EPILEPSY

The term “epilepsy” is derived from Greek word “epilambanein” which means “to seize upon” or “to attack”. In this modern era, epilepsy is the most frequent neurodegenerative disease after stroke. Epilepsy, a common chronic neurological disorder characterized by recurrent unprovoked spontaneous seizures also known as seizure disorder (Blume et al., 2001). When nerve cells in the brain fire electrical impulses at a rate of up to four times higher than normal, this causes a sort of electrical storm in the brain, known as a seizure. A pattern of repeated seizures is referred to as epilepsy.

It is a disorder of the brain where brain cells create abnormal electricity that causes seizures with an overt symptom of ‘Jerking’ movements. These seizures are transient signs or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain, which results in strange sensations, emotions and behavior, convulsions, muscle spasms and a loss of consciousness.

Seizure also called as convulsion, fit, or spell and was known as the “Sacred Disease” because people thought that epileptic seizures were a form of attack by demons, or that the visions experienced by persons with epilepsy were sent by the Gods. It affects approximately 1-2% of population worldwide (Loscher, 2002). It affects more than 2 million Americans and 50 million people worldwide (Strine et al., 2005). Epilepsy begins anywhere between the ages of 3 and 14 years, and continues indefinitely (AllReferHealth-seizures (convulsions).html). The common feature of this disorder is a tendency for hyperexcitability to develop in one or other regions of central nervous system. There are likely to be multiple underlying cellular and molecular mechanisms responsible for various epileptiform phenomena (Rajendra et al., 2004).
On the other hand, it is well known that epilepsy or Seizures are linked with neurodegeneration in several areas of the brain (Wasterlain and Shirasaka, 1994; Jacobs et al., 2000, Armstrong, 2005).

Aberrant neuronal networks that develop abnormal synchronization of a group of neurons can result in the development and propagation of an epileptic seizure (Engel, 1989). The brain transmits and stores information somewhat like electrical circuitry. When abnormal electrical activity or a “short circuit” occurs in the brain seizure occurs. Such epileptic seizures are thought to occur via alterations in the behavior of neural networks in the brain that induce the spontaneous suppression of periods of synchronized burst firing interspersed by periods of normal electric activity (Dichter, 1997).

Although knowledge, attitude and beliefs towards epilepsy have improved in most countries, there is still misperception about the disorder. The epilepsy is among the most prevalent neurological diseases and affects about 1% of the population (MC Namara, 1999). Some epilepsies may be traced to development malformations (Schwartzkroin and Walsh, 2000) and some have a genetic component (Cooper & Jan, 1999; Kullmann, 2002). In fact physiological studies have provided rather little information; slices of human epileptic tissue rarely generate spontaneous epileptic form activities (Prince and Wong, 1981; Avoli et al., 1988; Masukawa et al., 1989: Williamson et al, 1995).

This abnormal electrical brain activity is transmitted to the rest of the body as incorrect signals, resulting in abnormal muscle activity (convulsion) (convulsions-eCure.com). Although the neurochemical basis of epilepsy is not completely understood, it has been well established that impaired GABAergic activity and/or exaggerated activity of glutamatergic neurotransmission are thought to contribute to the various types of epilepsies (Loscher and Schmidt, 2002). For the normal neurological
condition, the balance between the activity of inhibitory (GABA) and excitatory (aspartate and glutamate) neurotransmitters are very important (Meldrum, 1986). Recent studies on human epileptic tissue (Kohling et al 1998), described a spontaneous synchronous activity and presented intriguing evidence for a defect in GABAergic signaling. Glutamate and γ - Amino Butyric Acid (GABA) are the most abundant neurotransmitters in the central nervous system. The balance between excitatory and inhibitory neurons, basically the equilibrium between glutamatergic and GABAergic neurons, controls temporary neuronal synchronization. Alterations in voltage and receptor gated ion-channels, neurotransmitter release, uptake and receptor functions have also been implicated in experimental and human epilepsy (Martin et al., 2001). Common ictogenesis-related characteristics such as hyperexcitability, imbalance between excitatory and inhibitory neurotransmitters, alterations of synaptic function and synchronicity are common among all neuro-degenerative diseases including epilepsy (Mc Namara, 1999).

In addition to the neuronal loss other alterations such as gliosis, axonal and dendritic plasticity, neurogenesis and molecular reorganization of cell membranes and extracellular matrix also contribute to the etiology of epilepsy (Jutila et al., 2002).

Studies in several epileptic models have suggested direct links between cholinergic activation in the hippocampus and epileptogenesis (Aronstam et al., 1979). NMDA receptors play an important role in the expression of epilepsy (McNamara et al., 1993). There is also considerable evidence that voltage-gated current, toxin that prolong Na⁺ channel opening contribute to the generation of epileptogenic seizures (Garber and Miller, 1987).
CAUSES OF EPILEPSY

Brain function is made possible by millions of tiny electrical charges passing between nerve cells in the brain and to all parts of the body. Epilepsy interrupts this normal pattern of changes with excessive electric discharges of nerve cells (also known as neurons). This can affect a person's consciousness, movements of sensations for a brief period of time. The cause of an individual's epilepsy can be divided into two categories: symptomatic and idiopathic. If the seizures have a known cause, the condition is referred to as secondary or symptomatic or acquired epilepsy (Sun et al., 2001). Some seizures have no identifiable cause called idiopathic. More common potential causes of epilepsy (Annegers et al., 1996) include the following.

- Brain tumors, CNS infections like meningitis, encephalitis, and neurosyphilis.
- AIDS and other immune disorders.
- Traumatic brain injury, stroke.
- Chemical imbalance such as low blood sugar or sodium.
- Toxic chemicals or drugs.
- Prenatal insults, degenerative disorders like Alzheimer's, Parkinsonism, Diabetes, kidney failure, uremia, nutritional deficiency, inborn errors of metabolism, alcoholism, withdrawal from drugs particularly barbiturates and benzodiazepines etc.

The diagnosis of epilepsy usually requires that the seizures occur spontaneously. Nevertheless, certain epilepsy syndromes require particular precipitants or triggers for seizures to occur. These are termed reflex epilepsy. For example, patients with primary reading epilepsy have seizures triggered by reading. Photosensitive epilepsy can be limited to seizures triggered by flashing lights. Other precipitants can trigger an epileptic seizure in patients who otherwise would be susceptible to spontaneous seizures. For
example, children with childhood absence epilepsy may be susceptible to hyperventilation. In fact, flashing lights and hyperventilation are activating procedures used in clinical EEG to help trigger seizures to aid diagnosis. Finally, other precipitants can facilitate, rather than obligately trigger seizures in susceptible individuals. Emotional stress, sleep deprivation, sleep itself, heat stress, alcohol and febrile illness are examples of precipitants cited by patients with epilepsy. Notably, the influence of various precipitants varies with the epilepsy syndrome. Likewise, the menstrual cycle in women with epilepsy can influence patterns of seizure recurrence. Catamenial epilepsy is the term denoting seizures linked to the menstrual cycle. There are different causes of epilepsy that are common in certain age groups.

During the neonatal period and early infancy the most common causes include hypoxic-ischemic encephalopathy, CNS infections, trauma, congenital CNS abnormalities, and metabolic disorders. During late infancy and early childhood, febrile seizures are fairly common. These may be caused by many different things, some thought to be things such as CNS infections and trauma.

