Chapter 1

Introduction

Epilepsy is the second most common neurological disorder after stroke. About 50 million people worldwide suffer from epilepsy and it affects people in almost every country (1). As many as 1 in 20 people at some point in their lives have an epileptic seizure and that at least 1 in 200 people have epilepsy (1-3). Over four fifth of the 50 million people with epilepsy are thought to be living in developing countries, and 90% of these people do not receive appropriate treatment. The term "epilepsy" is derived from the Greek word "*epilambanein*", which means "to seize upon" or "to attack". It is characterized by a tendency to recurrent seizures and defined by two or more unprovoked seizures. A seizure is also referred to as a convulsion, fit, or attack. However, the words "convulsion" or "fit" are usually used to refer to seizures with tonic-clonic muscle movements.

HISTORICAL OVERVIEW

Epilepsy is one of the oldest conditions known to mankind. Basic concepts surrounding epilepsy in ancient Indian medicine were refined and developed during the Vedic period of as old as 4500-1500BC (4, 5). In the Ayurvedic literature of *Charaka Samhita* (which has been dated to 400BC and is the oldest existing description of the complete Ayurvedic medical system), epilepsy is described as *"apasmara"* which means *"loss of consciousness"*. The *Charaka Samhita* contains abundant references to all aspects of epilepsy including symptomatology, etiology, diagnosis and treatment (4, 5). Another ancient and detailed account of epilepsy is on a Babylonian tablet in the British Museum in London (1). The tablet accurately records many of the different seizure types we

recognize today. In contrast to the Ayurvedic medicine of *Charaka Samhita*, however, it emphasizes the supernatural nature of epilepsy, with each seizure type associated with the name of a spirit or god - usually evil. Treatment was, therefore, largely a spiritual matter. Hippocrates (5th Century BC), however, believed that epilepsy was not sacred, but a disorder of the brain. He recommended physical treatments and stated that if the disease became chronic, it was incurable (6).

While both Hippocrates and the *Charaka Samhita* provided this less spiritualized understanding, the perception that epilepsy was a brain disorder did not begin to take root until the 18th and 19th Centuries AD. The intervening 2,000 years were dominated by more supernatural views. Some, however, succeeded and became famous the world over. Among these people was Julius Caesar, Czar Peter the Great of Russia, Pope Pius IX, the writer Fedor Dostoevsky, the poet Lord Byron Alexander, Napoleon, Helmholtz, Nobel, Lenin to name a few (1, 6)

In the 19th Century, as neurology emerged as a new discipline distinct from psychiatry, the concept of epilepsy as a brain disorder became more widely accepted. The foundation of our modern understanding of the derangement of function seen in epilepsy (pathophysiology) was also laid in the 19th Century with the work of a London neurologist Hughlings Jackson (1873). He proposed that seizures were the result of sudden brief electro-chemical discharges in the brain and the character of the seizures depends on the location and function of the site of the discharges. Soon afterwards the electrical excitability of the brain in animals and man was discovered by David Ferrier in London, Gustav Theodor Fritsch and Eduard Hitzig in Germany (1, 6)

Working in Germany during the 1920s, Hans Berger, a psychiatrist, developed the human electroencephalograph (EEG – 'brainwaves'). The EEG revealed the presence of electrical discharges, different patterns in the brain associated with different seizure types and located the site of seizure discharges.

EPIDEMIOLOGY: PREVALENCE, INCIDENCE AND MORTALITY

Epilepsy is a second most common chronic neurological condition seen by neurologists. Epilepsy knows no geographical, racial or social boundaries. It occurs in men and women and can begin at any age, but is most frequently diagnosed in infancy, childhood, adolescence and old age (1, 2). There are 55,00,000 persons with epilepsy in India; 20,00,000 in USA and 3,00,000 in UK (7-9). It is estimated that the condition affects approximately 50 million people worldwide; around 40 million of them living in developing countries (2, 10).

Prevalence

Prevalence is the proportion of people with epilepsy in a given population at a specified time or a defined time interval. To ensure uniformity, the guidelines established by the *International League Against Epilepsy* (**ILAE**) *Commission on Epidemiology and Prognosis* (2) are recommended for these studies. Recent reviews on meta-analysis of published and unpublished studies in India revealed that the prevalence rates per 1000

individuals are: males 6.05, females 5.18, urban population 6.34, and rural population 4.94. The overall prevalence rate in India is 5.59 per 1000 population (11, 12).

However, this may be an underestimate as some studies in developing countries (such as Colombia, Ecuador, Liberia, Nigeria, Panama, United Republic of Tanzania, Venezuela etc.) suggest a prevalence of more than 10 per 1,000 and even higher rates ranging from 14 to 57 per 1000 have been reported from some African and South American countries (3, 13). An unusual type of epilepsy has been reported from South India called 'hot water epilepsy' (14, 15). It is a kind of reflex epilepsy in which pouring hot water rapidly over the head induces seizures and the prevalence is thought to vary from 1.14 to 2.99 cases per 1000 population (14, 15).

Thus, lifetime prevalence of epilepsy (i.e. the number of people presently in the world who have epilepsy now or have had it in the past or will experience it in the future) is approximately 100 million people (1).

Incidence

Incidence is a measure of the number of new persons with epilepsy per 100,000 individuals per year. Studies in developed countries suggest an annual incidence of epilepsy of approximately 50 per 100,000 (between 40 to 70 per 100,000) of the general

population (3). However, studies in developing countries suggest that this figure is incredibly higher from 100 to 190 per 100,000 (3).

Based on a solitary study in India which reported an incidence of 49.3 per 100,000 thus revealed the number of new persons with epilepsy in India each year would be close to half a million. In 50 to 60% of patients, epilepsy begins before the age of 16. The cumulative incidence of epilepsy (chance of acquiring epilepsy at some time during life) is 2 to 4%. The chance of having at least one seizure, during the lifetime is approximately 8%. Thus, it is likely that around **50 million** people in the world have epilepsy at any one time.

Mortality

There are no published Indian studies on the morbidity or mortality of epilepsy. The mortality of epilepsy is increased by a factor of 2 to 4 in developed countries. Factors associated with a higher mortality include: male gender, extremes of age (1, 11), marital status (single) and epilepsy of symptomatic of diffuse or focal cerebral disease. Much of excess mortality is related to the underlying cause of the epilepsy rather than factors attributable to epilepsy *per se*. The mortality is higher even in patients with idiopathic epilepsy (1, 11). Death in epileptic patients may be directly related to seizure/status epilepticus, due to accidents during a seizure and drowning, suicide, side effects of antiepileptic drugs such as neoplasia, blood dyscrasia, hepatic failure, toxic epidermal

necrolysis or due to Sudden Unexpected Death in Epilepsy (SUDEP, 16). SUDEP is a non-traumatic unwitnessed death occurring in a patient with epilepsy, who has been previously relatively healthy, for which no cause is found even after an autopsy (16). Its frequency is estimated as between 1:200 and 1:1000 cases per year.

PATHOPHYSIOLOGY OF EPILEPSY

Development of epilepsy is known as 'epileptogenesis' which refers to the transformation of the normal neuronal network of the brain to a long lasting chronically hyperexcitable state (17, 18). Seizure is a paroxysmal event due to abnormal, excessive hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons (17, 18). A seizure is believed to occur when a small number of neurons synchronously discharge abnormally and recruit surrounding neurons to involve one or both hemispheres of the brain (18).

Epileptic seizures results due to imbalance between excitatorary and inhibitory neurotransmitters (18). There may be a defect in the activity of GABA and therefore result in enhanced propagation of the epileptoform discharge. An increase in the activity of excitatory neurotransmitters such as glutamate and possibly aspartate, may also contribute to the spread of epileptic activity. These neurotransmitters in turn bind to postsynaptic receptors, e.g. NMDA receptor for glutamate (Fig 1), to cause intermittent

bursts of neuronal firing. Depending upon the part of the brain where the abnormal electrical discharge arises, the seizure typè will be determined.

ETIOLOGY OF EPILEPSY

Any person may develop a seizure in certain circumstances. Epilepsies can start at any age. A rough outline of the relationship between cause and age of onset is presented in Fig 2. (ɜ).

Figure 1. Glutamate (NMDA) receptor

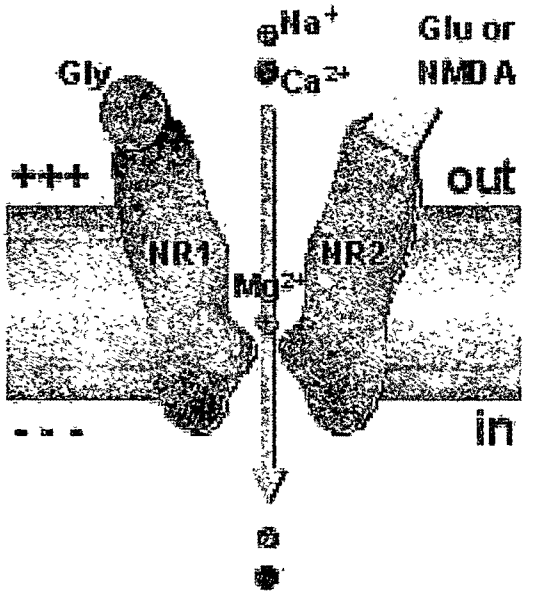
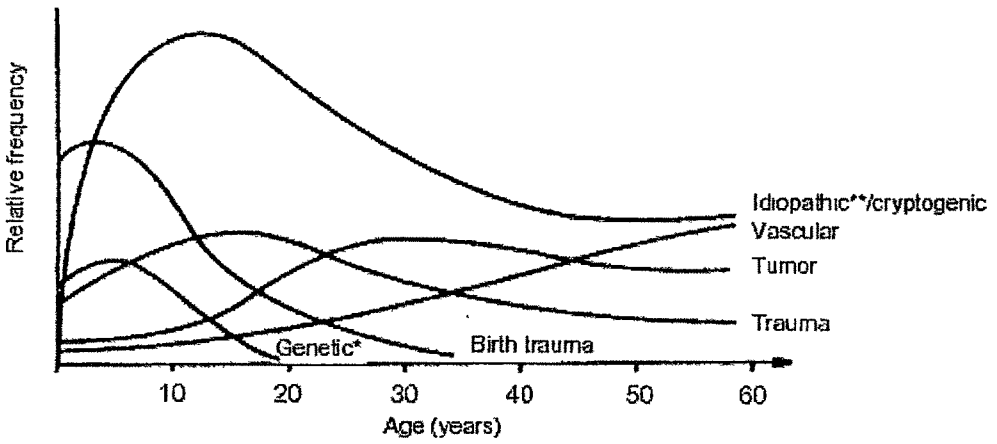


Figure 2. Approximate frequency of different causes of epilepsy, developing at different years (3).



* *Genetic brain disorders with epilepsy*
***Idiopathic = genetic epilepsy without other disorders = epilepsy sui generis*

It is imperative to establish which condition is the cause. The various causes of seizures are listed in Table 2. Some are common, some are very rare. X-rays, CT scans, and even more modern investigation methods can show structural lesions, while chemical and serological investigations will show metabolic and parasitic abnormalities (3).

Idiopathic epilepsies

There is no underlying cause other than a possible hereditary predisposition. Idiopathic epilepsies are defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology of the epilepsy (19, 20). This does not include other genetic brain disorders associated with epilepsy such as those grouped under congenital and degenerative diseases in Table 1.

