# Epilepsy Research:
# Providing Parts to the Puzzle

**By**

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- Epilepsy is a brain disorder in which clusters of nerve cells or neurons in the brain send abnormal signals. The abnormal activity causes disturbance of emotions and behavior and many times convulsions, muscles spasms, and loss of consciousness.
- Advancing research for causes, diagnosis, prevention, and treatment of epilepsy involves molecular biology, brain imaging, tissue banks, animal models, genetics, and developmental neurobiology.
- Geneticists speculate 500 or more genes may be involved in the many kinds of epilepsy and in the propensity for seizures.
- No cure exists for epilepsy at present. Therapies or interventions are designed to remedy seizures and undesirable behaviors
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## Introduction

When ancient Babylonians or Egyptians saw a person have a seizure, they were frightened and reasoned that such bizarre behavior must be of supernatural origin. They considered the disease to be of cosmic origin and perhaps a message that the gods were intervening. Babylonian cuneiform tablets and Egyptian papyri describe people with a “sacred disease” that we in the twenty-first century would recognize as epilepsy.

Tired of all the spirits and ghostly visits, Hippocrates in c. 410 BCE scoffed at the idea of a divine origin for epilepsy. In his *On the Sacred Disease,* he sarcastically paraded the different gods supposed to produce epileptic seizures and declared there was no evidence for these fantasies. He insisted that epilepsy was a disease of the brain. But the idea of supernatural persisted taking a demonic twist. Medieval paintings showed people with ghastly demons coming out of the body at the end of a seizure.

Today myths and stigmas concerning epilepsy are still prevalent in many places. Epilepsy is feared as a terrible and enigmatic disease. But researchers are fitting together pieces of the epilepsy puzzle. Actually, scientists know now that epilepsy is not one disease but many conditions with a common thread- electrical storms in the brain during which groups of nerve cells rapidly fire electrical impulses. The manifestations of the seizure depend on which parts of the brain are affected. The many kinds of epilepsies affect millions of people world wide. See Table I.

**Kinds of Epilepsy**

Hundreds of epilepsy syndromes as well different kinds of seizures exist. The disorders are characterized by a specific set of symptoms. Some cases appear to be hereditary, and some can be traced to another event like a blow to the head or a stroke. For most the cause is idiopathic or unknown.

The areas of the brain in which the syndromes originate usually give them the name. There are 10 classes of types:

1. Absence epilepsy. In this type people have seizures that cause momentary absence of consciousness. Called at one time petit mal seizures, these symptoms begin in childhood or adolescence and the person may not even be aware that he or she has temporarily blacked out. Since these occurrences tend to run in families, defective genes may be responsible. During the seizure, some children may experience a jerking arm or rapidly blinking eyes. Childhood absence epilepsy usually stops during puberty, but occasionally it may develop a more serious form or may disappear.
2. Psychomotor epilepsy. Strange or purposeless movements characterize this type of epilepsy with origins in the temporal lobe. Another term is recurrent partial seizure.
3. Temporal lobe epilepsy. TLE is the most common epilepsy syndrome with partial seizures. An aura may accompany this type of seizure that often begins in childhood. Repeated TLE seizures can cause the hippocampus to shrink over time. This structure important in memory and learning underscores the need to recognize this type early for treatment.
4. Frontal lobe epilepsy. This type usually involves a cluster of short seizures with a sudden onset and termination. Many types of these seizures exist and again the symptoms depend on where in the frontal lobe the seizures occur.
5. Occipital lobe epilepsy. Since this area of the brain is related to vision, occipital lobe epilepsy usually begins with visual

hallucinations, rapid eye blinking, and other eye-related symptoms. Otherwise, it is very much like frontal or temporal lobe epilepsy.