During childhood, well-defined epilepsy syndromes are generally seen. During adolescence and adulthood, the causes are more likely to be secondary to any CNS lesion. Further, idiopathic epilepsy is less common. Other causes associated with these age groups are stress, trauma, CNS infections, brain tumors, and illicit drug use and alcohol withdrawal. In older adults, cerebrovascular disease is a very common cause. Other causes are CNS tumors, head trauma, and other degenerative diseases which are common in the older age group, such as dementia.
TYPES OF EPILEPSY

There are over 40 different types of epilepsies, including: Absence seizures, atonic seizures, benign Rolandic epilepsy, childhood absence, clonic seizures, complex partial seizures, frontal lobe epilepsy, febrile seizures, infantile spasms, juvenile myoclonic epilepsy, juvenile absence epilepsy, hot water epilepsy, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, myoclonic seizures, mitochondrial disorders, progressive myoclonic epilepsy, psychogenic seizures, reflex epilepsy, Rasmussen's syndrome, simple partial seizures, secondarily generalized seizures, temporal lobe epilepsy, tonic-clonic seizures, tonic seizures, psychomotor seizures, limbic epilepsy, partial-onset seizures, Rett syndrome, generalized-onset seizures, status epilepticus, abdominal epilepsy, akinetic seizures, autonomic seizures, massive bilateral myoclonus, catamenial epilepsy, drop seizures, emotional seizures, focal seizures, gelastic seizures, Jacksonian seizure disorder, Lafora disease, motor seizures, multifocal seizures, neonatal seizures, nocturnal seizures, photosensitive epilepsy, pseudoseizures, sensory seizures, subtle seizures, Sylvan seizures, withdrawal seizures and visual reflex seizures, among others.

Each type of epilepsy presents with its own unique combination of seizure type, typical age of onset, EEG findings, treatment, and prognosis. The most widespread classification of the epilepsies divides epilepsy syndromes by location or distribution of seizures (as revealed by the appearance of the seizures and by EEG) and by cause. Syndromes are divided into localization-related epilepsies, generalized epilepsies, or epilepsies of unknown localization.

Localization-related epilepsies, sometimes termed partial or focal epilepsies, arise from an epileptic focus, a small portion of the brain that serves as the irritant driving the epileptic response. Generalized epilepsies, in contrast, arise from many independent foci.
(multifocal epilepsies) or from epileptic circuits that involve the whole brain. Epilepsies of unknown localization remain unclear whether they arise from a portion of the brain or from more widespread circuits.

Epilepsy syndromes are further divided by presumptive cause: idiopathic, symptomatic, and cryptogenic. Idiopathic epilepsies are generally thought to arise from genetic abnormalities that lead to alteration of basic neuronal regulation. Symptomatic epilepsies arise from the effects of an epileptic lesion, whether that lesion is focal, such as a tumor, or a defect in metabolism causing widespread injury to the brain. Cryptogenic epilepsies involve a presumptive lesion that is otherwise difficult or impossible to uncover during evaluation.

The genetic component to epilepsy is receiving particular interest from the scientific community. Conditions such as ring chromosome 20 syndromes are gaining acknowledgment, and although only 60 cases have been reported in the literature since 1976. Some epileptic syndromes are difficult to fit within this classification scheme and fall in the unknown localization/etiology category. People who only have had a single seizure, or those with seizures that occur only after specific precipitants ("provoked seizures"), have "epilepsies" that fall into this category. Febrile convulsions are an example of seizures bound to a particular precipitant. Landau-Kleffner syndrome is epilepsy which, because of its variety of EEG distributions, falls uneasily in clear categories. More confusingly, certain syndromes, such as West syndrome, featuring seizures such as infantile spasms can be classified as idiopathic, syndromic, or cryptogenic depending on cause and can arise from either focal or generalized epileptic lesions.
Epilepsy is classified into three main types

**Idiopathic:** where there is no apparent cause, but it is possible that there may be a genetic link. 60% of people with epilepsy have Idiopathic epilepsy.

Idiopathic epilepsy or primary generalized epilepsy is a tendency to have seizures when there is no structural abnormality in the brain. The primary cause could be genetic and a number of genes have been mapped.

The annual incidence of new cases of epilepsy after infancy is 20-70/100,000. The recurrence rate after a first seizure approaches 70% during the first year and more recurrent attacks occur within a month or two of the first seizure. Dermatoglyphics, the study of fingerprints are constant and individualistic. Abnormalities in the epidermal ridges may result from genetic alterations occurring around the first trimester, during organogenetic period, between 13th-60th days after fertilization. On this basis, it has been opined that any epidermal ridge alterations in individuals prone to epilepsy may have a distinctive dermatoglyphic feature, which remain unchanged throughout life. So, the likelihood of idiopathic epilepsy could be predicted. Diagnostic significance of dermatoglyphics has been reported especially correlating dermatoglyphics with idiopathic epilepsy. In this study, an attempt has been made to identify whether patients with idiopathic epilepsy express any specific dermatoglyphic features.

**Symptomatic:** where a cause has been found. Causes may include- head injury, brain damage at birth, stroke, brain infection and occasionally brain tumour.

**Cryptogenic:** where doctors believe there is likely to be a cause but they are unable to find it. Approximately 60% of all epilepsies are idiopathic or cryptogenic.
There are many different types of epileptic syndromes and doctors have identified over one hundred different epileptic syndromes which are characterised by specific signs and symptoms depending on where in the brain they originate.

Classification of epileptic seizures:

Clinically, epilepsy can be classified into various categories because it helps them to decide how best to treat the seizures.

Epilepsies divided into two broad categories.

They are generalized and partial (localization related) seizures (Idem, 1989).

In the new cases of epilepsy 50% have seizures of partial origin and 50% of generalized origin before the age of 40. After 40 years, the proportion of partial epilepsy rises to 75% by the age of 75.

I. Generalized seizures:

Affects both sides of the brain at the same time from the time the seizure begins. Person experiencing such a seizure may cry out or make some sound; loss of consciousness and loss of urine are common symptoms.

There are several types of generalized seizures. Perhaps the most commonly recognized type is the general tonic-clonic seizure, formerly called grand mal. During this type of seizure, one abruptly loses consciousness and falls. The body stiffens (tonic contractions of all the muscles, taking on a posture of extreme extension of the legs and back, air may be expelled from the lungs causing the person to vocalize with a distinct cry. After a few seconds, all the muscles will begin to jerk rhythmically. These events may be accompanied by excess salivation, tongue biting (caused by rhythmical contraction of the jaw muscles) and incontinence (involuntary passing of urine).
process lasts about two or three minutes following which the person relaxes and consciousness returns after several minutes. This may be followed by a period of confusion or sleep.

**Mechanism of Generalized Epilepsy**

For many years, the anatomical origin of generalized seizures was debated. The results of some experiments supported the hypothesis that generalized seizures originated in the thalamus (Bernard *et al.*, 2003). The mechanism that generates seizures is now believed to involve an alteration in the circuitry between the thalamus and the cerebral cortex (Snead, 1995; Futatsugi and Riviello, 1998; Kostopoulos, 2001). Some studies have shown that thalamocortical circuits govern the rhythm of cortical excitation by the thalamus and underlie normal physiologic patterns such as those that occur during sleep (Steriade *et al.*, 1993). This circuitry is conducted by thalamic relay neurons, thalamic reticular neurons and cortical pyramidal neurons. The thalamic relay neurons can activate the cortical pyramidal neurons either in a tonic mode, or in a burst mode that is made possible by T-type Ca$^{2+}$ channels on which bursts of action potentials (mediated by voltage-gated sodium channels) are superimposed (Nowycky *et al.*, 1985). In addition, ascending noradrenergic, serotonergic, and dopaminergic inputs to the thalamus modulate this circuit and affect the likelihood of a burst mode (McCormick, 1992). The abnormal circuit causes rhythmic activation of the cortex results in the characteristic EEG discharges and clinical manifestations of one type of generalized seizures (Kostopoulos, 2001). The precise abnormality of the circuit may be the T-type calcium channels (Burgess and Noebels, 1999; Kim *et al.*, 2001), and altered γ-aminobutyric acid (GABA) receptor function (Caddick and Hosford, 1996).
A. Absence seizures (Petit mal): General absence seizures were formerly called Petit mal epilepsy. Seizure can happen so quickly that it can sometimes go unnoticed (twitching of eyelids or facial muscles), lasts only few seconds without any after-effect. These seizures are characterized by a loss of awareness by the victim, but observers may not notice anything abnormal. One does not fall nor are there any unusual muscle jerks. On close observation, one may note a brief fluttering of the eye lids and a sudden arrest of motor activity. This event is brief, lasting from about 5 to 45 seconds. Following the seizures, there is an immediate return of awareness and the patient does not have any period of confusion following the event. In fact, the patient is usually not aware that a seizure has occurred. These are commonly experienced by children (child often thought to be day-dreaming). This type of seizures is frequently seen in children. Unfortunately the true nature of their problem may not be recognized and these children may be classified as daydreamers, intellectually a low or even insolent because they may not respond when spoken to.

