provide for training of personnel, disseminate information and organize awareness campaigns for the general population, exert influence on policy-makers and help in the design of specific policy. In addition, many of them fill the gaps wherever and whenever government health organizations fail to respond to the needs of PD patients and their families, providing funds for research and establishing outpatient clinics, rehabilitation centres, long-term care facilities, etc.

## CONCLUSIONS AND RECOMMENDATIONS

<b>1</b>	Diagnosis of PD can be made without the aid of costly resources if clinical criteria are adequately applied.
<b>2</b>	Effective management of PD in its early and intermediate stages can be achieved if available drugs are rationally used.
<b>3</b>	Major challenges from the medical point of view are: <ol style="list-style-type: none"> <li>a. increasingly complex pharmacological or even surgical requirements in the complicated patient;</li> <li>b. need for a multidisciplinary team approach for the comprehensive management of advanced cases with both motor and non-motor complications.</li> </ol>
<b>4</b>	Major challenges from the health system delivery perspective include: <ol style="list-style-type: none"> <li>a. need for more properly trained professionals (primary care physicians, neurologists, and PD-specialized neurologists, nurses, physiotherapists and speech therapists);</li> <li>b. need for widespread access to current PD medications;</li> <li>c. adequate allocation of resources to establish comprehensive management programmes for PD patients.</li> </ol>

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## 3.9 Stroke

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**Stroke is one of the main noncommunicable diseases of public health importance. After coronary heart disease and cancer, stroke is the most common cause of death in most industrialized countries. In general terms, stroke is a sudden neurological deficit owing to localized brain ischaemia or haemorrhage. Most strokes are attributed to focal occlusion of the cerebral blood vessel (ischaemic stroke) and the remainder are the result of rupture of a blood vessel (haemorrhagic stroke).**

WHO defines stroke as the clinical syndrome of rapid onset of focal (or global, as in subarachnoid haemorrhage) cerebral deficit, lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular one (1). In developed countries up to 75–80% of strokes are attributed to brain ischaemia, while 10–15% of strokes represent primary intracerebral haemorrhage (ICH) and approximately 5–10% are subarachnoid haemorrhage (SAH).

### DIAGNOSIS AND CLASSIFICATION

Acute stroke is a medical emergency, and the clinician must diagnose stroke properly and quickly. The diagnosis of stroke is made reasonably accurately on clinical grounds alone by specialists; however, in general medical and emergency-department settings up to 20% of patients with suspected stroke may be misdiagnosed, which indicates that infarction cannot be reliably distinguished from haemorrhage without brain imaging.

In the diagnosis of *haemorrhagic stroke*, computerized tomography (CT) is the most reliable method of demonstrating acute haemorrhage within the first week after stroke onset. Generally, a non-enhanced scan is all that is required. In the diagnosis of ischaemic stroke, CT may or may not show a definite infarct, but a normal scan does not necessarily mean that the patient has not had a stroke. The proportion of visible infarcts also depends on the timing of scanning. Within the first few hours, few infarcts can be seen. It should be noted that less than 50% of infarcts never become visible on CT, especially in patients with milder strokes. In such cases diffusion-weighted magnetic resonance imaging (MRI) would be a preferable method of investigation. In developing countries, patients may not give a clear clinical history, and neuroimaging techniques (CT and MRI) are not widely available, which frequently leads to imprecise diagnosis (2).

Subsequently, major advances in the diagnosis have been made with the development of perfusion CT, CT angiography, diffusion-weighted MRI (which permits sensitive imaging of cerebral ischaemia already very early after onset), perfusion MR, MR angiography. Positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) are important research tools to help in better understanding of the intimate pathogenetic aspects of brain ischaemia.

For classification and clinical differentiation of ischaemic stroke subtypes, Oxfordshire Community Stroke Project classification is frequently used. The ICH subtypes are mainly classified and characterized by the means of topographical patterns, namely localization of intracerebral haematomas (clots) in the brain.

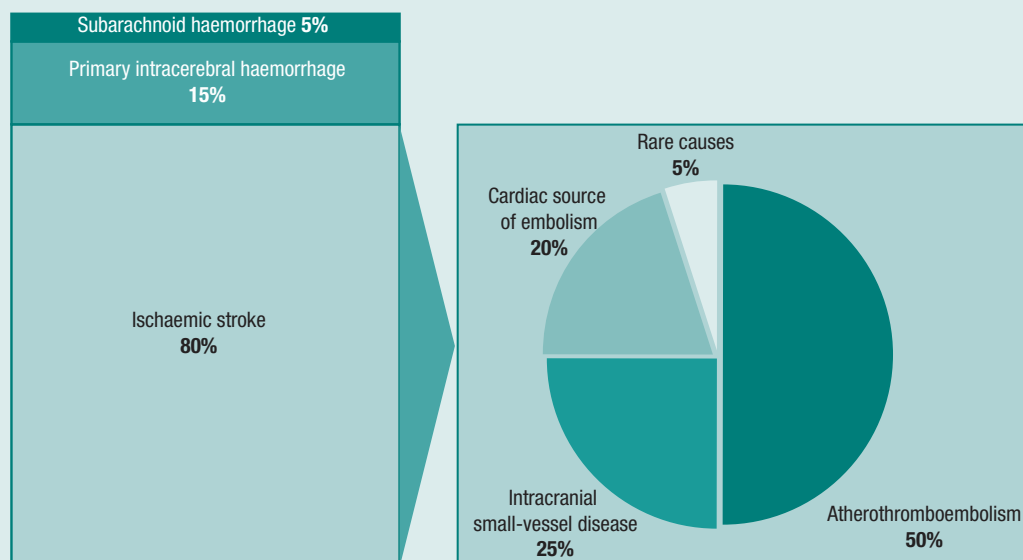
## RISK FACTORS AND PREVENTION STRATEGIES

In Caucasians, about 50% of all ischaemic strokes and transient ischaemic attacks (TIAs) are probably attributable to atherothrombotic disease of the extracranial or (less commonly) large intracranial arteries; about 20% of all ischaemic strokes arise from emboli from the heart; about 25% are so-called lacunar infarcts, probably caused by occlusion of one of the small, deep, perforating cerebral arteries; and the remainder are due to a miscellany of much rarer causes (see Figure 3.9.1). In Asian and Afro-Caribbean populations, intracranial small-vessel disease appears to be more common than in Caucasian populations.

Intracerebral haemorrhage occurs as a result of bleeding from an arterial source directly into brain substance. Because hypertension is one of its main causative factors, arterial changes associated with it have been commonly implicated in its pathogenesis. As to SAH, the leading cause — accounting for approximately 80% of cases — is rupture of an intracranial saccular aneurism.

Most conventional vascular risk factors — age, tobacco smoking, diabetes and obesity — are broadly similar for ischaemic stroke and for vascular disease in other parts of the arterial tree. The continuous relationship between stroke and blood pressure, however, is stronger than that for ischaemic heart disease. In contrast to coronary heart disease, initial studies found no overall association between plasma cholesterol concentration and stroke. Several more recent studies have found that plasma lipids and lipoproteins affect the risk of ischaemic stroke, but the exact relationships are still being clarified. Low high-density lipoprotein (HDL) is a risk factor for ischaemic stroke in men, but more data are needed to determine its effect in women (4). Potential sources of embolism from the heart are associated with an increased risk of stroke. Atrial fibrillation is by far the most important because it is so common, carries a high relative risk of stroke, and is definitely a causal factor in many cases. Recent years have seen an increasing interest and recognition of new risk factors for vascular disease, including stroke. Most are thought to operate by accelerating atherosclerosis.

Figure 3.9.1 Causes of ischaemic stroke



Source: (3).

They include infections, inflammatory and rheological markers, plasma homocysteine concentration and various genetic polymorphisms (3). For ICH, age, male sex, low cholesterol, hypertension and excessive alcohol intake were associated with the disease, while only hypertension, smoking and excessive alcohol intake showed their significance as risk factors for SAH.

The importance of any risk factor on a population basis will depend upon both its relative risk and the prevalence of that risk factor in the population. For stroke, five classic risk factors are of main interest in a population perspective: hypertension, smoking, physical inactivity, diabetes and atrial fibrillation. Taken together, these five risk factors account for more than two thirds of all stroke. For hypertension, smoking and atrial fibrillations, studies have convincingly shown that interventions substantially reduce the risk, whereas scientific support for the effect of interventions of physical inactivity and diabetes is weaker.