Symptomatic epilepsies

They are considered to be the consequence of a known or suspected disorder of the central nervous system. Any area with abnormal brain tissue (calcifications, scars, or vascular abnormalities) may act as a focus from where abnormal activity of the neurons takes place causing symptomatic epilepsy (Table 1).

Table 1. Causes of a seizure

Metabolic	
Hypoglycaemia	Pyridoxine deficiency/dependency
Hypocalcaemia	Uraemia
Electrolyte imbalance	Phenylketonuria
Hypomagnesaemia	Porphyria
Hyperbilirubinaemia (kernicterus)	
Infections	
INTRACRANIAL	EXTRACRANIAL
Meningitis	Febrile illnesses (febrile convulsions)
Encephalitis	Pertussis
AIDS	Pertussis immunization
Neurosyphylis	Tetanus
Cerebral malaria	
Rabies	
Toxoplasmosis	
Encephalopathy (SSPE)	
Trauma	
Birth trauma	Cold injury in newborns
Head injury in later life	Hypothermia
Anoxia	
Birth asphyxia	Conditions later in life
Toxic	
Alcohol and withdrawal from alcohol	
Carbon monoxide poisoning	
Drugs (high dose i.v. penicillin, strychnine, etc.)	
Lead poisoning, Organo-phosphorus insecticide poisoning	

Tanle 1 (cont.)

Space-occupying lesions	
Haemorrhage	Tuberculoma
Abscess	Cysticercosis
Tumour	Toxoplasmosis
Circulatory disturbances	
Cerebro-vascular accident (stroke)	Sickle-cell crisis
Vascular anomalies	
Cerebral oedema	
Hypertensive encephalopathy	Eclampsia
Congenital	
Malformations of the brain (hydrocephalus, microcephaly, etc.)	
Tuberous sclerosis (Bourneville disease)	
Neurofibromatosis (von Recklinghausen disease)	
Encephalo-trigeminal facial angiomatosis (Sturge-Weber's syndrome)	
Degenerative diseases	
Niemann-Pick disease	Dementias
Cerebromacular degeneration	
Epilepsy	
Most common causes	

Cryptogenic epilepsies

The term refers to a disorder whose cause is hidden or occult. These are presumed to be symptomatic, but there is no clear evidence of an etiological factor. The cryptogenic epilepsies are also age-related, but often do not have well defined electro-clinical characteristics (22).

Approximately 60 to 70% of all epilepsies are *idiopathic* or *cryptogenic* (Fig. 3). Almost any type of brain pathology can cause seizures/epilepsy (Fig 3). The etiology of seizures is multifactorial in any given individual and is best thought of as an interaction between genetically determined seizures thresholds, underlying predisposing pathologies or metabolic derangements and acute precipitating factors. Apart from this seizures are common in deep or penetrating brain or head injury, brain trauma and brain tumors. Cerebrovascular disease is the most commonly identified cause among adults, while preinatal insults seem to be most common among children.

Figure 3. Etiology of newly diagnosed epilepsy in India (22)

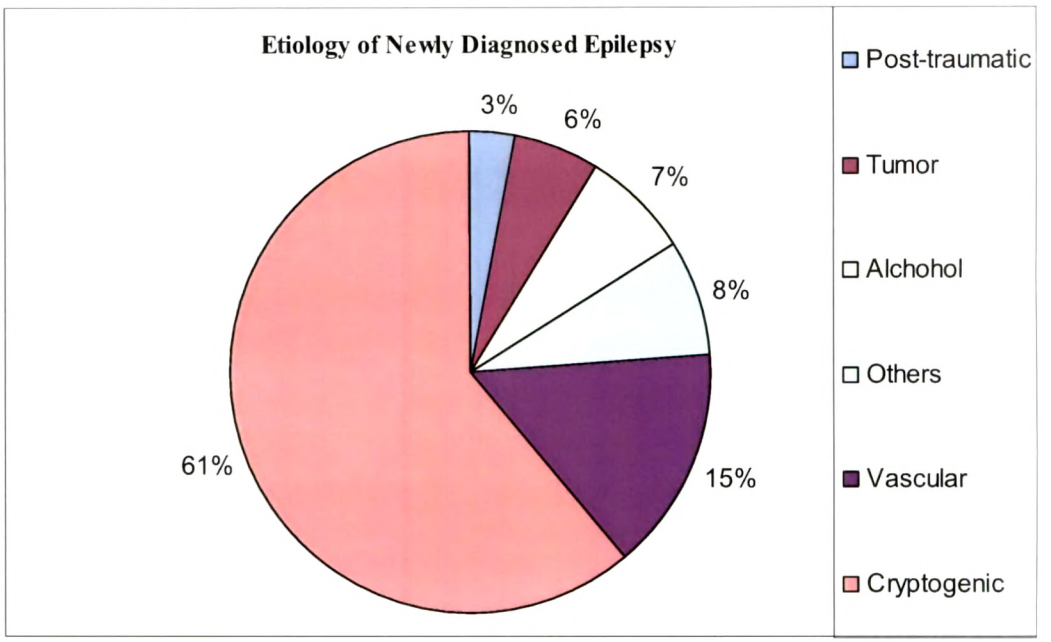


Figure 4. Distribution of types of seizures in a German clinic (1)

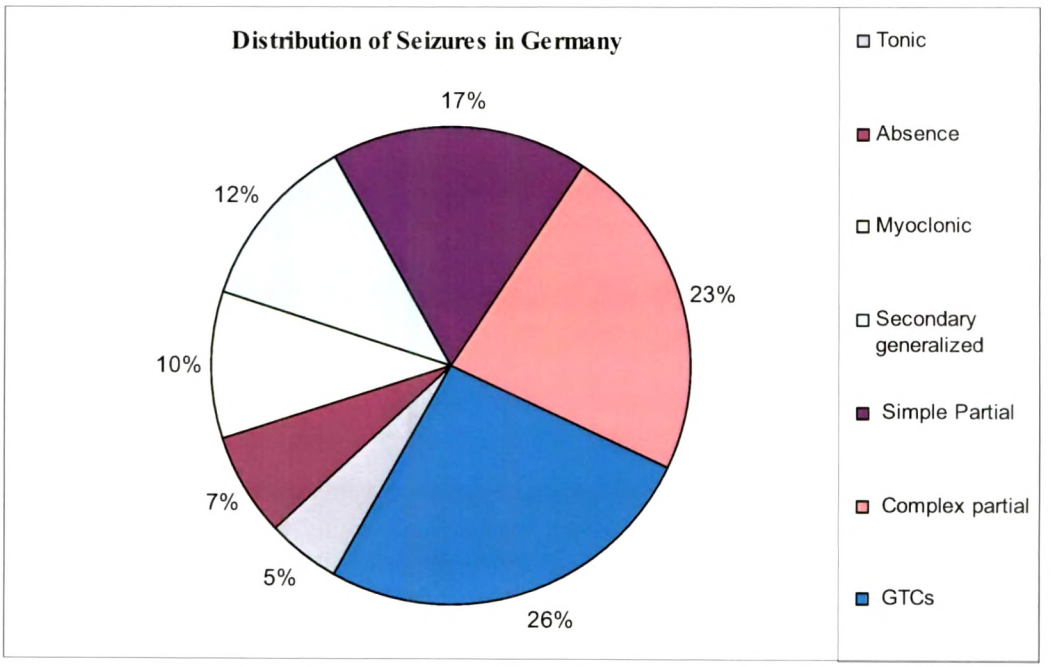
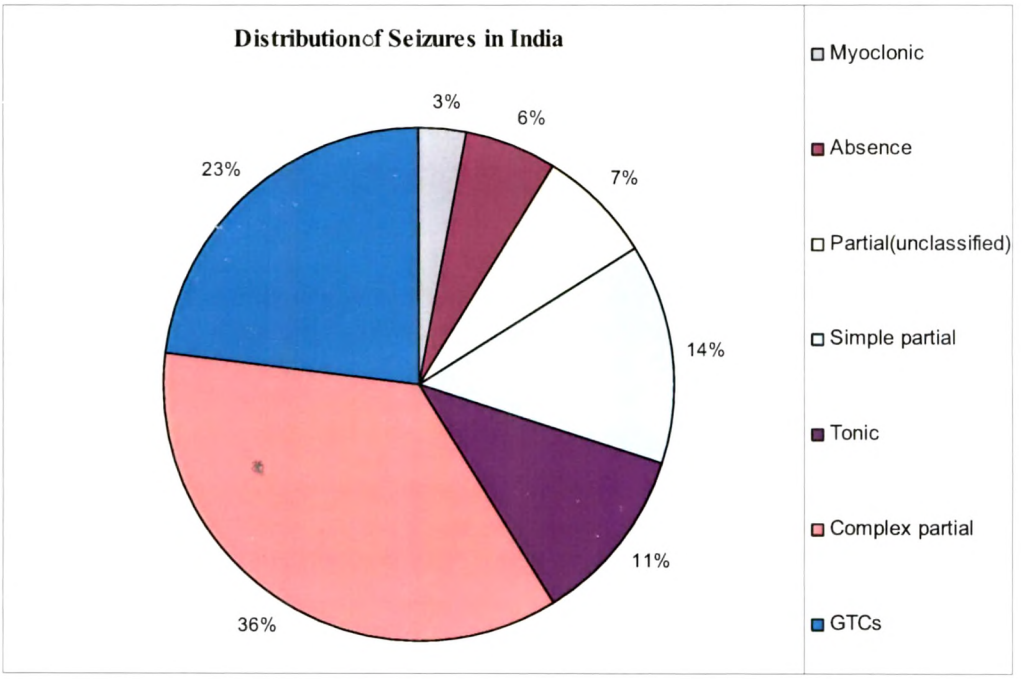


Figure 5. Distribution of types of seizures in India (21)



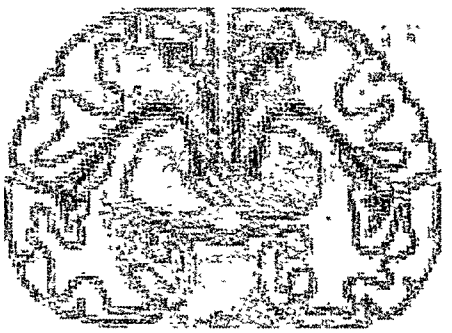
TYPES OF SEIZURES

Neurologists have described more than 30 different types of seizures. Seizures are divided into two major categories – *partial seizures* and *generalized seizures*. However, there are many different types of seizures in each of these categories. An overview on distribution of types of seizure in a European country and in India is given in Figs 4, 5.

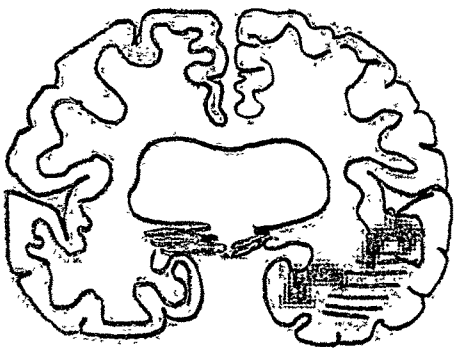
The International classification of epileptic seizures is proposed by the *Commission on Classification and Terminology of ILAE* (1989) and reviewed recently (22). This classification is based on the clinical expression of the seizure and the electroencephalographic picture during and between the seizures.