B. Atonic seizures (Astatic seizures or Akinetic seizures): Atonic seizures, sometimes called drop attacks, are characterized by a sudden and brief loss of muscle tone. The person suddenly drops to the floor and almost immediately after hitting the floor regains motor control. Sudden loss of muscle tone, causing person to fall. These seizures are not easy to prevent with medicines. There is usually only a very brief loss of consciousness.

C. Myoclonic seizures: Brief and abrupt jerking of one or more limbs, rapid contraction of muscles for a brief time. These jerks may involve only the head or face, one extremity, or a small group of muscles. They may occur hundreds of times a day. There is usually neither loss of consciousness nor any confusion following the event.
D. Tonic-clonic seizures (grand mal or convulsions): Stiffening (tonic phase), jolting and shaking (clonic phase) of limbs and face, violent muscle contractions, loss of consciousness, breathing stops temporarily and "sighing", incontinence of urine, tongue or cheek biting, confusion following the seizure.

II. Partial seizures (Focal seizures):

These are the most common type of seizures affecting one part of the brain. It can stimulate emotions and senses, generate perceptions and interfere with perceptions.

Mechanism of Partial seizures

Partial seizures are the most common seizure disorder in adults, often stemming from focal lesions such as head trauma, strokes, and tumors (Annegers, 2001). The most common lesion of these patients is hippocampal sclerosis (Mathern et al., 1998; Blumcke et al., 1999). Hippocampal sclerosis is due to selective loss of neurons in the dentate hilus and the hippocampal pyramidal-cell layer, with relative preservation of dentate granule cells and a small zone of pyramidal cells. The term sclerosis has also been used for the lesion, because often there is neuronal loss in the neighboring entorhinal cortex and amygdale (Falconer and Taylor, 1968). Excitatory interneurons located within the dentate gyrus, which normally activate inhibitory interneurons, appear to be selectively lost (Idem, 1987). Loss of excitatory cells would be expected to impair the inhibitory feedback and feed-forward mechanisms that act on dentate granule cells, resulting in hyperexcitability (Idem, 1991). The implications of selective cell loss in the hippocampus, although highly suggestive of a mechanism of epileptogenesis, are still not completely understood.

A. Simple partial seizures: During this period, the affected person may not be able to move or communicate, but will be in consciousness. These seizures begin in a small,
localized part of the brain. Since different parts of the brain carry out different functions, simple-partial seizures are usually categorized according to which part of the brain is affected. Parts of body may move, twitch or shake. Nausea, sweating, skin flushing may occur. For example, if the seizures manifested itself by the rhythmic twitching of the left face, it would be classified as motor seizures. If the initial symptoms were a strange feeling in the left face, the seizures would be called sensory. This strange sensation is called an aura. Some auras may be quite elaborate, especially if certain memory center of the brain is involved. If visual memory areas are involved, one may experience visual hallucinations that seem like a movie. Similarly there are auditory and olfactory hallucinations. In some cases, there are feelings of unfamiliarity even though one's surroundings are well known. Other people perceive great agonizing fear, while others may have feeling of overwhelming religious rapture during any of these auras, one's consciousness remains intact.

Some times simple seizures progress from a single spot in the brain to involve the brain. For example, the twitching in the left face might spread to involve the left arm and then the left leg. Following that, the patient might stiffen, fall and begin the rhythmical jerk in a manner that is indistinguishable from general tonic-clonic seizures. For the purposes of making an accurate diagnosis and hence applying the most appropriate treatment, it is important for witnesses to carefully note how it began so that the distinction between a general and partial seizure can be made. Quite often, if there is no sensory aura, the patient will not be able to make this observation himself because of the loss of consciousness associated with the seizures.

B. Complex partial seizures: - These seizures are like simple-partial seizures except that conscious awareness is affected. These complex activities, however, do not look normal
to casual observers. Rather they look more like a robot trying to carry out human activity. Temporal lobe may be involved in this type of seizures (temporal lobe epilepsy or psychomotor epilepsy). Eyes may stay open and move around, loss of consciousness, loss of control on movement and speech, nausea, sweating, skin flushing, inappropriate emotions, changes in personality or alertness, olfactory or gustatory hallucinations or impairment may occur.

**NEUROCHEMICAL BASIS OF EPILEPSY**

Neuronal cell damage or death is the main symptom of neurodegenerative disorders such as epilepsy, cerebral ischemia etc. Both NMDA and non-NMDA receptors play an important role in seizure induced brain damage. Sommer (1880) discovered an area of the hippocampus that is vulnerable to injury in patients suffering from prolonged seizures (status epilepticus) which consists of the pyramidal cell fields in CA1 region. It was reported that hippocampal CA1 region contains a very high density of NMDA receptors (Geddes et al., 1986) in the entire brain (Monaghan and Cotman, 1985).

Reduced cellular energy metabolism during ischemia and epilepsy causes increased release and decreased reuptake of glutamate, as well as increased extracellular K+ concentrations due to inhibition of the Na⁺/K⁺-ATPase (Feldman et al., 1996). Intracellular Ca²⁺ influx and NMDA receptor antagonists can attenuate the neuronal damage and death (Steinberg et al., 1988). Persistent glutamate activation of NMDA receptors with simultaneous membrane depolarization leads to a prolonged opening of NMDA receptor channels, permitting massive Ca²⁺ influx across the membrane (Glutamate-Calcium nertotoxicity hypothesis). Depolarization is also thought to cause additional Ca²⁺ entry into the cell through voltage-operated Ca²⁺ channels (VOCC) (Rajendra et al., 2004). Elevation in intracellular Ca²⁺ levels activate a variety of Ca²⁺
dependent processes, including specific proteases and endonucleases that can breakdown the cellular DNA (Choi, 1992; Lipton and Rosenberg, 1994); stimulation of phospholipase A2 (PLA2) and subsequent release of arachidonic acid (AA) which in turn can lead to the formation of free radicals and subsequent oxidative cell damage; Nitric oxide synthase (NOS), which catalyzes the formation of nitric oxide can also participate in the generation of harmful free radicals (Coyle and Puttfarcken, 1993); and Ornithine decarboxylase (ODC) resulting in tissue injury. Scatton (1994) reported that excess accumulation of Ca\(^{2+}\) in mitochondria can also lead to severe damage to brain regions.

In recent years in vitro electrophysiological models such as cultured spinal cord neurons, hippocampal and cortical slices have been developed to study the mechanism of epileptogenesis. GABA receptor agonist, bacuculline, picrotixin or pencillin in hippocampal slice cultures or potassium channel blockers such as tetraethylammonium induce in vitro epileptogenesis. In vitro Epileptiform events may also be induced by lowering of extracellular Mg\(^{2+}\) environments (Zang et al., 1995), lowering Ca\(^{2+}\) concentration (Konnerth et al., 1984), increasing K\(^+\) levels and addition of 4-AP (Leschinger et al., 1993). Interruption of AMPA and NMDA - mediated transmissions causes repeated high-frequency excitation (Croucher and Bradford, 1990) and increasing extracellular glutamate (Glutamate injury induced epileptogenesis) may also lead to epileptogenesis in in vitro models (Sun et al., 2001). From the earlier reports, it has been understood that impairment of ion-channel function and GABA mediated transmission or reciprocal increase in excitation due to glutamatergic and cholinergic influences may lead to epileptic characteristics in experimental animals (Avoli et al., 1993).
REGULATION OF EPILEPSY