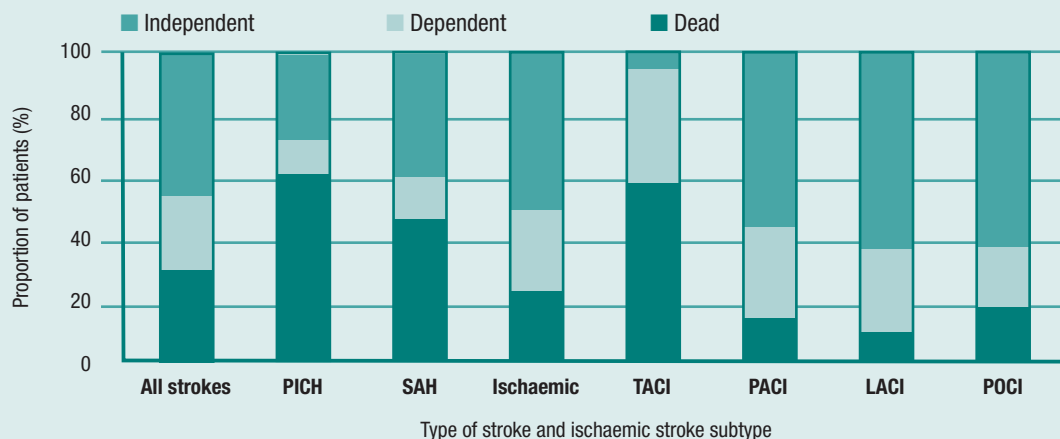
Current knowledge on stroke risk factors clearly indicates that there is a potential to reduce the incidence of stroke considerably: stroke is largely preventable. It remains a challenge, however, to implement effective preventive programmes in the population. One of the success stories has been in Japan, where government-led health education campaigns and increased treatment of high blood pressure have reduced blood pressure levels in the populations: stroke rates have fallen by more than 70% (5).

It is also very important that a strategy of comprehensive cardiovascular risk management is followed, rather than treating risk factors in isolation. To make assessment and management of cardiovascular risk feasible and affordable in low and medium resource settings, WHO has developed a CVD risk management package (6), see Chapter 1.

## COURSE AND OUTCOME

Early death after stroke is generally due to the complications of the brain lesion. Later the complications of dependency (e.g. pulmonary embolism and infection) are a more likely cause. About 30% of patients die within a year of a stroke. Recovery after stroke occurs through several overlapping processes. In the first hours and days these processes may include resolution of the ischaemia, cerebral oedema, and comorbidities (e.g. infection) that exacerbate the functional effects of the stroke itself. Later, neural plasticity by which neurons take on new functions, the acquisition of new skills through training (e.g. physiotherapy and occupational therapy), and modification of the patient's environment lead to further gains in function. Of stroke survivors, nearly half are left dependent. The outcome depends on the pathological type of stroke and the subtype of ischaemic stroke (see Figure 3.9.2) (3).

Figure 3.9.2 Outcome patterns in different stroke subtypes



Source: (3).

PICH=primary intracerebral haemorrhage; SAH=subarachnoid haemorrhage; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct; LACI=lacunar infarct; POCI=posterior circulation infarct.

The past few years have changed perception of the prognosis after stroke and TIA. Several studies have shown that the imminent risk of recurrence after TIA or minor stroke is much higher than previously thought, emphasizing the importance that all patients with suspected TIA or stroke are urgently admitted to hospital, adequately diagnosed and appropriately treated. Furthermore, neuroimaging studies have shown that clinically “silent” (but most probably not innocuous) new ischaemic events are at least as common as symptomatic ones. In the long term, the prognosis for recurrence is also grave: after 10 years more than half of patients will experience at least one ischaemic event, indicating a need for better and durable secondary preventive measures and systems for follow-up.

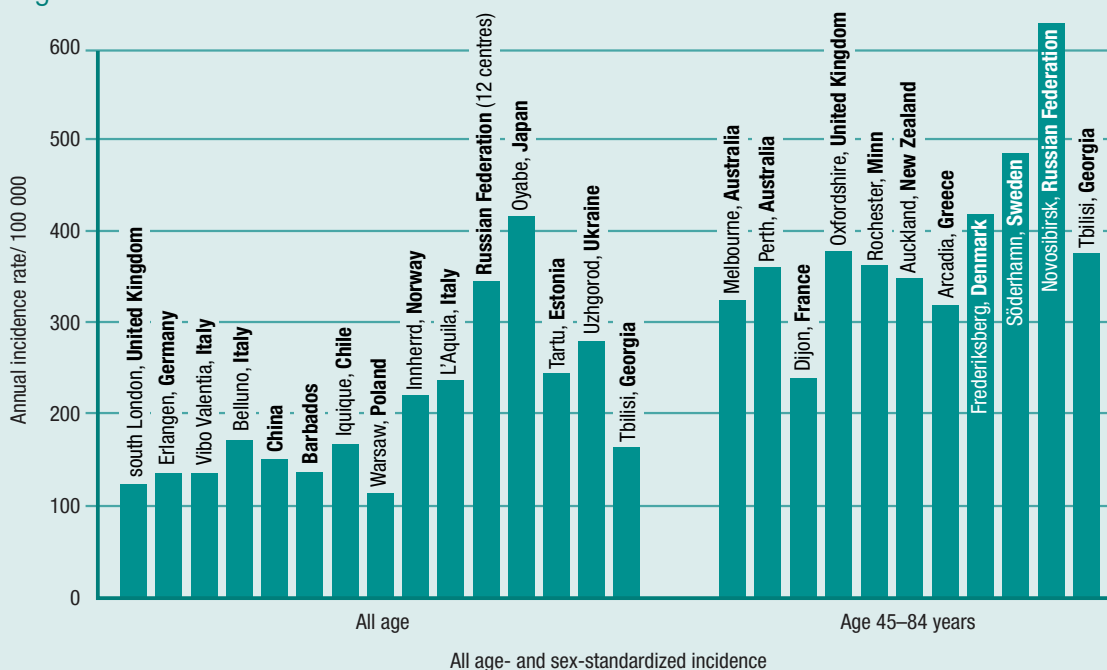
Vascular cognitive impairment and dementia are also common after stroke and at least as frequent as recurrent ischaemic events in a longer perspective. Its development depends on the volume of tissue affected either by infarction and haemorrhage or by their localization. The prevalence of post-stroke dementia in stroke survivors is about 30%, and the incidence of new onset dementia after stroke increases from 7% after one year to 48% after 25 years. Having a stroke doubles the risk of dementia.

## EPIDEMIOLOGY AND MAGNITUDE

### Stroke prevalence

The best measure of the total burden of stroke in any population is the prevalence, which provides information about the number of people at any one time in that population who have survived a stroke; however, reliable estimates of stroke prevalence are difficult to obtain. The prevalence of stroke among white populations ranges from 500 to 600 per 100 000. Reported rates per 100 000 in New Zealand are 793 crude, 991 men and 700 women; in Finland 1030 men and 580 women; and in France 1445 crude rate in elderly population. Rates per 100 000 from developing countries are also variable and range from 58 in India and 76 in the United Republic of Tanzania to 620 in China and 690 in Thailand. A recent comprehensive review of nine studies of stroke prevalence carried out after 1990 shows far less geographical variation (5–10 per 1000), with the exception

Figure 3.9.3 Stroke incidence in selected countries



of populations in rural Bolivia, in which the prevalence of stroke was as low as 1.7 per 1000, and Papua New Guinea, where no strokes were detected at all (7). The study in Bolivia, however, included only patients with stroke-related disability, and the one in Papua New Guinea screened only 213 patients over 20 years of age (the refusal rate in the older age group was 63%). The small variation in age-specific and age-standardized prevalence of stroke across the populations is consistent with the geographical similarity in stroke incidence and case-fatality.

It is uncertain whether the lower prevalence in some developing countries is related to low incidence rates or high mortality rates. It is anticipated that, with time, these populations will have a larger proportion of elderly people, life expectancies will lengthen, disease patterns will shift to patterns in developed countries, and the number of strokes will rise.

### Stroke incidence and case-fatality

The first population-based data about stroke incidence in developing countries (India, Nigeria and Sri Lanka) were obtained by WHO in 1971–1974 and showed moderate variations in incidence rates between different parts of the world. A higher prevalence of hypertension but a lower prevalence of diabetes in stroke patients in developing countries compared with developed countries was also reported. In the late 1980s, the WHO Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) stroke project showed relatively large geographical differences in stroke incidence and case-fatality rates, with the rates in less developed countries among the highest in the world (confined to patients 35–64 years old) (8, 9). The most recent data, taking into account only so-called “ideal” population-based studies of stroke incidence, show persistent geographical variations (see Figure 3.9.3).