6. Parietal lobe epilepsy. This type tends to spread to other parts of the brain but closely resembles the symptoms of other kinds of epilepsy.
7. Lennox-Gastaut syndrome. This type of severe epilepsy begins in childhood and is characterized by sudden falls or drop attacks. It is very difficult to treat effectively.
8. Rasmussen's encephalitis. Another condition that begins in childhood is progressive. Half of the brain shows continual inflammation. It may have to be treated with a radical surgical procedure called hemispherectomy.
9. Ramsay Hunt syndrome type II. This rare and progressive type of epilepsy begins in early adulthood and leads to reduced muscle coordination and cognitive ability in addition to seizures.
10. Infantile spasms. This type is an example of epilepsies that begin in infancy usually with clusters of seizures before the age of six months. The infant may bend or cry out. Anticonvulsive drugs often do not help the spasms. The physician may use adrenocorticotropic hormone (ACTH) or the steroid predinisone.

Two other special risks are associated with epilepsy. Status epilepticus is a severe, life-threatening condition in which the person has prolonged seizures (over five minutes) or does not fully regain consciousness between seizures. The second condition is sudden unexplained death that occurs for no

discernible reason. Any type of epilepsy increases the risk if unexplained death about two-fold. Intractable epilepsy occurs when a person continues to experience seizures even with the best available treatment.

While any seizure is of major concern, just having a seizure in isolation does not mean a person has epilepsy. First seizures, fever or febrile seizures, nonepileptic seizures or pseudoseizures caused by conditions, such as narcolepsy, Tourette syndrome, cardiac arrhythmia, and eclampsia may not be associated with epilepsy.

**Kinds of Seizures**

Two major categories- partial and generalized- include more that 30 different types of seizures:

Partial seizures occur in only one area of the brain and comprise about 60 percent of all seizures. The area of origin in the brain may be included in the name. Following are types of partial seizures:

- Simple partial seizure. The person remains conscious but may have unusual or unexplainable feelings of joy, anger, sadness, or nausea. They may hear, smell, taste, see, or feel things that are not there.
- Complex partial seizures. These seizures may last only a few seconds, but the person just blanks out or may have strange movements called automatisms. Sometimes there is violent behavior like hitting the wall or throwing a book across the room. The person may have auras that indicate the seizure is coming. Sometimes these symptoms are confused with other disorders such as narcolepsy, fainting, or mental illness.

Another term for partial seizures, especially those centered in the temporal lobe, is psychomotor seizures.

Generalized seizures result from abnormal neuronal activity in many parts of the brain and involve several kinds:

- Absence seizures. The person has momentary loss of consciousness and may stare into space for several moments or have jerking or twitching movements. An older term is petit mal seizure.
- Tonic seizures. Stiffening of muscles of the body generally the arms, back, and legs characterize these seizures.
- Clonic seizures. Jerking movements of muscles on both sides of the body characterize this type.
- Myoclonic seizures. Sudden jerking movements or twitches of the upper body, arms or legs may occur.
- Atonic seizures. In this type the person loses normal muscle tone and may fall down nodding the head involuntarily or appear as a rag doll.
- Tonic-clonic. These seizures involve a mixture of symptoms that include loss of consciousness, stiffening of the body, repeated jerking of arms and legs. The older name for this type is grand mal seizure.

Not all seizures will fit into one of these neat little packages or with a clear pattern. Some may begin as partial seizures then spread to the entire brain. The lack of understanding of the many types of seizures remains a continued problem for people with epilepsy. Seeing a non-convulsive seizure, one may

conclude that the action is deliberate and the person is not under control. The individual may be arrested, sued, or placed in a mental institution.

**Search for Causes**

Understanding how the normal brain develops has led to the struggle to unravel what goes wrong in epilepsy. For example, knowing how new nerve cells migrate to their proper locations has led to the identification of gene mutations that disrupt this pattern. A gene called doublecortin may cause migrating nerve cells to stop short of their destination and form two cerebral cortices one beneath the other. Another revealed secret involves the cell membrane, a structure that is critical to generating electrical impulses. However, a disruption in the process may lead to epilepsy. Epilepsy may result from changes in non-neuronal brain cells called glia, cells that regulate concentrations of chemicals in the brain that affect neuronal imaging.