Although glutamate is required for normal brain function, the presence of excessive amounts of glutamate can lead to excitotoxic cell death (Lipton and Rosenberg, 1994). Excitotoxicity is mediated by various types of glutamate receptors (Glu-R) particularly N-methyl-D-aspartate (NMDA), AMPA or kainic acid in different neurodegenerative disorders. Activated NMDA receptor channels allow an influx of Ca$^{2+}$ which in excess can activate a variety of potentially destructive processes (Standaert and Young, 1995). Blockade of voltage dependent Ca$^{2+}$ channels and release of extracellular Mg$^{2+}$ channels can regulate the activity of NMDA Channels. Prevention of repetitive firing of a neuron is possible by blocking the voltage-activated Na$^{+}$ channels in epileptics (McNamara, 1995). Through the regulation of inhibitory neurotransmitter (GABA), the resting membrane potential can be regulated and thus can reduce the probability of glutamate excitation (McNamara, 1995).
DIAGNOSIS OF EPILEPSY

The initial evaluation in patients who present with spells or seizures is to determine whether these episodes are epileptic in nature. Approximately 30-50% of epileptic cases has a known cause and is termed as acquired epilepsy (Sun et al., 2001). It can be induced by repeated application of short electrical stimuli (kindling) to amygdale or hippocampus. Some synaptic changes in kindling rats include enhancement of 1) Voltage sensitive calcium conductance 2) Glutamate release in CA3 region of hippocampus 3) GABA release in CA1 region of hippocampus, and 4) Sensitivity of NMDA receptors and of glutamate metaboreceptors (Akiyama et al., 1992). The diagnosis of epilepsy depends first of all on the clinical history, observation of seizures by careful historians, whether medical personnel, family members, and then on supportive EEG findings, moreover, imaging results should be interpreted in the context of the clinical and EEG data. Although imaging studies cannot be used to make a diagnosis of epilepsy, they are the most important means of establishing the etiology of seizures. Once epileptic seizures are diagnosed, the next step is to determine the epileptic syndrome and then the seizure type. This is helpful for choosing medications as well as for evaluating a patient for surgical treatment. The epileptic syndrome is determined based on the history, physical examination, EEG findings, and neuroimaging studies (Dileep, 2003).

Induction of Epilepsy

There is also considerable evidence that voltage-gated currents contribute to the generation of epileptogenic seizures. It has been shown that toxins that prolong Na⁺-channel opening cause seizures (Garber and Miller, 1987). Similarly drugs that prevent activation of K⁺-currents also induce convulsions with augmented transmitter release. Generalized limbic seizures and subsequent status epilepticus (SE) can be induced by the
muscarinic acetylcholine receptor (mAChR) agonist pilocarpine (Turski et al., 1984, 1989). Epilepsy can be induced by bacuculline, a GABA receptor antagonist (Psarropoulou and Descombes, 1999) and 3-mercaptopropionic acid, a competitive inhibitor of glutamic acid decarboxylase. Similarly picrotoxin and ethylbicyclophosphates induce epileptogenic seizures by mimicking GABA receptor complex in conjunction with blockage of chloride channel (Meldrum, 1981). A potent glutamate agonist, kainic acid induces limbic seizures by acting at high affinity kainite receptors in the CA3 of hippocampus (Cavalheiro et al., 1982). Pyridoxine antagonist, 4-deoxypyridoxin (4-DP) also induces experimental seizures primarily by decreasing the rate of synthesis of GABA (Meldrum and Horton, 1971). A tetrazole derivative like Pentylenetetrazol (PTZ) also induces convulsions presumably by impairing GABA-mediated inhibition at the GABA receptor (Olsen, 1981). Domoic acid, an excitatory amino acid analogue obtained from mussels reported to induce experimental SE in rats (Dakshinamurthi et al., 1991) and mice (Swann and Brady, 1984).

**Pentylenetetrazole**

Pentylenetetrazole (PTZ), a tetrazol derivative, has been shown to induce convulsions presumably by impairing GABA-mediated inhibition at the GABA receptor (Olsen, 1981). It acts as a central nervous system and respiratory stimulant. It is considered a non-competitive GABA antagonist (Hosford, 1995). PTZ can induce seizures at high doses and might have other serious side effects. It has been used experimentally to study seizure phenomenon and to identify pharmaceuticals that may control seizure susceptibility. It is generally believed that PTZ exerts its effects by binding to the picrotoxin-binding site of the post-synaptic GABA$_A$ receptor (Macdonald and Barker, 1977). Overall effect of PTZ should be an increase in glutamate-GABA ratio, which may contribute to the triggering of convulsions (Lacoste et al., 1988).
PTZ is a relatively well-studied molecule in terms of its seizure provoking mechanisms and is known to suppress the inhibitory effects of some neurotransmitters, especially GABA, thus leading to an easier depolarization of neurons (De Boer et al., 1982; De Deyn and Macdonald, 1989). PTZ blocks a neurotransmitter called gamma-aminobutyric acid, GABA, passes messages between neurons along specific brain pathways. Normal brains have a balance of neurotransmitters that excite neurons and make learning possible, and of GABA, which slows neuronal excitation so they do not become overly stimulated. It is likely that the alterations in neurotransmitter homeostasis in the brain may cause initiation and spread of seizures (Dodd and Bradford, 1976; Roberts, 1984; Meldrum, 1989).

TREATMENT OF EPILEPSY

The primary treatment for epilepsy is the use of antiseizure medicines called anticonvulsant or antiepileptic drugs (AED) to bring seizures under control. AEDs can reduce the occurrence of seizures or prevent them from occurring, but they do not cure epilepsy. Volprate and clonazepam may be active agents effective in young children. Approximately 50% of all women with epilepsy have increased seizure frequency during pregnancy. AEDS like carbamazepine and phenytoin induce the malformation in offspring epileptic mother. The selection of an appropriate AED is based on diagnosis of the epileptic syndrome of the patient. AEDs have initial starting doses, and subsequent titration is based on response to medication and side-effect profile (Dileep, 2003). Volprate and Clonazepam may be active agents which are effective against Myoclonic, Akinetic, and atonic seizures in young children (McNamara, 1995). Approximately 50% of all women with epilepsy have increased seizure frequency during pregnancy. Infant mortality is higher for epileptic mothers. Children of epileptic mothers who received antiseizure medication during the early months of pregnancy have an increased incidence
of a variety of birth defects (McNamara, 1995). AEDs like carbamazepine and phenytoin induce the malformation in offspring of epileptic mothers (Lindhout et al., 1984).

In patients who do not respond to medication, epilepsy surgery is a potential mode of treatment that can offer up to a 70% to 90% chance of seizure freedom in some patients. Other novel modes of therapy include the vagal nerve stimulator (VNS), which is usually reserved for those patients with intractable epilepsy who are not surgical candidates (Dileep, 2003). Neurocognitive side effects include dizziness, drowsiness, unsteadiness, blurred vision, ataxia, tremor, nystagmus, impaired memory, and fatigue (Dileep, 2003). Though various AEDs are available clinically, management of epilepsy is a very complex task because of co-existing neuropsychiatric complications (Krishnamoorthy, 2001).

Pathophysiology

Mutations in several genes have been linked to some types of epilepsy. Several genes that code for protein subunits of voltage-gated and ligand-gated ion channels have been associated with forms of generalized epilepsy and infantile seizure syndromes. Several ligand-gated ion channels have been linked to some types of frontal and generalized epilepsies. One speculated mechanism for some forms of inherited epilepsy are mutations of the genes which code for sodium channel proteins; these defective sodium channels stay open for too long thus making the neuron hyper-excitable. Glutamate, an excitatory neurotransmitter, may thereby be released from these neurons in large amounts which—by binding with nearby glutamatergic neurons—triggers excessive calcium (Ca^{2+}) release in these post-synaptic cells. Such excessive calcium release can be neurotoxic to the affected cell. The hippocampus, which contains a large volume of just such glutamatergic neurons (and NMDA receptors, which are permeable to Ca^{2+} entry
after binding of both sodium and glutamate), is especially vulnerable to epileptic seizure. Subsequent spread of excitation, and possible neuronal death. Another possible mechanism involves mutations leading to ineffective GABA (the brain's most common inhibitory neurotransmitter) action. Epilepsy-related mutations in some non-ion channel genes have also been identified.