The high incidence of stroke in eastern European countries can be attributed to well-known social and economic changes that have occurred over the past decade, including changes in medical care, access to vascular prevention strategies among those at high risk, and exposure to risk factors such as poor diet and high rates of smoking and alcohol consumption. The marked difference in stroke incidence between genetically similar areas (eastern and western Europe) suggests that potentially modifiable environmental factors are more important than genetic differences in determining stroke susceptibility.

Stroke incidence has shown little or no change over the last 10–20 years in most areas, perhaps owing to unchanged blood pressure levels and unsuccessful hypertension detection and management in the general population. More recently, however, a study from Oxfordshire, United Kingdom, showed that the age-specific incidence of major stroke had declined by over 40% in the last 20 years, while the incidence of minor stroke was similar (10), indirectly pointing to the possibility of substantial change being brought about in the rate of stroke by means of primary preventive strategies.

As to the frequency of different stroke subtypes, in some developing countries (Chile, China and Georgia) there is a tendency for haemorrhagic stroke to appear more frequently than ischaemic stroke (see Figure 3.9.4). This may be attributed to the high prevalence of hypertension in these countries as well as genetic, environmental and sociocultural factors.

Case-fatality of total strokes varies little between populations and mostly falls in the range of 20–30%, with the exception of Italy (33%), Georgia (35%) and the Russian Federation (35%) showing higher rates (7).

In almost all countries the stroke incidence increases with age, with highest rates in the age group of  $\geq 85$  years (7). As to distribution by sex, stroke is slightly more frequent in men than in women.

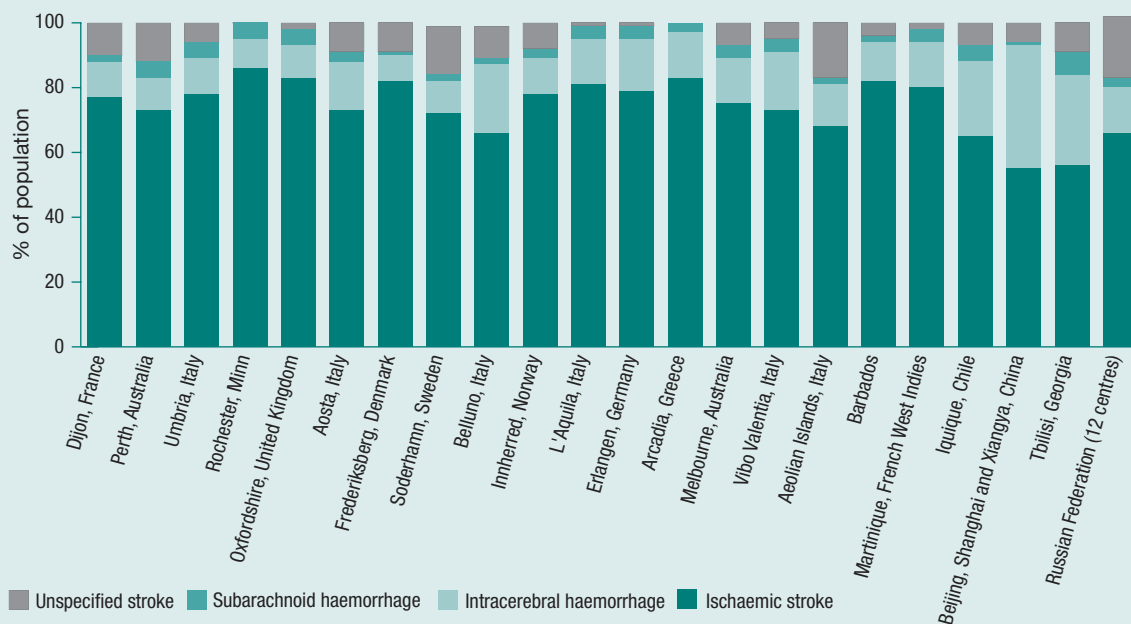
## MORTALITY, DISABILITY AND BURDEN

According to the most recent estimates, stroke is the second most common cause of mortality worldwide and the third most common in more developed countries (9, 11). Each year, stroke causes about 5.54 million deaths worldwide, with two thirds of these deaths occurring in less developed countries (12). Stroke mortality varies widely among countries for which routine death-certificate data are available. In the early 1990s, it was lowest — and had been declining steeply — in Australia, western Europe, Japan and the United States; however, it was two or three times higher in South America. Mortality was up to ten times higher — and increasing — in eastern Europe and the countries of the former Soviet Union. Routine mortality data are, however, limited by the inaccuracies of death certificates and the lack of reliable information about different pathological types of stroke (13). Furthermore, mortality depends on both the incidence of stroke and case-fatality and can give no information about strokes that are disabling but not fatal. Without urgent action, deaths from stroke will increase over the next decade by 12% globally and 20% in resource-poor countries (12).

Stroke is a major cause of long-term disability. About half of the patients surviving for three months after their stroke will be alive five years later, and one third will survive for 10 years. Approximately 60% of survivors are expected to recover independence with self-care, and 75% are expected to walk independently. It is estimated that 20% will require institutional care. The remainder will need assistance either by family, a close personal friend, or paid attendant. It is noteworthy that psychosocial disabilities (such as difficulties in socialization and vocational functions) are more common than physical disabilities (such as problems with mobility or activities of daily living).

As a major cause of long-term disability, stroke has potentially enormous emotional and socioeconomic impact on patients, their families, and health services. It causes a loss of 49 million disability-adjusted life years (DALYs) worldwide each year (12). Lifetime costs per patient are estimated at between US\$ 59 800 and US\$ 230 000. In the United Kingdom, the cost burden of stroke is estimated to be nearly twice that of coronary heart disease, accounting for about 6% of the total national health and social service expenditure. It is estimated that 41% of all costs for stroke are direct costs and 26% are indirect costs, whereas no less than 34% of expenditure corresponds to informal care. By the year 2020, stroke and coronary artery disease together are expected to be the leading causes of lost healthy life years worldwide. Even these bleak figures do not capture the full burden of stroke: more than a third of people who survive a stroke will have

Figure 3.9.4 Proportional frequency of stroke subtypes in different populations



severe disability. By 2015, over 50 million healthy life years will be lost to stroke, with 90% of this burden in low income and middle income countries (14).

## TREATMENT, MANAGEMENT AND REHABILITATION

The past decade has witnessed a dramatic change in treatment of acute stroke, leaving the era of an indifferent approach firmly behind. Equally as important as the development of particular emergency treatments, however, is the recognition that the organization of stroke services per se plays a key role in the provision of effective therapies and in improving the overall outcome after stroke.

An important advance in stroke management is the advent and development of specialized stroke services (stroke units) in the majority of developed countries. These services are organized as specialized hospital units focusing exclusively on stroke treatment. Evidence favours all strokes to be treated in stroke units regardless of the age of the patient and the severity and subtype of the stroke. Evidence from randomized trials shows that treatment in stroke units is very effective, especially when compared with treatment in general medical wards, geriatric wards or any other kind of hospital department in which no beds or specialized staff are exclusively dedicated to stroke care. The Stroke Unit Trialists' Collaboration (15) has shown that stroke units reduce early fatality (death within 12 weeks) by 28% and death by the end of one year follow-up by 17% (relative risk reduction). Stroke units also decrease disability and result in more discharges to home, rather than having patients institutionalized. In most European countries, the elements of comprehensive stroke unit care outlined by the Stroke Unit Trialists' Collaboration have been adopted, and include assessment and monitoring, physiological management, early mobilization, skilled nursing care, and short-term multidisciplinary team rehabilitation services. Despite proven efficacy and cost-effectiveness, stroke unit care remains underused in almost all parts of the world.