While we are still struggling to understand the basis of the electrical discharge assumed to underlie the epilepsy, recent advances in molecular genetics, molecular biology, and eletrophysiology have combined for increased insight. Basic studies of the neurotransmitters has revealed that some people have a high level of excitatory neurotransmitters that increase neuronal activity; other have abnormally low level of inhibitory neurotransmitters that decrease neuronal activity. Both too little or too much may cause epilepsy.

Dr. Raymond Dingledine, Emory University, has studied the basic biology of neurological disorders such as epilepsy. His work on excitatory neurotransmitter glutamate and N-methyl-D-asparate (NMDA) receptors has led to a focus on epilepsy. Glutamate, the simple amino acid, acts on neurotransmitter receptors to mediate communication between neurons of

the brain. Glutamate receptors have binding sites for glutamate, but they are also ion channels. When glutamate binds, the channel opens and ions flow through the channel to set up electrical communications. With epilepsy a problem of overactivation of brain neurons are driven by glutamate synapses. Dingledine thinks understanding glutamate receptor protein can benefit new strategies for seizure control. (Interview April 2002 http:/www.in-cites.com/scientists/DrRaymondDingledine.html).

Stafstrom *et. al* (2003 *Epilepsy Research* 53, 1-2, 129-137) studied how NMDA plays a prominent role in the pathogenesis of epilepsy by inducing seizures in mouse pups then testing behavior when compared to rats that had been induced for general seizures. The team found that NMDA evoked a unique seizure with increased duration and that later brought about deficits in spatial learning. The implications here are that this type of seizure implicated by NMDA might cause different long-term consequences.

The inhibitory neurotransmitter gamma-aminobutyric acid (GABA), is believed to play a role in epilepsy. Frahm *et. al* (2003 *Epilepsy Research* 52,3,243-252) investigated the uptake of inhibitory transmitter GABA and its limiting the efficacy of synaptic and tonic inhibition in brain tissue. GABA-uptake is down-regulated in temporal lobe epilepsy and may limit anti-convulsant activity of GABA-uptake blockers. This study showed that the inhibitory GABA may play a part in temporal lobe epilepsy.

Gene may control all these regulatory actions. For example, Wallace *et. al* (2001 *Nature Genetics*, 28,49 – 52) found a mutation in a gene encoding a $GABA_A$ receptor subunit in a large family with epilepsy. The two main phenotypes were childhood absence epilepsy (CAE) and febrile seizures (FS).

**Targeting Epilepsy Genes**

Jeffrey L. Noebels, Developmental Neurogenetics Laboratory, Baylor College of Medicine, Houston, underscores how the bounty of epilepsy models from geneticist's laboratories will continue to provide new part to the epilepsy puzzle and lead to new drug targets. Transgenic animal expressions of human mutations have allowed tracing of critical path ways. See Table II. Noebels (1996 *Neuron*,16,241-244) discussed possible divisions of targeting genetic factors:

- Intrinsic excitability of ion channel genes like potassium channel blockers
- Synaptic release mechanisms and transmitters such as calcium related proteins critical to neuronal signaling and GABA
- Synaptic receptors that are excitatory and neuromodulatory
- The network of axon terminal growth, synaptogenesis, and glia
- Human epilepsy mutations.

Noebels (2003 *Epilepsia*,21,16-21) explored new gene discoveries in idiopathic generalized epilepsy (IGE). He told how new genetic techniques are rapidly identifying specific genes responsible for these epilepsies and are gradually taking the "I" out of IGE. Ion channels ($K^+$, $Ca^+$, and $Na^+$) have been linked to idiopathic epilepsies. Gene errors alter excitability in various ways, depending on mutation, the regional network, and the stage of brain development. Most mutations prolong depolarization, favor repetitive firing, and alter neurotransmitter release or postsynaptic sensitivity at central synapses.