Epileptogenesis is the process by which a normal brain develops epilepsy after an insult. One interesting finding in animals is that repeated low-level electrical stimulation to some brain sites can lead to permanent increases in seizure susceptibility: in other words, a permanent decrease in seizure "threshold." This phenomenon, known as kindling (by analogy with the use of burning twigs to start a larger fire) was discovered by Dr. Graham Goddard in 1967. It is important to note that these "kindled" animals do not experience spontaneous seizures. Chemical stimulation can also induce seizures; repeated exposures to some pesticides have been shown to induce seizures in both humans and animals. One mechanism proposed for this is called excitotoxicity. The roles of kindling and excitotoxicity, if any, in human epilepsy are currently hotly debated. Other causes of epilepsy are brain lesions, where there is scar tissue or another abnormal mass of tissue in an area of the brain. The complexity of understanding what seizures are have led to considerable efforts to use computational models of epilepsy to both interpret experimental and clinical data, as well as guide strategies for therapy.

Management

Epilepsy is usually treated with medication prescribed by a physician; primary caregivers, neurologists, and neurosurgeons all frequently care for people with epilepsy. However, it has been stressed that accurate differentiation between generalized and partial seizures is especially important in determining the appropriate treatment. In some cases
the implantation of a stimulator of the vagus nerve, or a special diet can be helpful. Neurosurgical operations for epilepsy can be palliative, reducing the frequency or severity of seizures; or, in some patients, an operation can be curative. The proper initial response to a generalized tonic-clonic epileptic seizure is to prevent the person from self-injury. If a seizure lasts longer than 5 minutes, or if more than one seizure occurs without regaining consciousness emergency medical services should be contacted.

Surgery

Epilepsy surgery is an option for patients whose seizures remain resistant to treatment with anticonvulsant medications who also have symptomatic localization-related epilepsy; a focal abnormality that can be located and therefore removed. The goal for these procedures is total control of epileptic seizures, although anticonvulsant medications may still be required. The evaluation for epilepsy surgery is designed to locate the "epileptic focus" (the location of the epileptic abnormality) and to determine if resective surgery will affect normal brain function. Physicians will also confirm the diagnosis of epilepsy to make sure that spells arise from epilepsy (as opposed to non-epileptic seizures). The evaluation typically includes neurological examination, routine EEG, Long-term video-EEG monitoring, neuropsychological evaluation, and neuroimaging such as MRI, Single photon emission computed tomography (SPECT) and positron emission tomography (PET). Some epilepsy centers use intracarotid sodium amobarbital test (Wada test), functional MRI or Magneto encephalography (MEG) as supplementary tests. Certain lesions require Long-term video-EEG monitoring with the use of intracranial electrodes if noninvasive testing was inadequate to identify the epileptic focus or distinguish the surgical target from normal brain tissue and function. Brain mapping by the technique of cortical electrical stimulation or Electrocorticography are other procedures used in the process of invasive testing in some patients. The most
common surgeries are the resection of lesions like tumors or arteriovenous malformations which, in the process of treating the underlying lesion, often result in control of epileptic seizures caused by these lesions. Other lesions are more subtle and feature epilepsy as the main or sole symptom. The most common form of intractable epilepsy in these disorders in adults is temporal lobe epilepsy with hippocampal sclerosis, and the most common type of epilepsy surgery is the anterior temporal lobectomy, or the removal of the front portion of the temporal lobe including the amygdala and hippocampus. Some neurosurgeons recommend selective amygdala-hippocampectomy because of possible benefits in postoperative memory or language function. Surgery for temporal lobe epilepsy is effective, durable, and results in decreased health care costs. Despite the efficacy of epilepsy surgery, some patients decide not to undergo surgery owing to fear or the uncertainty of having a brain operation.

Palliative surgery for epilepsy is intended to reduce the frequency or severity of seizures. Examples are callosotomy or commissurotomy to prevent seizures from generalizing (spreading to involve the entire brain), which results in a loss of consciousness. This procedure can therefore prevent injury due to the person falling to the ground after losing consciousness. It is performed only when the seizures cannot be controlled by other means. Multiple subpial transections can also be used to decrease the spread of seizures across the cortex especially when the epileptic focus is located near important functional areas of the cortex. Resective surgery can be considered palliative if it is undertaken with the expectation that it will reduce but not eliminate seizures. Hemispherectomy involves removal or a functional disconnection of most or all of one half of the cerebrum. It is reserved for people suffering from the most catastrophic epilepsies, such as those due to Rasmussen syndrome. If the surgery is performed on very young patients (2–5 years old), the remaining hemisphere may acquire some rudimentary
motor control of the ipsilateral body; in older patients, paralysis results on the side of the body opposite to the part of the brain that was removed. Because of these and other side effects it is usually reserved for patients who have exhausted other treatment options.

**ANTIEPILEPTIC DRUGS (AEDs)**

Considering the multifactorial neurochemical and neurophysiological malfunctions consequent to the epileptic seizures, some antiepileptic drugs (AEDs) are designed to mitigate the debilitating aspects of epilepsy. Barbiturates and benzodiazepines control high frequency repetitive firing of action potentials interacting with voltage-gated sodium channels (Macdonald and McLean, 1986) and enhance GABAergic inhibition by binding to an allosteric regulatory site on GABA receptor (Olsen, 1987). Phenytoin and carbamazepine interact with voltage-dependent Na⁺ channels and reduce the frequency of sustained repetitive firing of action potentials in neuronal cell culture (Macdonald and McLean, 1986) and hippocampal neurons (Kuo and Bean, 1994). Classical AEDs like Carbamazapine, Phenobarbital, Phenytoin and Valproate as well as many newer AEDs like felbamate, gabapentin, lamotrigine, tiagabine, vigabatrine alleviate neuronal damage and delay the development of epileptogenesis (McNamara, 1995; Pitkanen, 2002). Ethosuximide, dimethidine (metabolite of trimethidine) has their action by reducing the T-type Ca²⁺ current in thalamic relay neurons (Coulter et al., 1989). Valproic acid (VPA) has been found to block sustained high frequency repetitive firing of neurons in culture (Macdonald and McLean, 1986) interacting with T-type calcium channels (Kelly et al., 1990). Felbamate, an anticonvulsant active at NMDA receptors (Mazarti et al., 2000), has been shown that drugs that activate ATP-dependent K⁺ currents shows powerful antiepileptic effects (Macdonald and McLean, 1986). Gabapentine (GBP), a cyclic GABA analog, acts on GABAergic neurotransmitter system and increases GABA turnover in different regions of
rat brain (Loscher et al., 1991). Lamotrigine (LTG), a phenyltriazine, inhibits the voltage-dependent sodium channel, which indirectly prevents the presynaptic release of glutamate (Leach et al., 1986). Oxcarbazepine (OBCZ) has been shown to reduce sustained high-frequency repetitive firing of voltage-dependent sodium action potential in spinal cord neurons of mouse. Vigabatrin, an effective anticonvulsant causes selective irreversible inhibition of GABA transaminase (Fippert et al., 1977).