Ischaemic stroke is caused by interruption of the blood supply to a localized area of the brain. This results in cessation of oxygen and glucose supply to the brain with subsequent breakdown of the metabolic processes in the affected territory. The process of infarction may take several hours to complete, creating a time window during which it may be possible to facilitate restoration of blood supply to the ischaemic area and interrupt or reverse the process. Achieving this has been shown to minimize subsequent neurological deficit, disability and secondary complications. Therefore the acute ischaemic stroke should be regarded as a treatable condition that requires urgent attention in the therapeutic window when the hypoxic tissue is still salvageable (16). Recent advances in management of ischaemic stroke imply implementation of thrombolytic therapy that restores circulation in zones of critical ischaemia thus allowing minimizing, or even reversing, the neurological deficit. Thrombolysis is effective for strokes caused by acute cerebral ischaemia when given within three hours of symptom onset. Intravenous thrombolysis has been approved by regulatory agencies in many parts of the world and has been established or is in the build-up phase in many areas. The therapy is associated with a small but definitive increase in the risk of haemorrhagic intracerebral complications, which emphasize the need for careful patient selection. Currently less than 5% of all patients with stroke are treated with thrombolysis in most areas where the therapy has been implemented. One half to two thirds of all patients with stroke cannot even be considered for intravenous thrombolytic therapy within a three-hour window because of patient delays in seeking emergency care. Changing the patients' behaviour in the event of acute suspected stroke remains a major challenge. Several studies are currently ongoing on the possibility to extend the current criteria for thrombolysis to larger patient groups including beyond the three-hour window.

In cases of acute stroke, aspirin is given as soon as CT or MRI has excluded intracranial haemorrhage. Immediate aspirin treatment slightly lowers the risk of early recurrent stroke and

increases the chances of survival free of disability: about one fewer patient dies or is left dependent per 100 treated. However, because aspirin is applicable to so many stroke patients, it has the potential to have a substantial public health effect. Aspirin is also likely to reduce the risk of venous thromboembolism.

Heparins or heparinoids lower the risk of arterial and venous thromboembolism, but these benefits are offset by a similar-sized risk of symptomatic intracranial haemorrhage, and such therapy is therefore not generally recommended. For patients at high risk of deep venous thrombosis, low-dose subcutaneous heparin or graded compression stockings are currently being evaluated in clinical trials.

A recent trial did not confirm superiority of surgical treatment over non-surgical management in cases of ICH, though appropriately selected patients with acute, spontaneous ICH may benefit from urgent removal of the clot, particularly in the cerebellum. Selection criteria and choice of surgical procedure vary widely between centres.

Several advances are noted with endovascular treatment of intracranial aneurisms by detachable coils. Recent evidence suggests that endovascular intervention is at least as effective as open surgery, with fewer complications.

### **Costs of acute stroke treatments**

Although limited, the evidence suggests that the cost of organized care in a stroke unit is not any greater than that of care in a conventional general medical ward. Stroke-unit care is therefore likely to be highly cost effective, given that it has an absolute treatment effect similar to that for thrombolysis but is appropriate for so many more acute stroke patients. Although aspirin has only a very modest effect, it is very cost effective (about US\$ 58 to prevent one death or dependent stroke survivor) because it is widely applicable and accessible, inexpensive and relatively safe. Thrombolysis is less cost effective, but an accurate analysis requires considerably more data than available (17).

### **Acute stroke management in resource-poor countries**

In almost all developed countries, the vast majority of patients with acute stroke are admitted to hospital. By contrast, in the developing world hospital admission is much less frequent and depends mainly on the severity of the stroke — the more severe, the better the chance of being hospitalized. Thus hospital data on stroke admission are usually biased towards the more serious or complicated cases. Home and traditional treatment of stroke is still accepted practice in the most resource-poor countries (2).

The aims in the general management of acute stroke are good nursing care, maintenance of pulmonary and cardiovascular functions, fluid, electrolyte and nutritional balance, avoidance of systemic complications, and early rehabilitation, as well as specific stroke treatment (e.g. thrombolysis). All these goals are rarely reached in developing countries, because expert stroke teams and stroke units are rarely available, so patients are unlikely to be treated urgently. The patients are usually cared for by a general practitioner, with only a minority of patients being under the care of a neurologist. Treatment for acute stroke in developing countries is generally symptomatic; thrombolytic and neuroprotective drugs are the exception rather than the rule. Many drugs are delivered by the intravenous route, thus preventing patients from early mobilization. Antiplatelet agents are not used in a systemic manner, and anticoagulants in atrial fibrillation are usually under-prescribed because of poor compliance and the need for frequent monitoring of blood coagulation. Removal of cerebral haematomas and extensive craniotomy for brain decompression are the main neurosurgical procedures for stroke patients in some parts of the developing world; endarterectomy is rarely used though there are few specific data available.

## Rehabilitation

Stroke survivors frequently suffer from neurological impairments, functional deficits and handicap. Stroke rehabilitation is the restoration of patients to their previous physical, mental and social capability. Rehabilitation may have an effect upon each level of expression of stroke-related neurological dysfunction. It is of extreme importance to start rehabilitation as soon as possible after stroke onset. In stroke units, in cases of severe stroke with decreased level of consciousness, passive rehabilitation is started and active rehabilitation is initiated in patients with preserved consciousness.

Several organizational models of stroke rehabilitation exist. Rehabilitation is typically started in hospital and followed by short-term rehabilitation in the same unit (comprehensive stroke units), rehabilitation clinics or outpatient settings. A multidisciplinary team approach and involvement and support to carers are key features also in the long term. Several studies have shown that different types of rehabilitation services improve outcome, but less is known about the optimum intensity and duration of specific interventions. The scientific basis for rehabilitation and neural repair has increased considerably, and reorganization of activation patterns in the brain after injury may be monitored by functional imaging studies (PET, functional MRI).

Because of a lack of modern rehabilitation equipment and organization of services in the resource-poor countries, proper and prompt rehabilitation (both passive and active) are often deficient in the majority of developing countries.

## SECONDARY PREVENTION

Almost a third of all strokes occur in patients who have previously had a stroke, and about 15% of all strokes are preceded by TIAs. Recurrent cerebrovascular events thus contribute substantially to the global burden of the disease. Recently, an encouraging amount of new information has emerged to modify clinical practice in secondary prevention of ischaemic stroke and TIA.

Lowering of blood pressure has been known for years to reduce the risk of first stroke. The recent trials show that the same applies for secondary stroke prevention, whether ischaemic or haemorrhagic. The relative risk reduction of about a quarter is associated with a decrease in blood pressure of 9 mm Hg systolic and 4 mm Hg diastolic.

Although higher plasma cholesterol concentrations do not seem to be associated with increased stroke risk, it has been suggested that lowering the concentration may decrease the risk. The risk of stroke or myocardial infarction, and the need for vascular procedures, is also reduced by a decrease in cholesterol concentration but it is still debated whether statins are effective in stroke prevention. Aspirin, given to TIA/ischaemic stroke patients, reduces the relative risk of stroke and other important vascular events by about 13%. Compared with aspirin, clopidogrel reduces the risk of stroke and other important vascular events from about 6.0% (aspirin) to 5.4% (clopidogrel) per year. The combination of aspirin and modified-release dipyridamole may also be more effective than aspirin alone.

Long-term oral anticoagulants for TIA/ischaemic stroke patients in atrial fibrillation reduce the annual risk of stroke from 12% to 4%. Anticoagulation may be indicated for about 20% of patients with TIA/ischaemic stroke who have high-risk sources of embolism from the heart to the brain, mostly atrial fibrillation.

Stroke risk ipsilateral to a recently symptomatic carotid stenosis increases with degree of stenosis, and is highest soon after the presenting event. Carotid endarterectomy reduces the risk of stroke substantially in such patients. The recent evidence suggests that the benefit from surgery is also greater in men, patients aged  $\geq 75$  years, and those randomized and operated upon within two weeks after their last ischaemic event.

Carotid artery stenting is less invasive than carotid endarterectomy but has only been compared with endarterectomy in a few small randomized controlled trials with inconclusive results. Several large studies comparing the two treatments are currently ongoing.

The undoubted effectiveness of medical and surgical interventions must not detract from lifestyle modification, which should provide additional benefits and at lower cost — though with more effort by the patient. In spite of a lack of formal randomized evidence, ceasing to smoke, increasing physical activity, lowering body weight and eating a diet rich in potassium seem to be effective measures to prevent stroke.

All these measures are less achievable in developing countries where there is also a lack of knowledge and information regarding stroke prevention strategies, including lifestyle modification (18). Antiplatelet agents are not used systematically and anticoagulants are usually under-prescribed mainly because of difficulties with monitoring. The high-technology preventive measures indicated above are not accessible in the poorest countries. WHO has developed evidence-based recommendations for policy-makers and health professionals for prevention of recurrent heart attacks and strokes in low and middle income populations (19).