In the *partial seizures* the abnormal electrical discharges start in a localized area of the brain (Figure 6). The symptoms/signs are dependent on which part of the brain is affected. These discharges may remain localized, or they may spread to other parts of the brain and then the seizures become generalized (secondary generalized seizures). In *generalized seizures*, on the other hand, the seizure is generalized from the onset (i.e., primary generalized seizures), starting in both hemispheres of the brain simultaneously (Figure 6).

Figure 6. Generalized seizure (A), epileptic discharge affects both hemispheres; in partial seizures epileptic discharge is localized in one area of the brain(B).



[A]



[B]

As EEG does not available often or possible to help in making this division, we are completely dependent on the clinical expression: the medical history, and the ability of the observer to describe the seizure. The patient himself has no memory of the seizure, except in simple partial seizures and only of the *aura* of other seizures. A definite *aura* is an indication that the seizure is of focal (partial) onset. During his lifetime, a patient does not necessarily have only one type of seizure. The proportion of incidence cases according to seizure type of shown in Fig 3.

PARTIAL SEIZURES

The partial seizures are first divided into two groups, those where the consciousness is maintained, and where there is an impairment of the consciousness. Both these groups may develop into generalized seizures, then forming a third group.

Simple partial seizures

The patient does not lose consciousness, and therefore is able to tell what happened, but the experience may be so strange that he may not be able to express himself properly (Figure 7). What happens is dependent on the location of the affected area.

In *motor* seizures, the focus is in the primary motor cortex. There are twitchings, starting in a distal part of the extremity, or in the face. The twitching may remain there, or spread up the whole extremity and even become completely generalized. The spreading is called

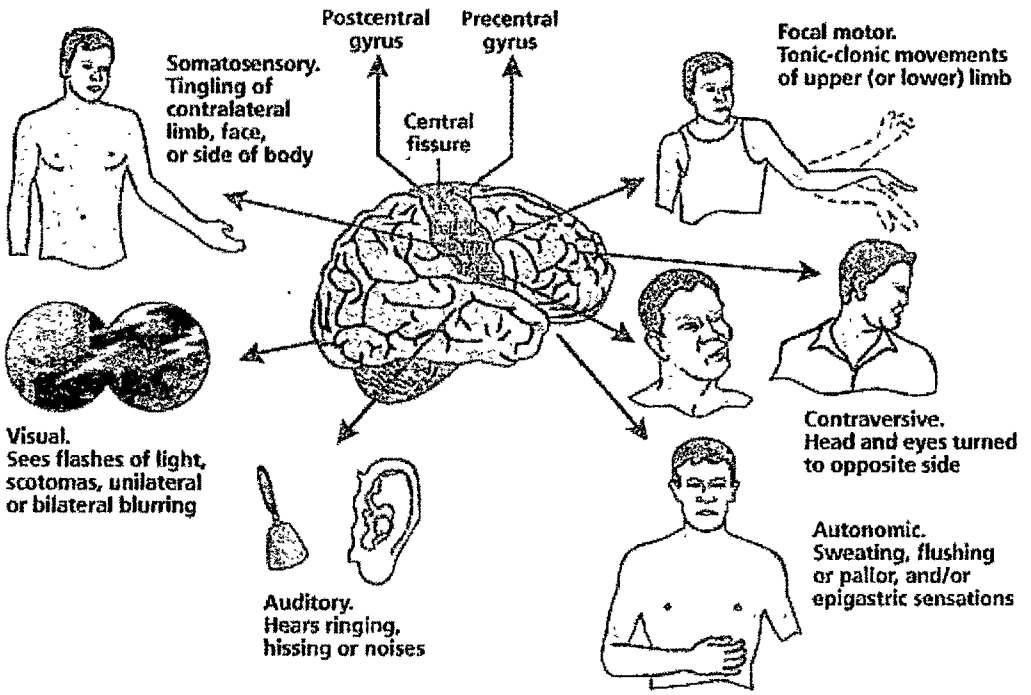
a Jacksonian march (named after Huglings Jackson 1835 - 1911). The *sensory* seizures have their focus in the post central gyrus (primary sensory cortex). There might be feelings of tingling, pins and needles, cold or heat, or numbness of a limb. Sometimes there may be strange feelings with visual signs, or hearing or smelling sensations. The *autonomic* seizures are associated with foci in the temporal lobe. There maybe: a sensation rising from the epigastrium to the throat, palpitations, sweating or flushing. The *psychic* symptoms may consist of changes in mood, memory, or thought (thinking). There may be distorted perceptions (time, space, or person) or problems with language. Structured hallucinations could occur (music, scenes). These simple partial seizures are usually only recognized as epileptic seizures when they develop into generalized seizures.

Complex partial seizures

Here the patient has impaired consciousness, there is no complete loss of consciousness, he is slightly aware of what is going on, but he cannot respond to anything, neither can he change his behavior during an attack (Figure 8). There is an aura, a strange feeling in the stomach rising up to the throat and head, or a sensation of light, smell, sound or taste. The seizure may occur with changes in perception, e.g. of time (time seems to pass too slowly or too fast), of light or sound or space. The surroundings may suddenly seem completely strange and different in scale (things seem larger or smaller than usual), or there is *déjà vu*. These feelings can cause the patient a great deal of anxiety. Sometimes the seizure occurs with hallucinations or with psychomotor symptoms such as automatisms, automatic movements. There is a slow recovery after a complex partial seizure, with a

period of confusion. After the attack there is complete amnesia of it. These seizures were previously called *'psychomotor seizures'*, and as the localization of the abnormal

Figure 7. Simple partial seizures.

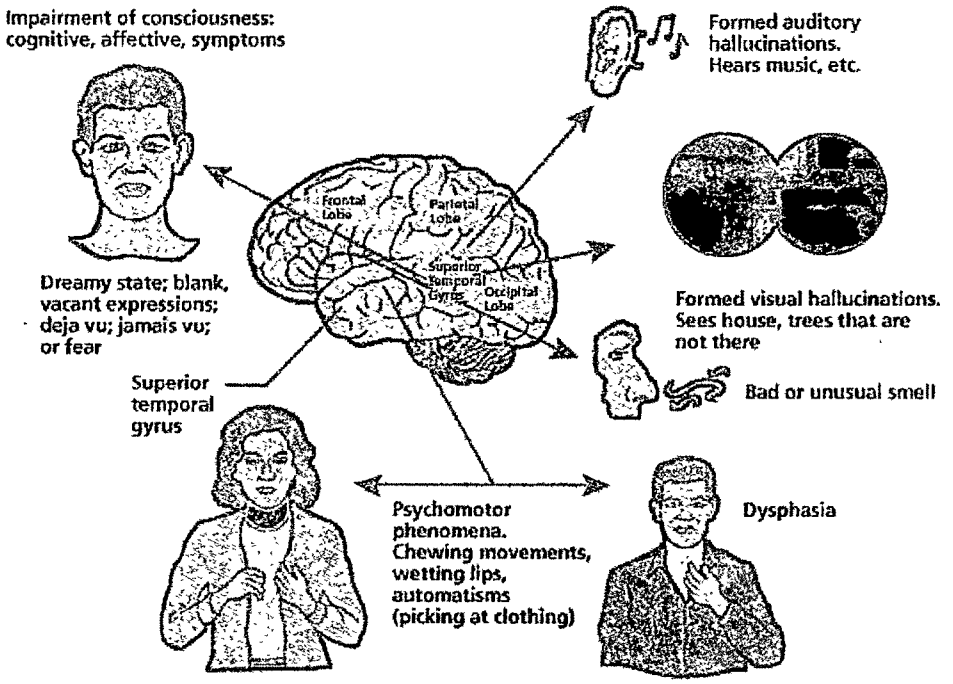


discharge is often in the temporal lobe, the epilepsy is often called *'temporal lobe epilepsy'* (the focus might occur in the frontal lobe too).

Partial seizures secondary generalized

Both the simple partial seizures and the complex partial seizures may become generalized tonic-clonic seizures. The beginning is as described above, but they end alike the primary generalized tonic-clonic seizures as described below.

Figure 8. Complex partial seizures.



GENERALIZED SEIZURES

The primary generalized seizures are characterized by a complete loss of consciousness and the absence of an aura (Figure 9). They come on suddenly and unexpectedly, and if the patients fall, they may injure themselves. The generalized seizures consist of six different seizure types; of which the primary generalized tonic-clonic seizure (GTCS) is the most common.

Absence seizures

These are short periods of loss of consciousness lasting only a few seconds (not more than half a minute). They are of sudden onset, there are usually no, or only minimal motor manifestations. There is a blank stare, brief upward rotation of the eyes, and an interruption of ongoing activity (Figure 10). The child is unresponsive when spoken to. It is suddenly over, and the child continues what he was doing before the seizure came. The child has no memory of these seizures. Typical absences occur in school-aged children, during childhood because of *Childhood Absence Epilepsy*, and in adolescence because of *Juvenile Absence Epilepsy.* They occur many times a day. During such an absence seizure the child does not hear what the teacher is saying, and as they occur so often the child cannot follow the lessons any more. Most parents are unaware of these small seizures, and even when they observe them, do not think them important and will not mention them to the doctor. Unless these children also suffer from generalized tonic-clonic seizures they are not brought to a clinic, and especially not to an epilepsy clinic, as people are unaware that these absences are epileptic seizures.

Figure 9. Three major phase (A, B, C) in Generalized tonic-clonic seizures (GTCS).