However, there are also anecdotal observations that many multiple AED regimens employed in ameliorating seizures generally met with partial success and suffer from substantial problems such as pharmacoresistance (development of tolerance) (Boggs et al., 2000), neurotoxic effects and idiosyncratic reactions such as skin rashes etc. (Loscher and Schmidt, 2002). Although the prognosis for seizure control is good in at least 60% of patients, up to 40% of individuals suffer from intractable, pharmacoresistant epilepsy (Regesta and Tanganelli, 1999; Kwann and Brodie, 2000). Chronic toxicity was observed with some of the older AEDs such as osteoporosis, gingival hyperplasia, and alterations in reproductive endocrine function. Some specific problems have also been found with some newer AEDs. Hopefully new AEDs that act on different neurotransmitter receptors or ion-channels will result in improved control of seizures and drugs that are active on ion-channels have greater potential in restoring the function of epileptic neurons to normalcy.
Antiepileptic Drugs (AEDs):

<table>
<thead>
<tr>
<th>AED</th>
<th>Typical Starting Dose (mg/day)</th>
<th>Titration</th>
<th>Some Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>900</td>
<td>300mg/day at 24 hr intervals</td>
<td>Neurocognitive effects, weight gain, mood changes, dry mouth, periorbital edema, myalgias</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>500</td>
<td>250mg/day at 1 wk intervals</td>
<td>Neurocognitive effects, anorexia, nausea, vomiting, weight loss, diarrhea, abdominal pain, headache, mood changes, rash, hirsutism, and gingival hyperplasia</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400</td>
<td>200mg/day at 1 wk intervals</td>
<td>Neurocognitive effects, rash, nausea, vomiting, hyponatremia</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000</td>
<td>1000mg/day at 2 wk intervals</td>
<td>Neurocognitive effects, mood changes, behavior changes, anesthesia</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>50</td>
<td>50mg/day at 2 wk intervals</td>
<td>Neurocognitive effects, headache, rash, mood changes, nausea, vomiting</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>600</td>
<td>600mg/day at 1 wk intervals</td>
<td>Neurocognitive effects, rash, nausea, vomiting, hyponatremia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>90</td>
<td>30mg/day at 4 wk intervals</td>
<td>Neurocognitive effects, mood changes, nausea, vomiting, rash, phrophoria exacerbation, physical dependence</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300</td>
<td>100mg/day at 4 wk intervals</td>
<td>Neurocognitive effects, hirsutism, gingival hyperplasia, nausea, vomiting, coarse facies, headache, lymphadenopathy, osteomalacia</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>4</td>
<td>4-8mg/day at 1 wk intervals</td>
<td>Neurocognitive effects, mood changes, asthenia, nausea, vomiting</td>
</tr>
<tr>
<td>AED</td>
<td>Typical Starting Dose (mg/day)</td>
<td>Titration</td>
<td>Some Common Side Effects</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25-50</td>
<td>25-50mg/day at 1 wk intervals</td>
<td>Neurocognitive effects, language problems, psychomotor slowing, mood changes, paresthesia, weight loss</td>
</tr>
<tr>
<td>Valproate</td>
<td>500</td>
<td>250mg/day at 1 wk intervals</td>
<td>Neurocognitive effects, weight gain, nausea, vomiting, headache, hairloss, menstrual irregularities</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100</td>
<td>100mg/day at 2 wk intervals</td>
<td>Neurocognitive effects, mood changes, headache, insomnia</td>
</tr>
</tbody>
</table>

Although the last decade brought the introduction of several new antiepileptic drugs (AEDs) and essential progress in the pharmacotherapy of epilepsy was noted, about 30% of patients still have seizures that continue despite taking AEDs (Loscher, 2002).

**EPILEPSY AND AYURVEDA**

Medicinal plants are of great interest to the researchers and clinicians as most of the drug industries depend, in part, on plants for the production of pharmaceutical compounds (Chand et al. 1997). Among the World's 25 best selling pharmaceutical medicines, 12 are plant derived (O’Neill and Lewis 1993).

The medicinal plants for the study have to be selected in such a way that their availability is maximized in many parts of the world. The plant for the present study was selected *Bacopa monnieri* Linn (Scrophulariaceae) which has been used as brain tonic to enhance memory development, learning, and concentration, and to provide relief to patients with anxiety or epileptic disorders. The plant has also been used in India and
Pakistan as cardiac tonic, digestive aid, and to improve respiratory function in case of bronco constriction.

**Bacopa Monnieri**

*Bacopa monnieri* and *Centella asiatica* are the main constituents of Indian ayurvedic herbal medicine which is known as medhya rasayana. The medicinal efficacy of *Bacopa monnieri* is also extensively reported in Indian traditional literature such as Atharved, Charak samhita and Susrutu samhita. It has been extensively used for the treatment of various neurological and neuropsychiatric diseases. The whole plant is the source of the ayurvedic drug bramhi, usually dried and powdered.

Hence Bacopa shares its Sanskrit name, Brahmi, with another herbal nervous system restorative- *Centella asiatica* (Gotu kola) (Morgan & Bone, 1999). *Bacopa* forms the basis for a number of important Ayurvedic herbal preparations, including *Brahmighritam* and *Brahmirasayanam*. Ancient texts dating back as far as the sixth century BC record the use of Brahmi to promote mental function and to treat mental disease. Bacopa also provides relief from anxiety and epileptic disorders. The animal and human studies validate the traditional claims of Ayurvedic medicine in which known
usage of Bacopa as a ‘Brain and memory tonic’ dates back approximately 2000 to 3000 years.

This medicinal plant is locally known as brahmi. The name Brahnmi is derived from the word ‘Brama’ the mythical “Creator” in the Hindu pantheon. Bacopa monnieri is a small herb with purple flowers. It grows in wet and marshy areas and near the streams in tropical regions. It is a creeping herb with numerous branches and small fleshy and oblong leaves.

**PLANT DISCRIPTION**

*Bacopa monnieri*, also referred to *Bacopa monnieri*, Herpestis monniera water hyssop, and “Brahmi”, (greatest of the great) has been used in the Ayurvedic system of medicine for centuries. (Mukherjee and Dey, 1966). *Bacopa monnieri* is one of the great multipurpose miracle herbs of oriental medicine. It has been used by Ayurvedic medicinal practitioners in India for almost 3000 years and is classified as a medharsayana, a substance which improves memory and intellect. Brahmi literally means the ‘Energy or shakti of Brahman (i.e. Sarasvati)’.

In India the plant is used for all sorts of skin problems- eczema, psoriasis, abscess, ulcerations and stimulation of the growth of skin, hair and nails. It is also used for chronic rheumatism often as an ointment.

In Pakistan the herbal drug Brahmi-buti, is used to treat skin diseases, leprosy, epilepsy, eczema, asthma, and diseases of the nervous system. *Bacopa* extracts appear to exert a protective effect against DNA damage, which may account for its anti-cancer effects.
**TAXONAMY**

**Scientific name**: *Bacopa monnieri*

**Family**: Scrophulariaceae

**Common names**
- Jala brahmi, herpestis, mandukaparni, herb-of-grace, water hyssop, Indian pennywort, thyme-leaved gratiola.

**English**: Water hyssop, Thyme-leaved gratiola

**Hindi**: Brahmi

**Sanskrit**: Barambhi, nirabarhmi

**Telugu**: Sambrani chettu

**Bengali**: Brahmi sak,

**Marathi/Tamil**: Nir brahmi

**Malayalam**: Nir brahmi,

**Kannada**: Niru brahmi

**Taxonomic features**: Small, creeping herb with succulent and relatively thick and oblanceolate, and are arranged oppositely on the stem and blue or white flowers.

**MORPHOLOGY**

*Bacopa monnieri*, a member of the Scrophulariaceae family, is a small, creeping herb with numerous branches, small oblong leaves, and light purple flowers. In India and the tropics it grows naturally in wet soil, shallow water, and marshes. The herb can be found at elevations from sea level to altitudes of 4,400 feet, and is easily cultivated if adequate water is available. Flowers and fruits appear in summer and the entire plant is used in ayurvedic medicine. The drug is present throughout the entire dried plant, but principally concentrated in leaves and stems. It is native to India and Southeast Asia and
is also referred to as *Gratiola monniera, Herpestis monniera, monniera cuneifolia*. Water hyssop, and Bramhi. It commonly grows in marshy areas, throughout India Nepal, Sri Lanka, China, Taiwan, Vietnam, and some southern states of USA. The stems have soft, ascending branches, and are about 10-30 cm long and 1-2 mm thick.

Bacopa’s soft, sessile leaves are succulent, Reni form and spatulate, measuring about 2.5 mm in length. Brahmi’s leaves are used in tribal veterinary medicine, particularly in the treatment of epilepsy. Brahmi’s flowers are small blue or white in color with four or five petals, and grow on peduncles that are usually longer than the leaves. The fruits are ovoid, with acute capsules included in a persistent calyx. Its leaves look like tiny brains.