Speaking at the World Congress of Neurology XVII (2001) Dr. Sam Berkovic, University of Melbourne, Australia, commented that the scientific studies of genetics that began in 1945 with twin studies has moved to

molecular biology and is revolutionizing out approach to the genetic of epilepsy. Current research shows epilepsies have polygenic or complex multifactorial inheritance. He emphasized that to find a gene you need a large number of affected individuals and predicted the new genetics will transform clinical practice in the next ten years.

**Drugs and the Puzzle**

First synthesized in 1906 the drug phentyoin sat on a pharmaceutical shelf unused until researchers who were screening many agents for seizures in cats found it to have anti-convulsive effects. Scientists realized that the drug showed medications need not be sedatives like phenobarbitol and began the hunt for other drugs to control seizures. In 1960 another agent valproate was accidentally used to speed up absorption of other drugs. Today doctors prescribe these two drugs- phentyoin and valproate- along with carbamazapine for newly diagnosed cases of epilepsy as drugs of first choice.

The search was on to test new drugs for the 30 percent of patients that did not respond well to the drugs of first choice. The National Institutes of Health NINDS Epilepsy Therapeutics Research Program began in 1975 with its goal of studying potential anti-epileptic drugs. Since that time, participants in the program have screened more than 22,000 compounds for development. The US Food and Drug Administration (FDA) has now approved several new drugs for either as monotherapy or in combination with other drugs. The drugs are tiagabine, lamotrigine, gabapentin, topiramate, levetiracetam, flebamate, and zonisamide. Oxcarbamazapine is similar to carbamazapine but with fewer side effects. A few drugs like

fosphenytoin are used only in hospital setting for status epilepticus. See TABLE III Selected New Anti-Epilepsy Drugs (AEDs).

Most of the new AEDs were approved as add-ons for conventional therapies, but additional research revealed new possible uses as monotherapy. Scientists found tiagabine (Gabitril®) is an effective anticonvulsive in humans based on its structure to increase GABA (although the exact mechanism is still under investigation). Another one of the new drugs is a GABA analog. Approved in January 2001, gabapenitin (Neotin®) binds to an auxiliary protein of voltage-gated calcium channels (a2/3) and apparently modulates the action of calcium channels and neurotranmitter release.

The AED topiramate affects glutamte receptors. Angehagen *et. al* (2003 *Epilepsy Research* 54,1,63-71) found that topimamate (Topamax®) protected against glutamate and kainite-induced neurotoxicity upon neuronal cells in a primary culture. This drug is recommended as an add-on for partial seizures.

Kindling is a phenomenon in which a small change in neuronal activity, if repeated, may lead to full-blown epilepsy. S. Stratton *et. al* (2003 *Epilepsy Research* 53,1,2,95-106) investigating lamotrigine (Lamictral®) and levetiracetam (Keppra®) found that these drugs possessed the ability to counteract kindling acquisition, which distinguish them from other compounds with sodium channel blocking  activity. Long term data released on February 6, 2003 revealed that Keppra offers sustained efficacy, as add-ons, over the longer term- up to 54 months in reducing frequency u adult patients with difficult to treat partial seizures. Keppra is well tolerated by patients.

Zonegran® or zonesimide, an anti-lepsy drug for partial seizures, was approved March 28, 2002. This drug has a group of unique multiple mechanisms of actions in that it blocks sodium channels, reduces voltsge-dependent transient inward T-type $Ca^{2+}$ channels, and facilitates both dopaminergic and seratonergic neurotransmission. The effect may be due to the increase of GABA release from the hippocampus.

T. *Welty et. al* at the American Epilepsy Society 56th Annual Meeting, December 2002, described the outcomes of an ongoing study of patients with juvenile myoclonic epilepsy treated with lamotrigine, topiramate, zonesimide, or levetiracetam and found that topiramate and zonesimide produced dramatic reductions in the frequency of generalized tonic-clonic seizures. This study and other presenters at the meeting led the participants to believe that some of the AEDs may have a broader spectrum of effectiveness that those approved. Side effects and over treatment continue to be major concerns.