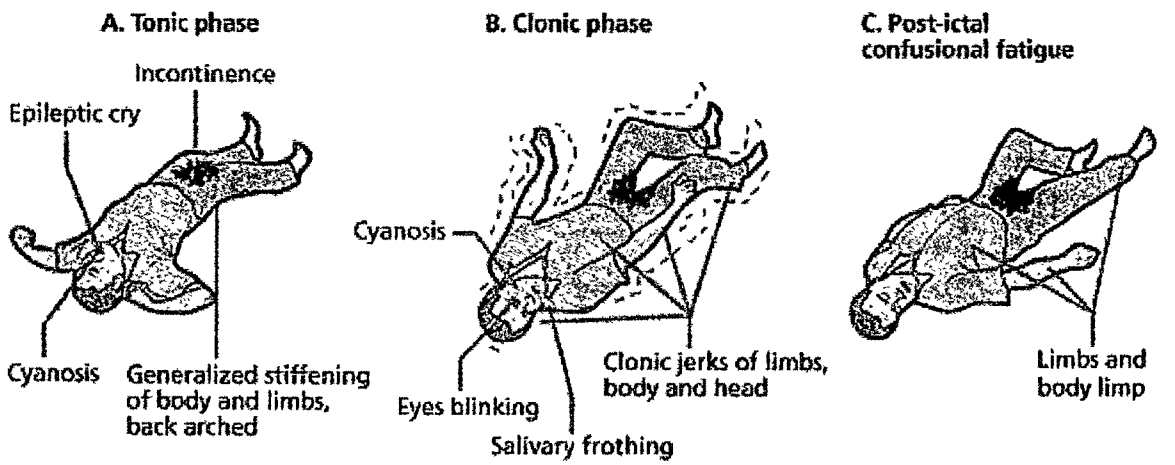
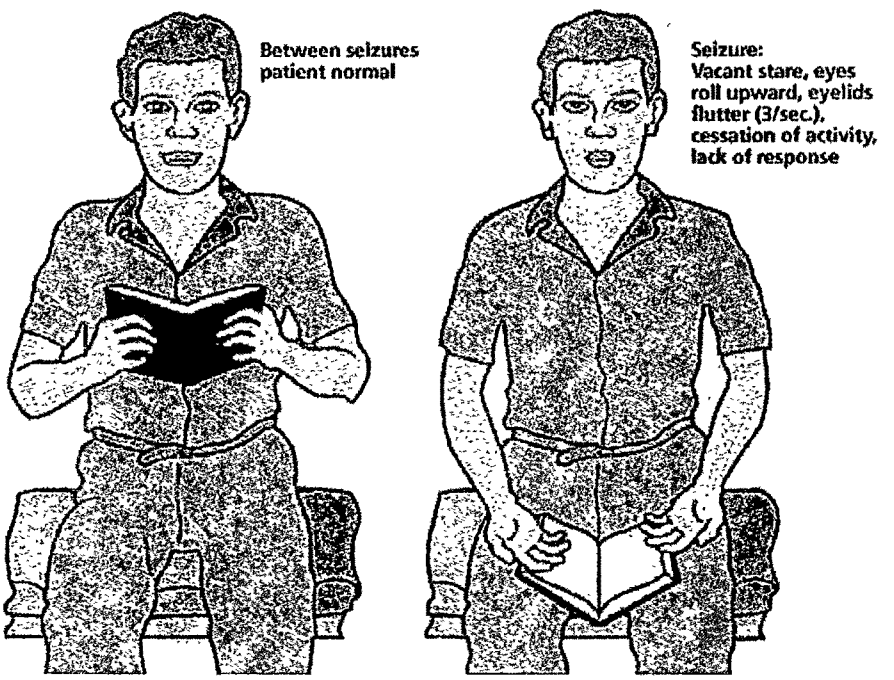


Figure 10. Absence seizures.



A child with absence seizures may, in addition, have other types of seizures, such as primary GTCS, or myoclonic seizures. Previously, these seizures were called *petit mal* seizures, or pyknolepsy (because they occurred so frequently).

Myoclonic seizures

These seizures consist of sudden, brief, shock-like muscle contractions, either occurring in one limb, or more widespread and bilateral. They may be single jerks, or jerks repeated over longer periods. They are often seen in combination with other seizure types occurring in special epileptic syndromes.

Clonic seizures

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive rhythmic flexing and stretching of limbs). When the frequency diminishes the amplitude of the jerks do not.

Tonic seizures

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is immediate loss of consciousness. Often there is a deviation of the eyes and head towards one side, sometimes rotation of the whole body. They are seen mainly in pediatric practice.

Tonic-clonic seizures (GTCS)

The majority of the patients (70–80%) present with *generalized tonic-clonic seizures* (*GTCS*). This is a new name for what were previously called "*grand mal*" (French for the big illness) seizures. As shown in Fig. 9, the patient loses consciousness, falls down, sometimes with a scream, and develops a generalized stiffness (the tonic phase). Breathing stops, as all the muscles of the trunk are in spasm, and the patient becomes cyanotic, the head is retracted, the arms flexed and the legs extended. After a while, this tonic phase is followed by the clonic phase, when the muscles alternately contract and relax, resulting in clonic movements. With this jerking the patient might bite his tongue, pass urine, or sometimes stool. The clonic phase may last several minutes. When all the jerking stops and the patient regains consciousness, he may feel very tired with a headache and confusion. He has no memory of what happened, and may find himself on the floor in a strange position. Often he falls into a deep sleep. These seizures are not as frequent as absence seizures. Their frequency may vary from one a day to one a month or once a year, or even once every few years. Generalized tonic-clonic seizures can occur in generalized epilepsies and in partial epilepsies. To distinguish the two they are called primary or secondary generalized. Primary GTCS occur without any warning, i.e., they are not preceded by an aura or other partial seizure. Secondary GTCS occur in partial epilepsies and are always preceded by an aura or other partial seizure; however, the generalization may be so rapid that the preceding seizures are not noticed. This type of seizure is not seen in the newborn period or infancy.

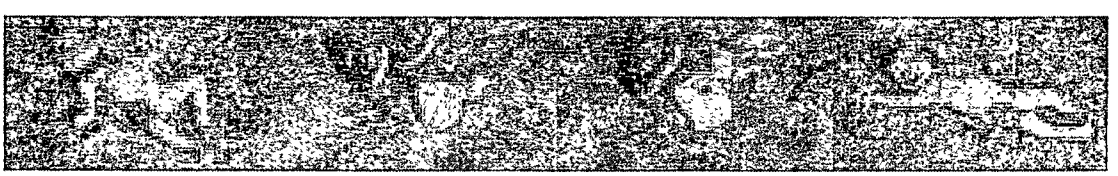
Atonic seizures (astatic seizures)

There is a sudden loss of muscle tone causing the head or a limb to drop, and often the patient falls suddenly to the floor. They are therefore also called "drop attacks". There is loss of consciousness, a sudden onset and no post-ictal phase. The patient stands up and continues what he was doing. The seizure is very short, only seconds, but may occur several times a day. The patients often present with scars or fresh wounds on chin, cheek or forehead, or the back of the head. A protective helmet is recommended for these patients to prevent fatal accidents. Sometimes these patients may have, in addition to atonic seizures, absence or myoclonic seizures.

Infantile spasms

Before 1981, *infantile spasms* were seen as one of the seizure types. In the present classification they are classified under the generalized syndromes. They are flexor spasms of the head, bending of the knees and flexion with abduction of the arms (Figure 11). They occur in the first year of life, and are very difficult to treat. ACTH or prednisolone is the drug of choice.

Figure 11. Infantile spasms.



STATUS EPILEPTICUS

A status epilepticus occurs whenever a seizure persists for at least 30 minutes, or is repeated so frequently that recovery between attacks does not occur (23, 24). A status is a medical emergency and the patient should be transferred to a clinic where, with i.v. injections the status could be stopped as quickly as possible. It is a dangerous condition, which may result in brain damage (cerebral necrosis) related to calcium induced excitotoxicity (24) with severe morbidity or death. A status may be the patient's first epileptic event, or may be precipitated by suddenly discontinuing anticonvulsant therapy.

Unclassified epileptic seizures

This category includes all seizures, which cannot be classified because of inadequate or incomplete data, or seizures that defy classification in the categories as presently defined.

DIAGNOSIS

The diagnosis of epilepsy remains difficult in many patients. As discussed earlier, careful history including witness' account of the episode is critical. It is only in the last decade that clinical neuroscientists have been able to look directly at the structure and function of the living human brain (25-33).

This has been through the use of:

- Magnetic resonance imaging (**MRI**) has enabled the majority of structural brain abnormalities responsible for epileptic seizures to be visualized.
- Positron emission tomography (**PET**) and single photon emission computed tomography (**SPECT**) could help pinpoint an epileptic region by looking at localized dysfunction in brain blood flow, metabolism and chemical processes during and between seizures.
- Computerized electroencephalography (**EEG**) and magneto-encephalography (**MEG**) can readily locate the sites of origin of epileptic discharges.
- Magnetic resonance spectroscopy (**MRS**) is also being used to non-invasively identify areas of brain damage as well as disturbances in brain metabolism and neurotransmitter function.

Although MEG and MRS remain experimental diagnostic tools, most of these techniques are being used in epilepsy centers in developed countries not only for research but also for evaluation of people who may benefit from brain surgery as treatment for intractable, drug resistant forms of the disease. Indian Council of Medical Research (**ICMR**) broadly encourages research in this line. **KEM** and **Bombay hospitals** (Mumbai), **NIMHANS** and **TIFR / NCBS** (Banglore), **AIIMS** (New Delhi) are the centers to name a few.

Blood tests

The blood samples are often screened for metabolic or genetic disorders that may be associated with seizures. They also may be used to check for underlying problems such a infections, lead poisoning, anemia, and diabetes that may be causing or triggering the seizures (1).

Developmental, Neurological and Behavioral Tests

Doctors often use tests devised to measure motor abilities, behavior, and intellectual capacity as a way to determine how the epilepsy is affecting that person. These tests also can provide clues about what kind of epilepsy the person has (1).

TREATMENT GAP

Treatment gap is defined as the percentage of persons with active epilepsy who are not receiving treatment. The treatment gap in underdeveloped countries ranges from 70 to 94% with and average of 80%. It is estimated that about 3 million persons with epilepsy living in rural areas of India are not receiving any treatment (34-37). Indeed it is this knowledge that has resulted in the ILAE and WHO Global Campaign Against Epilepsy. The treatment gap has further been refined. Absolute treatment gap may be used to describe the number of people who are not diagnosed at all and hence the question of therapy does not arise. Surgical treatment gap may be used to measure the proportion of people with intractable epilepsy, who might benefit from surgery, yet do not have it. The reasons for treatment gap include failure to identify persons with epilepsy; failure to

deliver treatment to identified persons with epilepsy; knowledge, attitude and practices (Cultural Epidemiology) of the people, and the cost of antiepileptic drugs (38).

Misconceptions about epilepsy form the greatest barrier to treatment of persons with epilepsy. In a study from one of the most literate states of India, 27% thought that epilepsy is a form of insanity! **In many societies, epilepsy is still considered a curse of God and people do not seek help from doctor.** People often use two or more systems of healing at the same time, both allopathic and traditional. The treatment gap may be narrowed by better identification of persons suffering from epilepsy, better delivery of treatment and education of public.

TREATMENT: Antiepileptic drugs

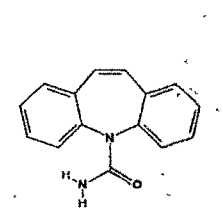
Before the antiepileptic (antiseizure) drugs (AEDs) were discovered and developed, treatment of epilepsy consisted of trephining, cupping and the administration of herbal medicines and animal extracts. In 1857, Sir Charles Locock reported the successful use of potassium bromide in the treatment of what is now known as catamenial epilepsy. In 1912, Phenobarbital was first used for epilepsy, and in the next 25 years, 35 analogs of Phenobarbital were studied as anticonvulsants (39).

In 1938, phenytoin (PHT) was found to be effective against experimental seizures in cats. Between 1935 and 1960, tremendous strides were made both in development of experimental models and in methods for screening and testing new antiseizure drugs (39). In 1968, carbamazepine (CBZ) was approved, initially for the treatment of trigeminal neuralgia; later, in 1974, it was approved for partial seizures. Ethosuximide has been used since 1958 as a first-choice drug for the treatment of absence seizures without generalized tonic-clonic seizures. Valproate was licensed in Europe in 1960 and in the United States in 1978, and now is widely available throughout the world. It became the drug of choice in primary generalized epilepsies and in the mid 1990s was approved for treatment of partial seizures. These anticonvulsants were the mainstays of seizure treatment until the 1990s, when newer AEDs with good efficacy, fewer toxic effects, better tolerability, and no need for blood level monitoring were developed (39). The new AEDs have been approved in the United States as add-on therapy only, with the exception of lamotrigine, which is approved for conversion to monotherapy. However, a series of new compounds became available in the 1990s. In practice *conventional* as well as *newer generation* AEDs are being used, either alone (mono-therapy) or in combination (add-on therapy), for the treatment of different class of seizures (39), Figure 12.