Brahmi is also the name given to *Centella asiatica* by some botanists while others consider that to be a mistake that arise during the 16th century, when brahmi was confused with mandukaparni, a name for *Centella asiatica*. Its ability to grow in water makes it a popular aquarium plant. It can even grow in slightly brackish conditions. Analysis of the leaves and stalks show that it contains moisture, protein, fat, carbohydrates, crude fiber, and ash, calcium, phosphorus, iron, ascorbic acid, nicotinic acid and sterols. The leaf powder standardized extract contained approximately 40% bacosides which are the known major bioactive components in *Bacopa monnieri*.

**Mechanism of action**

The triterpenoid saponins and their bacosides are responsible for bacopa’s ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and ultimately nerve impulse transmission. Based on animal study results, bacosides appear to have antioxidant activity involved in scavenging of reactive oxygen species in the brain.
HISTORY

Bacopa monniera, also referred to as water hyssop and brahmi, has been used in the ayurvedic system of medicine for centuries. It is said that the use of bacopa for memory enhancement goes back 3000 years or more in India. Bacopa has been regarded as a highly effective brain tonic since antiquity in the Ayurvedic medical system of India (Singh & Dhawan, 1997). The herb has been described in Ayurvedic texts since around 800 BC and recorded as a treatment for a range of mental disorders in the ‘Charak Samhita’ (Singh & Dhawan, 1997), which, according to the literature, was written in the 6th century AD (Chowdhuri et al., 2002; Russo & Borrelli, 2005). In a later treatise of the 16th century, the Bhavprakasa Varg-Prakarana, Bacopa’s actions are set down as follows: bitter, laxative, astringent, brain tonic, memory enhancing, and longevity promoting as well as brain conditions such as epilepsy, insanity and neuroses. Other indications described in this treatise include anemia, leprosy, renal disease, blood disease, poisoning and cough (Singh and Dhawan, 1982). Ayurvedic medicine classifies Bacopa as belonging to a group of plant medicines known as medhya rasayana that improve mental health, intellect and memory (medhya) and promote longevity and rejuvenation (rasayana) (Singh and Singh, 1980).

CHEMICAL CONSTITUENTS

Bacopa consists of two main alkaloids (bramhmine and herpestine). Other constituents are several acids, flavanoids, saponins and esters and sterols. The most important constituent is saponin, it includes bacoside which assists in release of nitric oxide that allows the relaxation of the aorta aria veins, to allow the blood to flow more smoothly through the body, and bacoside B is valued for nourishing the brain cells. In a thorough review of the chemical composition of bramhi, (Russo and Borrelli (2005) points out that the first constituents identified was an alkaloid brahmine.
Many active constituents, the alkaloids brahmine and herpestine, saponins d-mannitol and hersaponin, acid A, and monmierin were isolated in India over 40 years ago. Other active constituent have since been identified, including betulic acid, stigmastarol, beta-sitisterol, as well as numerous bacosides and bacopasaponins. The constituents responsible for bacopa’s cognitive effects are bacosides A and B.

In addition to the bacosides, *Bacopa* contains a wide variety of medically active substances, including stigma sterol, sapogenins, and flavonoids. Other compounds include triterpenoid saponins. Such as bacoside A₃, *bacopasaponin C* isomer, *bacopasaponin C* and *bacopasaponin I*. *Bacopa* also contains D-mannitol; octacosane, nicotine, and amino acids such as alpha-alanine, aspartic acid, glutamic acid, and serine. Saponins are glycosides, a sugar unit attached to a glycone portion (the sapogenin).

The sapogenin portion describes the type of saponin- either steroidal (4-ringed structure), or triterpenoid (5-ringed structure) (Mills and Bone, 2000). Triterpenoid saponins, the major components in Brahmi, were reported to be responsible for the cognitive enhancing activity of Brahmi.

Chemical constituents of Bacopa are the dammarane-type triterpenoid saponins (Garai *et al.*, 1996a, 1996b; Mahato *et al.*, 2000) with jujubogenin and pseudojujubogenin as a glycones (Deepak and Amit, 2004). Alkaloids such as Brahmines, Herpestine and a mixture of three alkaloids were reported from the leaves of this plant.

The carbohydrate mostly of bacoside A was shown to be arabinosyl glucose with, the arabinose unit as the terminal sugar. Bacoside B was found to be dextrorotatory where as bacoside A was laevo rotatory. The hemolytic action of bacoside B is twice that of
Hacoside A (Report on Herbal industry, pp: 37-41). This is because of the differences in the configuration of the carbohydrate parts.

Three new saponin have been isolated from the Bacopa monniera designated as bacopasides III, IV, V with structures 3-O-α-L-Isue
Bacoside A yields bacogenins A1, A2, A3 and A4 upon hydrolysis (Chatterji et al., 1965). The other chemical constituents of the plant include bacoside A1, hersaponin, betulinic acid, stigmasterol, b-sitosterol and stigmasterol (Chatterji et al. 1963). Other constituents include alkaloids (herpestine and brahmine), flavonoid, glycosides, betulinic acid and phytosterols (Anonymous Indian Herbal Pharmacopoeia Volume I, Kapoor). Saponins are natural products which have been shown to possess antioxidant property. The main components were either bacoside A1 or bacoside II, bacosides IV and V were present at lower concentrations. The beneficial cognitive effects of brahmi have been attributed to the triterpenoid saponins and their bacosides, specifically bacosides A and B. These constituents are responsible for bacopa’s ability to enhance nerve impulse transmission.

**PHARMACOLOGICAL PROPERTIES**

*Bacopa monnieri* (L.) Wettst, commonly known as Brahmi, has been used for a long time in Ayurvedic medicine as a nerve tonic for promoting mental health and improving memory. Recently, several studies have been published on the biological effects of this plant, especially for a therapeutic potential in the treatment or prevention of neurological diseases and cognitive processes.

Alcoholic extract showed considerable increase in learning performance in some clinical trials on rats. Bacopa may improve higher order cognitive process that is critically dependant on the input of information from our environment such as learning and memory. The acute and chronic effect of brahmi on cognitive function has been studied in children as well as in adults. In adults, it appears that brahmi must be administered chronically in order to obtain cognitive-enhancing effects.
It is kapha and pitta suppressant. It is very effective in skin related ailments and also in fairing the skin texture. It is considered the best brain tonic and is very widely given in improving memory and concentration. It is also given in heart related ailments and high blood pressure. It increases the appetite. It is beneficial in acidity and also in epistasis. It helps in expelling out the extra mucus accumulating in the respiratory tract. It is also effective in urine related problems. It also relieves from fever.

According to ayurveda it contains

- Gunna (properties) – laghu (light)
- Rasa (taste) – tickta (bitter)
- Virya (potency) – sheet (cold)
- Prabhav (action) – brain tonic

Traditionally, in ayurveda, brahmi is considered astringent, diuretic, laxative and a tonic for the heart and nerves. It is used to improve memory and intelligence, and to treat anemia, anorexia, arthritis, cough, dermatosis, diabetes, dropsy, dyspepsia, emaciation, fever and insanity. In other Indian traditional medicine systems, the drug is also used to treat anxiety, asthma, epilepsy and hoarseness, and as a potent nerve tonic, cardio tonic and diuretic.

Recently, many studies have revealed its pharmacological roles as cognition-enhancer (Singh and Dhawan, 1997; Stough et al., 2001; Das et al., 2002; Sumathi et al., 2002), antidepressant (Sairam et al., 2002), antioxidant (Pawar et al., 2001; Russo et al., 2003), antiulcerogenic agent (Sairam et al., 2001), and calcium antagonist (Dar and Channa, 1999). It has been used for a long time in Ayurvedic medicine as nerve tonic for promoting mental health and improving memory. Recently, several studies have been published on the therapeutic potential of this plant extracts in the treatment or prevention
of neurological diseases and cognitive processes. Although bramhi is indicated as an anti-epileptic in ayurveda, animal research shows anticonvulsant activity only at high doses over extended periods of time.