It has been three years since the FDA approved most of the new AED's for use. None of these obtained an indication for monotherapy in the past year, and much of the research has been on new indicators, such as new epileptic syndromes, tolerability, and establishing the best dose. Preclinical research on the neuroprotective potential of AEDs continues to move forward, but is not consistent enough to result in clinical trials.

**Surgery**

When medication will not control seizures, doctors may recommend evaluation for surgery. A team of doctors usually at a university medical center looks at the type of seizures the person has and at the brain region involved. Surgeons avoid operating if the focal point is in an area of the

brain involved in speech, language, hearing, or other important abilities. Three broad categories are usually treated successfully by surgery: partial seizures, seizures that begin as partial before spreading to the rest of the brain, and the multifocal epilepsy like the rare Rasmussen's encephalitis. Surgery can reduce or halt seizures for some people with these conditions, but the procedures are not without risk. A lot of new research is going on to develop techniques in surgery. Radiosurgery is being used experimentally in some medical centers to treat epilepsy.

Presentations at the 56th Annual Meeting of the American Epilepsy Society focused on the area of neurostimulation. Four categories were represented: vagus nerve stimulation (VNS), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and direct stimulation of the epilepsy focus in response to the start of a seizure, a procedure that drew lots of interest. VNS is an accepted therapeutic practice that has placed more than 1700 implants in people with epilepsy. The mechanism of exactly how neurostimulation works is not fully understood. One group of researchers implanted DBS electrodes in the amygdala-hippocampal area of four patients and found a greater than 50 percent reduction of seizures and not side effects. Several reports revealed a new system called the NeuroPace that detects the onset of a seizure and then delivers an electrical stimulation or an AED directly to the ictal focus area to stop the impending seizure.

**Neuroimaging and Beyond**

Neuroimaging is playing an important role in the treatment of patients with epilepsy. While electroencephalography is still used, magnetic resonance imaging (MRI) is becoming the most important technique edging out computerized tomography (CT) . The new MRI protocols such as fluid-

attenuated inversion recovery (FLAIR) imaging have enhanced the processes of epilepsy. FLAIR reveals features especially of hippocampal sclerosis show the underlying atrophy and loss of internal regions. Other new imaging techniques include:

- magnetic resonance spectroscopy (MRS) that can provide noninvasive biochemical measurement of specific brain metabolites
- magnetic resonance relaxometry (MRR) that can evaluate abnormal T1 and T2 signal of epilepsy
- functional magnetic resonance imaging (FMRI), receptor PET studies using specific neuroreceptor ligands
- magnetoencephalography (MEG) providing the recording of the magnetic fields generated by intraneuronal electrical currents.

Diets are sometimes recommended as alternative therapies. The ketogenic diet for epilepsy has seen its ups and downs over a period of years. However, investigators are still looking to find the possible connection between diet and prevention of seizures. The ketogenic diet is high in fat and low in carbohydrates and protein. The resulting ketosis exerts an antiepileptic effect although the process of how it works is not clear. Several presenters at the 2002 American Epilepsy Society Meeting monitored side effects and complications of the diet. One researcher reported that the participants had a reduction in bone mass, a major health problem.

Others are suggesting transplanting fetal pig neurons that produce GABA into the brains of patients. Stem cells also may be used in treatment. And don’t count out gene therapy. Dr. Noebels said that scientists now know that loss of a protein called cystatin B causes increasingly bad seizures in

myclonic epilepsy. A next logical step is to give back patients the missing protein. He asked the question, “What are we waiting for?”

**Conclusion**

No cure exists for epilepsy at the present, and therapies are designed to remedy seizures and undesirable behaviors. However, at the National Institute of Health NINDS conference in 2000, Dr. Timothy Pedley of Columbia University entitled a hope-filled talk “Epilepsy 2000: The Beginning of the End.” He encouraged scientists to adopt a new enthusiasm for inquiry in the new millennium. This spirit is certainly prevalent in piecing together the puzzle of epilepsy. Investigations in molecular genetics, targeted drug development, and brain imaging allows for the first time humans to volunteer for basic research studies. The genetics revolution has made it possible that other potential therapies such as stem cell transplants, stimulation of the brain, and gene therapy will happen in the near future. All the makings of science fiction are seen in epilepsy research, but as we have seen from the past what is today’s science fiction may soon become science history.