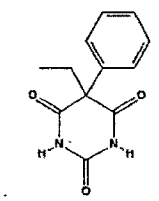
The AEDs can be grouped according to their main mechanism of action, although many of them have several actions and others have unknown mechanisms of action. The main groups include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, hormones, and drugs with unknown mechanisms of action (39).

Figure 12. Structure of some commonly used AEDs (40)

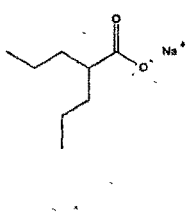
Carbamazepine



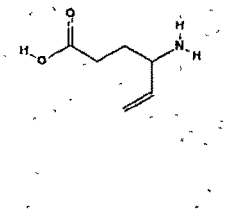
Phenytoin



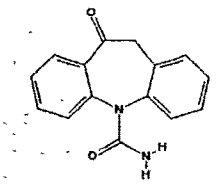
Na-valproate



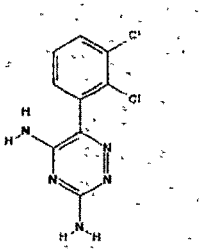
Vigabatrin



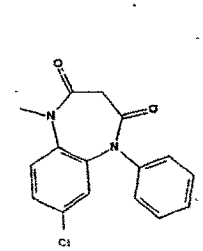
Oxacabazepine



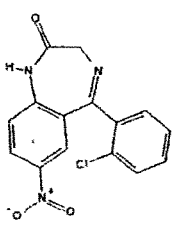
Lamotrigine



Clobzam



Clonazepan



Felbamate

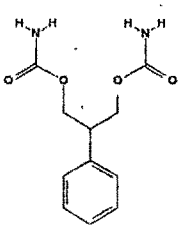
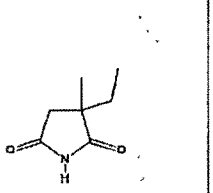
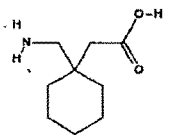


Fig 12. (Cont.)

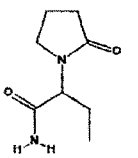
Ethosuximide



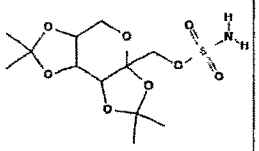
Gabapentin



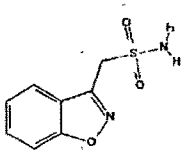
Levetiracetam



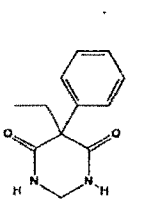
Topiramate



Zonisamide



Primidone



AEDs that target sodium channels prevent the return of these channels to the active state by stabilizing the inactive form of these channels. In doing so, repetitive firing of the axons is prevented. AEDs that inhibit these calcium channels are particularly useful for controlling absence seizures. GABA is produced by decarboxylation of glutamate mediated by the enzyme glutamic acid decarboxylase (GAD). Some drugs may act as modulators of this enzyme, enhancing the production of GABA and down-regulating glutamate. Some AEDs function as an agonist to this mode of chloride conductance by blocking the reuptake of GABA (i.e. tiagabine) or by inhibiting its metabolism mediated by GABA transaminase (i.e. vigabatrin), resulting in increased accumulation of GABA at the postsynaptic receptors. Most importantly, AEDs that block the action of excitatory neurotransmitter glutamate action to its receptor serve as antagonists. Inhibition of the enzyme carbonic anhydrase increases the concentration of hydrogen ions intracellularly and decreases the pH. The potassium ions shift to the extracellular compartment to buffer the acid-base status. This event results in hyperpolarization and an increase in seizure threshold of the cells. Acetazolamide has been used as an adjunctive therapy in refractory seizures with catamenial pattern (i.e. seizure clustering around menstrual period). Topiramate and zonisamide also are weak inhibitors of this enzyme; however, this is not believed to be an important mechanism for their antiseizure efficacy.

Sodium channel blockade is the most common and the well-characterized mechanism of currently available AEDs. AEDs that target these sodium channels prevent the return of the channels to the active state by stabilizing the inactive form. In doing so, repetitive

firing of the axons is prevented. The presynaptic and postsynaptic blockade of sodium channels of the axons causes stabilization of the neuronal membranes, blocks and prevents posttetanic potentiation, limits the development of maximal seizure activity, and reduces the spread of seizures. A brief description of some most commonly used conventional and new generation AEDs is given below.

Carbamazepine

Carbamazepine (CBZ) is a major first-line AED for partial seizures and generalized tonic-clonic seizures (39-54). It is a tricyclic compound and initially was used primarily for the treatment of trigeminal neuralgia, but its value in the treatment of epilepsy was discovered quite by chance. The main mode of action of CBZ is to block sodium channels during rapid, repetitive, sustained neuronal firing and to prevent posttetanic potentiation. It has been approved in the United States for the treatment of epilepsy since 1974. However, it has been used for epilepsy since 1968.

Pharmacokinetics

CBZ is a crystalline substance that is insoluble in water, which limits the route to oral administration. Because it is an unstable substance, care must be taken to protect it from hot or humid conditions, which decrease its bioavailability by 50%. Approximately 75-85% of the drug is plasma protein bound, and it has a free fraction of 20-24% of the total plasma concentration. The cerebrospinal fluid (CSF) levels ranges between 17% and 31%. It is metabolized extensively in the liver and induces its own metabolism. The major metabolic pathway is epoxidation to CBZ 10,11-epoxide and hydrolysis to CBZ 10,11-*trans*-dihydrodiol.

Because CBZ induces its own metabolism, causing an increase in clearance and a decrease in levels, the serum half-life decreases by 50% during the first few weeks of treatment. The elimination half-life ranges from 5-26 hours following repeated treatment in healthy volunteers and patients with epilepsy. In children, the half-life ranges from 3-32 hours. Its induction of hepatic cytochrome P-450 system activity also increases the metabolism of other AEDs. Peak levels of the drug are present in the blood for 4-8 hours. Formulations that are available include suspension, syrup, tablets (100 mg, 200 mg, 400 mg), chewable tablets (100 mg, 200 mg), extended release capsules (Tegretol XR; 100 mg, 200 mg, 400 mg), Carbatrol (200 mg, 300 mg), and rectal suppositories.

Antiepileptic effect and clinical use

CBZ is one of the most widely used AEDs in the world. It is highly effective for partial onset seizures, including cryptogenic and symptomatic partial seizures. It also has demonstrated good efficacy in the treatment of generalized tonic-clonic seizures. The drug is highly effective and well tolerated. The major disadvantages of this drug are transient adverse dose-related effects when initiating therapy and occasional toxicity.

Side effects and toxicity

CBZ can produce dose-related adverse effects, which include dizziness, diplopia, nausea, ataxia, and blurred vision. Rare idiosyncratic adverse effects include aplastic

anemia, agranulocytosis, thrombocytopenia, and Stevens-Johnson syndrome. Asymptomatic elevation of liver enzymes is observed commonly during the course of therapy in 5-10% of patients. Rarely, severe hepatotoxic effects can occur.

Drug interactions

Several drugs, such as macrolide antibiotics (erythromycin and clarithromycin), isoniazid, chloramphenicol, calcium channel blockers, cimetidine, and propoxyphene, inhibit the hepatic enzyme cytochrome P-4503A4 (CYP3A4), which is responsible for the metabolic breakdown of CBZ, thereby raising its levels. Phenobarbital, phenytoin, felbamate, and primidone also lower its levels through CYP3A4. Toxic symptoms or breakthrough seizures may occur if the dose of CBZ is not adjusted. Grapefruit juice and St. John's wort are inducers of CYP3A4 and can decrease CBZ levels.

CBZ induces the metabolism of tricyclic antidepressants, oral contraceptives, cyclosporin A, and warfarin. Any drug that is metabolized by the hepatic enzyme CYP3A4 will have reduced levels since CBZ induces this enzyme.

CBZ still is one of the most widely used AEDs. The extended-release preparations, Tegretol XR (Novartis) and Carbatrol (Shire), are better tolerated than the immediate-release preparations.

Lamotrigine

Lamotrigine (LTG) is a triazine compound that is chemically unrelated to any of the other AEDs (39-53, 55, 56). It was developed as an antifolate agent based on a theory that the mechanism of some AEDs is related to their antifolate property. It was approved in the United States in 1994. Its major mechanism of action is blocking voltage-dependent sodium-channel conductance. It has been found to inhibit depolarization of the glutaminergic presynaptic membrane, thus inhibiting release of glutamate. It has a weak antifolate effect that is unrelated to its antiseizure efficacy.

Pharmacokinetics

On oral administration, LTG has a bioavailability close to 100%, reaching peak levels within 1-3 hours and achieving a volume of distribution of 0.9-1.3 L/kg. Its solubility is poor in both ethanol and water; therefore, it is not available in parenteral form. Protein binding is 55% and the elimination half-life is 24-41 hours. It is metabolized by the liver and excreted through the kidneys. It produces auto-induction at higher doses and has no active metabolites.

Drug interactions

LTG levels increase with concomitant use of valproate to 70 hours. It does not induce or inhibit hepatic enzymes; therefore, it does not affect the metabolism of lipid-soluble drugs such as warfarin and oral contraceptives. Conversely, drugs that induce hepatic

enzymes may reduce the half-life of LTG from 23 hours to 14-16 hours. LTG levels must be adjusted accordingly.

Antiepileptic effect and clinical use

LTG's significant effect on seizures as compared to placebo was demonstrated in 9 of 10 placebo-controlled trials in which LTG was administered as add-on therapy. LTG resulted in a 17-59% reduction in seizures, with most trials showing 25-30% median reduction in seizures. It is effective in partial onset and secondarily generalized tonic-clonic seizures, primary generalized seizures (ie, absence seizures and primary generalized tonic-clonic seizures), atypical absence seizures, tonic/atonic seizures, and Lennox-Gastaut syndrome. It is sometimes effective for myoclonic seizures, but can cause worsening of myoclonic seizures in some patients with juvenile myoclonic epilepsy or myoclonic epilepsy of infancy. It currently is approved in the United States for adjunctive therapy for partial onset and secondarily generalized tonic-clonic seizures, crossover to monotherapy, and Lennox-Gastaut syndrome.

The dose regimen and titration schedule depends on co-administration of other AEDs, the titration rate being slower with enzyme-inhibiting AEDs such as valproate than with enzyme-inhibiting AEDs such as PHT and CBZ. Preset packages are available with the recommended doses of LTG, with and without valproate. In children on valproate, the starting dose of LTG is 0.15 mg/kg, with increments every 1-2 weeks up to a maximum of 1-5 mg/kg. In patients taking concomitant enzyme inducers, the starting dose is 0.6 mg/kg, up to a maximum of 5-15 mg/kg. It is available in tablets

(25 mg, 50 mg, 100 mg, 150 mg and 200 mg) and chewable tablets (5 mg, 25 mg, 100 mg); it is administered twice a day.