## DELIVERY OF CARE

Developed countries are able to provide accessible health-care services to their people but, even in these countries, services are far from optimal. In developing countries, however, cultural beliefs and failure to recognize stroke symptoms may have an impact on the number of patients seeking medical attention, and those who do come may present after complications have developed. In the United States, approximately 60% of stroke patients present within three hours of stroke onset, while in Europe 40–56% arrive at hospital within six hours. In Turkey, only 40% of stroke patients are seen in the hospital within 12 hours (2).

Economic policies of developing countries may not allow large investments in health care, hospitals, brain scanners or rehabilitation facilities. Health care in the acute phase of stroke is the most costly component of the care of stroke patients; in low-resource countries hospital care of even a small proportion of all patients with stroke accounts for a disproportionately high share of total hospital costs. Stroke units, which have been shown to reduce mortality, morbidity and other unfavourable outcomes without necessarily increasing health costs, are available in very few developing countries.

Costs of consultation, investigation, hospitalization and medication may be beyond the means of poor people, especially those who do not have welfare benefits or medical insurance plans. This seriously hampers the provision of care to patients who are otherwise able to seek medical attention.

Although hospital care represents a large proportion of the costs of stroke, institutional care also contributes significantly to overall stroke care costs. Most developing countries do not have well-established facilities for institutional care. The bulk of long-term care of the stroke patient is likely to fall on community services and on family members, who are often ill equipped to handle such issues. There is thus a need for appropriate resource planning and resource allocation to help families cope with a stroke-impaired survivor.

## Priorities for stroke care in the developing world

Governments and health planners in developing countries tend to underestimate the importance of stroke. To compound this difficulty, 80% of the population in developing countries live in rural areas, a factor that limits access to specialized services. In these parts of the world, top priority for resource allocation for stroke services should go to primary prevention of stroke, and in particular to the detection and management of hypertension, discouragement of smoking, diabetes control and other lifestyle issues. To achieve this task, stroke prevention awareness must be

raised among health-care planners and governments. Another priority is education of the general public and health-care providers about the preventable nature of stroke, as well as about warning symptoms of the disease and the need for a rapid response. Furthermore, allocation of resources for implementation and delivery of stroke services (e.g. stroke units and stroke teams) should also be a priority. Finally, it is very important to establish key national institutions and organizations that would promote training and education of health professionals and dissemination of stroke-relevant information.

## **PARTNERSHIPS WITHIN AND BEYOND THE HEALTH SYSTEM**

Despite the enormous and growing burden of stroke, the disease does not receive the attention it deserves — including funds for prevention, management and research. In the context of an integrated approach to chronic disease, a Global Stroke Initiative has been formed involving WHO, the International Stroke Society and the World Federation of Neurology. The primary focus of this international collaboration will be to harness the necessary resources for implementing existing knowledge and strategies, especially in the middle and low income countries. The purpose of this strategy is threefold: to increase awareness of stroke; to generate surveillance data on stroke; and to use such data to guide improved strategies for prevention and management of stroke (20).

Each of these components is necessary to reduce the global stroke burden. The Global Stroke Initiative is only possible through a strong interaction between governments, national health authorities and society, including two major international nongovernmental organizations.

Increasing awareness and advocacy among policy-makers, health-care providers and the general public of the effect of stroke on society, health-care systems, individuals and families is fundamental to improving stroke prevention and management. Advocacy and awareness are also essential for the development of sustainable and effective responses at local, district and national levels. Policy-makers need to be informed of the major public health and economic threats posed by stroke as well as the availability of cost-effective approaches to both primary and secondary prevention of stroke. Health professionals require appropriate knowledge and skills for evidence-based prevention, acute care and rehabilitation of stroke. Relevant information needs to be provided to the public about the potential for modifying personal risk of strokes, the warning signs of impending strokes, and the need to seek medical advice in a timely manner.

## **RESEARCH**

Stroke research is grossly underfunded even in developed countries (21). One of the major problems of stroke epidemiology is the lack of good-quality epidemiological studies in developing countries, where most strokes occur and resources are limited. To address the problem of accurate and comparable data in these countries, an approach to increase the quality of the data collected for stroke surveillance has recently been proposed by WHO. This flexible and sustainable system includes three steps: standard data acquisition (recording of hospital admission rates for stroke), expanded population coverage (calculation of mortality rates by the use of death certificates or verbal autopsy), and comprehensive population-based studies (reports of nonfatal events to calculate incidence and case-fatality). These steps could provide vital basic epidemiological estimates of the burden of stroke in many countries around the world (20).

CONCLUSIONS AND RECOMMENDATIONS	
1	Stroke is the second leading cause of mortality worldwide and the major cause of long-term disability in adults.
2	Further increase of stroke mortality is expected, with the majority of deaths from stroke to occur in less developed countries.
3	By 2015, over 50 million healthy life years will be lost from stroke, with 90% of this burden in low and middle income countries.
4	In developed countries, up to 80% of strokes represent ischaemic stroke, while the remaining 20% are attributed to either intracerebral or subarachnoid haemorrhage. In some developing countries the proportion of haemorrhagic strokes is higher.
5	Non-contrast computerized tomography is a reliable diagnostic tool allowing proper differentiation between ischaemic and haemorrhagic stroke and excluding other causes of brain damage.
6	Advent of thrombolytic therapy together with development of stroke units leads to a reduction of mortality and disability caused by stroke.
7	Immediate aspirin treatment of ischaemic stroke is beneficial in terms of reducing early stroke recurrence and increasing disability-free survival.
8	Effective measures to prevent stroke are lifestyle modification (smoking cessation, increased physical activity and the lowering of body weight), control of hypertension and blood sugar, lowering of plasma cholesterol, carotid endarterectomy in selected cases, and long-term antiplatelet or anticoagulant treatment.
9	There is a gap between developed and developing countries in terms of stroke prevention, diagnosis, treatment and rehabilitation caused by the lack of trained specialists and expertise, lack of equipment, inadequate diagnostic evaluation and insufficient funds in resource-poor countries.
10	Stroke research and training are grossly underfunded.

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## 3.10 Traumatic brain injuries

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**Traumatic brain injury is the leading cause of death and disability in children and young adults around the world and is involved in nearly half of all trauma deaths. Many years of productive life are lost, and many people have to suffer years of disability after brain injury. In addition, it engenders great economic costs for individuals, families and society. Many lives can be saved and years of disability spared through better prevention.**

**More and better epidemiological data can help in tailoring effective preventive measures against traumatic brain injury (TBI), with particular emphasis on reducing the impact of road traffic accidents. The world is facing a silent epidemic of road traffic accidents in the developing countries: by 2020, road traffic crashes will have moved from ninth to third place in the world ranking of the burden of disease and will be in second place in developing countries. A lot can be done to reduce the devastating consequences of TBIs.**

Systematic triage of patients can lead to important economic savings and better use of scant hospital resources. More standardized pre-hospital and in-hospital care, to minimize secondary brain injury, can improve outcomes substantially.

Systematic triage of patients can lead to important economic savings and better use of scant hospital resources. More standardized pre-hospital and in-hospital care, to minimize secondary brain injury, can improve outcomes substantially.

### DEFINITION AND OUTCOME

If the head is hit by an external mechanical force, the brain will be displaced inside the skull and can be injured against the solid meningeal membrane, the dura, or against the inside of the neurocranium. Acceleration and deceleration forces may disrupt the nervous tissue and blood vessels of the brain. All grades of injury can occur, ranging from no visible abnormality of the brain in cases of mild TBI to superficial bruising (contusion), and, in severe cases, dramatic swelling (oedema) as well as large collections of blood (haematomas).

Initial classification of TBI is based mostly upon the clinical examination which is carried out by the physician in the hospital's accident and emergency department. Around 90% of TBIs are classified as "mild", implying that the patient is awake but may have had a loss of consciousness and/or a short amnesia. Only 3–5% are "severe" TBIs, meaning that the patient is unconscious upon admission.

Outcome of TBI, in terms of mortality rates and disability, is related to:

- pre-injury status: age, health and psychosocial function;
- initial clinical grade immediately after injury, reflecting the primary brain damage;

- acute management: pre-hospital and in-hospital;
- complications and secondary brain damage that may develop within minutes of the impact;
- rehabilitation.

In mild TBI, the mortality rate is below 1%, while 20–50% die after suffering a severe TBI. The intermediate category, “moderate” head injury, implies a mortality rate of 2–5%. Disability is a common problem after hospitalization for TBI, even after a mild event (7).