# Table I- Facts and Figures of Epilepsy

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| World-wide- 6 out of 100 or 42 million people are afflicted |
| 2.3 million Americans have a form of epilepsy |
| 30 percent of epileptics are not helped by medication- some 600,000 |
| 3.5 million new cases of epilepsy occur each year- 40 percent in children |
| 50 percent of cases world-wide are idiopathic of no known origin |
| 85 percent of the world's patients do not receive treatment- |
| 98 percent of people in Ethiopia do not receive treatment |
| About 195,000 people in US each year have status epilepticus, prolonged life-threatening seizures, causing 42,000 deaths. |

**Source: D&MD**

# TABLE II Selected Gene Epilepsy Syndromes as of June 2002

| Epilepsy syndrome | Chromosomal location | Gene |
|---|---|---|
| Childhood absence epilepsy | 8q24 | ? |
| AD juvenile myoclonic epilepsy | 6p21<br>5q14<br>5q34 | ?<br>?<br>GABRA1 |
| Adolescent-onset idiopathic generalized epilepsies | 8p12<br>18q12<br>5p | ?<br>?<br>? |
| Idiopathic generalized epilepsy | 3q26<br>14q23<br>2q36 | ?<br>?<br>? |
| Familial adult myoclonic epilepsy | 8q24 | ? |
| AD partial epilepsy with auditory features | 10q24 | LGU |
| AD nocturnal frontal lobe epilepsy | 20q13<br>1q<br>15q24 | CHRNA4<br>CHRNB2<br>? |
| AD febrile seizures | 8q13<br>19p<br>5q14-15 | ?<br>?<br>? |
| Temporal lobe epilepsy | 12p | Kv1.1 |

**Source: D&MD adapted from information provided by Dr. Jeffrey Noebels**

**TABLE III The New Drugs: Selected AED Treatment**

| AED | Brand name | Company | Effect | Comments |
|---|---|---|---|---|
| **Tiagabine** | **Gabitril** | **Cephalon** | **Oral AED approved for partial seizure; preclinical data shows GABA prevents problem of neural impulses that contribute to seizures** | **May cause dizziness, drowsiness, or trouble in thinking** |
| **Lamotrigine** | **Lamictral** | **SmithGlaxoKline** | **For drug-resistant partial epilepsy** | **May have side effects; rash** |
| **Gabapentin** | **Neotin** | **Pfizer** | **Modulates action of calcium channels and neurotransmitter release** | |
| **Topiramate** | **Topamax** | **Ortho-McNeil** | **Protects against glutamate activity at AMPA and KA receptors** | **Approved for Lennox-Gastaut syndrome; add on for drug resistant partial** |
| **Levetiracetam** | **Keppra** | **UBC Pharma** | **Efficacy reduction in seizure frequency** | **Add-on for drug-resistant localization epilepsy** |
| **Felbamate** | **Felbatol** | **Felbatol Pharmacy/ Carter Wallace Labs** | **For those with seizures when other medications fail** | **An older drug; person must risk aplastic anemia** |
| **Flutamide** | **Euflex** | **Schering** | **Non-steroid antiandrogen** | **Elevates clonic seizure threshold** |

| | | | | |
|---|---|---|---|---|
| **Zonesamide** | **Zonegran** | **Élan** | **Blocks sodium channels; may be due to increase of GABA release from hippocampus** | **Approved 3/28/02 for partial seizures** |
| **Fosphenytoin** | **Cerebyx** | **Eisai** | **For use in hospitals only for status epilepticus** | **Hospital based** |
| **Oxcarbamazepine** | **Trileptal** | **Novartis** | **May be used in monotherapy or add-on** | **Partial seizures- less side effects that the first choice carbamazamine** |

**Source: D&MD**