Adverse effects and toxicity

Different from most AEDs, LTG produces few CNS side effects. Rash is the main concern associated with this drug. It occurs in 5% of patients and is associated with rapid titration. Severe rash (more common in children taking valproate) may develop and lead to Stevens-Johnson syndrome, which may be fatal, but this is rare (0.1%). Other commonly reported adverse reactions are headache, blood dyscrasias, ataxia, diplopia, GI disturbance, psychosis, tremor, hypersensitivity reactions, somnolence, and insomnia. The International Lamotrigine Pregnancy Registry Update reported 414 monotherapy exposures, giving a risk of 2.9% (57). This compares with risks of 2-3% in the general population.

LTG is a very effective and well-tolerated drug. Combination therapy with valproate enhances the antiepileptic effect; however, it also increases the chances of developing allergic skin reactions. Very slow titration is important for better tolerability. The excellent side-effect profile and lack of significant CNS toxicity make this drug one of the preferred choices in treating elderly patients. The reported low incidence of congenital malformations when exposed to pregnant patients makes this drug one of the preferred treatments during pregnancy.

Clobazam

This benzodiazepine has a 1,5 substitution instead of the usual 1,4-diazepine. This change results in an 80% reduction in its anxiolytic activity and a 10-fold decrease in its sedative effects. It has been licensed in Europe since 1975 but is not available in the United States. In addition to its agonist action at the GABA-A receptor, clobazam may affect voltage-sensitive conductance of calcium ions and the function of sodium channels (39-53).

Pharmacokinetics

Clobazam is relatively insoluble in water; therefore, no IV or IM preparations are available. Its oral bioavailability is about 90%. Time to peak plasma concentrations (T_{max}) is 1-4 hours. Absorption rate is decreased when taken with meals, but total absorption is not affected. Plasma protein binding of clobazam is approximately 83% with the proportion of bound to unbound drug independent of clobazam concentration. Very low plasma protein levels are associated with increases in the unbound (ie, free) fraction, for example, in renal or hepatic disease. Brain and saliva concentrations are proportional to the unbound fraction. A good correlation exists between dosage and plasma levels; significant interindividual variations exist.

Clobazam is metabolized by oxidation in the liver to norclobazam (*N*-desmethylclobazam). This metabolite has a very long half-life (ie, 50 h), but it has a

low affinity for the benzodiazepine receptor, and its antiepileptic effect is unclear. The elimination half-life usually is in the range of 10-50 hours. Norclobazam is conjugated in the liver and excreted in the bile as glucuronate and in the urine as sulfate. The clobazam plasma level is 20-350 ng/mL. Norclobazam levels typically are 10 times higher than clobazam levels at usual clinical dosage.

Drug interactions

No significant clinical interactions are reported. Minor interactions are common.

Antiepileptic effect and clinical use

Clobazam is a potent anticonvulsant for partial epilepsy. No double-blind, controlled studies have been reported, but the trials performed showed a striking benefit. In one study, the mean reduction of seizures was 50% in more than 50% of patients. These patients had partial epilepsy and were taking other AEDs. In one Canadian study in drug-naive children, clobazam monotherapy was found to be as effective as CBZ

or PHT.

The major clinical problem of this drug is the development of tolerance; sedation tolerance is more evident than antiepileptic tolerance. No clear correlation between

plasma levels and seizure control has been found. No measures have been effective against the development of tolerance. The anxiolytic effect (mild) may be beneficial for some patients. It is effective in a wide range of epilepsies and should be considered as adjunctive therapy. It can be used in patients with Lennox-Gastaut syndrome or primary or secondarily generalized seizures. Clobazam is administered orally at a dose 10-20 mg per day, taken at night or twice daily. No parenteral preparations are available.

Adverse effects and toxicity

Essentially, the adverse effects are similar to those of other benzodiazepines. The most common effect is sedation. Other adverse effects include dizziness, ataxia, blurred vision, diplopia, irritability, depression, muscle fatigue, and weakness. Idiosyncratic reactions are very rare and no fatal reactions have been reported so far.

Clobazam is useful in intermittent treatments (eg, catamenial epilepsy) and as prophylaxis for some situations, such as traveling, celebrations, and other occasions.

Phenytoin

Since its introduction in 1938, phenytoin (PHT) has been a major first- line AED in the treatment of partial and secondary generalized seizures (39-53, 58). It blocks movements of ions through the sodium channels during propagation of the action

potential, and therefore blocks and prevents posttetanic potentiation, limits development of maximal seizure activity, and reduces the spread of seizures. It also demonstrates an inhibiting effect on calcium channels and the sequestration of calcium ions in nerve terminals, thereby inhibiting voltage-dependent neurotransmission at the level of the synapse. An antiepileptic effect also is seen on calmodulin and other secondary messenger systems, the mechanisms of which are unclear. The adverse-effect profile (eg, gingival hyperplasia and coarsening of the facial features in women) makes its use less desirable than CBZ in some patients.

PHT is one of the most commonly used first-line or adjunctive treatments for partial and generalized seizures, Lennox-Gastaut syndrome, status epilepticus, and childhood epileptic syndromes. It is not indicated for myoclonus and absence seizures. One disadvantage of this drug is that it causes CNS and systemic adverse effects. The long-term use of PHT has been associated with osteoporosis; therefore, it must be used with caution in susceptible populations and routine screening must be performed to detect the condition early. CNS effects occur particularly in the cerebellum and the vestibular system, causing ataxia and nystagmus. It is not a generalized CNS depressant; however, some degree of drowsiness and lethargy is present, without progressing to hypnosis. Nausea and vomiting, rash, blood dyscrasias, headaches, vitamin K and folate deficiencies, loss of libido, hormonal dysfunction, and bone marrow hypoplasia are among the most common adverse effects. When given during pregnancy, PHT, like other AEDs, can cause cleft palate, cleft lip, congenital heart disease, slowed growth rate, and mental deficiency in the offspring.

Oxcarbazepine

Oxcarbazepine (OXC) is a recently developed analog of CBZ (59, 60). OXC was developed in an attempt to hold on to the benefits of CBZ while avoiding its auto-induction and drug interaction properties. Licensed in over 50 countries, including the United States, OXC now is considered one of the first-line therapies in some countries. OXC does not produce the epoxide metabolite, which is largely responsible for the adverse effects reported with CBZ. Like CBZ, OXC blocks the neuronal sodium channel during sustained rapid repetitive firing (61).

Somnolence, headache, dizziness, rash, hyponatremia, weight gain, GI disturbances, and alopecia are the most commonly reported adverse effects. The allergic rash is similar to the one caused by CBZ. Dose-related adverse effects include fatigue, headache, dizziness, and ataxia. Hyponatremia is mild and can be corrected by fluid restriction. Hyponatremia is uncommon in children younger than 17 years, but it occurs in 2.5% of adults and 7.4% of the elderly (62). Idiosyncratic reactions appear to be less common than with CBZ.

Zonisamide

Zonisamide (ZNS) was synthesized as a benzisoxazole in 1974. It is chemically unrelated to any of the other AEDs (63-65, 67). It is a small ringed structure related to sulfonamide antibiotics with pH-dependent solubility in water. Although ZNS was approved by the US Food and Drug Administration (FDA) in March 2000 for the

indication of partial seizures in patients older than 12 years as adjunctive therapy to other AEDs, it has been approved and studied in Japan for more than 10 years. The major mechanism of action of ZNS is reduction of neuronal repetitive firing by blocking sodium channels and preventing neurotransmitter release. It also exerts influence on T-type calcium channels and prevents influx of calcium. ZNS also exhibits neuroprotective effects through free radical scavenging.

ZNS has been approved for adjunctive therapy for patients with partial seizures who are 12 years or older. It is preferred clinically because of the ease of patient tolerance, degree of seizure reduction, long half-life, and lack of drug interactions with other AEDs. ZNS provides dose-dependent, effective, and generally well-tolerated adjunctive therapy in patients with partial seizures.

The most commonly reported adverse reactions to ZNS are dizziness, anorexia, headache, ataxia, confusion, speech abnormalities, mental slowing, irritability, tremor, and weight gain. Gradual titration of the drug appears to reduce the manifestations of adverse reactions. Somnolence and fatigue have been reported frequently. ZNS is associated with renal stones in 1.5% of patients; therefore, the risk in patients with a history of renal stones needs to be weighed against the therapeutic benefits of the medication. This drug should not be used in patients who are allergic to sulfonamides.

Clonazepam

Clonazepam, a 1,4-substituted benzodiazepine, is one of the first benzodiazepines used for epilepsy. Clonazepam has higher affinity for the GABA-A receptor site than diazepam and binds to GABA-A receptors that do not bind with other benzodiazepines. It may have some action on sodium-channel conductance (39-53).

Clonazepam is a potent AED and the drug of choice for myoclonic seizures and subcortical myoclonus. It also is effective in generalized convulsions and, to a lesser extent, in partial epilepsies. It rarely is used as adjunctive treatment of refractory epilepsy because of its sedative effect and tolerance, which are similar to those of other benzodiazepines. It is very effective in the emergency treatment of status epilepticus, like diazepam, and can be given IV or rectally. Withdrawal from clonazepam may induce status epilepticus or exacerbation of seizures. Psychiatric withdrawal also may occur, manifested as insomnia, anxiety, psychosis, and tremor. The major adverse effect is sedation, even at low doses. Children can tolerate this medication much better than adults; therefore, pediatricians use it most often. Clonazepam has the typical adverse effects of benzodiazepines (eg, ataxia, hyperactivity, restlessness, irritability, depression, cardiovascular or respiratory depression). Children and infants may have hypersalivation. Occasionally, tonic seizures may be exacerbated. Idiosyncratic reactions are rare and include marked leukopenia.

Phenobarbital

This is the most commonly prescribed AED of the 20th century. It is a very potent anticonvulsant with a broad spectrum of action (39-53, 66). Currently, its use is limited because of its adverse effects. It is a free acid, relatively insoluble in water. The sodium salt is soluble in water but unstable in solution. It has a direct action on GABA-A receptors by binding to the barbiturate-binding site that prolongs the duration of chloride channel opening. It also reduces sodium and potassium conductance and calcium influx and depresses glutamate excitability.

In a multicenter double-blind study, Phenobarbital (PHB) was found to be as effective as PHT and CBZ in the treatment of partial and secondarily generalized seizures. The Veterans Administration (VA) cooperative study, however, comparing PHB, primidone, PHT, and CBZ, showed a significantly lower retention in patients on PHB or primidone despite their similar efficacy, because of poorer tolerability. No statistical difference was reported between PHT and CBZ. PHB is effective in a wide variety of seizures and is currently the cheaper AED. Although PHB effectiveness is not questioned, it is a second-line drug because of its adverse effects such as sedation and cognitive slowing.

The most important adverse effects are cognitive and behavior alterations. Children are more likely than adults to exhibit behavioral changes (ie, paradoxical hyperkinesis). Sedation is prominent, particularly at the beginning of therapy, and

usually subsides. Psychomotor slowing, poor concentration, depression, irritability, ataxia, and decreased libido are other effects. Long-term use of PHB may be associated with coarsening of facial features, osteomalacia, and Dupuytren contractures. Folate deficiency, megaloblastic anemia, and idiosyncratic skin reaction are rare. Vitamin supplementation is warranted. Hepatitis has been reported secondary to an immune-mediated process.