## DIAGNOSIS AND CLASSIFICATION

The diagnosis of TBI can be obvious in cases where a blow to the head is reported and when superficial wounds can be identified. But some cases are less clear-cut, and TBI may be present without any superficial signs of a head injury.

Further classification of the brain injury is made in order to evaluate prognosis, identify patients at risk for deterioration and choose appropriate observation and treatment. As shown in Table 3.10.1, the Glasgow Coma Scale (GCS) uses a points system to evaluate the best ocular, verbal and motor responses. A normal healthy person will obtain a GCS score (adding up the eye opening score, the verbal score and the motor score) of 15. Someone who opens his eyes only after painful stimulation, utters only incomprehensible sounds and withdraws his hand only after pinching will be given a score of 8. This scale permits the following classification of TBI after clinical examination:

- mild head injury (GCS 13–15);
- moderate head injury (GCS 9–12);
- severe head injury (GCS 3–8).

Table 3.10.1 Glasgow Coma Scale to evaluate brain injury

Points awarded	Eye opening	Verbal response	Motor response
1	None	None	None
2	To pain	Sounds (incomprehensible)	Extends
3	To speech	Words (inappropriate)	Abnormal flexion
4	Spontaneous	Confused	Withdraws
5		Orientated	Localizes pain
6			Obeys commands

### Triage

Classification into these categories based on clinical assessment alone must be supported by the results of a computerized tomography (CT) examination in many cases, or a skull X-ray if a CT scanner is not available. A fracture detected on the skull X-ray images indicates an increased risk of deterioration, and the patient will need admission. A CT scan reveals a skull fracture more clearly than an ordinary X-ray examination will do. In addition, it visualizes the bleeding, bruising and swelling of actual brain injury: CT signs of brain damage are present in one third of the mild cases, two thirds of the moderate cases and all the severe cases (2–4).

## EPIDEMIOLOGY AND BURDEN

There are many scientific reports on TBI, but in view of methodological shortcomings the epidemiological data are not easily comparable (5). In spite of these reservations, it can be interesting and informative to compile data from different parts of the world.

### Incidence

In Tagliaferri's European study, the TBI incidence rate collected from 23 reports with epidemiological data was found to vary greatly between countries (5). Some of the differences could be ascribed to variations in study years, inclusion criteria and research methods. Most rates were in the range 150–300 per 100 000 population per year. The estimated European incidence of TBI was 235 per 100 000 per year, including all hospitalized patients with head injury and those dying of a head injury prior to admission. Admission policies, particularly in cases of mild TBI, will, of course, influence the incidence rates markedly. Therefore, incidence rates such as 546 per 100 000 per year in Sweden and 91 per 100 000 per year in Spain must be interpreted with caution.

Data from many parts of the world consistently show a peak incidence rate in children, young adults and elderly people. Males are injured 2–3 times as often as women.

### Prevalence

Prevalence of TBI measures the total number of injuries at a point in time or in a period interval; the calculation should include all those with TBI sequelae such as impairments, disabilities, handicaps or complaints, plus all the newly diagnosed cases at the defined time or time interval.

Estimates from the United States indicate that 1–2% of the population, i.e. around five million people, live with a TBI disability (6–7). Many disabled people have neurobehavioural problems. It is therefore no exaggeration to describe TBI disability as an enormous public health problem (6).

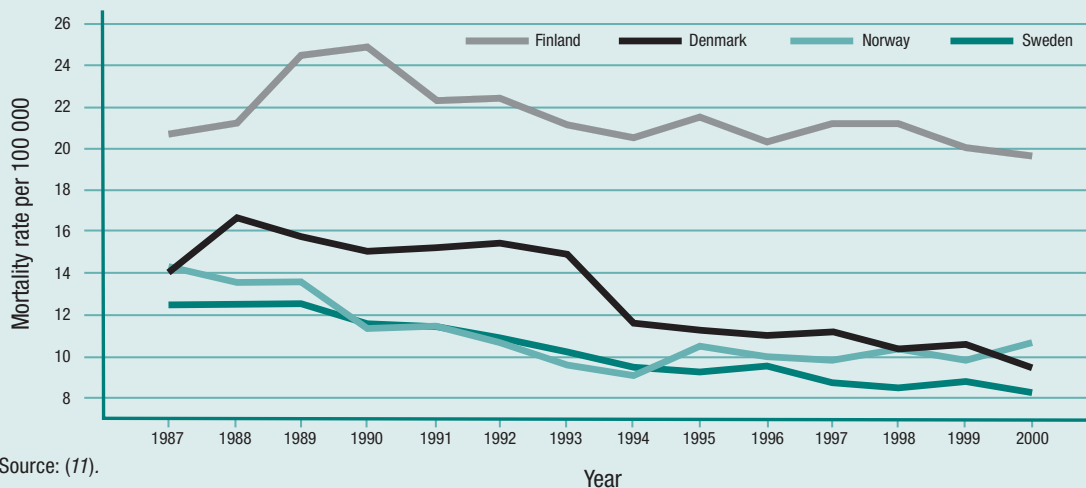
Information on how sequelae develop (diminish or increase) over time is scarce (8); better data on prevalence would certainly be useful for improved planning of rehabilitation needs.

### Mortality

*Case-fatality rate in different parts of the world.* The average European pre-hospital case-fatality rate was 8%, while the in-hospital rate was 3%, i.e. a total rate of 11 deaths per 100 cases of TBI, all grades of severity included. The in-hospital rate varies from 2.4 in Australia to 6.2 in the United States and 11 in China, Province of Taiwan (5). Admission policies may influence these rates. About one third of the hospitalized patients dying after TBI had talked at some time after the injury: this is an indication that some of them might have been saved (9).

*Mortality rate per 100 000 population per year* is more informative than the case-fatality rate. The average European rate was estimated to be 15 TBI-associated deaths per 100 000 population per year (5). The rate is around 10 in Scandinavia, 20 in India, 30 in the United States, 38 in China, Province of Taiwan, 81 in South Africa and 120 in Colombia (10). In three of the four Nordic

Figure 3.10.1 Mortality rates associated with traumatic brain injury, Nordic countries, 1987–2000



Source: (11).

countries, the TBI mortality rate decreased considerably between 1987 and 2000, as shown in Figure 3.10.1. The decrease is explained by a marked reduction in serious road traffic accidents. It has been suggested that heavy alcohol abuse may explain the persistent and high mortality rate in Finland (11).

## Disability

Traumatic brain injury is the leading cause of disability in people under 40 years of age. Disability can be classified in a simple fashion using the Glasgow Outcome Scale (see Table 3.10.2):

Table 3.10.2 Glasgow Outcome Scale (GOS)

Classification (GOS level)	Description
Dead	
Persistent vegetative state	Awake but not aware
Severely disabled	Conscious but dependent
Moderately disabled	Independent but disabled
Good recovery	May have minor sequelae

Source: (10).

Thornhill and colleagues have recently estimated the annual incidence of disability after TBI (moderate and severe disability together) to be approximately 100 per 100 000 population per year. Their findings revealed a higher incidence than indicated in previous reports, particularly in patients with mild TBI (7). Most patients (90%) had sustained a mild head injury, while a few had suffered moderate (5%) or severe (3%) brain injury. Half of the survivors were disabled after mild or moderate TBI, while three quarters of survivors were disabled after a severe injury. Even among young patients with mild injuries and a good pre-injury status, one third failed to achieve a good recovery.

Moderate disability after TBI is 3–4 times more common than severe disability. Severe disability after TBI is reported in 15–20 per 100 000 population per year (8). Mostly, patients with severe disability will have a combined mental and physical handicap.

The rarest form of disability after TBI is the vegetative state. It may be transitory, subsiding after a month or so, but may persist in many cases. The persistently vegetative patient needs artificial nutrition and hydration and will have a markedly reduced life span, i.e. 2–5 years. In some cases, complicated ethical and legal discussions arise about the purpose of continuing life-sustaining treatment.

Disability after moderate or severe TBI may take various forms:

- Mental sequelae with personality change, memory disorders, reduced reasoning power and apathy (9). A defective recent memory may be particularly incapacitating.
- Disturbed motor function of arm or leg.
- Speech disturbances.
- Epilepsy, which may develop years after the primary injury, is seen in 1–5% of patients.

## Recovery

Some patients continue to recover for years after a TBI, but 90% reach their definitive GOS level after six months (9).

Elderly patients with TBI are known to have a slower rate of functional recovery, longer stays in rehabilitation and greater levels of disability with comparable injuries.