Brahmi's fresh juice may be applied externally to relieve the pain of inflamed joints. Bacopa also provides relief from anxiety and epileptic disorders. Bacopa mediates the GABAergic system (Shukla et al, 1987). Gamma-aminobutyric acid is an inhibitory neurotransmitter that has been shown to possess anticonvulsive, antinociceptive (Prevention of pain due to hypersensitive nerve endings), locomotors, and sedative effects. Because Bacopa also has all these properties, it is reasonable to speculate that a similar mechanism of action explains its effects on the brain and the body.

Bacopa monniera has been identified in clinical analysis as an adaptogen that increases the body's resistance to a wide range of chemical, biological, and physical stressors. Scientists explain that bacopa monniera likely affects multiple body systems to promote emotional well-being, physical endurance, and mental sharpness.

**NEUROPHARMACOLOGY**

Other pharmacological properties of the extracts include sedation cardio tonic, vasoconstriction, anti-inflammatory activity and astringency (Wealth of India, 1985). Juice of the leaves relieves bronchitis and diarrhea (Wealth of India, 1985). A paste of the leaves is used as a remedy for rheumatism (Wealth of India, 1985). The entire plant is used in indigenous medicine as a nervous tonic (Chopra et al., 1956). Brahmighritha, a medicated ghee prepared from *Bacopa monniera*, is beneficial in cases of epilepsy and hysteria (Singh and Dhawan, 1997). Hersaponin, one of its active compounds, is reported to have a sedative effect (Malhotra and Das, 1959). It is also has laxative, carminative, digestive, purgative, emmenagogue, sudorific and antipyretic properties. It is useful in
treating neuralgia, insanity, amentia, cancer, ulcers (Rao and Agarwal, 2000), dyspepsia, flatulence, asthma, skin diseases, leucoderma, syphilis, hoarseness, dysmenorrheal and sterility (Wealth of India, 1985). Additionally, it shows cardio protective and hepatoprotective (Sumathi and Nongbri, 2008) effects. The plant is an aphrodisiac, effective in treating scabies and syphilis, and purifies the blood, having proven useful for diarrheas and pyresis. The powdered dried leaf yielded satisfactory results in clinically tested cases of asthma, nervous breakdown and other low dynamic conditions (Singh and Dhawan, 1997). Bacopa monniera plant is known as a memory enhancer and act toward improving intellect. Although the plant is widely used for several ailments related to the central nervous system, its potential is unexplored. The present study was undertaken to investigate the anticonvulsant activity of an alcoholic extract of whole Bacopa monniera (BM), in different models of convulsion.

The brain is vulnerable to oxidative damage because of a relative lack of antioxidant enzymes like catalase and glutathione peroxides and abundance of oxidizable substrates like polyunsaturated fatty acids, catecholamine’s etc. (Halliwell and Gutteridge, 1985; Cohen, 1980). Oxidative insult has been implicated in various forms of brain damage or altered neuronal functions.

Its various neuro beneficial functions have been attributed to the characteristic presence of bacoside A and B. further, neuroprotective efficacy of BM and has been well know in terms of its ability to improve memory, effect against anxiety, epilepsy, and insomnia. Several clinical studies suggest that BM extract significantly improves the speed of visual processing, learning rate and memory consolidation. In view of the increased human usage of BM formulations, we are currently investigating the mechanism underlying its neuro protective action.
Whether the delay in the onset of convulsions was due to BM anticonvulsant properties or to inhibition of sympathetic discharge is unclear. It has been reported that brahmi has an antioxidant effect in the rat frontal cortex, striatum and hippocampus (Bhattacharya et al. 2000).

It is understood that brahmi has an unusual combination of constituents that are beneficial in curing mental inefficiency and illnesses and useful in the management of convulsive disorders like epilepsy. Bacosides, brahmi’s active principles responsible for improving memory related functions, are attributed with the capability of nerve impulses, thereby strengthening memory and cognition. Russo et al. (2003a) suggested that because of its ability to reduce NO-induced cellular alterations, brahmi has a therapeutic potential in treatment or prevention of neurological diseases.

The bacosides aid in repair of damaged neurons by enhancing kinase of synaptic activity, and ultimately nerve impulse transmission and boosting the synthesis of new protein in brain (Singh and Dhawan, 1997). Animal research has shown bacopa extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain (Chowdhuri et al, 2002). In vitro research has shown protective effect of bacopa extract against DNA damage in astrocytes and human fibroblasts (Russo et al., 2003a). Bacopa appears to stabilize most cells in vitro, (Samiulla et al., 2001) and possesses anti-inflammatory activity via inhibition of prostaglandins synthesis and liposomal membrane stabilization (Jain et al., 1994). In vitro research suggests an anticancer effect for bacopa extracts, possibly due to inhibition of DNA replication in cancer cell lines.

The preclinical studies have reported enhancing memory and learning effect with bacopa monnieri in children and patients with anxiety state (Sharma et al., 1987; Singh
and Singh, 1980). It is also used in treatment of asthma, leprosy, hoarseness, water retention and blood cleaning (Singh and Dhawan, 1982). Bacopa monniera has been used in ayurvedic formulation for conditions ranging from catarrhal complaints, gastrointestinal disturbances due to excessive tobacco use, habitual abortion and high blood sugar due to anxiety disorders, hysteria, epilepsy etc. (Chopra et al., 1956; Nadkarni, 1976).

*Bacopa monnieri* is reported to play a protective role on morphine-induced brain mitochondrial enzyme status in rats (Sumathy et al., 2002). It is also active against leishmaniasis. In the clinical trials described below, bacopa has been found to improve various aspects of cognitive function in children and adults. (Sharma et al. (1987), Negi et al. (2000) reported children with attention deficit hyperactive disorder (ADHD) were found to benefit from bacopa administration. No significant side effect was observed and results were highly favorable as overall anxiety-related physical symptoms and biochemical markers of anxiety (Singh and Singh, 1980). It is noteworthy that support for an anxiolytic action in human was provided by a well designed clinical trial (discussed below in detail) in which state anxiety was significantly improved by bacopa (Stough et al., 2001).

**OBJECTIVES OF THE PRESENT STUDY**

Epilepsy is one of the major neurological disorders where modern drug therapy is complicated by side effects, long-term toxicity and about 40% patients are refractory to therapeutic intervention and thus its effective and safe therapy remains a challenge. Medicinal plants used for therapy of epilepsy in traditional medicine have been shown to possess promising anticonvulsant activities which can be considered as invaluable source for search of new antiepileptic compounds.
Even though much work has been done on the anticonvulsant effects of selected medicinal plants as reported in the foregoing account, no systematic investigation was carried out on the neurobiological role of *Bacopa monnieri*, with particular reference to anticonvulsant and neuroprotective activity. From the survey of literature, it is obvious that screening of Phytochemical plants with particular reference to anticonvulsant/antiepileptic activity was performed by number of workers for the past few years from other countries and much is awaited from our country which is endowed with rich heritage of flora and fauna. Hence the present study is undertaken to examine the anticonvulsant effect of different fractions of *Bacopa monnieri* on selected neurochemical parameters in different areas of rat brain with the following objectives.

- The present study examines the impact of PTZ-induced epilepsy on selected facets of neuronal metabolism.
- The present study is carried out with a focus on characterization of antiepileptic fractions from the *Bacopa monnieri* plant and to define the neurobiological role of these fractions with particular reference to antiepileptic and Neuroprotective activity.
- To study the pathophysiological sequelae of neurotransmitter mechanisms (Acetylcholine, biogenic amines and glutamate metabolism) during PTZ-induced epilepsy and on Pre-treatment with the extracts of *Bacopa monnieri*.
- To study the alterations of energy status during epileptic and antiepileptic treatments.
- To characterize the pharmacological profile of individual fractions and to suggest the therapeutic modality of these compounds with particular reference to neuroprotection.