Valproate

Valproate (VPA) is the drug of choice for primary generalized epilepsies, and is also approved for the treatment of partial seizures (39-53, 68-70). It was discovered by accident; first synthesized in 1882, its antiepileptic properties were recognized when it was used as a solvent for the experimental screening of new antiepileptic compounds. It was licensed in Europe in the early 1960s, where its use became extensive. It has been used in different forms, including divalproex sodium, magnesium or calcium salt, or valpromide. These forms do not differ significantly. The mechanism of action is uncertain. VPA enhances GABA function, but this effect is observed only at high concentrations. It may increase the synthesis of GABA by stimulating GAD. It also produces selective modulation of voltage-gated sodium currents during sustained, rapid, repetitive neuronal firing.

VPA is a potent AED, effective against a wide range of seizure types. It is the drug of choice in idiopathic generalized epilepsy. Open and comparative studies have shown excellent control rates in patients with newly diagnosed typical absence seizure. It is

the drug of choice for juvenile myoclonic epilepsy and can be used in other types of myoclonus. Also, it is a first-line drug in photosensitive epilepsy and Lennox-Gastaut syndrome. It is a second choice in the treatment of infantile spasms. In focal epilepsy, VPA has been shown to be as effective as other first-line agents. VPA is one of the most commonly used AEDs around the world.

Based on clinical experience, dose-related adverse effects include nausea, vomiting (mainly during initiation of therapy and improved by administration of enteric-coated preparations), tremor, sedation, confusion or irritability, and weight gain. Metabolic effects from interference in mitochondrial metabolism include hypocarnitinemia, hyperglycinemia, and hyperammonemia. Severe sedation or even coma may result from hyperammonemia, typically with normal liver function tests. Patients with an underlying urea cycle enzyme defect may become encephalopathic from acute hyperammonemia, which may be fatal occasionally.

Vigabatrin

In the 1970s, GABA was recognized as an important inhibitory neurotransmitter in the CNS (39-53, 71). Favoring the balance toward the GABA system was a major target of drug research, and soon vigabatrin (VGB) was developed. The drug was licensed worldwide, except in the United States because of its toxicity. It is a close structural analog of GABA, binding irreversibly to the active site of GABA-T. Newly synthesized enzymes take 4-6 days to normalize the enzymatic activity. In vivo

studies in human and animal subjects have shown that VGB significantly increases extracellular GABA concentrations in the brain. VGB has no other known action. VGB is less effective against primarily generalized tonic-clonic seizures and also may worsen myoclonic seizures or generalized absence seizures.

The most common adverse effect is drowsiness. Other important adverse effects include neuropsychiatric symptoms, such as depression (5%), agitation (7%), confusion and, rarely, psychosis. Minor adverse effects, usually at the onset of therapy, include fatigue, headache, dizziness, increase in weight, tremor, double vision, and abnormal vision (72). VGB has little effect on cognitive function. Acute hypersensitivity or idiosyncratic immunological adverse effects are extremely rare. Unfortunately, because of this drug's toxicity, its use is restricted. It has not been approved by the US Food and Drug Administration (FDA) because of its adverse visual effects.

Topiramate

Topiramate is a very potent anticonvulsant. It is structurally different from other AEDs (73, 74). It is derived from D-fructose and initially was developed as an antidiabetic drug. In animal models, it was found to have potent antiepileptic effects. Topiramate has multiple mechanisms of action. It exerts an inhibitory effect on sodium conductance, decreasing the duration of spontaneous bursts and the frequency

of generated action potentials, enhances GABA by unknown mechanisms, inhibits the AMPA subtype glutamate receptor, and is a weak inhibitor of carbonic anhydrase.

Topiramate also has been effective in drug-resistant generalized epilepsies as adjunctive therapy, including juvenile myoclonic epilepsy, absence and generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. In the United States, it currently is approved for (1) partial onset and secondarily generalized tonic-clonic seizures, (2) primary generalized tonic-clonic seizures, and (3) Lennox Gastaut syndrome.

The most common adverse effects of topiramate include ataxia, impairment of concentration, confusion, dizziness, fatigue, paresthesia in the extremities, somnolence, disturbance of memory, depression, agitation, and slowness of speech. If the drug is continued, many adverse effects subside within a few weeks (75).

PRESENT STUDIES

Repeated seizure episodes during epileptic attack lead to hyper-synchronous discharges from neurons that may cause structural and functional changes in plasma and subcellular membranes as well. Brain damage during seizure episodes is related to increased intracellular Ca^{2+} levels, which has an important role in the regulation of diverse spectrum of cellular events as well as in epileptogenesis (76). Additionally, intense seizure activity is reported to be associated with inhibition of microsomal Mg^{2+},Ca^{2+}-ATPase mediated Ca^{2+} uptake and deregulation of Ca^{2+} homeostasis (77, 78). Induction and progression of seizures and maintenance of essential electrolyte balance are critically dependent on the membrane function. Alterations in neurotransmitter concentrations in synapse (79-82), reduced plasma membrane Na^{+},K^{+}-ATPase activity, cellular pH and residual ATP content in subcellular fractions and lysosomal dysfunction in rat brain have also been reported in some animal models of epilepsy (83-86). Cellular metabolic parameters along with neurotransmitter imbalances are well established in the epileptic condition (87). Damage to cellular and subcellular functions are not only limited to the cerebral structures during seizures (88-90) but it could also aggravate in to peripheral system like blood plasma, RBCs, fibroblasts, muscle fibers etc. (91-93).

Understanding the mechanism of action of AEDs is important in clinical practice so that they can be used effectively, especially in multi-drug regimens. As discussed in neuronal physiology above, many structures and processes are involved in the development of a seizure, including neurons, ion channels, receptors, glia, and

inhibitory and excitatory synapses. The AEDs are designed to modify these processes to favor inhibition over excitation in order to stop or prevent seizure activity.

Number of reports from last few decades indicates that AEDs may directly or indirectly modulate the neurotransmitter levels and ion channel functioning (39, 94). For example, CBZ has been shown to reduce high frequency repetitive firing in neocortical and hippocampal pyramidal neurons (95-97), depress post tetanic potentiation (98), reduce synaptic transmission in spinal cord (99) and in thalamus (100), modifies the metabolism of GABA, monoamines, adenosine receptors (101) and modulate extracellular serotonin concentration (102). LTG, topiramate and gabapentin are shown to be interacting with K-ion currents (103). PHB, diazepam and LTG alters the seizure triggering-threshold in the kindling focus of rat hippocampus (104).

Interestingly, besides being used as antiepileptics these drugs have emerged as potential agents for the treatment of other neuropsychological disorders (105), e.g. CBZ and VPA for bipolar disorders, schizophrenia and peripheral neuropathy (106-108), LTG for effective management of cluster headache and refractory affective disorder (109-111) and CLB against psychosomatic stress and anxiety (95, 112-113). When used for the management of the aforementioned disorders (95, 105-113) it is likely that the actions of the AEDs may be mediated by modulating the cellular / subcellular functions as well. In fact studies with conventional AEDs indicated cellular effects with respect to energy metabolism in CNS (114-119). Valproic acid

and its metabolites are reported to induce cytotoxicity by altering fatty acid metabolism, mitochondrial transmembrane potential and modulating antioxidant system in liver (120-122). On the other hand neuroprotective action of topiramate is directly related to its inhibitory effect on the mitochondrial permeability transition pore (123). Diazepam and Phenobarbital treatment lead to structural and functional alterations in mitochondrial and other subcellular membrane in liver (124, 125)

Therefore, it is clear from the foregoing reports that: what leads to specific form of epilepsy is still not well understood. Nevertheless, an extensive survey of the studies carried out so far in humans as well as in animals reveals some metabolic and functional abnormalities. In spite of this, only few investigations have been carried out to evaluate the basic biochemical defects underlying epilepsy at subcellular levels. The effects of AEDs on GABA, glutamate and amine neurotransmitters and receptor binding activities have been reported, although, in depth biochemical investigations to evaluate their action and/or effects at subcellular levels are lacking.

Cerebral work directly in human subjects is impracticable. Most AEDs were discovered through screening in animal models (126-128). For practical reasons, rodents (rats, mice and Mongolian gerbils) are the most commonly used species, although many mammalian species—including dogs and primates—experience seizures and their brain architecture and physiology are arguably closer to that of humans (126, 127). Epileptic seizures can be studied by the use of various chemical epileptogens such as kainic acid, picrotoxin (PTX), pentylenetetrazole, bicuculine

etc., electrically kindled and genetic models like photosensitive baboons, DBA/2J, E1 and totterer mice, genetically epilepsy prone rats (GEPRs) etc. (127). Exposure to PTX is known to induce generalized tonic-clonic seizures in the rats. Chronic tonic-clonic seizures are established after 20 day exposure to PTX (129). PTX binds to the chloride channel and benzodiazepine binding site of $GABA_A$ receptor complex in the brain (129, 130). As a consequence, non-competitive inhibition of synaptic GABA transmission results in generalized tonic-clonic convulsions (129, 130).

The present study was focused to elucidate biochemical mechanism(s) underlying epilepsy. The studies were carried out to decipher the possible defects at subcellular membrane systems – mitochondria and lysosomes – and to check whether these defects are corrected by the AEDs viz. Carbamazepine (CBZ), Lamotrigine (LTG) and Clobazam (CLB). Studies reported in the present thesis have been carried out in brain tissue of picrotoxin (PTX) induced epileptic model of rat. Parallel studies were also carried out on liver – major metabolic and detoxification organ – that served as internal control. Given below is the brief account on lysosomes and mitochondria.

Lysosomes

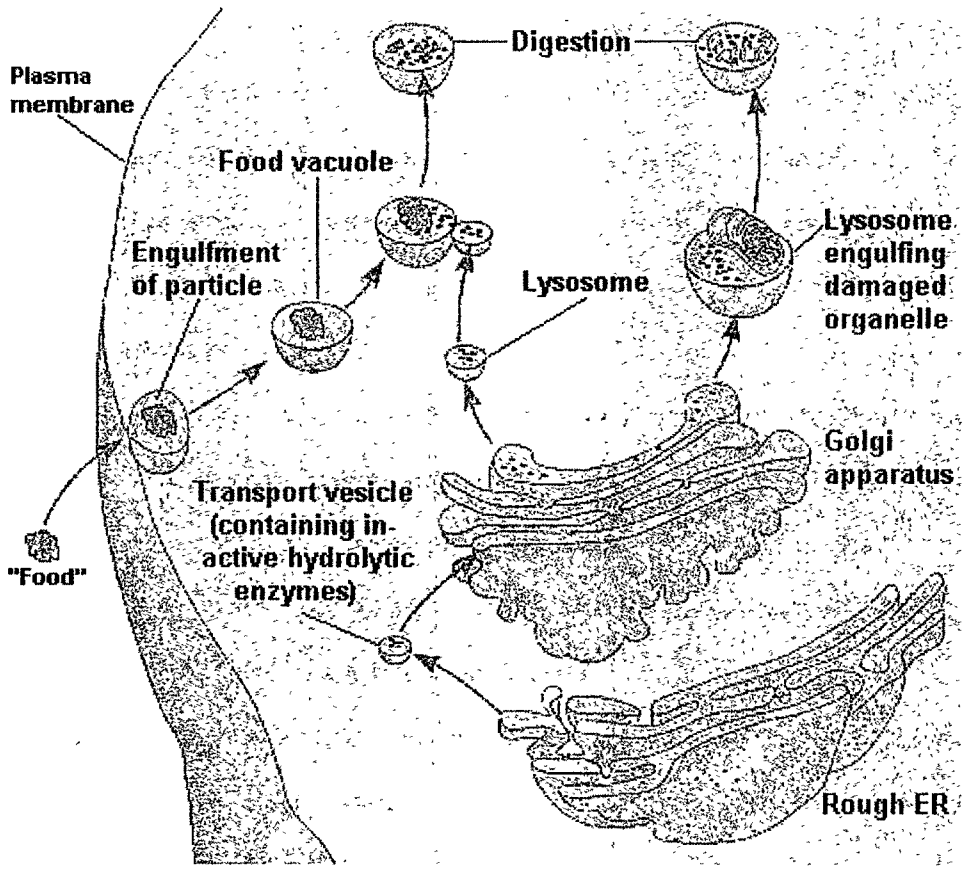
Discovered in 1950 by Rene de Duve, a lysosome is a tiny organelle found in all eukaryotic cells. The lysosomes are more or less the "demolition crew" of a cell. They digest macromolecules such as monosaccharides, protein, neucleotides and break down damaged or old cell parts as well as bacteria. Each lysosome is surrounded by

its own membrane due to the acidic conditions within it. They contain about 70 different types of hydrolytic enzymes that break down whatever is necessary (131). These enzymes are only active within the acidic membrane of the lysosome so that in case of leakage or rupture, the enzymes will not be active within the cell.