## ETIOLOGY AND RISK FACTORS

The three main causes of TBI are road traffic accidents (RTAs), falls and violence. Their relative importance varies from region to region, see Figure 3.10.2. The graph shows that exposure to hazards varies considerably between regions (5). These variations must be taken into account by health planners who design prevention programmes.

### Road traffic accidents

As the leading cause of head injury in the world, RTAs account for 40–50% of the cases hospitalized for TBI. The impact of RTAs is even higher in children and young adults with TBI, in cases of moderate or severe TBI and in patients with multiple injuries. Every day about 3000 people die and 30 000 people are seriously injured on the world's roads, nearly half of them with head injuries. Most of the victims are from the low income or middle income countries, with pedestrians, cyclists and bus passengers bearing most of the burden (12). Fatality rates among children are six times greater in developing countries than in high income countries.

There has been a steady decrease in RTAs in many industrialized countries during the last two decades, while the problem is increasing in developing countries (4). Terms such as “a public health crisis” and “a neglected epidemic” have been used to describe this growing problem (13).

### Falls and violence

Falls are second in frequency to RTAs, as shown in Figure 3.10.2, and occur more frequently in Australia, India and northern Europe (5). In Pakistan, falls from the roof are a common cause of head injury, and account for more than 10% of the injuries in a large neurosurgical series of relatively serious TBIs (14).

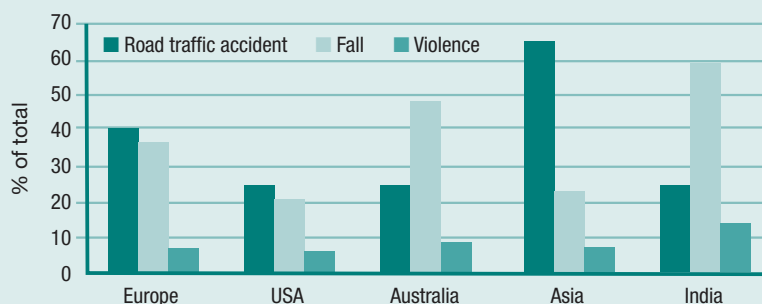
People 70 years or older have a relatively high incidence of head injuries, and in these patients falls are the most common cause. Many factors contribute to the increased risk for falls in elderly people: gait impairment, dizziness, previous stroke, cognitive impairment, postural hypotension, poor visual acuity and multiple medication.

Interpersonal violence is involved in 2–15% of cases (5). Most TBIs are the result of blunt trauma, but in some countries there is a high percentage of penetrating injuries, e.g. in the United States where gunshot wounds are the major cause and account for 40% of all head injury deaths, while 34% are secondary to RTAs (15,16).

Many factors increase the risk of sustaining a TBI:

- Alcohol and drugs: alcohol is an important contributing factor in TBI from all causes in more than one third of cases (5).
- Poverty: living in a low income neighbourhood increases the risk of TBI in children as well as in adults (17,18).
- Comorbidity: seizures and being elderly and handicapped aggravate the risk of TBI.

Figure 3.10.2 External causes of traumatic brain injury in selected areas



Note: Variations must be interpreted with caution since case definitions and classification schemes have not been standardized.  
Source: (5).

## ACUTE MANAGEMENT OF TRAUMATIC BRAIN INJURY

### Treatment of mild head injuries

Many of the mild cases can be classified as “minor head injuries”. These patients can be dismissed after a short clinical examination and adequate information, since their risk of further problems will be very low, i.e. <0.1%. Before dismissal, they deserve brief information, preferably written, about:

- warning signs indicating possible complications;
- how normal and mild symptoms are expected to develop;
- how to resume normal daily activities.

The remaining patients with mild TBI have a 1–6% risk of deterioration (19). Therefore, a closer examination may be required to identify the individuals with the highest risk of developing complications. Patients who need special attention are those with:

- decreasing level of consciousness;
- neurological deficit;
- epileptic seizure;
- deficient blood coagulation;
- age >60 years;
- alcohol abuse.

Patients at risk will need a CT examination and/or admission.

- Observation should be maintained for 12–24 hours with repeated examinations to detect a decreasing level of consciousness.
- A CT scan gives excellent information about fractures and brain damage:
- CT scanning of patients with mild TBI has been found very cost effective in Sweden, where scanners are available and manpower in hospitals is expensive (20).
- A skull X-ray should be performed if a CT scanner is not available. A fracture will indicate a higher risk of deterioration and admission is necessary for a short time of observation.

The clinical examination, a CT scan and, in some cases, observation in a hospital ward will identify the very few patients in this group requiring treatment by a qualified neurosurgeon.

### Treatment of moderate and severe injuries

Patients with moderate or severe TBI represent less than 10% of all the traumatic head injuries. In this category of TBIs, adequate health care can make a difference and substantially improve outcomes. Airway obstruction and falling blood pressure are the acute threats to the vulnerable brain-injured patient. Pre-hospital care with skilled paramedics, early arrival at the scene of the accident, prompt stabilization of the patient’s condition in accordance with ABC guidelines, and rapid evacuation reduced overall TBI mortality by 24% in two years in San Diego (6, 21).

Well-organized and updated hospital inpatient treatment is equally important. On admission, life-supporting measures should be continued, in accordance with Advanced Trauma Life Support recommendations (22). Simultaneously, a rapid diagnostic overview must be carried out: many patients, particularly in RTA cases, will have concomitant injuries of the chest, abdomen, spine or extremities.

In the United Kingdom, the mortality in patients with epidural haematoma declined progressively from 28% to 8% after the introduction of national guidelines for the early management of head injury (22). The guidelines clearly indicate how patients at risk should be identified and managed before progressive brain damage occurs.

A study from the United States in patients with severe TBI showed improved outcomes after implementation of evidence-based treatment guidelines. At the same time, reduced hospital costs

were obtained through shortened length of stay, from an average of 21.2 days to an average of 15.8 days (7).

Research that focused on identifying the ideal conditions for the extremely vulnerable brain in severe TBIs has resulted in two different approaches in neurointensive care, the Lund model and the perfusion concept. Although they are different in many ways, both have led to improved outcomes in patients with severe TBI (23).

## REHABILITATION AFTER TRAUMATIC BRAIN INJURY

Although disability after mild TBI may have been underestimated, most patients will make a good recovery with provision of appropriate information and without requiring additional specific interventions (24, 25).

Patients with moderate to severe TBI should be routinely followed up to assess their need for rehabilitation. There is strong evidence of benefit from formal interventions, particularly more intensive programmes beginning when the patients are still in the acute ward. The balance between intensity and cost-effectiveness has yet to be determined (24, 25).

The importance of rehabilitation is consistently underestimated, not least because of its cost. It is a regrettable truth that this part of the treatment lacks the drama of the primary treatment and is consequently more difficult to fund. It is nonetheless of great importance since TBI damages young lives for whom rehabilitation is as important for the regaining of function as primary treatment is for the saving of life.

Examples of rehabilitation services are shown in Box 3.10.1 and Box 3.10.2.

Neuropsychologists evaluate orientation, attention, intellect, memory, language, visual perception, judgement, personality, mood and executive functions of the patients with TBI. An example of a TBI patient with neuropsychological sequelae is given in Box 3.10.2.

### Box 3.10.1 Traumatic brain injury rehabilitation services in Costa Rica

Since 1974, rehabilitation services following TBIs are provided in Costa Rica at the National Rehabilitation Centre (CENARE), San José, which is part of the national health services. This Centre receives patients from all over the country; it is classified as a tertiary care hospital and offers highly specialized medical care to the population on an inpatient and outpatient basis. The neurotrauma unit in the Centre has a 16-bed capacity, and serves an annual average of 50 people through an interdisciplinary team consisting of two physicians (specialized in medical rehabilitation), a head nurse, an occupational therapist, a physical therapist, a psychologist and a social worker. Every week the team makes rounds to the inpatients and meets six outpatients in order to assess them throughout the subacute process of their rehabilitation; active participation of the families is encouraged at all stages of the rehabilitation process. The team counts on the help of a staff respiratory and speech therapist.

The patient population is composed of patients who were over 12 years of age at the moment of the lesion and who sustained severe traumatic head injuries, as well as patients with non-traumatic brain damage. The following services are offered.

*Low-level rehabilitation* for comatose and slow-to-recover patients, who are referred as soon as their medical condition is stable. They receive structured stimulation, in the form of physical and occupational therapy. Nutritional and feeding requirements are evaluated and installed. Families receive psychological support and advice, orientation in attention protocol, and advice in areas such as feeding, nursing care, positioning, and prevention and care of pressure ulcers. Home visits are scheduled in order to offer advice on eliminating architectural barriers and to give training to family members in their own environment.