Lysosomes are formed off of the membrane of the trans-golgi. Lysosomal membrane contains 20-35% of total lysosomal protein (132) Presence of cholesterol, sphingomyelin and N-acetyl neuraminic acid is typical of lysosomal membranes (131-133) Materials to be digested reach the enzymes through endocytosis, where a macromolecule is taken into the cell by an endosome (Figure 13). The lysosome then fuses with the membrane of the endosome and begins to break down the macromolecule (133). In a process called autophagocytosis, an old or damages organelle are enveloped by endosomes and then fused to lysosomes. Phagocytosis is the process where extra cellular particles such as bacteria, are engulfed in the cell and then fused to lysosomes for digestion (Fig 13).

There are very few reports that suggests role of lysosomes in epileptic condition. Interestingly, it has been reported that in cobalt epilepsy the acid phosphatase activity in rat brain was significantly elevated (134). By contrast, in the skin biopsy samples and in the leukocytes from epileptic patients the arylsulfatase A activity was decreased (135, 136). In kainate evoked seizures, the levels of cathepsin D mRNA in rat brain were found to be elevated (137). These reports are thus the suggestive of the possible lysosomal dysfunctions in epilepsy. Studies with respect to lysosomal function in the epileptic condition is detailed in Chapter 7 of thesis.

Figure 13. Endocytosis, phagocytosis and autophagocytosis functions of lysosomes



four respiratory chain (RC) complexes, complex V (ATP-synthase), ubiquinone and CAT-II (138, 141). Substrate transport via the IM is quite selective and it is permeable only for unloaded molecules like O_2, CO_2 and H_2O. There are carriers for anions, redox equivalents and cations (138). Altogether, 14 carriers are known so far. Among these are those for aspartate/glutamate, phosphate, pyruvate etc (138). Within the inter membrane space reside the adenylate kinase, the mitochondrial carnitine-phosphokinase, the deafness dystonia protein (DDP1/TIM8A), and cytochrome c (cyt c), which initiates apoptosis if release to cytosol.

Matrix

Within the matrix a large no. of enzymes and other proteins and peptides, including RC complexes, DNApol, chaperones (heat shock protein), mRNAs, tRNAs and mitochondrial DNA (mtDNA) are located.

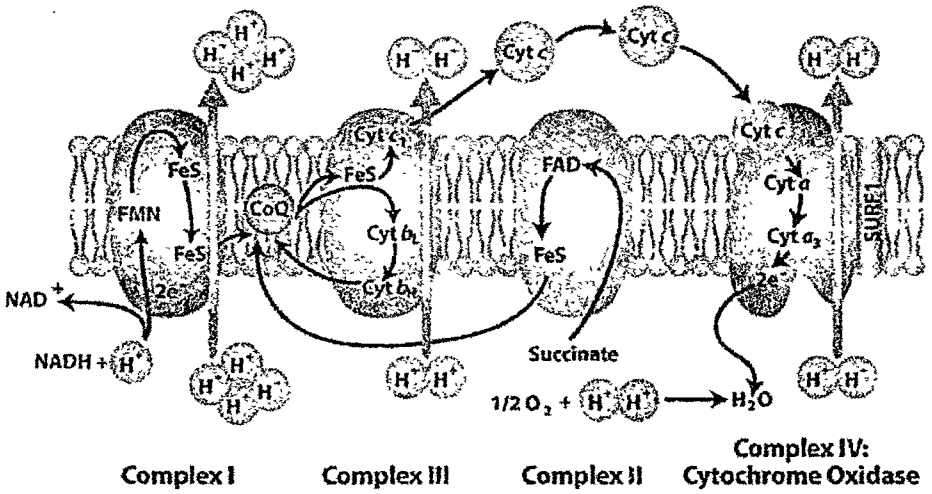
Function of mitochondria

Mitochondria serve four fundamental biological roles: (i) provision of ATP, (ii) mediation of cell death by apoptosis (138-142), (iii) heat production, and (iv) contribution to human genetics. In addition mitochondria harbor the beta-oxidation, TCA cycle, degradation of amino acids, parts of haem-biosynthesis, parts of steroid metabolism, parts of the uric acid cycle, mitochondrial protein synthesis, and the pyruvate dehydrogenase (PDC) complex, responsible for the decarboxylation of pyruvate.

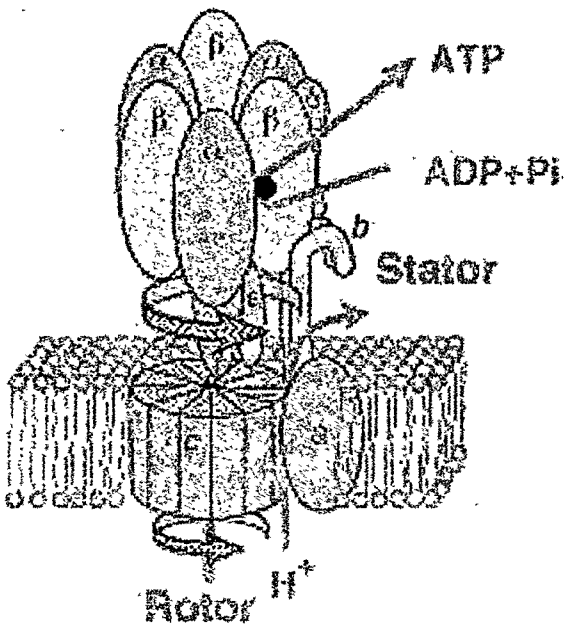
Mitochondrial respiratory chain and ATP production

The principle function of mitochondrion is to produce energy in the form of ATP, which is achieved via the PDC, citrate cycle, beta-oxidation, EC and oxidative phosphorylation (oxphos) (140). Fatty acids, pyruvate and amino acids are transferred from the cytosol into mitochondrion where they are metabolized to acetyl-CoA, which is further metabolized through the TCA cycle. Electrons from the TCA cycle then enter the RC (Fig 14). The core of RC and oxphos pathway are five multi-subunit complexes I-V (143). RC and oxphos are built up of 83 polypeptides of which 70 are encoded by nuclear DNA (nDNA) and 13 by mtDNA. The 13 mtDNA-encoded proteins compromise <5% of crucial mitochondrial proteins (e.g. Cytochrome oxidase). Electons from various substrates pass along the chain, providing energy to pump protons across the IM from matrix via complexed I, III and IV into the intermembrane space (Fig 14). (138, 143). Per molecule NADH, 10 protons and per molecule succinate, six protons are pumped to the intermembrane space (138). The electrochemical proton gradient thus established derives the ATP generation via complex V (143) also known as F_oF_1ATPase (Fig 14). The transfer of electons within a complex is affected by flavones, iron/sulphus centres, cytochromes and copper centres (138). The electron producing substrates glutamate, pyruvate and hydroxybutyrate enter the EC at complex I, succinate at complex II, and fatty acids at both, complex I and the electron transfer protein, coupled to ubiquinone (coenzyme Q) (140, 143). CoQ shuttles electrons from complexes I and II to complex III. From complex III electrons are passed to complex IV (cytochrome oxidase, COX) by cyt c, and intermembrane protein Complex V (Fig 14) allows protons to flow back into the matrix, using the released energy to synthesize ATP (145).

Figure 14. Mitochondrial respiratory chain and $FoF_1ATPase$



Mitochondrial Respiratory Chain



Fo F1 ATPase

Apoptosis

There is ample evidence that mitochondria play an important role in apoptosis. A series of events are associated with this process: opening of permeability transition pore, release of cyt c into cytosol, binding of cyt c to Apaf-1 that complexes with caspasse-9 to initiate the caspase-cascade, terminating in apoptototic cell death (138, 143, 144). Activated caspases kill cells by cleaving critical cell repair and homeostatic proteins as well as cytoskeletal proteins. Caspase-independent apoptotic cell death is mediated by the release of the apoptosis-inducing factor, a flavo-protein stored in the intermembrane space and released in response to DNA damage, oxidative stress or exocytoxic stress (146, 147).

Heat production

Decoupling of oxphos leads to the production of heat (thermogenesis). It is particularly developed in brown adipose tissuesof newborns and hibernators (138). Uncoupling protein 1 (UCP 1), lipoprotein lipase and thermogenin are upreglated in this process (138).

Mitochondrial DNA

The human mitochondrion contains 5-10 identical, circular molecules of DNA (140, 143). Each consists of 16.6 Kbp carrying the information for 37 genes which encodes 2 different molecules of rRNA, 22 different molecules of tRNA and 13 polypeptides. The rRNA and tRNA molecules are used in the machinery that synthesizes the 13

polypeptides. They forms subunits of the protein complexed in the IM. Including subunits of NADH dehydrogenase, cyt c oxidase and ATP synthase. However, each of these protein complexes also requires subunits that are encoded by nuclear genes, synthesized in the cytosol and imported from the cytosol into the mitochondria (140, 143).

Mitochondria and epilepsy

There is accumulating evidence that epileptic seizures can occur as a presenting sign of mitochondrial dysfunction in the central nervous system (CNS). Generalized seizures have been observed in several forms of myoclonus epilepsy, which have been associated with mutations in the mitochondrial $tRNA^{Lys}$ (148, 149) and $tRNA^{Ser}$ genes (150, 151) Partial seizures are frequently noticed in mitochondrial encephalopathies, including the MELAS (mitochondrial encephalopathy with lactic acidosis and stroke like episodes) syndrome, associated with mutations in the mitochondrial $tRNA^{Leu}$ gene (152, 153). Nevertheless, mitochondrial cytopathies represented as the spontaneous or sporadic mutations on mtDNA and/or nDNA are shown to be associated with epileptic phenotype (143, 144). Since it has also been noticed that mitochondria are intimately involved in pathways leading to neuronal cell death (143, 144) as seen in experimental and human epilepsy, it is reasonable to assume a considerable role of mitochondrial dysfunction in epileptogenesis and in the development of at least a subclass of therapy resistant forms of epilepsy. A major part of this thesis is dedicated to decipher mitochondrial oxidative energy metabolism and membrane function in the chronic condition of generalized seizures in rats.

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