*Full rehabilitation.* Once patients have recovered complete consciousness, cognitive sequelae are evaluated and treated and physical sequelae are further evaluated and treated. Both can be done as inpatients or outpatients, depending on the distance between the Centre and the patient's place of residence. A formal, structured cognitive retraining programme will be implemented in the near future. Patients and their families are supported throughout their subacute and chronic phases of recovery by all team members, and services are offered when needed in an open manner as well as through structured appointments.

## COSTS

Any information that is available about the economic consequences of TBI is mostly related to costs of hospitalization, which probably constitute only a relatively small part of the total costs. According to Berg and colleagues (10), TBI-associated costs can be subdivided as follows:

- direct costs: hospitalization, outpatient care, rehabilitation;
- indirect costs: lost productivity, in particular after moderate or severe injuries;
- intangible costs to patients, families and friends: related to death or reduced quality of life.

## PREVENTION AND EDUCATION

### Prevention of road traffic accidents

Road traffic accidents are the major cause of TBIs on a global scale. Although their mortality rates have decreased substantially in many industrialized countries during the past two decades, there is increasing concern about a rising epidemic of RTA injuries in developing countries. By 2020, it is estimated that road traffic crashes will have moved from ninth to third place in the world ranking of the burden of disease and will be in second place in developing countries. To quote an article in the *British Medical Journal*: "... sleepiness among drivers may account for nearly a fifth of road traffic crashes. Similarly, if the international public health community continues to sleep through the global road trauma pandemic it will be accountable for many millions of avoidable deaths and injuries" (12).

The frequency and severity of RTAs are related to the following factors:

- The number of cars and motorcycles.
- The design and condition of motor vehicles:
  - use of seat belts lowers risk;
  - functioning brakes and adequate tyres lower the risk of RTAs.
- The quality and design of the road:
  - shared road use by motor vehicles and unprotected road users increases the risk of injury;
  - speed cameras are effective in lowering the risk;
  - speed reduction through road design effectively reduces the risk.

## Box 3.10.2 Rehabilitation after traumatic brain injury: a case-study

Vera is a 34-year-old administrator who was head of personnel in a government training office for many years. She sustained a severe head injury in 1999, which did not produce any physical limitation but severely affected her memory and, to a lesser extent, speech. After evaluation it was evident that Vera had important intellectual limitations. She was given memory compensation techniques to use at home and at work, and it was suggested she relocate to a less demanding position. Vera refused to change her job; she asked the team not to visit her superiors and tried in vain to maintain her position at work without letting anybody know her condition. After some months she eventually resigned from her job, very depressed because her staff no longer trusted her and had lost respect for her authority — she constantly made mistakes, could not remember what she had asked for days before, etc. Vera decided to

enrol in some of the training courses her office offered to the public, but she failed again and again. Her former subordinates made fun of her failure, which depressed her further. When last seen, Vera was receiving treatment for severe depression, but insisted she wanted to recuperate and could recover her former capacities and employment.

**Comment:** The consequences of TBI — in the form of memory impairment (as in Vera's case), attention problems, mild to severe intellectual deficiency, lack of concentration and limited ability to learn — can result in impossibility to return to work, affect emotional stability, and limit performance at work and at home. All of these problems will affect the person's emotional status, as well as his or her family and friends. It can also mean social isolation in the long term, further aggravating depression.

- Road safety laws and traffic conditions:
  - poor enforcement of traffic safety regulations increases risk;
  - helmets dramatically reduce the risk of TBI in motorcyclists and cyclists (63–88% reduction of TBI risk in cyclists; 50% reduction of fatalities from motorcycles in the United States from 1982 to 1992);
  - speed is a major killer (5% of pedestrians will die if hit by a car at 32 km/h, while 85% will die if hit at 64 km/h (26));
  - alcohol increases the risk of RTA for drivers, pedestrians and cyclists;
  - discouraging the use of cars and heavy vehicles in cities will lower risk;
  - safe public transport incurs fewer deaths per km than travel by private car;
  - dedicated urban spaces for walking and cycling will reduce risk.
- Population density.
- The education of all road users and the general public about safe driving and transport.

A *locally relevant evidence* base is an urgent requirement for prevention of RTAs. Public health authorities need to acquire more knowledge about the epidemiology of RTAs and the main local causes, especially when injuries are fatal. They should also know that road traffic injuries are preventable and that some measures are very effective. With reliable data about the epidemiology of the “war on the roads”, a sense of urgency can be established among policy-makers and effective preventive measures can be designed that are tailored to local traffic conditions and take account of regional data on external causes and risk factors (12).

*Structural measures* have proven to be the most efficient approaches in the prevention of RTAs. Examples are physical measures to separate motor vehicles from pedestrians, speed bumps, speed cameras, strict speed limits and alcohol check-ups.

*Educational programmes* may be a useful supplement in adults, but there is no evidence that education of pedestrians reduces the risk of motor vehicle collisions involving children on foot (12).

*Community-based activities* (such as American Association of Neurological Surgeons “Think first” and “Group at risk” designed programmes), as well as interaction with motor vehicle companies, are important elements in prevention programmes. Realities in both developed and developing countries must be taken into account to make sure the programmes will be acceptable and efficient.

### Prevention of brain injuries from other causes

Prevention of TBIs from falls, violence, sports, work-related accidents, etc. must also be based on a thorough knowledge of regional epidemiology, causes and risk factors. In some countries, for example the United States, the use of firearms accounts for the majority of deaths attributed to TBI. Improved medical treatment would not have much impact in such cases, since most gunshot wounds to the head are fatal. There is a need for more efficient prevention, starting with specific legislation to regulate the use of firearms (16).

### Education

Educational activities should comprise age-oriented educational programmes including personal computer games, medical and paramedical training in neurotrauma, development of an Advanced Life Support in Brain Injury® (ALSBI), and multimedia educational campaigns on safety of motor vehicles. The creation of foundations for the relatives of victims of injuries or associations for education and the prevention of TBI should be strengthened.

The ALSBI® course objectives could be summarized as follows:

- educate pre-hospital and emergency service physicians in the care of acute neurological patients;

- promote the “time is brain” concept by emphasizing the importance of the initial management of TBI, stroke and other brain disorders;
- avoid secondary neurological damage;
- improve survival and quality of life of head-injured victims;
- spread this knowledge all over the world.

## INFRASTRUCTURE AND HUMAN RESOURCES FOR CARE

Taking care of patients with TBI does not differ from any other trauma care. In fact, a large proportion of moderately or severely head-injured patients will have concomitant injuries of the spine, chest, abdomen or extremities.

In densely populated areas of developed countries a complete trauma centre includes:

- a fully staffed and equipped emergencies and admissions unit;
- easy access to radiology services, including an technologically advanced all-body CT scanner;
- operating theatre;
- intensive care unit;
- anesthesiologists, trauma surgeons, neurosurgeons and specialized nurses available 24 hours a day, seven days a week.

In remote areas and in developing countries the situation may be different.

## RESEARCH

Research in the field of TBI should cover the following subjects:

- Epidemiology, with particular emphasis on more standardized measures, to allow comparisons between regions and a valid evaluation of care and prevention.
- The management of TBI patients with pre-hospital care, in-hospital care and rehabilitation. Such studies should range from logistics, quality of life studies, pathophysiology, etc. to evaluation of various aspects of multidisciplinary rehabilitation.

## CONCLUSIONS AND RECOMMENDATIONS

<b>1</b>	Research in epidemiology and management has led to better prevention and treatment in some parts of the world during the past two or three decades. Health policy-makers, doctors, nurses and paramedics should be proud of their achievements and join forces to organize a worldwide fight against the silent and neglected epidemic of traumatic brain injury.
<b>2</b>	There is an urgent need for the development of global and national policies in order to minimize the risks and the consequences of road traffic accidents, particularly in the developing countries. This should be a joint effort between different government agencies, medical societies, motor vehicle manufacturers and nongovernmental organizations.
<b>3</b>	Policies to improve the outcome of TBIs and strengthen road traffic safety must aim primarily at improving the research-based knowledge of regional epidemiology, preventive programmes and the acute management of TBI in pre-hospital and inpatient settings.
<b>4</b>	Prevention will have a greater impact if based upon robust data on causes and risk factors involved in TBI and upon knowledge of the efficiency of the various preventive measures.

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